

Challenges of the current medicine

**Elżbieta Krajewska-Kułak, Jolanta Lewko,
Wojciech Kułak, Mateusz Cybulski**

Vol. 12

ISBN- 978-83-67454-29-2

***Challenges of the current
medicine***

Volume XII

Medical University of Białystok
Faculty of Health Sciences



Challenges of the current medicine Vol. 12

**Edited by
Elżbieta Krajewska-Kulak
Jolanta Lewko
Wojciech Kulak
Mateusz Cybulski**

Białystok 2023

REVIEWERS

Dr hab. Katarzyna Van Damme -Ostapowicz
Western Norway University of Applied Sciences,
Faculty of Health and Social Sciences,
Førde, Norway

Dr hab. Ruslan Yakubtsevich
Department of Anesthesiology and Emergency Medicine
Grodno State Medical University

ISBN- 978-83-67454-29-2

The first Edition
Białystok 2023

Graphic Design: Agnieszka Kułak-Bejda

Printed by:
RobotA Piotr Duchnowski, Zaścianki 6, 15-521 Zaścianki

*Nothing can stop the man with the right mental attitude from achieving his goal;
nothing on earth can help the man with the wrong mental attitude*
Thomas Jefferson

Dear Colleagues

The monograph periodical “*Challenges of the Current Medicine - 12 Edition*” is a collection of works written by authors from many different medical centers.

The fourth report of the National Health Test of Poles from 2023 clearly showed that health prevention should be constantly reminded because good habits are formed over the years.

The National Health Test of Poles is the largest health study on the Polish Internet (according to available data). In 2023, almost 208,000 people took part in it, and over a million surveys have been completed since the beginning of the study.

Before the pandemic, the group of healthier people dominated, and now, more than half of Poles have long-term health problems or chronic diseases (lasting six months or more). As much as 52%. Poles have long-term health problems. Not only the oldest are affected because in the group of the youngest adults (18-24 years old), 36% of people have long-term health problems, and this percentage is significantly increasing in older age groups.

Almost every third Pole declared that he had been diagnosed with arterial hypertension, every eighth with heart disease, every eleventh with diabetes, every twentieth with cancer, and every thirty-third with chronic obstructive pulmonary disease. The proportion of people with chronic non-communicable diseases increases rapidly with age.

It turned out that 9% of Poles sleep less than six. Most people (21%) who do not get enough sleep (less than six hours) are among the 45-64-year-olds. As many as 74% of Poles sleep six to eight hours daily. 7% sleep more than nine hours a night. subjects.

Most often, Poles choose meat meals (24%) and meals balanced in accordance with the recommendations of dietitians (21%). Vegetarian or vegan meals are most often chosen by 4% of Poles. Every fifth Pole (19%) eats fast food several times a month, and 3% even several times a week - in this group, the most significant percentage are people aged 18-24. Only 31% of Poles eat vegetables every day, and 35% of Poles eat fruit.

Total abstinence was declared by 20% of Poles. 9% of adult Poles drink alcohol at least once a day. 14% of men drink alcohol at least once a day, and 5% of women drink alcohol every day.

The percentage of active smokers of all tobacco products is, on average, 28%, and 21% of Poles are heavy smokers, and 8% use tobacco products occasionally. Thus, year on year, there is a slight decrease in interest in tobacco products.

Compared to previous years, changes in diet, physical activity, or avoidance of stimulants, i.e., lifestyle in general, are not large, although in general, a slight improvement can be seen in this area. However, compared to previous years, Poles have finally started to get tested, and year to year, there are substantial increases in almost all essential and screening incidences.

*Prof. Elżbieta Krajewska-Kulak
Dr hab. Jolanta Lewko
Prof. Wojciech Kulak
Prof. Mateusz Cybulski*

CONTENS

SELECTED PROBLEMS CONNECTED WITH CORONAVIRUS INFECTION

Kaja Sładkowska, Andrzej Dłubak, Julia Honisz, Filip Kruczek, Maciej Dyda: Ocular complications of SARS-CoV-2	11
Mariola Bartusek: Artificial intelligence in health care. Opportunities and threats of using technology during the pandemic	23
Oskar Pastuszek, Anna Susłow: Long Covid as a significant problem in orthopedics and rheumatology	32
Marta Zasieczna, Grzegorz Mikita, Natalia Wawrzeczko, Magdalena Raczkowska, Natalia Jendrzejczyk, Aleksandra Faryś, Paweł Dąbrowski: The impact of the lockdown caused by the Covid-19 pandemic on the human skeletal system	43

SELECTED CLINICAL AND THERAPEUTIC PROBLEMS

Sven Solisch, Anna Susłow, Adam Szwed, Krzysztof Gomulka: Significance of gut microbiome in heart diseases	54
Maria Kręcicka, Julia Drewniowska, Magdalena Góral, Maciej Dyda: Alzheimer's Disease - ophthalmological point of view	63
Aleksandra Jany, Magdalena Urbaniak: Drusen in ophthalmology	80
Magdalena Urbaniak, Aleksandra Jany: Herpes simplex infection of the eye	95
Kinga Łysak, Agata Walulik, Michał Błaszczewicz, Krzysztof Gomulka: A Short Review of Inflammation Process and Therapeutic Concepts in Diabetic Retinopathy	106
Katarzyna Jania: Non-imaging diagnosis of infective endocarditis - challenges and guidelines	125
Adam Szwed, Krzysztof Gomulka: Review of selected immunological aspects of plant-based diets	134
Maja Mielczarek, Jan Sroczyński, Paulina Wójcik: Robotic versus laparoscopic approach in bariatric surgery	140
Maja Mielczarek, Julia Wodniakowska, Paulina Wójcik, Jan Sroczyński: Laparoscopic groin hernia repair	147
Maria Greniuk, Maria Łuszcz, Paula Hauzer, Jakub Cisek, Mateusz Mierniczek, Michał Łabuda, Przemysław Kubicki: Current approach in postoperative management of patients after bariatric surgery- an overview of guidelines	155
Aleksandra Korta, Julia Kula, Krzysztof Gomulka: Interleukin 23 and its role in Inflammatory Bowel Disease	167
Laura Więcko, Marzena Jargilo, Łukasz Dylewicz, Kacper Solarz, Jakub Bętkowski: The Antibiotic Resistance Crisis	177
Łukasz Dylewicz, Jakub Bętkowski, Jakub Rudzki, Zuzanna Kata, Laura Więcko, Kacper Solarz, Justyna Talaska: Current and future role of AI in Medicine	183

Anita Froń, Urszula Tokarczyk, Karol Zagórski: Endometriosis – what we should know	193
Agata Boczar, Patryk Dryja: Juvenile idiopathic arthritis - the latest perspective on the current state of knowledge	206
Zuzanna Kata, Jakub Rudzki, Laura Więcko, Łukasz Dylewicz, Kacper Solarz, Jakub Bętkowski, Justyna Talaska: Nosocomial infections as a serious problem in the healthcare sector	212

SELECTED PROBLEMS IN PSYCHIATRY

Joanna Mikulska, Diana Pietrzak, Paweł Rękawek, Krystian Siudaj, Łucja Walczak-Nowicka: Oxidative stress and inflammation - common pathogenesis of Celiac disease and depressive disorder	220
Michał Bolek, Justyna Klimczak, Dominika Musialska: Bigorexia: The Perils of Chasing an Ideal Body	237
Michalina Toborek, Katarzyna Sudelska, Tomasz Król, Grzegorz Tarsa: Coping with stress in the 21 st century	242
Julia Błońska, Maciej Dydą, Tomasz Malinowski, Michał Orzechowski: A modern view on whether marijuana should be considered a medicine or a narcotic	256
Maciej Pachana, Julia Marschollek, Hubert Sawczuk, Julia Letkiewicz, Piotr Kukula: Application of artificial intelligence in diagnosing and treating mental disorders	274
Gabriela Świrkosz, Julia Wójcik, Katarzyna Logoń, Anna Łysik, Joanna Zapala: Laziness, daydreaming, restlessness? Try executive dysfunction, inattentiveness and hyperactivity - ADHD in adult	284
Zuzanna Lizoń, Hubert Sawczuk, Paulina Typek: REM sleep behavior disorder - what do we know?	299
Wiktoria Lewicka, Michał Szyszka, Klaudia Włodarczyk, Paweł Drymluch, Marta Malicka, Julia Sobczak: Postpartum psychosis: risk factors, diagnosis, and treatment	308
Zuzanna Lizoń, Paulina Typek: Deep brain stimulation in psychiatry	322
Paulina Zegarska, Eliza Mędrek: Psychotherapy as a supportive method in psychiatric disorders and schizophrenia	333
Klaudia Włodarczyk, Natalia Nowak, Weronika Biziorek, Haytham Al Hamaydeh, Diana Ranja Rabih: Sexuality and gender issues in autism spectrum disorder	337
Julia Wójcik, Karol Zagórski, Tomasz Dudzik, Ewa Szczesna, Izabella Sośniak: The Nature of Addiction to Common Drugs	346
Dominika Ziółkowska, Renata Fedyk, Kamila Florek, Jakub Grzonka, Wojciech Węgrzyn, Michał Szyszka, Paulina Tomecka: Controversies over PANDAS	356

**SELECTED PROBLEMS CONNECTED
WITH CORONAVIRUS INFECTION**

OCULAR COMPLICATIONS OF SARS-COV-2

Kaja Śladkowska, Andrzej Dłubak, Julia Honisz, Filip Kruczek, Maciej Dyda

Wrocław Medical University

ABBREVIATION LIST

- COVID-19- coronavirus disease
- SARS-CoV-2 Severe acute respiratory syndrome coronavirus 2
- L-DOPA- levodopa
- BADI- Bilateral acute depigmentation of the iris
- BES- Burning eye syndrome
- CRAO- Central retinal artery occlusion
- CRVO- central retinal vein occlusion
- OCT- optical coherence tomography
- FA- Fluorescein angiography
- AMN- Acute macular neuropathy
- SD-OCT- Spectral-domain optical coherence tomography

On May 5th, 2023 The WHO Director-General, Dr Tedros Adhanom Ghebreyesus determined that COVID-19 is now an established and ongoing health issue that no longer constitutes a public health emergency of international concern and on May 11th The US COVID-19 national emergency and public health emergency ended [1].

Those events give an opportunity for summary and conclusions. In this study, we focused on ophthalmic complications in COVID-19 patients.

BACKGROUND

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus [2]. The virus mainly attacks the respiratory system nevertheless since the 2020 pandemic

outbreak more and more studies reveal the virus's impact on other organs. The pathophysiological base of complications associated with COVID-19 infection might be diverse; studies name hypercoagulability, dysregulated immune response, and endothelial cell damage leading to thrombosis, including arterial and venous thrombotic systemic events [3, 4]. The question of whether thrombosis is specific to SARS-CoV-2 or is a pathway of the thromboinflammatory response to viral infection remains uncertain [5].

OPHTHALMOLOGICAL COMPLICATIONS OF COVID-19 INFECTION

In this study in favor of improving the outlook on the following problem, the authors decided to divide the ophthalmologic complications post-COVID-19 infection according to the region of the sight organ they occur in.

Focusing on the anatomy of the sight organ the ophthalmologic complications can be attached to the anterior section which consists of eyelids, conjunctiva, cornea, iris, sclera, and lens, and to the posterior section containing vitreous, retina, and uvea. Issues linked with an optic nerve are treated as part of the sight organ and will be considered neuro-ophthalmic manifestations.

ANTERIOR SECTION

Blepharospasm

There is scarce information regarding blepharospasm incidence in COVID-19 patients. Farci et al. described two women aged 43 and 63 and one man aged 54 who developed this complication 2 weeks, 3 weeks, and 4 months after COVID-19 infection respectively [6].

Blepharospasm is a dystonia characterized by abnormal contraction of the eyelid muscles. Symptoms start with mild and infrequent spasms that progress over time to forceful and frequent contractures of the eyelids, in advanced cases causing functional blindness from an inability to temporarily open the eyes [7].

This dystonia may be attributable to basal ganglia and diencephalic dysfunction as a result of transneuronal penetration of COVID-19 even in the absence of olfactory and gustative symptoms. The authors hypothesized that the binding of SARS-CoV-2 to basal ganglia ACE receptors alters the degradation of L-DOPA to dopamine and causes blepharospasm [6].

Myokymia

Eyelid myokymia, characterized by episodic or persistent fine, spontaneous undulating contractions of the upper or lower lids, has been observed in 15 patients during or immediately after the recovery of systemic disease. Most patients (except for 2) experienced complete resolution of lid myokymia within 3 months of onset [8].

The exact causes of this condition are not well understood, but it is often associated with factors such as stress, fatigue, and caffeine intake [9].

Interestingly, the recovery time of myokymia was not influenced by the severity of the systemic illness but was found to be significantly delayed in older patients and those with prolonged hospitalization [8].

Conjunctivitis

Conjunctivitis has been thought to be among the most common ocular complications of COVID-19 not only in adults but also in children [10–18].

It is manifested by conjunctival hyperemia, chemosis, foreign body sensation, and epiphora [10, 13, 19]. In several cases it has been recorded as one of the first manifestations of infection as shown by Colavita et al. or Cheema et al. who reported keratoconjunctivitis as the initial medical presentation of COVID-19 [16, 20].

Conjunctivitis is frequently observed as the predominant ophthalmic manifestation in children and can manifest at any stage of the disease. Moreover, ophthalmic symptoms may serve as the initial and solitary indication of COVID-19 infection [15].

In Kumar et al. observational study 2742 patients were examined. At admission none had ocular symptoms, however on follow-up (every 72 hours or when ocular symptoms occurred) 20 (0.72%) developed ocular manifestations, of which 19 (95%) had features suggestive of bilateral viral conjunctivitis [21].

It supports conjunctivitis being the most common in terms of ocular manifestations, however, it also shows that regarding the rate of incidence of ocular manifestations, the studies are incohesive. Almazroa et al. in their systematic review also found discrepancies about the presence of conjunctivitis in COVID-19 patients and suggested the severity of the cases as one of the reasons. However, they supported the view of conjunctivitis is the most common ocular presentation in COVID-19 patients [22].

Keratitis

It is a rarely occurring ocular complication. In Wasfy et al. study out of 425 patients 2 (0.5%) developed keratitis while conjunctivitis developed in 111 (26.1%) patients [13].

Keratitis in COVID-19 was characterized by pain, photophobia, and tears in the affected eye with or without systemic COVID-19 symptoms [13, 23].

In a case study by Cano-Ortiz et al., the first published case of early-onset bilateral interstitial keratitis in a COVID-19-positive patient was presented. The treatment involving Dexamethasone 1 mg/ml was initiated. Fourteen days after treatment, the right cornea was completely transparent, and the left cornea showed remarkable improvement in transparency with no other recurrences over a 6-month follow-up [24].

Zuo et al. described a patient who developed keratitis 3 days before common COVID-19 symptoms. The authors pointed out the corneal inflammation looked distinct from common keratitis (under a slit lamp microscope a shallow white turbid focus with a clear boundary, and a large number of fine particles could be seen). The patient was treated with Ganciclovir eye drops [23].

Bilateral acute depigmentation of the iris

Bilateral acute depigmentation of the iris, also known as BADI, is a rare disease that affects mostly young women [25].

In the clinical course of that disease, we observe progressive symmetrical pigment loss of the iris stroma. The prognosis is usually favorable and the pigmentation can recover over the time of 3 to 4 years, however, several cases show adverse effects of that state, such as the development of vision loss and glaucoma [25, 26].

The etiology of BADI is still not fully known, although experts tend to point to viral infections and systemic antibiotic use as possible causes. As the COVID-19 pandemic began, cases of BADI with possible coronaviral onset were also described. BADI usually does not develop during active COVID-19 inflammation, but rather a couple months after. To the best of our knowledge, the relationship between SARS-CoV-2 and BADI is still yet to be explained. One of the more extensive studies dedicated to BADI conducted by Turkish experts shows that in only 38,5% of instances, depigmentation was linked with viral infections [26].

According to case reports, the development of BADI does not correlate with the severity of

the preceding coronaviral infection, as described patients recovered quickly and suffered from mild symptoms. Moreover, both patients didn't have a relevant ophthalmological history before BADI [27]. No other symptoms or ophthalmologic pathologies in further examination were found. Described patients were treated with topical 0,1% dexamethasone 5 times a day, but no noticeable changes were spotted over the time of 1 month. As for now, there is not enough research to determine if BADI is directly correlated with SARS-CoV 2 or long COVID syndrome, but this infection should be kept in mind as a possible cause.

Episcleritis

Episcleritis is an acute inflammation of the episclera, the most superficial layer of the sclera. This condition occurs both in men and women, with a peak in the fourth decade. The most common symptoms appearing during episcleritis are redness of the sclera (caused by congestion of the episcleral vascular network), discomfort, foreign-body sensation, and rarely mild pain. According to studies conducted on 159 patients, this condition is usually unilateral, although 36,5% of examined patients developed bilateral episcleritis [28].

The etiology of episcleritis is yet to be fully known. Most of the cases are idiopathic, a but significant number are linked with autoimmune diseases or various infections, such as Lyme disease, syphilis, or cat-scratch disease. SARS-CoV 2 can also be counted as a possible pathogen factoring into the development of episcleritis. One of the first published case reports dedicated to the possible association between COVID-19 disease and episcleritis, described a patient developing episcleritis only 7 days after testing positive for COVID-19. The patient, a 31-years old female had no relevant ophthalmologic history, and was only suffering from mild symptoms related to viral infection. Treated with fluorometholone and artificial tears, symptoms resolved after 6 days of treatment [29].

Another case report is presenting a similar medical course, only the described patient, a 29-years old man, developed symptoms of episcleritis 3 days before the first signs of the COVID-19 infection [30].

Burning eye syndrome

Burning eye syndrome, also known as BES is included as one of the COVID-19 symptoms Not linked with the respiratory tract [31, 32]. As a neuropathic disease, its main manifestation is

spontaneous, burning pain combined with a sensation of dryness, allodynia, and hyperalgesia [33].

The etiology of BES is diverse and includes injuries, allergies, and autoimmune diseases. There are also reports suggesting that SARS-CoV-2 is a factor causing the development or deterioration of BES symptoms. According to a broad systematic review and meta-analysis, the correlation between the severity of COVID-19 and occurring of BES is not evident, age or gender also does not seem to have an impact on COVID-19-related BES. First signs of BMS statistically occur 1 week after the first COVID-19 symptoms. The correlation between BES and SARS-CoV 2 is still under-studied, but the possibility that BES could be a part of the so-called long COVID syndrome must be remembered [32].

NEURO-OPHTHALMIC SECTION

Coronavirus SARS-CoV 2 mainly affects the respiratory system; however, there are reports of neurological manifestations [34]. A wide variety of neuro-ophthalmologic manifestations have also been found in association with COVID-19, mostly related to demyelinating disease. While the mechanism of these manifestations is unknown, hypotheses include direct neuronal invasion, endothelial cell dysfunction leading to ischemia and coagulopathy, or a widespread inflammatory "cytokine storm" induced by the virus [35].

Optic perineuritis

Optic perineuritis is a rare manifestation of orbital inflammatory disease in which the specific target tissue is the optic nerve sheath. The optic nerve sheath becomes inflamed secondary to one of a variety of potential etiologies. It is comprised of a spectrum of diseases that can be divided into two categories: primary and secondary. Primary is idiopathic in nature and secondary is considered to be a part of an identifiable systemic condition [36].

It typically presents with optic neuropathy; thus, classic demyelinating conditions must be ruled out before making a diagnosis [37].

Typical symptoms involve decreased visual acuity or unilateral vision loss, diplopia, eye pain, and color deficits however some cases report other orbital signs, such as ophthalmoplegia and proptosis. The diagnosis is made based on clinical examination and radiographic findings [37].

Optic neuritis

Optic neuritis is an inflammatory demyelinating condition of the optic nerve that typically presents as subacute, unilateral vision loss or decreased vision, and periorbital worse with eye movement. It is commonly known as the first presenting sign of multiple sclerosis, and thus it is necessary to initially rule that cause out. However, multiple studies report the possibility of optic neuritis occurring as a complication due to a viral infection. Symptoms in cases of optic neuritis associated with COVID-19 might range from mild to severe. The most common presenting symptoms have included eye pain, decreased visual acuity, and headache. The mild character of the neuritis might not impact the patient's vision and the pain might appear only with eye movements [38].

Central retinal artery occlusion

Central retinal artery occlusion (CRAO) by definition represents end-organ ischemia and is analogous to terminal branch occlusion in cerebral stroke. It results in infarction of the retina and profound, usually monocular, painless vision loss, and is associated with significant functional morbidity. Approximately 15–30 % of the general population have a cilioretinal artery, which is a branch of the short posterior ciliary artery. It supplies a part or the whole of the fovea, and in those eyes where there is a CRAO, the cilioretinal artery is spared and the visual acuity may be preserved at 20/50 or better, with loss of peripheral vision only [39].

POSTERIOR SECTION

Retinal Venous Occlusion

When it comes to venular or arterial occlusions, one of the most often described as central retinal vein occlusion (CRVO). In COVID-19 patients suffering from CRVO, the median age is 36, while non-COVID-19 patients are usually above 60. Moreover, only 36% of the COVID-19 patients with CRVO have cardiovascular diseases which is considered a risk factor for central retinal vein occlusion [40].

Pathogenesis, as Evidence shows, is linked with inflammatory cytokine storm and viral evasion of cellular immune responses which leads to vasoconstriction, ischemia, tissue edema, and a procoagulant state [41].

Fluorescein angiography (FA) and optical coherence tomography (OCT) demonstrate features not different from CRVO from non-COVID-19-related causes [42].

Acute macular neuropathy

Acute macular neuropathy (AMN) is a rare condition with unknown etiology but, about 50% are associated with respiratory or influenza-like illness, and the number of cases increased since the COVID-19 outburst and some cases have already been linked with COVID-19 infection in young women [42–45]. AMN is a manifestation of retinal microvascular ischemia. It presents with central scotoma, photopsia, and mild visual acuity loss [45]. Vision loss may be caused by vascular compromise of the deep retinal capillary plexus of the retina [46].

Fluorescein angiography and OCT angiography can demonstrate ischemia, enlargement of the foveal avascular zone, and capillary drop-out areas [45].

Uveitis

Uveitis is an inflammation of the iris and ciliary body due to a breakdown in the blood-aqueous barrier. Anterior uveitis accounts for 75 percent of all uveitis cases and can be classified as acute, recurrent, or chronic. Etiology can be infectious (f.e. viral) or no-infectious, for example autoimmune [47].

The majority of uveitis or reactivation of uveitis are linked to COVID-19 vaccination, but cases of post-covid anterior uveitis also occurred [48].

Patients typically show eye symptoms like redness, photophobia, blurred vision, or lacrimation, then, after considering symptoms, early use of corticosteroids at a moderate dose for a short course may enhance recovery of the COVID-19 patient [49].

Vitritis

The case of post covid vitritis was also reported. A 57-year-old woman, 12 days after covid infection onset experienced bilateral redness in her eyes. SD-OCT showed hyperreflectivity at the level of posterior vitreous hyaloid corresponding to the vitritis and fluorescein angiography showed corresponding hyperfluorescence. After ruling out other causes, for example, CMV, HSV, toxoplasmosis, and borrelia, COVID-19 was presumed the cause of the described changes shown in OCT [50].

REFERENCES

1. Statement on the fifteenth meeting of the IHR (2005) Emergency Committee on the COVID-19 pandemic. [https://www.who.int/news/item/05-05-2023-statement-on-the-fifteenth-meeting-of-the-international-health-regulations-\(2005\)-emergency-committee-regarding-the-coronavirus-disease-\(covid-19\)-pandemic](https://www.who.int/news/item/05-05-2023-statement-on-the-fifteenth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic). Accessed 24 Jun 2023.
2. Coronavirus. <https://www.who.int/health-topics/coronavirus>. Accessed 24 Jun 2023.
3. Borrego-Sanz L, Guerres-Villahoz N, Fernández-Tresguerres F, Santos-Bueso E (2021) Optic neuropathy in a COVID-19 patient. *Journal Français d’Ophtalmologie*, 2021, 44, 1271–1273.
4. de Oliveira MR, Lucena ARV, Higino TM, Ventura CV. Central retinal artery occlusion with cilioretinal artery sparing secondary to COVID-19: Additional ocular complication. *Indian Journal of Ophthalmology*, 2023, 71, 663–666.
5. Rapkiewicz AV, Mai X, Carsons SE, et al. Megakaryocytes and platelet-fibrin thrombi characterize multi-organ thrombosis at autopsy in COVID-19: A case series. *eClinicalMedicine*, 2020, 24, 100434.
6. Farci R, Fossarello M, Carta A. Blepharospasm as a tardive manifestation of COVID-19 disease: A case report. *Indian Journal of Ophthalmology*, 2023, 71, 669–670.
7. Blepharospasm - EyeWiki. <https://eyewiki.aao.org/Blepharospasm>. Accessed 24 Jun 2023
8. Khan HA, Shahzad MA, Jahangir S. et al. Eyelid Myokymia—a Presumed Manifestation of Coronavirus Disease 2019 (COVID-19). *SN Comprehensive Clinical Medicine*, 2022, 4(1), 29.
9. Jafer Chardoub AA, Patel BC. Eyelid Myokymia. StatPearls. StatPearls Publishing, Treasure Island (FL), 2023
10. Wu P, Duan F, Luo C, et al. Characteristics of Ocular Findings of Patients With Coronavirus Disease 2019 (COVID-19) in Hubei Province, China. *JAMA Ophthalmology*, 2020, 138, 575–578.
11. Chen L, Deng C, Chen X, et al. Ocular manifestations and clinical characteristics of 535 cases of COVID-19 in Wuhan, China: a cross-sectional study. *Acta Ophthalmologica*, 2020, 98, e951–e959.
12. Daryabari SH, Asadollah A, Moghadam FA, et al. Detection of COVID-19 in tears of ICU-admitted patients with SARS-CoV-2 infection. *International Ophthalmology*, 2022, 42,

- 723–727.
12. Wasfy T, Eldesouky MA, Serag Y, Elbedewy HA. Concurrent and Post COVID-19 Ophthalmological Implications. *Clinical Ophthalmology*, 2021, 15, 4467–4473.
 13. Valente P, Iarossi G, Federici M, et al. Ocular manifestations and viral shedding in tears of pediatric patients with coronavirus disease 2019: a preliminary report. *Journal of American Association for Pediatric Ophthalmology*, 2020, 24, 212–215.
 14. Ichhpujani P, Singh RB, Dhillon HK, Kumar S. Ocular manifestations of COVID-19 in pediatric patients. *Therapeutic Advances in Ophthalmology*, 2023, 15, 25158414221149916.
 15. Cheema M, Aghazadeh H, Nazarali S, et al. Keratoconjunctivitis as the initial medical presentation of the novel coronavirus disease 2019 (COVID-19). *Canadian Journal of Ophthalmology*, 2020, 55, e125–e129.
 16. Navel V, Chiambaretta F, Dutheil F. Haemorrhagic conjunctivitis with pseudomembranous related to SARS-CoV-2. *American Journal of Ophthalmology Case Reports*, 2020, 19, 100735.
 17. Seah I, Agrawal R. Can the Coronavirus Disease 2019 (COVID-19) Affect the Eyes? A Review of Coronaviruses and Ocular Implications in Humans and Animals. *Ocular Immunology and Inflammation*, 2020, 28, 391–395.
 18. Xia J, Tong J, Liu M, et al. Evaluation of coronavirus in tears and conjunctival secretions of patients with SARS-CoV-2 infection. *Journal of Medical Virology*, 2020, 92, 589–594.
 19. Colavita F, Lapa D, Carletti F, et al SARS-CoV-2 Isolation From Ocular Secretions f a Patient With COVID-19 in Italy With Prolonged Viral RNA Detection. *Annals Of Internal Medicine*, 2020, 17, M20-1176.
 20. Kumar KK, Sampritha UC, Prakash AA, et al Ophthalmic manifestations in the COVID-19 clinical spectrum. *Indian Journal of Ophthalmology*. 2021, 69, 691–694.
 21. Almazroa A, Alamri S, Alabdulkader B, et al. Ocular transmission and manifestation for coronavirus disease: a systematic review. *International Health*, 2021, 14, 113–121.
 22. Zuo D-M, Xue L-P, Fan H, et al. COVID-19 infection with keratitis as the first clinical manifestation. *International Journal of Ophthalmology*, 2022, 15, 1544–1548.
 23. Cano-Ortiz A, Leiva-Gea I, Ventosa ÁS, et al. Stromal interstitial keratitis in a patient with

- COVID-19. *The Journal Français D'ophtalmologie*, 2022, 45:e175–e177.
24. Atilgan CU, Kosekahya P, Caglayan M, Berker N. Bilateral acute depigmentation of iris: 3-year follow-up of a case. *Ophthalmology and eye diseases*, 2018, 10,
 25. Tugal-Tutkun I, Araz B, Taskapili M, et al. Bilateral Acute Depigmentation of the Iris: Report of 26 New Cases and Four-year Follow-up of Two Patients. *Ophthalmology*, 2009, 116, 1552-1557.e1.
 26. Soydan A, Kaymaz A (2023) Bilateral acute depigmentation of the iris determined in two cases after COVID-19 infection. *Indian Journal of Ophthalmology*, 2023, 71, 1030–1032.
 27. Watson PG, Hayreh SS (1976) Scleritis and episcleritis. *British Journal of Ophthalmology*, 1976, 60, 163–191.
 28. Méndez Mangana C, Barraquer Kargacin A, Barraquer RI. Episcleritis as an ocular manifestation in a patient with COVID-19. *Acta Ophthalmologica*, 2020, 98, e1056–e1057.
 29. Otaif W, Al Somali AI, Al Habash A. Episcleritis as a possible presenting sign of the novel coronavirus disease: A case report. *American Journal of Ophthalmology Case Reports*, 2020, 20, 100917.
 30. Meduri A, Oliverio GW, Mancuso G, et al (2020) Ocular surface manifestation of COVID-19 and tear film analysis. *Scientific Reports*, 2020, 10, 20178.
 31. Williams LD, Zis P. COVID-19-Related Burning Eye Syndrome and Burning Mouth Syndrome: A Systematic Review and Meta-analysis. *Pain and Therapy*, 2023, 12, 621–630.
 32. Kalangara JP, Galor A, Levitt RC, et al. Burning Eye Syndrome: Do Neuropathic Pain Mechanisms Underlie Chronic Dry Eye? *Pain Medicine*, 2016, 17(4), 746-755.
 33. Favas TT, Dev P, Chaurasia RN, et al. Neurological manifestations of COVID-19: a systematic review and meta-analysis of proportions. *Neurological Sciences*, 2020, 41, 3437–3470.
 34. Hu K, Patel J, Swiston C, Patel BC. Ophthalmic Manifestations of Coronavirus (COVID-19). *StatPearls*. StatPearls Publishing, Treasure Island (FL), 2023.
 35. Purvin V. Optic Perineuritis: Clinical and Radiographic Features. *Archives of Ophthalmology*, 2001, 119, 1299.
 36. Hussain A, Fazzone H, Elefant D, et al (2022) Orbital apex inflammation: a curious case of COVID-19. *Digital Journal of Ophthalmology*, 2022, 28, 69–73.
 37. Zhang J, Joiner D, Zhang C. Hyperacute optic neuritis in a patient with COVID-19 infection

- and vaccination: a case report. *BMC Ophthalmology*, 2023, 23, 80(2023).
38. Cugati S, Varma DD, Chen CS, Lee AW. Treatment Options for Central Retinal Artery Occlusion. *Current Treatment Options in Neurology*, 2013, 15, 63–77.
 39. D'Alessandro E, Kawasaki A, Eandi CM. Pathogenesis of Vascular Retinal Manifestations in COVID-19 Patients: A Review. *Biomedicines*, 2022, 10, 2710.
 40. Shiroma HF, Lima LH, Shiroma YB, et al. Retinal vascular occlusion in patients with the Covid-19 virus. *International Journal of Retina and Vitreous*, 2023, 23, 8(1), 45.
 41. Sen M, Honavar SG, Sharma N, Sachdev MS. COVID-19 and Eye: A Review of Ophthalmic Manifestations of COVID-19. *Indian Journal of Ophthalmology*, 2021, 69, 488–509.
 42. Reddy S, Garvin A, Weeks JL, West MR. In the Eye of the Cytokine Storm: A Tale of SARS-CoV-2-Induced Acute Macular Neuroretinopathy. *Cureus*, 2023, 15, e36797.
 43. David JA, Fivgas GD. Acute macular neuroretinopathy associated with COVID-19 infection. *American Journal of Ophthalmology Case Reports*, 2021, 24, 101232.
 44. Yılmaz Çebi A, Kılıçarslan O, Uçar D. Coincident Acute Macular Neuroretinopathy and Paracentral Acute Middle Maculopathy in COVID-19. *Turkish Journal of Ophthalmology*, 2023, 53, 120–123.
 45. Rahimy E, Sarraf D. Paracentral acute middle maculopathy spectral-domain optical coherence tomography feature of deep capillary ischemia. *Current Opinion in Ophthalmology*, 2014, 25, 207–212.
 46. Obaid N, Zulfiqar R, Khan A. Covid-19 association with anterior uveitis (post-covid acute anterior uveitis). *Journal of the Pakistan Medical Association*, 2022, 72(8), 1642-1644.
 47. Bolletta E, Iannetta D, Mastrofilippo V, et al. Uveitis and Other Ocular Complications Following COVID-19 Vaccination. *Journal of Clinical Medicine*, 2021, 10, 5960.
 48. Iriqat S, Yousef Q, Ereqat S. Clinical Profile of COVID-19 Patients Presenting with Uveitis - A Short Case Series. *International Medical Case Reports Journal*, 2021, 14, 421–427.
 49. Zago Filho LA, Lima LH, Melo GB, et al. Vitritis and Outer Retinal Abnormalities in a Patient with COVID-19. *Ocular Immunology and Inflammation*, 2020, 28, 1298–1300.

ARTIFITIAL INTELLIGENCE IN HEALTH CARE. OPPORTUNITIES AND THREATS OF USING TECHNOLOGY DURING THE PANDEMIC

Mariola Bartusek

Medical University of Silesia, Department of Health Sciences in Katowice.

Faculty of Nursing, Institute of Nursing and Social Medical Issues

INTRODUCTION

The intensity of technology development has led to the presence of the most modern technological solutions in the global economy. Also in Poland, there are many users of innovative solutions, from private life to wide-ranging sectoral activities.

Polish health care system has been undergoing changes for many years. Some of them are strongly identified with the development of modern technology in the world. Even before the pandemic, numerous solutions were proposed, the results of which would improve the quality of medical services as well as health condition and life of patients. Nevertheless, the pandemic had a direct impact on the use of innovative solutions that will remain in health care for good. However, this interest is not only the subject of discussion in the field of medicine, but also life as the highest value, which significantly changes the position of modern solutions and artificial intelligence in the hierarchy of human needs [1].

The results of the study conducted before the pandemic pointed to great interest among medics in the use of modern technology not only for the direct implementation of medical services. The solutions also concerned the priorities of documenting and improving the work of medics. The conducted analysis of the introduced innovative solutions also confirms the hypotheses assuming the benefits of using the solutions after the end of the pandemic as well. The aim of this publication is to attempt to consider the value of factors that threaten, but also favor the use of modern technology in health care. The initial analysis reveals that there is high probability that attention will be paid to the emerging threats, but also the benefits of taking actions during the pandemic that are beneficial for the future functioning of the health care system and the patients themselves. This also includes the use of modern technology by entities of medical activity during the pandemic.

MODERN TECHNOLOGY IN THE HEALTH CARE SECTOR

Progressive economic growth together with the changing social, cultural and economic dimension of humanity has an impact on intensive recognition and reception of new human needs. However, health and human life are still perceived as the highest value, which leads to applying innovative solutions also in the health care sector. It has become a trend not only in Poland, but also in Europe and even worldwide [1]. Innovative solutions are a part of both public health and health care, which constitutes its elementary link. As far as the subject of public health is concerned, it is worth noticing that it involves general protection, comprehensive in human terms, giving health care permission to deal with its organization, functioning and financing entities providing direct care in the form of medical services [1]. The historical conditions behind the development and application of artificial intelligence have led to its very wide use in the world. Ethical and legal considerations always directed the use of artificial intelligence towards helping people. In medicine, therefore, prostheses of limbs, hearing implants or artificial retina have been designed. This has significantly improved the quality of human life, expanded its scope of functioning and allowed to maintain it in the long term [2].

For many years, Poland has been interested in cooperation in the area of modern technology application in medicine. At the beginning, it concerned mainly the area of surgery but later also the area of administration. Thanks to the use of modern technology, e-prescription systems, electronic sick notes or teleconsultation services have already brought many benefits to both staff and patients. It is also a significant step in organizing effective work in health care entities. Similarly in the area of diagnostics, where thanks to innovative solutions there has been great development in the field of radiology [3]. Unification of standards in the field of IT systems, replacement of computer hardware and staff training is another step towards modernity [3]. Modern diagnostics in ophthalmology, diabetology and oncology leading to taking new paths in treatment is another step in the progress of medicine. The significance of implementing solutions based on artificial intelligence is emphasized. Since they constitute considerable social and economic challenge, they require special treatment. Here, life is very clearly and quickly affected by a tool that affects the quality of human life [3]. Medics in Poland are prepared to introduce changes, and the need for additional education enabling them to work in the new system is not an obstacle for them. They see great potential in technology, while acknowledging that changing the way in which they work or introducing new tools entails the

need to be very well prepared. They are interested not only in the use of technology, but also in its creation. It is also important to secure the collected data, analyze it and draw conclusions, which may have a significant impact on the assessment of patients' health needs and the selection of an effective therapeutic process [4].

Pandemic has accelerated the process of implementing the changes already prepared. In the pandemic conditions the following were introduced: telemedicine, teleconsultation services, telesurgeries or telerehabilitation, monitoring remotely the condition of health or monitoring the application of medicines. Hardware based on AI has also been used in diabetes therapy, elderly people caregiving, especially among those under home care, or interfaces for voice recognition. Alternatively, there are hospital bedside interfaces for transferring information, communication or even entertainment [5].

OPPORTUNITIES AND THREATS OF THE USE OF ARTIFICIAL INTELLIGENCE DURING THE PANDEMIC

The presented discourse is not aimed at either assessing the introduced systemic changes or verifying the undertaken actions. This is only a preliminary attempt to analyze the subjective opinions of nurses and midwives gathered at the beginning of the pandemic in March 2020 on the introduction of technological changes to the healthcare sector. For years, the nursing community has initiated a number of meetings and activities for improvement and introduction of changes in the healthcare sector. At the same time, it is an expression of concern for the role and importance of the undertaken actions that will contribute to the future of the health care system, its proper functioning and stabilization in the future.

The study, as a result of which the first information on the needs, opportunities and threats of the use of modern technology in the health care sector was obtained, was conducted at the beginning of the pandemic in Poland (May-June 2020). This is the first part of the study, currently being continued, whose purpose was to hear the opinion of healthcare professionals on the use of innovative methods and tools during and right after the pandemic in the health care sector. Respondents were selected from employees of medical entities. Among the respondents were nurses and midwives, including students of master's studies in nursing, all professionally active. The respondents were to answer questions of an authorial questionnaire. It was assumed that vast majority of respondents use modern technology both in their private and professional lives. Moreover, the assumption was that they would see an opportunity to use

artificial intelligence in their professional work in the field of health care, yet the existing threats and the probability of loss that might result from it are too high and may pose a threat to the patients' lives. The research has revealed that respondents use modern technology more often in their private lives than in their professions, at the same time being interested in using modern technology at work. However, they can clearly see the threats related to the introduction of equipment/applications with the use of artificial intelligence in the health care sector in Poland, yet at the same time the number of perceived losses related to the introduction of artificial intelligence in the indicated sector increases [6]. New technologies are a very important factor in the functioning and future of all mankind. It is worth remembering, however, that a significant role in development may entail many significant threats [7].

It turns out that the growing interest in technology among members of society regarded as individuals means greater involvement of entrepreneurs not only in building a new assortment of the company, but also in choosing new marketing paths [8]. One of the most important areas protecting humanity from extinction is the protection of public health. However, what is typical for all health care systems around the world are limited resources and increasing health needs[9]. These needs grew disproportionately to expectations precisely during the last pandemic[10]. It turned out that the on-going and planned tasks resulting from current social needs were superimposed with new, existing, but not so intensively identified health needs, in the physical, social and spiritual spheres. This had a direct impact on the search for the best solutions under the pressure to save humanity, not only the health of individuals. This time turned out to be difficult for the whole world, yet the funds allocated by individual countries for new tasks resulted in saving the lives of individuals.

In Poland, as well as in other countries, the pandemic was a kind of final exam that the system had to pass without any special preparation. This would require rapid changes in terms of increasing the availability of services for the population, the introduction of electronic solutions in basic health care, e.g. teleconsultations, e-sick leaves, e-referrals, changes in terms of perinatal care as well as spiritual support for the patients, especially in the last moments of life. Due to the sudden increase in the demand for basic and specialist services, patients in these two areas expected the responses and solutions as fast as possible [11]. The particular changes, which were being prepared on an ongoing basis, required many comprehensive actions compatible with the new legal regulations, the introduction of innovative technological solutions into practice and verification of the operating strategy. However, that was a global problem, not only a matter of one specific country. Therefore, many guidelines had to be

compatible with international recommendations. This gave a realistic chance for the dominant virus to be dethroned.

THE USE OF ARTIFICIAL INTELLIGENCE AFTER THE PANDEMIC

The development of modern technology, including the use of artificial intelligence, despite taking place gradually for many years, has significantly accelerated during the pandemic. At that time it turned out that isolation, which was an elementary condition for protection against the spread of the virus, required support in communication. The so far applied tools turned out to be insufficient on a scale to which people were accustomed. Therefore, it was necessary to use innovative methods that, although not used on such a large scale before, gave a chance for humanity to survive during the pandemic. In addition, the tools used both in social communication and in the administrative system supported people in taking up challenges necessary for functioning. They also entered the healthcare sector with ease, yet with the need to strengthen the protection of the data obtained. The proposed solutions shortened the waiting time for the patient's appointment, compressed the doctor's contact with the patient, allowing for faster decision-making, diagnosis and the suggested treatment, that would in effect positively affect the patient's health condition. Taking into regard the proposed and applied global recommendations, without these changes, patients' chances of survival could be significantly reduced. The solutions constituted a virtually perfect remedy for the strained healthcare systems in every country.

However, contemporary sectoral solutions based on helping people and increasing the comfort and quality of life require a very good legal and ethical base. Contemporary medicine based on providing widely understood help for people uses all possible resources. The development of technology has been helpful in this area for years and has a significant impact on the performance of medical procedures. However, this requires personnel with high general and specialist qualifications, equipment and financial resources. All these factors together allow for high-quality medical services for people.

Expectations towards the use of modern technology in medicine, including the use of artificial intelligence, are very high. However, the lack of full awareness of its effects and effectiveness raise doubts among scientists, especially in the context of human good understood in the traditional sense [2]. Only a few years ago, combining the use of robots with traditional methods in the therapeutic process was a vision planned for distant future. Today, they perform

some of the tasks of medics, without any organizational conflict. As a driving force, they can shorten the waiting time for a visit or surgery, which leads to an improvement in the patient's health. It is estimated that works in this field will be intensive in the coming years [3]. The research conducted during the pandemic was aimed at, among other things, determining the patient's protection status against the threat of the new coronavirus. It has been confirmed that since the beginning of the pandemic, the matter of great difficulties and problems in the health sector has significantly intensified. At the same time, it is pointed out that this situation, despite its tragical dimension is underdetermined in the context of the threat to human life, global discourse has begun on the need to introduce changes around the world. Like other countries, Poland recognized health of the population as a priority and a necessary condition and a guarantee of socio-economic stability. In order to achieve it, directions of changes were established and systemic proposals were adopted for recommendation. A wide group of experts developed solutions both for the protection of individual health and the social functioning of groups, institutions and enterprises. This partnership gave a new direction to the planning of work and organization of the health care system in the country [12].

From the patient's point of view, the increase in health needs should entail an increase in the access to medical services, broader range of health care services, access to modern preventive methods and tools, diagnosis and treatment with increased investment in the health care system. Threat to human life significantly modifies our perception of the process of satisfying health needs. It should be adequate to individual needs, fast and effective. Globally, from an organizational point of view, however, the matter was not so clear-cut, if only because of the high health risk and limited financial resources of each country. Therefore, the prepared action strategies were created for current needs and were to minimize the negative effects as much as possible. They assumed the use of all existing resources together with the means and resources available in the conditions at that time in particular countries of the world. The evident disproportion in the availability of services, the degree of participation in the therapeutic process of modern technology or the number of medical personnel quickly affected the degree of response to the side effects of the pandemic. At the same time, a very large number of deaths among people both under professional care and not aroused a lot of emotions. The analyzes carried out during the pandemic were not helpful, as the conclusions forced the population to prepare for the worst scenarios including the death of loved ones, prolonged loneliness of hospitalized people or passing away alone. Numerous initiatives, including the ones taken by non-governmental organizations, provided significant support to patients and their families

during this difficult period.

The deteriorating health of the population, the change of disease entities constituting the largest percentage of the causes of morbidity, or the overall morbidity statistics are clearly signalized [13]. The applied technology, used before the pandemic in the therapeutic process, has significantly accelerated in its development and use in practice in many medical specialties [14].

Numerous analyses have stressed the special importance and role of technological solutions applied during the pandemic, for which we were already prepared. There were the already existing rules of law as well as the administrative and technological infrastructure. Although no comprehensive attempts to introduce innovations had been made before, the ones implemented so far worked and were often used regionally. They served among others collecting information for further work and analyzing the costs of care. The changes made during the pandemic with the use of modern technology met with both support and resistance to introducing such changes. From the institutional point of view, the process of introducing changes has not yet been fully implemented, so it could cause anxiety, especially among medical staff.

SUMMARY

Reality has shown that, apart from central assumptions from the supervision and organization sector of the polish health care sector, medical entities in cooperation with the technological market, aim at obtaining innovative solutions as rapidly as possible. Vast majority supports especially these solutions which will result in increasing the quality of medical services as well as affect the quality of patient's life through shortening the process of diagnosis, treatment, rehabilitation, better therapeutic effect and risk treatment of the negative health effects. Additionally, the devised administrative solutions are to shorten and streamline the work time of the personnel, which in effect should result in better comfort of the patient during hospitalization.

The conducted analysis of the subject and the presented research results indicate the real possibilities of using modern technology in the practice. However, they are only a prelude to a broad topic based also on the existing international and national legal and ethical frameworks. These are not only an expression of the global care for the safety of treated people, but also of medics directly interested in the provision of services for the patient.

The doubts related to the limited financial resources are a condition to be met after conducting many financial analyses. Moreover, a problem of a very delicate ethical nature needs to be solved. After the introduction of detailed legal regulations and financial analyses, there will be a great need to focus on the preparation of a comprehensive set of ethical principles. Although the ethical scope goes beyond legal standards, detailed regulations limiting the occurrence of abuses seem to be a guarantee of the security of people nowadays. There is no need to negate innovative solutions, since they are a condition for functioning in the future also in such a delicate matter as health or disease. The problem, however, goes much broader, because it touches existence in the sense of human life. The more effort we make to prepare the base for human safety, the more calmly we will be able to take on new innovative challenges.

Pandemic has not only revealed the shortcomings of the world economy, but also deprived humanity of dreams of stability, which people allegedly could have an impact on. Full health security cannot be guaranteed. Therefore, every effort should be made to minimize the risks resulting additionally from the applied technology. It is unimaginable to introduce solutions that will threaten the health and life of humanity. Identification of threatening factors should be constantly analyzed to introduce the safest solutions. The conducted research constitutes a small part of the medical potential of professionals, specialists and experts for whom human life is the greatest value. However, it is worth hearing their voice, not being dependent on ideological and other affiliations, and lean towards saving human life. Because this life, often generally understood in literature, is also the life of each of us, the only one we have.

REFERENCES

1. Dymyt M., Dymyt T., Determinanty rozwoju innowacji w systemie opieki zdrowotnej, Zarządzanie i finanse, Management and Finance, v2018, 16(3/1), 67-81.
2. Osiński G. Transhumanizm – największe zagrożenie ludzkości, <https://wsksim.edu.pl/transhumanizm-najwieksze-zagrozenie-ludzkosci/> Accessed 30 March 2023.
3. Pochrzęst – Motyczyńska A., Sztuczna inteligencja obsłuży pacjenta w rejestracji szpitala, Prawo.pl. Zastosowanie sztucznej inteligencji w medycynie, www.prawo.pl/zdrowie/zastosowanie-sztucznej-inteligencji-w-medycynie,493017.html, Accessed 30 May 2023.
4. Grzela E., Kurzyńska E., Sztuczna inteligencja to rewolucja w medycynie. Relacja z Impact19, Materiał z dnia:29.05.2019, źródło: <http://pulsmedycyny.pl/sztuczna-inteli>

- gencja-to-rewolucja-w-medycynie-relacja-z-imact-19-962162; Accessed 30 May 2023.
5. Mikołajewska E., Mikołajewski D., Zastosowanie medyczne systemów Ambient Intelligence, *Acta Bio-Optica et Informatica Medica*, 2011, 3(17), 208-209.
 6. Bartusek M., Kulawik A. Analiza potrzeb zastosowania nowoczesnej technologii i sztucznej inteligencji w sektorze ochrony zdrowia. *Fides, Ratio Et Patria. Studia Toruńskie*, 2021, 15, 121–148.
 7. Cuda A. Nowe technologie w systemie ochrony zdrowia na przykładzie Stanów Zjednoczonych i Polski. *Ekonomia, Wrocław Economic Review* 2018, 24/4, 3882, 83-92.
 8. Całka A. Wykorzystanie nowych technologii w komunikacji marketingowej ośrodków opieki zdrowotnej w Polsce. *Wydział nauk Ekonomicznych i Zarządzania, Studia i Prace Wydziału Nauk Ekonomicznych i Zarządzania*, 2015, 39(2), 5, 327-337.
 9. Mazur M. Technologie informatyczne i prawo jako czynniki rozwoju medycyny i służby zdrowia. *Zeszyty naukowe Uniwersytetu Szczecińskiego* 2015, 10 (605), 139-153.
 10. Opieka medyczna w czasie pandemii. Komunikat z badań, CBOS Nr 88/2020 Lipiec 2020. Źródło: cbos.pl/SPISKOM.PL/2020/K_088_20.PDF Accessed 30 May 2023.
 11. Chmielowiec B., Raczek M., Chmielewski J. i wsp. Dostępność świadczeń zdrowotnych w Polsce w początkowym okresie pandemii SARS-CoV-2- perspektywa pacjenta. *Medycyna Ogólna i Nauka o Zdrowiu*, 2022, 28(3), 208–216.
 12. Rekomendacje zmian w polskim systemie ochrony zdrowia poprawiające dostęp do świadczeń medycznych dla pacjentów. Wnioski związane z pandemią COVID-19. INFARMA, INNOWO, Pracodawcy Rzeczypospolitej Polskiej, 2021. infarma.pl/assets/files/2021/Rekomendancje_zmian_w_polskim_systemie_ochrony_zdrowia_pandemia_COVID-19.pdf Accessed 30 May 2023.
 13. Zdrowie i ochrona zdrowia w 2020 r. Analizy statystyczne, GUS, Warszawa, Kraków 2021, stat.gov.pl/files/gfx/portalinformacyjny/pl/defaultaktualności/5513/1/11/1/zdrowie_i_ochrona_zdrowia_2020_korekta.pdf Accessed 30 May 2023.
 14. Szponar A. Jak algorytmy czuwają nad zdrowiem? Sztuczna inteligencja w medycynie. COMARCH Healthcare. comarch.pl/files-pl/file_188/PL_CH_WP_AI_w_medycynie.pdf Accessed 30 May 2023.

LONG COVID AS A SIGNIFICANT PROBLEM IN ORTHOPEDICS AND RHEUMATOLOGY

Oskar Pastuszek¹, Anna Susłow²

1. Student Science Association of Orthopedics, Wrocław Medical University, Wrocław, Poland
2. Student Science Association of Adult Allergology, Wrocław Medical University, Wrocław, Poland

ABBREVIATION LIST

- EBV - Epstein-Barr virus
- SLE - Systemic lupus erythematosus
- Il-1 - Interleukin 1
- Il-1 β - Interleukin 1 β
- Il-6 - Interleukin 6
- IL-8 - Interleukin 8
- IL-17 - Interleukin 17
- CRP - C-reactive protein
- TNF- α - tumor necrosis factor alpha
- CXCL10 - C-X-C motif chemokine ligand 10
- IFN- γ - interferon gamma
- TNF-alfa - Tumor necrosis factor alpha
- FACIT - F - Functional assessment of chronic illness therapy - fatigue scale
- EWGSOP2 - European Working Group on Sarcopenia in Older People 2
- COVID-19 - Coronavirus disease 2019
- SARS-CoV-2 - Severe acute respiratory syndrome coronavirus 2
- ACE2 - Angiotensin-converting enzyme 2
- TMPRSS2 - Transmembrane serine protease 2
- RNA - Ribonucleic acid
- BMI - Body Mass Index
- MRI - Magnetic resonance imaging

INTRODUCTION

Long COVID, also referred as “post-acute sequelae of SARS-CoV-2 infection” or “post-acute coronavirus disease - COVID - syndrome” (PACS) is what we now call a wide range of ongoing health problems that affect people after being infected with SARS-CoV-2. It can last weeks, months or even years, causing disabilities and diminishing quality of life. The most common symptoms are fatigue, fever, joint or muscle pain, respiratory and heart problems, neurological impairment, diarrhea and stomach pain [1]. As for now Long COVID doesn’t have diagnostic biomarkers, moreover universally accepted definition. Cassandra Calabrese et al. suggested definition of Long Covid as a heterogenous, multisystem, relapsing and remitting illness that can affect patients regardless of severity of their acute SARS-CoV-2 infection and is unattended by end-organ pathology [2]. Studies show that immune dysregulation and immune activation takes a crucial part in pathogenesis of Long COVID [3]. Our aim is to disguise the impact of long covid on musculoskeletal system and rheumatological complications.

PATHOPHYSIOLOGY

Long Covid as mentioned earlier can give many symptoms seemingly unrelated to a respiratory infection. This is where the question arises. Why are there actually so many symptoms related to bones, muscles and joints? There are several possible explanations for this problem.

As is well known, the SARS-CoV-2 virus is able to enter cells through angiotensin-converting enzyme 2 (ACE2) receptors, and the serine protease TMPRSS2 [4]. In the cells, translation and replication of viral RNA takes place in the cytoplasm, and it is further released into the body [4]. Viral proteins can interact with other proteins present in the human body, which can result in impairment of their function [4]. All this can lead to cellular dysfunction and result in cell apoptosis, which causes disruption at the tissue level, but also increases local inflammation [4]. Nathaniel P. Disser and colleagues showed that human skeletal muscles show expression of the previously mentioned TMPRSS2, but only smooth muscle cells and pericytes have expression for ACE2 [4]. Expression for both TMPRSS2 and ACE2 was possessed by several synovial membrane cells [4]. The opposite of skeletal muscle was the case for articular cartilage and meniscus which showed expression of only ACE2 (the exception was homeostatic chondrocytes also having expression for TMPRSS2) [4]. In addition, expression

for ACE2 was detected in bone, and samples enriched in osteoblasts also showed expression for TMPRSS2 [4]. Data for tendons and ligaments were hard to obtain, but rat and mouse results were used, which indicated a lack of expression for either molecule [4]. In summary, synovial membrane, skeletal muscle, cortical bone and possibly cartilage tissue are possible locations for direct infection by the virus.

Another important factor in pathophysiology is generalized inflammation. Interleukin 1 beta (IL-1 β), IL-6, IL-8, IL-17, interferon gamma (IFN- γ), C-X-C motif chemokine 10 (CXCL 10) and tumor necrosis factor alpha (TNF- α) are mainly responsible for this state [4]. Molecules such as IL-1 β , IL-6, IL-17 and TNF- α , IFN- γ may be involved in the induction of muscle fiber proteolysis and decreased protein synthesis [4]. TNF- α and IL-1 β , in addition to the above action, may block the development of satellite cells responsible for muscle fiber development [4]. IL-1 β and IL-6 cause an increase in the activity of muscle fibroblasts which leads to muscle fibrosis [4]. Inflammation also affects bones and joints [4]. CXCL10, IL-17 and TNF- α contribute to osteoclastogenesis and a decrease in the number of osteoblasts and this results into a decrease in bone mineral density [4]. IL-1 β , IL-6 and TNF- α can lead to the breakdown of cartilage tissue [4]. As for inducing inflammation in tendons, IL-1 β , IL-17 and TNF- α perform the main role [4]. These bone changes and the role of cytokines were also confirmed in the study of golden Syrian hamsters carried out by Wei Qiao and colleagues [5].

RISK FACTORS

Practically every disease unit will have people who are more or less predisposed to have it. Long COVID also has such factors.

General risk factors for the overall syndrome include elevated levels of D-dimers, troponin-1, inflammatory markers, IL-6 and CRP, reduced lymphocyte count (not all studies agree on the role of each factor) [6]. Female gender, prior use of antidepressants, depression and anxiety identified in the patient's history has a role in development of fatigue in Long Covid (some studies have not found a higher frequency of the syndrome in women) [6].

Another important aspect is the number of symptoms at the onset of COVID-19 infection as studies indicate that the occurrence of more than 5 symptoms or 10 symptoms (depending on the study) may be a significant predictor [6]. Also, it was noted that while the long duration of infection itself does not affect the development of Long Covid, the admission of patients to the intensive care unit, mechanical ventilation and long hospitalization time already does [6].

There are also risk factors associated with specific musculoskeletal symptoms. The development of sarcopenia and joint pain as symptoms of Long Covid may be predisposed by long hospital stay, low physical activity and low serum albumin levels [7,8]. Also, age >60 years, diabetes, obesity are important [8]. As for fibromyalgia, the strongest predisposing factors were found to be obesity and male gender [9]. This is interesting because, as previously mentioned, female gender is more likely to contribute to the overall development of Long Covid [6]. An additional factor is most likely the corticosteroids widely used to treat patients infected with COVID-19 to reduce the inflammation going on inside the body. These drugs lead to muscle weakness, muscle atrophy [4]. Going further, lowered levels of testosterone, progesterone and estrogen, the onset of a cytokine storm in the patient, dexamethasone therapy, vitamin D deficiencies and dysbiosis of the intestinal microflora, among others, may be responsible for symptoms originating in the bones [10]. One study focused on assessing pain in patients with Long Covid depending on the variant of the virus that caused the infection [11]. The study found that patients affected by the historical variant, compared to those infected with the Alpha and Delta variants, were more likely to report new musculoskeletal pain, but that pain was also common in the non-history groups [11]. It can be concluded from this that even specific viral variants are predisposing factors for musculoskeletal pain in Long Covid [11]. Other musculoskeletal risk factors appearing in the studies include high BMI, stay in the intensive care unit, malnutrition, prolonged physical inactivity, mechanical ventilation and female gender [12,13,14].

SKELETAL MUSCLES, BONES AND JOINTS – SYMPTOMS

The multitude of Long Covid symptoms is huge, however, we have focused on those originating from the musculoskeletal system.

The first common symptoms in the research articles are joint pain, muscle pain and fatigue [4,12,14,15,16]. It has been found that these symptoms can appear in up to 2/5 of patients [4,15]. In their study, Francesco Ursini and colleagues describe the pain more broadly as fibromyalgia occurring in Long Covid [9].

The pains were mostly widespread, but some patients pointed to the knee joint, foot joint, ankle joint and shoulder joint as the most commonly affected [15]. As for muscle pains, these typically involved the arm, shoulder girdle and lower leg [15]. These symptoms were also associated with a weakening of grip strength by up to a third compared to healthy individuals [4,13].

Another symptom to be aware of is sarcopenia. According to the EWGSOP2 definition, this is the presence of low muscle mass and low muscle strength (below expected levels for a given group of people) [7,8]. Sarcopenia is present in up to one in five people [7]. Additionally, it is often correlated with the previously mentioned joint pain and fatigue [7]. It also turned out that age had no effect on its incidence which makes it expected in many age groups [7].

After testing patients with sarcopenia, reduced grip strength, quadriceps strength and a significant decrease in physical performance were found, which can easily affect daily life [17].

Another orthopedic problem faced by Long Covid patients are those in the bones. As we know, corticosteroids were the mainstay of therapy for COVID-19 infection to reduce the inflammation going on in the body [4,10]. The harmful effects of steroids are well known worldwide, and avascular necrosis of the femoral head is cited as one of the possible complications of their use [10,18]. As a result of the use of these drugs, bone destruction occurs through impairment of bone vascularization and architecture, death of osteocytes and fat cells [10,18].

A large role is played by the cumulative dose of steroids given to patients during treatment, although as it turns out, it is lower than usually described in the literature in the occurrence of this condition [18].

Thus, it can be concluded that COVID-19 infection further predisposes to avascular necrosis of the femoral head. It turns out that the condition affects not only the elderly, but also young and active people, which is why early diagnosis and treatment is so important [18]. To do this, it is best to use MRI for early detection of the disease even in asymptomatic patients from high-risk groups [18].

After steroid therapy, a decrease in bone mineral density was also observed in patients, and other bone necrosis in addition to that seen in the previously described were osteonecrosis of the humeral head, ankle bone, heel bone and knee [4,10]. As for osteonecrosis of the knee, the situation is similar to that of the femoral head. Early diagnosis is important so that bisphosphonate therapy can be applied [19]. The most appropriate form of treatment to prevent necrosis is short-term low-dose therapy, and intermittent therapy may also be an alternative. The cumulative dose of methylprednisolone should be less than 5g and the duration of therapy should not exceed 30 days because then the risk is estimated to be quite low [20]. Bone loss (osteoporosis) can also occur independent of dexamethasone therapy, as indicated by studies in mice and hamsters [21].

The combination of osteoporosis and sarcopenia has been called osteosarcopenia. As it turns out, this combination also occurs in patients as a symptom of Long Covid [22].

RHEUMATOLOGICAL COMPLICATION IN LONG COVID

Rheumatological diseases can affect multiple tissues and organs in the human body within the musculoskeletal system. Furthermore rheumatological disorders frequently manifest by multi organ extra-articular disease. [23] Post-infectious onsets of rheumatological complications are reported in many bacterial and viral cases. Well-known phenomenon called reactive arthritis, also known as Reiter's syndrome, is connected with sexually transmitted disease, caused by among others *Chlamydia trachomatis*. [24] Viral infections and rheumatic diseases correlation is still being explored, due to continuous advances in science. [25] Viruses can trigger autoimmune response, in predisposed patients, moreover escalate the ongoing inflammation causing flares. Thoroughly examined Epstein-Barr virus (EBV) infection was found to enhance risk of developing SLE (systemic lupus erythematosus) and multiple sclerosis. [24, 26, 27] EBV promotes autoimmunity mostly by cross-reactivity with self-antigens and by expanding auto-reactive ABCs that continuously stimulate auto-reactive T cells and promote chronic inflammation in both secondary lymphoid tissue and target tissue. [28] Other viruses also have been connected with several rheumatological diseases such as influenza virus, HBV, HCV and HIV [29, 30, 31]. Novel addition to this group is Long COVID, a mysterious manifestation of SARS-CoV2 infection.

Studies present that the clinical spectrum of autoimmune-related manifestation in COVID-19 patients is highly diverse [25].

Rheumatological presentations include inflammatory arthritis, lupus-like syndrome, vasculopathy such as Kawasaki-like disease, chilblain lesion, vasculitis, and chronic fatigue spectrum disorder [32].

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus is a chronic autoimmune disease that can affect every organ and tissue [33]. The most common symptoms are fatigue, skin rashes, fevers and pain or swelling joints. SLE manifestation varies and can include cutaneous, musculoskeletal, hematological, renal, and neurological systems [34]. Female to-male ratio is 9:1 and it mainly affects women in childbearing age [31].

SLE pathogenesis is complex and not fully understood. Till now we know that many factors can affect development and activity of the disease, especially genetic predisposition, hormonal milieu and environmental triggers - such as viruses [35].

SARS-CoV2 infection alters the immune system causing specific pattern, which include lymphopenia, lymphocyte activation and dysfunction, granulocyte abnormalities, cytokine (Il-1, Il-6 and TNF-alpha), monocyte production and increased antibodies. Dysregulation of innate immunity, hyperinflammation, immunosuppression, organ damage can predispose to new onsets of SLE or lupus like syndrome [25]. Further studies are needed to establish if LONG covid can be associated with SLE, so far only a few case reports regarding this topic were published [31, 36, 37, 38].

CHRONIC FATIGUE SPECTRUM DISORDER

Fatigue, joint pain, and myalgia were the most frequent rheumatic and musculoskeletal symptoms appearing after COVID infection. 3 in 5 patients had at least one symptom [15]. Furthermore, female patients were more likely to experience fatigue, myalgia, and joint pain at 6 months post COVID-19 [15, 39, 40]. Patients with Long COVID report that chronic fatigue is the most dominant and bothersome symptom. It is profound, persists even after adequate rest and unables daily activities, causing not only problems for the individual, but also for the whole community [2]. Patients point out that long Covid prevented their return to work and also that they were incapable to work. What so ever patients weren't receiving medical support as they needed. Observational study conducted with 213 participants showed that chronic fatigue correlated with COVID-19 is clinically relevant and is as severe as fatigue in several other clinical conditions, such as cancer. In addition, chronic fatigue in long COVID patinstes co-occurs with some features of postexertional symptom exacerbation [41]. Patients presenting these symptoms should be carefully examined to preclude cardiovascular and pneumological complications overlapping from COVID-19 tissue damage.

Measurement of fatigue can support diagnostic procedure and follow-up during rehabilitation. FACTI-Fatigue scale was already successfully introduced in several populations to validated patients with chronic fatigue [42]. It is a 13-item questionnaire created to assess reported symptoms [43].

CONCLUSIONS

Long COVID is causing controversy in both medical and media circles. Taking into consideration all the facts that we gathered, more large-scale cohort studies are needed to establish a unified clinical approach in diagnostic and treatment of musculoskeletal and

rheumatological complications in Long COVID. Thus we now know that clinicians are facing challenging times, trying to find reason and solution to patients suffering.

REFERENCES

1. CDC - Centers for Disease Control and Prevention, “Long COVID or Post-COVID Conditions”,<https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html> Accessed 12 Jun 2023.
2. Calabrese, C., Kirchner, E., & Calabrese, L. H. Long COVID and rheumatology: Clinical, diagnostic, and therapeutic implications. Best practice & research. Clinical rheumatology. 2022, 36(4), 101794.
3. Peluso, M. J., & Deeks, S. G. Early clues regarding the pathogenesis of long-COVID. Trends in immunology. 2022, 43(4), 268–270.
4. Disser, N. P., De Micheli, A. J., Schonk, M. M., Konnaris, M. A., Piacentini, A. N., et al. Musculoskeletal consequences of COVID-19. Journal of Bone and Joint Surgery, 2020, 102(14), 1197–1204.
5. Qiao, W., Lau, H. E., Xie, H., Poon, V. K.-M., Chan, C. C.-S., et al. SARS-CoV-2 infection induces inflammatory bone loss in golden Syrian hamsters. Nature Communications, 2022, 13(1).
6. Yong, S. J. . Long COVID or post-COVID-19 syndrome: Putative pathophysiology, risk factors, and treatments. Infectious Diseases, 2021, 53(10), 737–754.
7. Martone, A. M., Tosato, M., Ciciarello, F., Galluzzo, V., Zazzara, M. B., et al. Sarcopenia as potential biological substrate of long COVID-19 syndrome: Prevalence, clinical features, and risk factors. Journal of Cachexia, Sarcopenia and Muscle, 2022, 13(4), 1974–1982.
8. González-Islas, D., Sánchez-Moreno, C., Orea-Tejeda, A., Hernández-López, S., Salgado-Fernández, F., et al. . Body composition and risk factors associated with sarcopenia in post-COVID patients after moderate or severe COVID-19 infections. BMC Pulmonary Medicine, 2022, 22(1).
9. Ursini, F., Ciaffi, J., Mancarella, L., Lisi, L., Brusi, V., et al. . Fibromyalgia: A new facet of the post-COVID-19 syndrome spectrum? Results from a web-based survey. RMD Open, 2021, 7(3), e001735.
10. Sapra, L., Saini, C., Garg, B., Gupta, R., Verma, B., et al. Long-term implications of COVID-19 on bone health: Pathophysiology and therapeutics. Inflammation Research, 2022, 71(9), 1025–1040.

11. Fernández-de-las-Peñas, C., Cancela-Cilleruelo, I., Moro-López-Menchero, P., Rodríguez-Jiménez, J., Gómez-Mayordomo, V., et al. Prevalence of musculoskeletal post-covid pain in hospitalized COVID-19 survivors depending on infection with the historical, alpha or delta sars-cov-2 variant. *Biomedicines*, 2022, 10(8), 1951.
12. Azadvari, M., Haghparast, A., Nakhostin-Ansari, A., Emami Razavi, S. Z., Hosseini, M. . Musculoskeletal symptoms in patients with long COVID: A cross-sectional study on Iranian patients. *Heliyon*, 2022, 8(8), e10148.
13. Ali, A. M., & Kunugi, H. . Skeletal muscle damage in COVID-19: A call for action. *Medicina*, 2021, 57(4), 372.
14. Khoja, O., Silva Passadouro, B., Mulvey, M., Delis, I., Astill, S., et al.. Clinical characteristics and mechanisms of musculoskeletal pain in long COVID. *Journal of Pain Research*, 2022, Volume 15, 1729–1748.
15. Karaarslan, F., Güneri, F. D., Kardeş, S.. Long COVID: Rheumatologic/ musculoskeletal symptoms in hospitalized COVID-19 survivors at 3 and 6 months. *Clinical Rheumatology*, 2021, 41(1), 289–296.
16. Swarnakar, R., Jenifa, S., & Wadhwa, S.. Musculoskeletal complications in long COVID-19: A systematic review. *World Journal of Virology*, 2022, 11(6), 485–495.
17. Montes-Ibarra, M., Oliveira, C. L. P., Orsso, C. E., Landi, F., Marzetti, E., et al.. The impact of Long COVID-19 on muscle health. *Clinics in Geriatric Medicine*, 2022, 38(3), 545–557.
18. Snowden, G. T., Clement, N. D., Zhang, S., Xue, Q., Simpson, A. H. R. W.. Orthopaedic long COVID - The unknown unknowns. *Bone & Joint Research*, 2022, 11(1), 10–11.
19. Agarwala, S. R., Vijayvargiya, M., Sawant, T.. Secondary osteonecrosis of the knee as a part of long COVID-19 syndrome: A case series. *BMJ Case Reports*, 2022, 15(3), e248583.
20. Zhang, S., Wang, C., Shi, L., Xue, Q.. Beware of steroid-induced avascular necrosis of the femoral head in the treatment of covid-19—experience and lessons from the SARS epidemic. *Drug Design, Development and Therapy*, 2021, 15, 983–995.
21. Awosanya, O. D., Dadwal, U. C., Imel, E. A., Yu, Q., Kacena, M. A.. The impacts of COVID-19 on musculoskeletal health. *Current Osteoporosis Reports*, 2022, 20(4), 213–225.
22. Tarantino, U., Visconti, V. V., Bonanni, R., Gatti, A., Marcozzi, M., et al. Osteosarcoma and Long-COVID: A dangerous combination. *Therapeutic Advances in Muscu-*

- loskeletal Disease, 2022, 14, 1759720X2211304.
23. Subesinghe M, Bhuva S, Arumalla N, Cope A, D'Cruz D, et al.; 2-deoxy-2[18F]fluoro-D-glucose positron emission tomography-computed tomography in rheumatological diseases. *Rheumatology (Oxford)*. 2022, 5, 61(5), 1769-1782.
24. Sapkota, H. R., & Nune, A. . Long COVID from rheumatology perspective - a narrative review. *Clinical rheumatology*, 2022, 41(2), 337–348.
25. Roseti L, Grigolo B. COVID-19 and rheumatic diseases: A mini-review. *Front Med (Lausanne)*. 2022, 26, 9:997876.
26. James J.A., Kaufman K.M., Farris A.D. Taylor-Albert E., Lehman T.J., et al.: An increased prevalence of Epstein-Barr virus infection in young patients suggests a possible etiology for systemic lupus erythematosus. *The Journal of Clinical Investigation*. 1997, 100, 3019-3026.
27. Laurynenka V., Ding L., Kaufman K.M., James J.A., Harley J.B. A high prevalence of anti-EBNA1 heteroantibodies in systemic lupus erythematosus (SLE) supports anti-EBNA1 as an origin for SLE autoantibodies. *Frontiers in Immunology*, 2022, 17, 13, 830993.
28. Long, A., Kleiner, A., Looney, R. J.: Immune dysregulation. *The Journal of allergy and clinical immunology*, 2023, 151(1), 70–80.
29. Giardullo, L., Corrado, A., Maruotti, N., Rotondo, C., Cantatore, F. P.: Rheumatological Diseases in HIV Infection. *Current Rheumatology Reviews*, 2021, 17(3), 271–282.
30. Kim A, Choi SJ, Song GG, Kim JH, Jung JH.: Characterization of virus-mediated autoimmunity and the consequences for pathological process in patients with systemic lupus erythematosus. *Clinical Rheumatology*. 2023, 27.
31. Gracia-Ramos, A. E., Martin-Nares, E., Hernández-Molina, G.: New Onset of Autoimmune Diseases Following COVID-19 Diagnosis. *Cells*, 2021, 10(12), 3592.
32. Zacharias, H., Dubey, S., Koduri, G., D'Cruz, D.: Rheumatological complications of Covid 19. *Autoimmunity reviews*, 2021, 20(9), 102883.
33. Koo, M., Hsu, C. W., Lu, M. C.: Increased Risk of Developing Systemic Lupus Erythematosus and Rheumatoid Arthritis in Patients with Primary Sjögren's Syndrome- A Secondary Cohort Analysis of Nationwide, Population-Based Claims Data. *Journal of Clinical Medicine*, 2023, 12(12), 4157.
34. Gracia-Ramos, A. E., Saavedra-Salinas, M. Á. Can the SARS-CoV-2 infection trigger systemic lupus erythematosus? A case-based review. *Rheumatology International*,

- 2021, 41(4), 799–809.
35. Fava, A., Petri, M.: Systemic lupus erythematosus: Diagnosis and clinical management. *Journal of Autoimmunity*, 2019, 96, 1–13.
36. Mantovani Cardoso, E., Hundal, J., Feterman, D., & Magaldi, J.: Concomitant new diagnosis of systemic lupus erythematosus and COVID-19 with possible antiphospholipid syndrome. Just a coincidence? A case report and review of intertwining pathophysiology. *Clinical Rheumatology*, 2020, 39(9), 2811–2815.
37. Slimani, Y., Abbassi, R., El Fatoiki, F. Z., Barrou, L., Chiheb, S.: Systemic lupus erythematosus and varicella-like rash following COVID-19 in a previously healthy patient. *Journal of medical virology*, 2021, 93(2), 1184–1187.
38. El Aoud, S., Morin, C., Lorriaux, P., Obert, J., Sorial, D. et al.: COVID-19 Presenting as Lupus Erythematosus-Like Syndrome. *Disaster medicine and public health preparedness*, 2021, 15(4), e12–e15.
39. Ghosn J, Piroth L, Epaulard O, Le Turnier P, Mentré F, et al.; Persistent COVID-19 symptoms are highly prevalent 6 months after hospitalization: results from a large prospective cohort. *Clinical Microbiology and Infection*, 2021, 27(7), 1041.
40. Peghin M, Palese A, Venturini M, De Martino M, Gerussi V, et al.: Post-COVID-19 symptoms 6 months after acute infection among hospitalized and non-hospitalized patients, *Clinical Microbiology*, 2021, 27(10), 1507-1513.
41. Twomey R, DeMars J, Franklin K, Culos-Reed SN, Weatherald J, et al.: Chronic Fatigue and Postexertional Malaise in People Living With Long COVID: An Observational Study. *Physical Therapy*. 2022, 1;102(4), pzac005.
42. Vlaski T, Slavic M, Caspari R, Fischer H, Brenner H, et al.: Development Trajectories of Fatigue, Quality of Life, and the Ability to Work among Colorectal Cancer Patients in the First Year after Rehabilitation-First Results of the MIRANDA Study. *Cancers (Basel)*. 2023, 13, 15(12), 3168.
43. Wagan, A. A., Raheem, A., Bhatti, A., Zafar, T. Fatigue assessment by FACIT-F scale in Pakistani cohort with Rheumatoid Arthritis (FAF-RA) study. *Pakistan Journal of Medical Sciences*, 2021, 37(4), 1025–1030.

THE IMPACT OF THE LOCKDOWN CAUSED BY THE COVID-19 PANDEMIC ON THE HUMAN SKELETAL SYSTEM

Marta Zasieczna¹, Grzegorz Mikita¹, Natalia Wawrzeczko¹, Magdalena Raczkowska¹, Natalia Jendrzejczyk¹, Aleksandra Faryś¹, Paweł Dąbrowski²

1. Student Research Group of Paleoanatomy "VERTEX", Department of Normal Anatomy, Wrocław Medical University
2. Chair of Human Morphology and Embryology, Department of Normal Anatomy, Wrocław Medical University

INTRODUCTION

Covid-19, caused by the SARS-CoV-2 virus, has triggered a global pandemic that has had a significant impact on various aspects of human health. In addition to the direct respiratory symptoms, there is growing evidence of the impact of Covid-19 infection on other systems and organs in the body, including the musculoskeletal system [1]. It is anticipated that Covid-19 may affect skeletal abnormalities in several ways. Firstly, the infection itself can induce inflammation in the body, which may lead to changes in bone metabolism and affect bone remodeling processes [2,3]. Secondly, frequent hospitalizations and prolonged immobilization of Covid-19 patients can result in bone loss and muscle weakness, which in turn may increase the risk of skeletal abnormalities [4]. Thirdly, some studies suggest that the SARS-CoV-2 virus itself may have the ability to directly attack skeletal cells, which can impact their function and structural integrity [3]. Furthermore, an important aspect is the lockdown, which directly influenced an increased number of skeletal abnormalities in the population due to a greater amount of time spent in front of phone screens and immobilization of our lives [5].

The aim of this scientific study is to investigate the impact of lockdown measures on postural disorders in humans. Based on available sources, we aim to summarize how pandemic-related restrictions, such as school closures, remote work, and limited outdoor physical activity influence body posture and may contribute to the development of postural abnormalities such as scoliosis, temporomandibular joint disorders, forward head posture, pathologies of the hand

and wrist joint. In our work, we utilized online resources such as the PubMed, Google Scholar and NCBI (National Center for Biotechnology Information) platforms, the NLM (National Library of Medicine), The Library of Medical University in Wrocław, and other sources mentioned in the literature.

TEMPOROMANDIBULAR JOINT DISORDERS (TMD)

Temporomandibular joint disorders (TMD) encompass a broad and diverse group of pathological conditions. They represent the most common cause of non-dental orofacial pain [6]. These disorders can have joint-related, muscle-related, as well as psychogenic origins. Common symptoms include pain of the masseter and temporal muscles, temporomandibular joint pain, clicking and popping in the joint, dislocation, limited mouth opening, and headache [7]. In terms of etiology, special attention is given to the association with patients' mental states. In a prospective cohort study called OPFERA, a statistically significant association was found between the indication of depression, heightened stress and anxiety in the SCL-90-R questionnaire, and the aforementioned disorders with 95% confidence interval, as well as related behaviors such as bruxism and nail biting [8]. It means that there is a connection between TMD and humans' psyche, while global deterioration of mental health has been observed during the COVID-19 pandemic. Several studies and subsequent meta-analyses conducted during that time have demonstrated the prevalence of anxiety disorders in surveyed groups ranging from 31% to 41%, a 25% increase in their frequency compared to the pre-pandemic period, the occurrence of depressive disorders among 34% of the participants, and sleep disturbances among 33% [9,10,11,12]. This issue also affects college students, leading to the assumption that the frequency of psychogenic temporomandibular joint disorders among these students may have increased during the pandemic and the resulting lockdown. This assumption is supported by research findings. In 2020, a survey was conducted among the students of the Medical University of Łódź, which showed that 77.3% of them reported TMD symptoms [13]. Similar results were reported by students in Turkey [14]. Among 699 participants, 11.5% reported severe symptoms, 21.9% reported moderate symptoms, and 44.1% reported mild symptoms. The same study also examined the occurrence of depression, anxiety, and heightened stress. Statistically significant associations were found between the presence of TMD and each of these problems, particularly among women. Additionally, among students at the University of Campinas in Brazil, a correlation was observed between TMD prevalence at a rate of 64.2% and a lower quality of life index [15]. The phenomenon seems to

be global, however a more comprehensive analysis of this issue appears necessary, as the majority of available data comes from self-reported questionnaires that lack verification by medical professionals or actual diagnoses.

CERVICAL SPINE

In the era of COVID-19, dependence on electronic devices has become a fairly common problem. During lockdown and isolation, online platforms and remote learning took the upper hand in teaching to meet academic needs [16,17]. In addition, social isolation increased time spent using cell phones contributing to the worsening problem of cell phone addiction. Among students, a link was noted between increased smartphone or other hand held metal devices (HHMD) use and worsened academic performance, stress, sleep disturbances as well as bone and muscle pain [16].

When using electronic devices, it is easy to have an abnormal posture, which has been described as "text neck syndrome" or forward head posture (FHP) [17]. The main factors contributing to this phenomenon are excessive neck tilt and lordosis in the lower cervical spine, which in turn is balanced by kyphosis in the upper thoracic spine. When using smartphones and other devices, we use many parts of the body- through the head, neck and shoulders to the wrists, hands and torso [16,18]. In forward head posture, we can distinguish two types:

1. cervical spine tilt,
2. the lower cervical spine remaining in contraction while the upper cervical spine is stretched to maintain a horizontal gaze [17].

The upper part of cervical spine is responsible for 50% of total neck flexion and extensions, as well as 50% of overall cervical rotation. Instability in this region can cause biomechanical symptoms such as vertebrobasilar insufficiency, cervical radiculopathy, cervicogenic dizziness, head and facial pain and nerve irritation. In cases of FHP, long lasting pull on the nuchal ligament and nuchal muscle can cause tendinitis and bony spur in the nuchal ligament [19]. Affected ligaments are: posterior longitudinal ligament, ligamentum flavum, supraspinous ligament and interspinous ligament. The alar and transverse ligaments may become overstretched as well. When the head and neck are held in a flexed posture for a prolonged period, creep can occur in the posterior ligaments of the spine after as little as 10 minutes [20]. It has been reported that muscle activity and muscle fatigue of the neck extensors are more common as the flexion angle of the neck increases during smartphone use. SCM become short, strained and weak [18]. Generally, the muscular imbalances associated with FHP

result from the combination of the elongation and weakening of the anterior neck muscles, and the contraction and stiffness of the posterior neck muscles [17]. It has been discovered that the angle of neck tilt increases more when sitting than when standing. The additional tilt of the trunk causes excessive contraction of the back extensor muscles, and the constant load on these muscles may increase the risk of neck and back pain [18]. FHP also affects the joints. There may be a reduction in the space in the atlanto-occipital and atlantoaxial joints, and as a result an increase in compressive forces placed posteriorly. This affects the suboccipital muscles, which become shortened. It compresses the facets of joints and even slackens posterior ligamentous structures. If instability occurs, the greater occipital nerve, vertebral artery, and spinal cord all may be placed at risk [20]. It was also stated that the more severe FHP becomes, the bigger impact it will have on the proprioception [17].

When the neck is held in a neutral position, the head has been shown to weigh approximately 10–12 lbs according to three studies [16,20,21]. The more flexed the neck is, the more weight is placed on the cervical vertebrae, intervertebral discs, and facets of joints, which can lead to degeneration and herniation. For example, flexion to 15 degrees increases the load on the spine to 27 lbs, 40 lbs at 30 degrees, 49 lb at 45 degrees, and finally 60 lbs at 60 degrees [20,21]. It turns out, that males have been shown to demonstrate dramatically greater angles than females in the head and neck flexion angle [20]. It was shown that women perceive more overall musculoskeletal pain in the cervical spine and upper extremities than men. It is a common knowledge that the text neck syndrome has become a widespread modern-day epidemic [16,17], affecting people exposed to HHMD use for multiple hours- adults use them for 5.1 hours a day. For example, in the United States, university students aged 19–22 years old reported using a HHMD for over 8.5 hours per day on average [20]. On the other hand, a study conducted by Kennet Hansraj from the New York Spine Surgery & Rehabilitation Medicine, conducted that nearly all the community (>95%) use smartphone in the performance of daily activities. The most common position when using the cellphone among Indian adolescents was a supine position for a period of 1–3 h, followed by sitting at a table reported by 27.3% for 1–3 h. In Saudi Arabia most of the participants had been smartphone users for a minimum of 12 months. They complained about symptoms like pain, numbness, tingling, aching, stiffness, and burning in the neck region which they experienced during or after smartphone use in the preceding 12 months. Most of them reported using smartphones for 7 hours daily or more [16]. Text neck syndrome is an increasingly popular phenomenon these days and in all likelihood could affect us [17]. Using HHMD for an average of 2 hours a day for 10 years increases the risk of developing lordosis in the cervical spine and future neck

pathologies. In contrast, a study in India found that neck disorders, especially sternocleidomastoid and upper trapezius muscles pain, are more likely to affect people who use smartphones for 5 hours a day or more. One study found that the neck flexion angle tends to increase more significantly when using a HHMD in a sitting versus a standing position. While seated, the best position for device use is placed on a table and angled upward towards the person's head, or mounted or held just at or below eye level to avoid the need for increased upper and lower cervical flexion [20]. Neck symptoms were found to be more prevalent among female adolescents and those who used smartphones for a longer duration and less common among physically active individuals. Ergonomic experts recommend keeping the smartphone at eye level to avoid head flexion, using smartphone holders and periodic neck exercises [16].

PATHOLOGIES OF THE HAND AND WRIST JOINT

Following the declaration of the COVID-19 pandemic by the WHO, the shift to remote work in the public sector has potentially contributed to the occurrence of numerous work-related musculoskeletal disorders. Pain from the musculoskeletal system is most commonly associated with back pain, while hand and wrist joint pathologies are often overlooked [22]. The environmental change of work from the pandemic reduced work productivity in around 15% of workers [23]. Moreover, work-related musculoskeletal disorders of the hand and wrist joints are the most common cause of employee absenteeism, and also are associated with greater loss of productivity at work than pathologies of other anatomical regions.

Excessive mouse usage, exceeding 20 hours per week, poses a significant risk for carpal tunnel syndrome and other work-related musculoskeletal disorders. Similarly, an increased likelihood of such disorders can be linked to prolonged remote computer work or taking on a demanding job that involves extensive computer use [24].

The COVID-19 pandemic has influenced health, well-being, and contributed to the development of smartphone addiction, which, through prolonged usage, can lead to various pathologies, including musculoskeletal disorders. The monotonous activities of holding a smartphone in one hand and scrolling with one finger may cause excessive usage of thumb, wrist joint, and especially the carpometacarpal joint to excessive wear and tear. These wrist and thumb activities very often cause musculoskeletal symptoms. Also, increased pressure in the carpal tunnel area, which compress its contents and cause swelling of the median nerve and long finger flexor tendon is often found. Moreover, excessive smartphone usage may be associated with impaired ability to perform precise thumb movements [25,26].

MUSCULOSKELETAL DISORDERS AND POSTURE DEFECTS

Correct posture influenced by many factors is very important in maintaining the efficiency of many organs. When it is disrupted, the functioning of the entire body is affected [27.] The key to good posture is the position of the spine. Correct posture should maintain three natural curves, but not increase them. Increased curvature of the spine affects many parts of the human body through pressure. Therefore, the effects are not only seen in the musculoskeletal system, but also affect the functioning of the nervous and cardiovascular systems [28].

The COVID pandemic and its associated lockdown has contributed significantly to the decline in physical activity among students and school children. People were forced to stay indoors, all educational institutions were shut down and they started online education, this led to dependency on online classes [30]. This lifestyle has developed an abnormal posture among students [29]. They were spending more time on laptops and smartphones both to support their academic activities and in their free time [30]. Staying at static position by repeated movements such as using a keyboard, clicking on a mouse, usage of the body in inadequate ergonomic conditions may lead to musculoskeletal disorders [31].

One study conducted in elementary school among children showed changes throughout the spine [32]. Before the pandemic, postural disorders were present in 71.11%. More than 95% of the children had pathological alignment of the shoulders and shoulder blades both before the pandemic and after one year of anti-pandemic restrictions. Analysis of body segment positions showed that the most affected segment was the lumbar spine, followed by thoracic spine deformities [33].

Musculoskeletal pain in college students leads to discomfort that can limit students' daily leisure time and increases psychological stress [34]. The results of a survey of students during the COVID-19 and lockdown pandemic clearly suggest that there is a high prevalence of musculoskeletal pain among college students during the pandemic, which increased from 15.6% to 64.4%. This has been correlated with both decreased physical activity among students during this time and increased time spent at mobile devices in a forced posture. This study concluded that increased screen-time on electronic devices during COVID-19 led to high prevalence of musculoskeletal disorders in students. The highest prevalence was found in lower back region [30].

Some students do not have an ergonomically standard chair at home [35]. Non-ergonomic position reduced the muscular effort required to maintain a seated position, cause

the ligaments and muscles supporting the spine to increase tension which cause upper and lower back pain [36].

Prolonged static contraction of the back's skeletal muscles causes impaired blood flow to the muscles (ischemia), along with swelling and the accumulation of waste metabolites that cause spasm pain [37].

RESULTS

This work is a preliminary summary of the effects that Covid-19 has had on society. During the lockdown, prolonged periods of reduced physical activity contribute to muscle loss, decreased bone density, and an increased risk of fractures. Sedentary behavior and poor nutrition further worsen these effects, leading to accelerated progression of skeletal disorders. Additionally, extended bed rest associated with COVID-19 hospitalization can result in muscle wasting, particularly in older individuals. The lockdown measures implemented during the COVID-19 pandemic unintentionally contributed to the deterioration of skeletal health in humans manifesting as carpal tunnel syndrome, spinal curvatures, temporomandibular joint disorders and postural abnormalities. Recognizing and addressing the negative consequences on the skeletal system is crucial for preventing long-term complications and disability. Future research should focus on developing effective interventions and public health strategies to mitigate the negative impact of lockdowns on skeletal disorders and promote musculoskeletal health, especially among vulnerable populations.

REFERENCES

1. Alexander, A. J., Joshi, A., Mehendale A.: The Musculoskeletal Manifestations of COVID-19: A Narrative Review Article, *Cureus*, 2022, 14(9).
2. Salamanna, F., Maglio, M., Sartori, M., Landini, M.P., Fini, M.: Vitamin D and Platelets: A Menacing Duo in COVID-19 and Potential Relation to Bone Remodeling, *International Journal of Molecular Sciences*, 2021, 16, 22(18), 10010.
3. Sapra, L., Saini, C., Garg, B., Gupta, R., Verma, B., Mishra, P.K., Srivastava, R.K.: Long-term implications of COVID-19 on bone health: pathophysiology and therapeutics, *Inflammation Research*, 2022, 71, 1052-1040.
4. Karaarslan, F., Demircioğlu Güneri, F., Kardeş, S.: Long COVID: rheumatologic/musculoskeletal symptoms in hospitalized COVID-19 survivors at 3 and 6 months, *Clinical Rheumatology*, 2022, 41, 289-296.

5. Susilowati, I.H., Kurniawidjaja, L.M., Nugraha, S., Nasri, S.M., Pujiriani, I., Hasiholan, B.P.: The prevalence of bad posture and musculoskeletal symptoms originating from the use of gadgets as an impact of the work from home program of the university community, *Heliyon*, 2022, 8(10), 11059.
6. Li D.T.S., Leung Y.Y.: Temporomandibular disorders: Current concepts and controversies in diagnosis and management. *Diagnostics*, 2021, 11, 459.
7. Schiffman E., Ohrbach R., Truelove E., Look J., Anderson G., Goulet J., Svensson P., Gonzalez Y.: Diagnostic criteria for temporomandibular disorders (DC/TMD) for clinical and research applications: Recommendations of the international RDC/TMD consortium network and orofacial pain special interest group. *Journal of Oral & Facial Pain and Headache*, 2014, 28(1), 6–27.
8. Fillingim R.B., Ohrbach R., Greenspan J.D., Knott C., Diatchenko L., Dubner R., Bair E., Baraian C., MacK N., Slade G.D., Maixner W.: Psychological factors associated with development of TMD: The OPPERA prospective cohort study. *Journal of Pain*, 2013, 14(12).
9. Chang J.J., Ji Y., Li Y.H., Pan H.F., Su P.Y.: Prevalence of anxiety symptom and depressive symptom among college students during COVID-19 pandemic: A meta-analysis. *Journal of Affective Disorders*, 2021, 292, 242-254.
10. Daniali H., Martinussen M., Flaten M.A.: A global meta-analysis of depression, anxiety, and stress before and during COVID-19. *Health Psychology*, 2023, 42(2), 124-138.
11. Deng J., Zhou F., Hou W., Silver Z., Wong C.Y., Chang O., Drakos A., Zuo Q.K., Huang E.: The prevalence of depressive symptoms, anxiety symptoms and sleep disturbance in higher education students during the COVID-19 pandemic: A systematic review and meta-analysis. *Psychiatry Research*, 2021, 301.
12. Liyanage S., Saqib K., Khan A.F., Thobani T.R., Tang W.C., Chiarot C.B., Alshurman B.A., Butt Z.A.: Prevalence of anxiety in university students during the COVID-19 pandemic: A systematic review. *International Journal of Environmental Research and Public Health*, 2022, 19(1), 62.
13. Saczuk K., Lapinska B., Wawrzynkiewicz A., Witkowska A., Arbildo-Vega H.I., Domarecka M., Lukomska-Szymanska M.: Temporomandibular disorders, bruxism, perceived stress, and coping strategies among medical university students in times of social isolation during outbreak of COVID-19 pandemic. *Healthcare*, 2022, 10, 740.

14. Gaş S., Ekşi Özsoy H., Cesur Aydın K.: The association between sleep quality, depression, anxiety and stress levels, and temporomandibular joint disorders among Turkish dental students during the COVID-19 pandemic. *Cranio - Journal of Craniomandibular & Sleep Practice*, 2021.
15. Câmara-Souza M.B., Kim F.H.N., Garcia R.C.M.R.: Awake bruxism, temporomandibular disorders, and quality of life in dental students during COVID-19 lockdown: association with mental health. *Research, Society and Development*, 2022, 11(7).
16. Sirajudeen MS, Alzhrani M, Alanazi A, Alqahtani M, Waly M, Unnikrishnan R, Muthusamy H, Alrubaia W, Alanazi N, Seyam MK, Kashoo F, Miraj M, Channmgere Govindappa S, Alghamdi KA, Al-Hussin NM. 2022. Prevalence of text neck posture, smartphone addiction, and its association with neck disorders among university students in the Kingdom of Saudi Arabia during the COVID-19 pandemic, *PeerJ* 10:e14443.
17. Tsantili, A., Chrysikos, D., Troupis, T. Text Neck Syndrome: Disentangling a New Epidemic, Mini Narrative Review, 2022, *Acta Medica Academica*, 51(2), 123-127.
18. In, T., Jung, J., Jung, K., Cho, H. Spinal and Pelvic Alignment of Sitting Posture Associated with Smartphone Use in Adolescents with Low Back Pain, *International Journal of Environmental Research and Public Health*, 2021, 18(16), 8369.
19. Chu EC, Lo FS, Bhaumik A. Plausible impact of forward head posture on upper cervical spine stability, *Journal of Family Medicine and Primary Care*, 2020, 9(5), 2517-2520.
20. Fiebert, I., Kistner, F., Gissendanner, C., DaSilva, C. Text neck: An adverse postural phenomenon, *Work*, 2020, 69(4), 1261-1270.
21. Susilowati, I., Kurniawidjaja, L., Nugraha, S., Nasri, S., Pujiriani, I., Hasiholan, B. The prevalence of bad posture and musculoskeletal symptoms originating from the use of gadgets as an impact of the work from home program of the university community, *Heliyon*, 2022, 10, 2-4.
22. Gomez, I.N., Suarez, C.G., Sosa, K.E., Tapang, M.L. Work from home-related musculoskeletal pain during the COVID-19 pandemic: A rapid review. *International Journal of Osteopathic Medicine*, 2022, 47, 1-9.
23. Wakaizumi, K. , Yamada, K., Shimazu, A., Tabuchi, T. Sitting for long periods is associated with impaired work performance during the COVID-19 pandemic. *Journal of Occupational Health*, 2021, 63, 1.

24. Barr, A.E., Barbe, M.F., Clark, B.D. Work-Related Musculoskeletal Disorders of the Hand and Wrist: Epidemiology, Pathophysiology, and Sensorimotor Changes. *Journal of Orthopaedic & Sports Physical Therapy*, 2004, 34, 610-614.
25. Sirajudeen, M.S., Alzhrani, M., Alanazi, A., Alqahtani, M., Waly, M., Manzar, M.D., Hegazy, F.A., Mohd, Jamali, M.N.Z., Reddy, R.S., Kakaraparthi, V.N., Unnikrishnan, R., Muthusamy, H., Alrubaia, W., Alanazi, N., Kashoo, F.Z., Miraj, M. Prevalence of Upper Limb Musculoskeletal Disorders and Their Association with Smartphone Addiction and Smartphone Usage among University Students in the Kingdom of Saudi Arabia during the COVID-19 Pandemic—A Cross-Sectional Study. *Healthcare*, 2022, 10, 1-12.
26. Ming, Z., Pietikainen, S., Hänninen, O. Excessive texting in pathophysiology of first carpometacarpal joint arthritis. *Pathophysiology*, 2006, 13, 269-270.
27. Zagyapan, R., Iyem, C., Kurkcuoglu, A., Pelin, C., Tekindal, M.A.: The Relationship between Balance, Muscles and Anthropomorphic Features in Young Adults, *Anatomy Research International*, volume 2012, 6 pages
28. Akulwar-Tajane, I., Darvesh, M., Ghule, M., Deokule, S., Deora, B., Mhatre, V.: Effects of COVID -19 Pandemic Lock Down on Posture in Physiotherapy Students: A Cross Sectional Study, *Medical & Clinical Research*, 2020, 6: 91-102.
29. Socal Schwertner, D., Alexandre Nunes da Silva Oliveira, R., Silva Beltrame, T., Capistrano, R., Maestri Alexandre, J.: Questionnaire on body awareness of postural habits in young people: construction and validation, *Fisioter. Mov.*, Curitiba 2018, 31
30. Prajapati, S. P., Purohit, A.: Prevalence of Musculoskeletal Disorder among College Students in Times of COVID-19 Pandemic – An Observational Study, *International Journal of Health Sciences and Research*, 2021, 11.
31. Moretti, A., Menna, F., Aulicino, M., Paoletta, M., Liguori S., Iolascon, G.: Characterization of Home Working Population during COVID-19 Emergency: A Cross-sectional analysis, *International Journal of Environmental Research and Public Health*, 2020 Jan, 17 (17), 6284.
32. Makarczuk, A.: The Knowledge of parents about frequency of body posture defects in early school age children, *Journal of Education, Health and Sport*, 2022, 12(1), 259-264.
33. Rusnak, R., Potasova, M., Littiva, V., Kutis, P., Komar, M., Macej, P.: World's COVID-19 anti-pandemic measures in the context of postural and spine disorders in primary school children in Slovakia, *Bratislava Medical Journal*, 2022, 123(8).

34. Leirós-Rodríguez, R., Rodríguez-Nogueira, Ó., Pinto-Carral, A., José Álvarez-Álvarez, M., Galán-Martín, M. Á., Montero-Cuadrado, F., Alberto Benítez-Andrades, J.: Musculoskeletal Pain and Non-Classroom Teaching in Times of the COVID-19 Pandemic: Analysis of the Impact on Students from Two Spanish Universities, *Journal of Clinical Medicine*, 2020, 9(12), 4053.
35. Singh, S., Saini, A., Ahlawat, T.R.: Impact of online teaching on health of university students during Covid 19 pandemic crisis, *The Pharma Innovation Journal*, 2021, 10 (4), 958-961.
36. Meshram, K., Tembhare, V., Taksande, A., Pohekar, S., Kasturkar, P., Sakharkar, S., Wankhede, D., Sakharwade, P.: Preventive Recommendations to Reduce the Impact of Poor Ergonomics on Children during Online Learning, *Journal of Pharmaceutical Research International*, 2021, 33(57B), 247-252
37. Condrowati, Bachtiar, F., Maharania, F. T., Utari, D.: Musculoskeletal Disorder of Workers During Work From Home on Covid-19 Pandemic: A Descriptive Study, *Advances in Health Sciences Research*, 2020, 30, International Conference of Health Development. Covid-19 and the Role of Healthcare Workers in the Industrial Era (ICHHD 2020).

**SELECTED CLINICAL
AND THERAPEUTIC PROBLEMS**

SIGNIFICANCE OF GUT MICROBIOME IN HEART DISEASES

Sven Solisch¹, Anna Susłow¹, Adam Szwed¹, Krzysztof Gomulka²

1. Student Scientific Group of Adult Allergology, Wrocław Medical University, Wrocław, Poland
2. Department of Internal Medicine, Pneumology and Allergology, Wrocław Medical University, Wrocław, Poland

ABBREVIATION LIST

- CVD – cardiovascular disease,
- HF – heart failure
- LPS – Lipopolysaccharide,
- LVEF - left ventricle ejection fraction
- TMAO – Trimethylamine-N-oxide
- TNF-alpha – Tumour Necrosis Factor-alpha
- IL-6 – Interleukin-6
- CRP – C-reactive protein

INTRODUCTION

The question of the functions performed by the human intestinal microbiota has recently been an interesting issue. Thanks to the dynamic development of various diagnostic possibilities, we are able to learn more and more precisely the reasons why mother nature has equipped us with about 2 kg of bacteria inhabiting our digestive tract. They have been shown to be most abundant in the large intestine and belong to four types: *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, and *Actinobacteria*. Most microorganisms exhibit absolutely anaerobic metabolism (e.g. *Bacteroides*, *Clostridium*, or *Fusobacterium*), but there are also aerobic and relatively anaerobic bacteria (e.g. *Enterobacteriaceae*, *Lactobacillus*, *Enterococcus* or *Streptococcus*). What's more, some viruses or fungi also live in our intestines [1,2,3]. The key moment in the acquisition of physiological intestinal microbiota is the passage of the child through the mother's birth canal during natural childbirth [4]. Unfortunately, the recent increase in caesarean sections may have an adverse effect on the child's health in the future [5,6,7,8].

Microorganisms in our intestines perform many functions - they are responsible for proper digestion, absorption, and metabolism [9]. Thanks to the presence of bacteria, it is possible to digest resistant starch, mucins, or nitrogen compounds, as well as synthesize vitamins from the B-group (including thiamine, pyridoxamine, folic acid, or cobalamin) and vitamin K. In addition, microbiota degrades exfoliated epithelial cells, and foreign substances contained in food, drugs, or dietary supplements and enables the proper functioning of the intestinal barrier, which is an important component of the absorption of microelements (e.g. sodium and potassium) [1,10,11,12,13]. Another task performed by the useful microorganisms of our intestines is the synthesis of organic acids. Lactic acid effectively maintains the pH at the appropriate level, making the environment unfavorable for the invasion of possible pathogens [14,15]. In turn, butyric acid - one of the *SCFA* (short-chain fatty acids) - has a nutritional function in relation to colonocytes, anti-inflammatory and also stimulating the motility of the digestive tract [10,13,16,17]. Another important role of the microbiota is participation in immune reactions due to interactions with *GALT* (gut-associated lymphoid tissue), which positively affects the ratio of Th1 to Th2 lymphocytes [18,19,20].

The role of the intestinal microbiota is not limited to local impacts in the place of occurrence. Thanks to numerous connections with neurotransmitters, it affects the central nervous system. Dysregulation of the gut-brain axis is seen as the cause of many serious neurological diseases - including neurodegenerative diseases, depression, or multiple sclerosis [21].

Recent years have also shown the participation of the intestinal microbiota in the regulation of the cardiovascular system. For example, due to the possibility of decomposing nutrients such as saccharides or lipids, microorganisms living in our digestive tract may reduce the risk of cardiovascular incidents depending on the qualitative composition of the microbiota [22, 23]. The influence of the microbiota on the risk of coronary heart disease and heart failure will be discussed in detail in the following paragraphs.

ROLE OF GUT MICROBIOTA IN CARDIOVASCULAR DISEASE

Atherosclerosis is a chronic inflammatory disease in which there is a build-up of plaques inside arteries. Arteries that have become extremely narrow can cause shortness of breath and chest pain during physical activity, called angina pectoris [24]. These plaques are causing turbulent flow with atherosclerotic cardiovascular disease (ASCVD) as a result [25]. Coronary artery disease is one of the most common cardiovascular diseases (CVD). Despite the fact that

CVD incidence and mortality rates are constantly declining in many European countries, it still remains a major cause of morbidity and mortality [26]. In 2020, ischemic heart disease (IHD) mortality rates were 112.37 per 100,000 [27]. Overall CVD is estimated to cost the European Union economy 210 euro billion a year [28]. More than 60 million potential years of life are lost to CVD in Europe annually [29]. The major modifiable risk factors for CVD are hypercholesterolemia, hypertension, cigarette smoking, diabetes mellitus and adiposity [26]. Various inflammatory markers have already been associated with CVD, such as tumor necrosis factor-alpha (TNF-alfa), interleukin-6 (IL-6), and C-reactive protein (CRP) [30].

Advances in medical and microbiological knowledge resulted in a novel approach to the pathogenesis of CVD. The precise mechanism by which the microbiota contributes to atherosclerosis remains unknown. So far dysbiosis is associated with leaky gut, abnormal glucose, and lipid metabolism, which are major risk factors for CVD [31]. The gut microbiome produces hundreds of different metabolites, which can affect multiple tissues and organs of our body and it can be compared to endocrine organs. Butyrate is a product of microbial metabolism and simultaneously the main source of energy for colonocytes [32]. It supports anti-inflammatory effects in the intestinal mucosa by activating regulatory T cells. Decrease in butyrate-producing bacteria such as *Roseburia intestinalis* and *Faecalibacterium praus*, disrupt the mucosal barrier, resulting in leakage of microbial toxins such as lipopolysaccharide (LPS) [33,34,35]. LPS is a bacterial surface molecule, produced by most Gram-negative bacteria [36]. Studies showed that increased plasma levels of LPS can be connected to insulin resistance, glycaemic control, and abdomen obesity, primary drivers for CVD [37,38].

Trimethylamine-N-oxide (TMAO) is a microbiota-related metabolite and potentially a causative agent in atherosclerosis. To begin with, gut microbiota produces trimethylamine from nutrients containing L-carnitine or phosphatidylcholine. Next, it is oxidized by hepatic flavin-containing monooxygenases to TMAO. Choline, phosphatidylcholine, and L-carnitine are present in red meat, fish, and eggs. Animal models showed that precursors of TMAO promote foam cell formation and atherosclerosis [34]. Also, TMAO interferes with platelet function through stimulus-dependent calcium signaling, promoting atherothrombotic events [31]. Besides, increased plasma levels of TMAO were associated with an increased risk of major adverse cardiovascular events. Moreover, it is independent of traditional risk factors, even in low-risk cohorts [38].

Growing evidence of a microbial role in the pathogenesis of atherosclerosis evolved in attempts to use antimicrobial substances in patients. Oral broad-spectrum antibiotics can temporarily suppress the production of TMAO. Unfortunately, the durability of that effect with

long-term use is unknown. What is more W.H. Wilson Tang et al. suggests that instead of eradicating of intestinal microbes we should focus on reducing the consumption of products rich in phosphatidylcholine and choline [39]. Another interesting compound, resveratrol, is a polyphenol, originating from fruits, especially grapes. Evidence shows that red wine is high in resveratrol and most likely it is responsible for the “French paradox” phenomenon. Further studies showed that resveratrol can modulate TMAO synthesis through gut microbiota-related dysbiosis [40,41]. Future research is needed to establish the importance of resveratrol supplementation in patients with CVD.

As presented, the role of gut microbiota in the pathogenesis of cardiovascular disease is still being explored. Researchers indicate that possibilities in novel treatment or methods of prevention of CVD are promising, and should be further studied.

GUT MICROBIOTA AND HEART FAILURE

Certain characteristics of gut microbiota composition are observed to be associated with an increased risk of heart failure (HF). Bacteria located in the intestines, while digesting, are responsible for the production of various metabolites, including lipopolysaccharide, short-chain fatty acids, and imidazole propionate [42,43,44]. Elevated serum levels of the third are recognized as indicating lower microbial diversity and being linked with reduced left ventricular ejection fraction (LVEF) and heart failure independently of traditional risk factors for cardiovascular disease. Increased serum concentrations of this compound might be a valuable predictor of 5-year mortality in patients with heart failure according to a 2023 cohort study conducted by Molinaro et al. [45,46]. The microorganisms that are identified as the cause of elevated imidazole propionate serum levels include *Ruminococcus gnavus*, *Clostridium bolteae*, and *Clostridium symbiosum*, and they are also found in greater abundance in patients with type-2 diabetes [47,48]. Studies performed on animal models as well as in vitro analysis show that imidazole propionate administration leads to activation of molecular pathways that are involved in heart remodeling associated with HF in mice [49].

Moreover, the already mentioned trimethylamine-N-oxide might also be taken into consideration regarding HF. Besides its involvement in the pathomechanism of atherosclerosis, trimethylamine-N-oxide is thought to directly affect the heart itself having an influence on the progression of heart failure. Based on murine models, TMAO was observed to induce myocardial hypertrophy and fibrosis as well as impair cardiomyocyte contractile function and intracellular calcium management in rats, but also to cause pathological left ventricular dilation

and reduced LVEF in mice [50,51,52]. More investigation is needed to develop knowledge about the gut microbiome's connection to heart failure and its possible application in diagnostic, therapeutical, and predictive measures.

CONCLUSIONS

While these findings require more study on both animal and human models in order to further understanding of the processes in which bacteria located in the human intestine affect the heart and its function, it is predicted that in the future they can play a role in shaping the procedures applied in diagnosis and treatment of cardiovascular diseases.

REFERENCES

1. Mroczyńska M, Libudzisz Z, Gałęcka M, et al. Mikroorganizmy jelitowe człowieka i ich aktywność metaboliczna. *Przegląd Gastroenterologiczny*, 2016, 4, 218–224.
2. Dethlefsen L, Eckburg PB, Bik EM, et al. Assembly of the human intestinal microbiota. *Trends in Ecology & Evolution*. 2006, 21(9), 517–523.
3. Ley RE, Peterson DA, Gordon JI. Ecological and evolutionary forces shaping microbial diversity in the human intestine. *Cell*. 2006, 124(4), 837–848.
4. Dominguez-Bello MG, Costello EK, Contreras M, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proceedings of the National Academy of Sciences of the United States of America*, 2010, 107(26), 11971–11975.
5. Bartnicka A, Gałęcka M, Mazela J. Wpływ czynników prenatalnych i postnatalnych na mikrobiotę jelitową noworodków. *Standardy Medyczne Pediatria*. 2016, 13, 112–116.
6. Bager P, Wohlfahrt J, Westergaard T. Caesarean delivery and risk of atopy and allergic disease: meta-analyses. *Clinical & Experimental Allergy*. 2008, 38(4), 634–642.
7. Thavagnanam S, Fleming J, Bromley A, et al. A meta-analysis of the association between Caesarean section and childhood asthma. *Clinical & Experimental Allergy*. 2008, 38(4), 629–633.
8. Cardwell CR, Stene LC, Joner G, et al. Caesarean section is associated with an increased risk of childhood-onset type 1 diabetes mellitus: a meta-analysis of observational studies. *Diabetologia*. 2008, 51(5), 726–735.
9. Gałęcka M, Bartnicka A, Basińska A. Znaczenie mikrobioty jelitowej w kształtowaniu zdrowia człowieka — implikacje w praktyce lekarza rodzinnego. *The importance of*

- intestinal microbiota in shaping human health — implications in the practice of the family physician. *Forum Medycyny Rodzinnej*. 2018, 12, 50-59.
10. Nowak A, Libudzisz Z. Mikroorganizmy jelitowe człowieka. *Standardy Medyczne—Pediatria*. 2008, 5, 372–379.
 11. Egert M, de Graaf AA, Smidt H, et al. Beyond diversity: functional microbiomics of the human colon. *Trends in Microbiology*, 2006, 14(2), 86–91.
 12. Sobieszczańska BM. The influence of intestinal dysbiosis on human's health. *Gastroenterologia Polska/ Gastroenterology*. 2008, 15(5), 287-290.
 13. Radwan P., Skrzydło-Radomańska B. Rolamikroflory jelitowej w zdrowiu i chorobie. *Gastroenterologia Praktyczna*. 2013, 2, 1–11.
 14. O'Hara AM, Shanahan F. Gut microbiota: mining for therapeutic potential. *Clinical Gastroenterology and Hepatology*. 2007, 5(3), 274–284.
 15. Schwarz A, Bruhs A, Schwarz T. The Short-Chain Fatty Acid Sodium Butyrate Functions as a Regulator of the Skin Immune System. *Journal of Investigative Dermatology*. 2017, 137(4), 855–864.
 16. Sokol H, Pigneur B, Watterlot L, et al. *Faecalibacterium prausnitzii* is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. *Proceedings of the National Academy of Sciences of the United States of America*, 2008, 105(43), 16731–16736.
 17. Cao Y, Shen J, Ran ZH. Association between *Faecalibacterium prausnitzii* Reduction and Inflammatory Bowel Disease: A Meta-Analysis and Systematic Review of the Literature. *Gastroenterology Research And Practice*. 2014, 2014, 872725.
 18. Gałęcka M, Bartnicka A, Szewc M, et al. Kształtowanie się mikrobioty jelitowej u niemowląt warunkiem zachowania zdrowia. 2016, 13, 359–367.
 19. Rusch K, Peters U. Jelito grube — centrum układu immunologicznego. *Medycyna Biologiczna*. 2003, 2, 54–58.
 20. Strzępa A, Szczepanik M. Influence of natural gut flora on immune response. *Postępy Higieny i Medycyny Doświadczalnej*, 2013, 67, 908–920.
 21. Szewczyk A., Witecka A., Kiersztan A. (2019). The role of gut microbiota in the pathogenesis of neuropsychiatric and neurodegenerative diseases. *Postępy Higieny i Medycyny Doświadczalnej*. 2019, 73, 865-886.
 22. Palmu J, Börschel CS, Ortega-Alonso A, et al. Gut microbiome and atrial fibrillation—results from a large population-based study. *EBioMedicine*. 2023,91, 104583.
 23. Piccioni A, Niccolai E, Rozzi G, Spaziani G, Zanza C, Candelli M, Covino M,

- Gasbarrini A, Franceschi F, Amedei A. Familial Hypercholesterolemia and Acute Coronary Syndromes: The Microbiota-Immunity Axis in the New Diagnostic and Prognostic Frontiers. *Pathogens*. 2023, 21, 12(4), 627.
24. Atherosclerosis - StatPearls NCBI, <https://www.ncbi.nlm.nih.gov/books/NBK507799/>. Accessed 20 June 2023.
25. Coronary artery disease: Overview - InformedHealth.org. NCBI, 13 February 2013, <https://www.ncbi.nlm.nih.gov/books/NBK355313/>. Accessed 20 June 2023.
26. Frank L J Visseren and others, 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC), *European Heart Journal*, 2021, 42(34), 3227–3337.
27. 2022 Heart Disease & Stroke Statistical Update Fact Sheet Global Burden of Disease.” American Heart Association, 26 January 2022, <https://www.heart.org/-/media/PHD-Files-2/Science-News/2/2022-Heart-and-Stroke-Stat-Update/2022-Stat-Update-factsheet-Global-Burden-of-Disease.pdf>. Accessed 20 June 2023.
28. Fact sheets for Press. European Society of Cardiology, <https://www.escardio.org/The-ESC/Press-Office/Fact-sheets>. Accessed 20 June 2023.
29. Townsend, N., Kazakiewicz, D., Lucy Wright, F. et al. Epidemiology of cardiovascular disease in Europe. *Nature Reviews Cardiology*, 2022, 19, 133–143.
30. Koushki M, Dashatan NA, Meshkani R. Effect of Resveratrol Supplementation on Inflammatory Markers: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Clinical Therapeutics*. 2018, 40(7), 1180-1192.e5.
31. Masenga, S. K., Hamooya, B., Hangoma, J., et al. Recent advances in modulation of cardiovascular diseases by the gut microbiota. *Journal of Human Hypertension*, 2022, 36(11), 952–959.
32. Roediger W. E. Utilization of nutrients by isolated epithelial cells of the rat colon. *Gastroenterology*, 1982, 83(2), 424–429.
33. Jie, Z., Xia, H., Zhong, S. L. ET AL The gut microbiome in atherosclerotic cardiovascular disease. *Nature communications*, 2017, 8(1), 845.
34. Trøseid M., Andersen G. Ø., Broch K., Hov J. R. The gut microbiome in coronary artery disease and heart failure: Current knowledge and future directions. *EBioMedicine* 2020, 52, 102649.

35. Nie, K., Ma, K., Luo, W., et al. Roseburia intestinalis: A Beneficial Gut Organism From the Discoveries in Genus and Species. *Frontiers in cellular and infection microbiology*, 2021, 11, 757718.
36. Bertani B., Ruiz N. Function and Biogenesis of Lipopolysaccharides. *EcoSal Plus*, 2018, 8(1), 10.1128
37. Furusawa Y., Obata Y., Fukuda S., et al. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature*, 2013, 504, 446–450.
38. Trøseid M., Torunn K. N., Knut R., et al. Plasma Lipopolysaccharide Is Closely Associated With Glycemic Control and Abdominal Obesity: Evidence from bariatric surgery. *Diabetes Care*, 2013, 36(11), 3627–3632.
39. Tang W. H., Wang Z., Levison B. S., et al. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. *The New England journal of medicine*, 2013, 368(17), 1575–1584.
40. Zhu Q., Gao R., Zhang Y., et al. Dysbiosis signatures of gut microbiota in coronary artery disease. *Physiological genomics*, 2018, 50(10), 893–903.
41. Teimouri M., Homayouni-Tabrizi M., Rajabian A., et al. Anti-inflammatory effects of resveratrol in patients with cardiovascular disease: A systematic review and meta-analysis of randomized controlled trials. *Complementary therapies in medicine*, 2022, 70, 102863.
42. Hersoug, L.G., Møller, P., Loft, S., et al.: Gut microbiota-derived lipopolysaccharide uptake and trafficking to adipose tissue: implications for inflammation and obesity. *Obesity Reviews*, 2016, 17(4), 297-312.
43. Van Deventer, C.A., Lindeque, J.Z., van Rensburg, P.J., Malan, L., van der Westhuizen, F.H., et al.: Use of metabolomics to elucidate the metabolic perturbation associated with hypertension in a black South African male cohort: the SABPA study. *Journal of the American Society of Hypertension*, 2015, 9(2), 104-114.
44. Koh A., Molinaro A., Ståhlman M., et al.: Microbially Produced Imidazole Propionate Impairs Insulin Signaling through mTORC1. *Cell*, 2018, 1, 175(4), 947-961.e17.
45. Menni, C., Zhu, J., Le Roy, C.I., Mompeo, O., Young, K., et al.: Serum metabolites reflecting gut microbiome alpha diversity predict type 2 diabetes. *Gut Microbes*, 2020, 11(6), 1632-1642.
46. Molinaro A., Nemet I., Lassen P.B., et al.: Microbially Produced Imidazole Propionate Is Associated With Heart Failure and Mortality. *Journals of the American College of Cardiology: Heart Failure*, 2023, 11(7), 810-821.

47. Molinaro A., Bel Lassen P., Henricsson M., et al.: Imidazole propionate is increased in diabetes and associated with dietary patterns and altered microbial ecology. *Nature Communications*, 2020, 11(1), 5881.
48. Wu H., Tremaroli V., Schmidt C., et al.: The gut microbiota in prediabetes and diabetes: a population-based cross-sectional study. *Cell Metabolism*, 2020, 32(3), 379-390.
49. Liao Y., Takashima S., Maeda N., et al.: Exacerbation of heart failure in adiponectin-deficient mice due to impaired regulation of AMPK and glucose metabolism. *Cardiovascular Research*, 2005, 67(4), 705-713.
50. Li Z., W, Z., Ya, J., et al.: Gut microbe-derived metabolite trimethylamine N-oxide induces cardiac hypertrophy and fibrosis. *Laboratory Investigation*, 2019, 99(3), 346-357.
51. Savi M., Bocchi L., Bresciani L., et al.: Trimethylamine-N-Oxide (TMAO)-Induced Impairment of Cardiomyocyte Function and the Protective Role of Urolithin B-Glucuronide. *Molecules*, 2018, 23(3), 549.
52. Organ C.L., Otsuka H., Bhushan S., et al.: Choline diet and its gut microbe-derived metabolite, trimethylamine N-oxide, exacerbate pressure overload-induced heart failure. *Circulation: Heart Failure*, 2016, 9(1), e00231.

ALZHEIMER'S DISEASE- OPHTHALMOLOGICAL POINT OF VIEW

Maria Kręcicka, Julia Drewniowska, Magdalena Góral, Maciej Dyda

Wroclaw Medical University

ABBREVIATION LIST

- AD- Alzheimer's disease
- APP- amyloid precursor protein
- PSEN1- presenilin 1
- PSEN2- presenilin 2
- CT- computed tomography
- MRI- magnetic resonance imaging
- PET- positron emission tomography
- CNS- central nervous system
- IPL- inner plexiform layer
- AH- aqueous humour
- ACh- acetylcholine
- MCV- maximum velocity of constriction
- MCA- maximum constriction acceleration
- NMDAR- N-methyl-D-aspartate receptor

INTRODUCTION

According to Alzheimer's Disease International every three seconds a person develops dementia [1].

Alzheimer's Disease (AD) poses difficulties differentiation with other dementias, which is why it is so urgent to find biomarkers that allow diagnosis at an early stage [2]. AD is a neurodegenerative disorder, which derives primarily from genetic mutations and amyloid plaque accumulation. A connection between AD and ophthalmologic symptoms in affected patients has been observed and widely investigated. Anatomical changes in the eye can even appear before signs of cognitive impairment and memory loss [3]. Some studies even refer to

the retina as the window, in which to view the pathogenesis of Alzheimer's [4]. Not only the retina, but other anatomical parts of the eye show morphological changes caused by the progression of the disease:

- vitreous humor,
- optic nerve,
- lens,
- cornea,
- aqueous humor.

However, as AD affects the nervous system, eye symptoms are most often localized in the innervated sites - the retina and the cornea.

PATHOGENESIS

There are many hypotheses proposing different pathogenesis of AD. Among the most researched potential causes of Alzheimer's are the extracellular amyloid plaque accumulation, intracellular hyper-phosphorylated tau protein accumulation and genetic factors. Rare, familial form of AD is caused by mutations in three genes - amyloid precursor protein (APP), presenilin 1 (PSEN1) and presenilin 2 (PSEN2). However, AD is considered a sporadic disease, which is most often observed in patients with apolipoprotein E4, an isoform of a lipid transporting protein.

DIAGNOSIS

Alzheimer's Disease is currently diagnosed by many methods, such as computed tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography (PET) to rule out the possible causes for the symptoms. The early diagnosis is based on early recognition of symptoms and signs, like forgetting recently learned information which is not pathognomonic [5].

The eye offers a natural window to the brain as retina, which is the only optically accessible nervous tissue. Numerous studies have reported the presence of β -amyloid plaques in the patients' retina and signs of degenerative changes and retinal neuron damage. It opens the possibility, for early detection of AD in noninvasive eye scans [6-8].

At this moment, there is no perfect tool for AD screening, because there is limited number of eligible studies, with broad ranges of sensitivity and specificity. There is need to conduct larger studies investigating retinal β -amyloid and it's early detection and disease prediction sensitivity [6].

CORNEA

The cornea, in combination with the precorneal tear film, plays an important role in providing a proper anterior refractive surface as well as protection of the eye against infection and structural damage [9]. In AD changes such as corneal thinning and decreased corneal sensitivity are observed. Further studies have shown overall decrease in corneal nerve fiber number, density and length, as well as increased density of dendritic cells in AD patients [10].

As cholinergic nerve fibers are targeted in AD, the implications include abnormalities in tear outflow, such as decreased lacrimation. Blink rates, corneal hypoesthesia and tear function tests are helpful in detecting activity or progression of neurodegenerative diseases. corneal innervation is very significant in maintaining the corneal epithelium - its reduction may lead to clinical implications, such as erosions, that may require ocular surgery [9].

RETINA

Common pathological features have been observed in AD patients' brains and retina. The retina shares similarities with the brain tissue and is composed of multiple layers: three layers of nerve glial cell bodies and three layers of synapses. Photoreceptors capture and transmit information via interneurons to retinal ganglion cells, which make direct synaptic connections with the CNS through the optic nerve [11].

The proximity of nerves and blood vessels in the retina is called the blood-retina barrier, similarly to the brain-blood barrier [4].

The retinal arterioles and venules have anatomical features and physiological properties strongly resembling small cerebral vessels. These analogies enable scientists to refer to the retina, as mentioned above, the window of the brain, as pathological changes in the brain are often mirrored in the structure of the retina [12].

Therefore retinal manifestations may prove to be an effective screening, diagnostic and monitoring tool.

The hallmark biomarkers of AD - amyloid beta plaques and protein tau - have been detected in various retinal layers, resulting in neuronal cell death, retinal ganglion pericytes apoptosis, synaptic dysfunction and thinning of the retinal nerve layer. In other contradictory studies either no or limited evidence of amyloid accumulation has been found [10,11].

VASCULAR IMPLICATIONS

In AD patients the parameters of retinal vessels are changed. The diameter of veins, arterioles and venules is reduced, they are more tortuous and sparse, all of which results in decreased blood flow [10,13].

The combination of retinal vascular parameters such as blood column diameter, blood flow and blood speed can be applied in distinguishing between mild cognitive impairment and Alzheimer's.

A laser Doppler instrument is found to be useful in showing that blood flow is lower and the retinal veins are relatively narrow in AD individuals than in healthy patients [4]. Moreover, oxygen saturation in arterioles and venules is often significantly higher.

THICKNESS OF THE RETINA

Histological analysis has confirmed extensive loss of retinal ganglion cell in AD patients, resulting in substantial thinning of the retina [10,14]. The loss of retinal nerve fiber layer has been observed in various patterns, including sectoral loss in the superior, nasal and inferior retina [10,14,15]. Decrease in the volume of the temporal and occipital cerebral cortex correlates with thinning of the inner plexiform layer (IPL) [10,15]. It remains under question, whether retinal thinning precedes or follows the clinical manifestation of Alzheimer's disease [16].

AQUEOUS HUMOUR (AH)

The accumulation of amyloid β and precursor protein – APP - in the aqueous humour seems to have the origin in many sources [10].

There are studies which describe the transport pathway of amyloid substance produced in retina, via the vitreous humour, to the aqueous humour in the anterior chamber [10,17].

As it was mentioned before, describing the blood – retina barrier, some elements of the sight organ show similarities with the central nervous system components. That is because of the high-density of contained neurons and glia cells, as well as the analogical connection with the bloodstream [18,19]. This assumption is correct for the aqueous humour compared here with the cerebrospinal fluid regarding a complex mixture of proteins [19,20]. Following this thesis, the barrier between blood and aqueous humour functions analogous to the blood – brain barrier, which equals carrying the signs of damage in the AD by both [10,17].

All of these deliberations lead to the conclusion that the presence of protein deposits in the AH is a reasonable biomarker for the Alzheimer disease [10,18].

The correlation between changes in AH and the Alzheimer disease has also been demonstrated in the patients with glaucoma and pseudoexfoliation syndrome, suggesting that these conditions might be linked with amyloid accumulation [10,21,22].

As for primary glaucoma, elevated intraocular pressure is considered to be the most frequent and important risk factor. There are cases which mention glaucoma progression among patients with AD who develops increased values of that intraocular parameter [23-25]. Owing to the patients with normal intraocular pressure who have contracted primary open angle glaucoma, the notion that this morbid entity shares some pathogenetic mechanisms with neurodegenerative diseases such as AD is still investigated [21,26].

PUPIL

The pupil size is controlled by two antagonistic muscles: the dilator, activated by the sympathetic stimuli, and the sphincter, which reacts to activation of the parasympathetic nervous system. Significant changes in the function of pupil in patients with AD are caused by the pathological degenerative process located in the Edinger–Westphal nucleus, the part of oculomotor nerve (CN III) [10]. As a result, the anatomical structures which are innervated by the third cranial nerve, such as ciliary body and above - mentioned sphincter muscle of the pupil, cannot act properly. This pathomechanism explains the reason of increased pupil diameter during cognitive effort [10,23,27].

The basal nucleus of Meynert is also meaningfully influenced by the changes embraced the nervous tissue. That leads to the impairment of the cholinergic system responsible for the multiple projection to the brain cortex [10]. Loss of cholinergic neurons, located mainly in the medial septum and in the para-hippocampal area, is strongly and directly associated with

memory impairment^{28,29}. The decreased levels of acetylcholine (ACh) in AD patients result in pathologic condition of the pupillary system and altered pupillary eye reflex (PLR) [10,30].

The value of pupillometry as a potential biomarker in AD seems to be more and more appreciated [28]. In patients who develop AD, repetitive stimulation of the pupillary reflex is less pronounced [9]. The latency of pupillary constriction to light increases, whereas the amplitude is decreased [9,28]. Compared to healthy controls, faster redilation after light offset is observed, together with significant changes in different parameters - decreased maximum velocity of constriction (MCV) and maximum constriction acceleration (MCA) [28]. These two parameters have been reported as the most accurate to differentiate AD patients from healthy controls [28,31-33]. Nevertheless, not every study have succeed to find such differences [34,35].

LENS

As the lens and brain share a common embryological origin in germinal ectoderm [36,37], progressive changes of AD do not avoid normally transparent crystalline human lens. Some specific similarities have been indicated between the neurodegenerative processes in the brain and the fundamental mechanism of cataract formation [10,15]. Advanced loss of the lens transparency is caused by the cataractous changes of the lens. As in the previous described patomechanisms responsible for most of the implications of AD, the process of excessive accumulation of abnormal protein plays here significant role [10,30].

In AD lenses, A β peptides aggregate in the cytoplasm of supranuclear lens fiber cells, which scatter the visible light. Advanced supranuclear cataracts observed in late stage of AD are typically bilaterall and have no one typical phenotypic penetrance [36].

AD-associated pathological mechanisms are linked with others commonly known diseases connected with modifications of the lens structure. For example development of age-related cataract [10,30]. Down syndrome, a risk factor of developing AD with early – onset, is classified to these cases too [36]. Patients with DS in their third decade of life and beyond are at higher risk of progression of AD-related neuropathology, neurodegeneration, and cognitive decline which may lead to complete clinical dementia [36].

Highly sensitive noninvasive optical techniques, slit lamp examination and optical coherent tomography, can be used to detect and tracked the cataract. This marks the lens out as an ideal “window” to monitor the progression of AD as the slightest opacity may act as a sign

of systemic disorder³⁸. Furthermore, new technologies allow to confirm the origin of visible changes. Special fluorescence drops, unique for the A β proteins, may be injected into the eye and eventually bind into the match elements [38,39].

OPTIC NERVE

Reports which demonstrates degeneration of the optic nerve related to simultaneous damage of retinal cells and visual impairments in AD patients, have enabled further observation of significant changes involving the optic disc [2]. This structure modified by the pathological process is distinguished by excessive pallor and increased cup – to – disc ratio [10,40-42]. Thinning of lamina cribrosa as a consequence of Tau protein deposits in the cerebrospinal fluid might be also noticed [23,43]. Contradictory findings suggest that AD does not always affect axonal damage within the optic nerve [23,44].

CLINICAL OCULAR MANIFESTATIONS

Eye movements

One of the most noticeable Alzheimer's disease-related ocular changes are modified elementary eye movements, such as saccades, smooth pursuit and pupillary responses. To leave no doubt, the fast, swift motion of the eyes that shifts gaze from one focus to another towards the target is called prosaccade, while antisaccade is simply saccade away from the target. Smooth pursuit requires sustained following and focusing on moving target objects. Pupillary responses answer for variations of the size of the pupils involving the autonomic and the central nervous systems.

Generation of prosaccades demands contribution of multiple areas in the cortex and brainstem [45]. As an example regions that are able to trigger saccades: the frontal eye field, supplementary eye field and parietal eye field. Also there are cortical areas involved into preparing saccades, such as the posterior parietal cortex, posterior hemispheric cortex and vestibular cortex [46]. In AD patients increased latency to initiate and decreased velocity of prosaccades are observed [47-49]. Their movements' accuracy often occurs as hypometric, not reaching the target [50,52] but sometimes might be also hypermetric - when they make perseverative errors [47]. Moreover, AD patients demonstrate a distinct gap effect - the temporal gap between fixation point offset and target onset which typically results in shorter saccadic

latencies than if the fixation point remains on [52]. It is also believed that decreased control of saccadic movements comes from inhibitory dysfunctioning which is a relatively frequent sign of Alzheimer's disease [53]. However, some research suggests that AD patients may have normal prosaccadic functions [54,55]. The intricacy of prosaccadic processes is still waiting to be explained.

The first inhibitory signal responsible for antisaccades starts in the dorsolateral prefrontal cortex and it is sent to the superior colliculus to stop reflexive prosaccades [56]. After that, the frontal eye field and posterior parietal eye field are involved. Afflicted patients exhibit inability to suppress these reflexive responses due to the dorsolateral prefrontal cortex degeneration or decay in working memory [47]. This results in incorrect antisaccades, that is to say high antisaccade error rate [53,57].

During smooth pursuit tests patients have to continuously track and hold their gaze on moving target. Correct response is determined as the ability to keep gaze and to reduce the number of preceding (in the direction of target) and compensatory "catch up" saccades⁴⁷. Patients with AD show enlarged latency to initiate smooth pursuit as well as decreased velocity and gain which is the ratio of eye velocity to target velocity. They often make intrusive anticipatory and "catch up" saccades in different numbers and amplitudes [58,59]. AD group of individuals exhibits significantly differential values in the smooth pursuit test than healthy people. These pursuit errors are connected to diminished metabolism in the right posterior middle temporal gyrus - an area that is close to the middle temporal complex which is admitted to be involved in transmission of information about moving target to the frontal and supplementary eye fields mentioned above [60].

Well known pupillary response to light stimulus is reduced in people with AD [61,62]. Patients have significantly lowered levels of maximum constriction velocity and acceleration, amplitude between baseline pupil diameter and minimal pupil diameter during pupillary light response [32]. The reason for such a pupils' response is cholinergic deficiency in the visual system which is substantial for AD.

The quality of vision

Anomaly in visual acuity as the ability of the eye to identify small objects in terms of established level of luminance and contrast is found under conditions of low luminance when decreased visual acuity in AD patients is observed [63]. Moreover, low spatial frequency

conditions, that is to say reduced air transparency which results in blurred edges of viewed objects (just like on rainy or foggy days) hampers visual acuity [64].

Deficits of contrast sensitivity have been described in AD - patients show increased Frequency Doubling Technology (FDT-2) exam time, lowered general sensitivity and improper variability. It is believed the triggers of these changes are neuropathological or functional modifications in the retina or central pathways that take part in visual processing [65].

Due to significantly reduced contrast sensitivity it is possible to detect it even in early stages of the disease [10]. Noteworthy is the fact that abnormalities in contrast sensitivity can decline the standard of daily life of afflicted individuals such as increase reading latency [66] and cause risk of fractures and falls in AD patients [13].

AD patients' poor color vision performance is partly related to cognitive impairment and might be caused by retinal cell damage associated with the P neural pathway [67]. Most of the deficiencies relate to the blue-yellow spectrum (the tritan axis) [13].

Another visual manifestation in AD is visual field loss. Synaptic dysfunction and accumulation of A β -plaques [68] lies at the bottom of this impairment. AD patients exhibit visual field deficits which can be measured with the Humphrey perimetry. They present an asymmetric loss, mostly with the left hemisphere of the brain predominance [69]. An interesting fact has been observed - there is a correlation between the degree of advancement in visual field loss and the degree of dementia [70].

Motion perception as an ability to deduce direction and speed of objects is crucial for daily functioning and navigation [13]. AD patients report higher thresholds for motion detection than healthy controls. An interconnection between enlarged threshold and the severity of dementia is observed [71].

TREATMENT

The most effective current strategies of AD treatment are prevention methods, which can significantly slow its evolution. However, they are hard to administer, as the first neuropathological signs of AD occur 15 to 20 years before the disease begins. Disease-modifying treatments are not yet available [72].

Two main approaches have been developed in treating Alzheimer's Disease [73]. In the early, asymptomatic stages these drug therapies may be more beneficial, before the neurodegeneration occurs [72]. During the progression of the disease, due to the destruction of

acetylcholine producing cells, cholinergic transmission through the brain is reduced. Acetylcholinesterase inhibitors (AChEI) are administered in order to increase ACh levels in the synaptic cleft [73]. Three drugs have been currently approved that affect cholinergic transmission - donepezil, rivastigmine and galantamine [74].

NMDAR antagonist prevents overactivation of NMDAR glutamate receptor, which would have led to a rise of Ca^{2+} levels, promoting cell death and synaptic dysfunction⁷³. An NMDA receptor antagonist, Memantine, was approved in 2003 [74].

Both of these courses of treatment, despite having a therapeutic effect, present no advancement in curing or preventing the disease and can be used only as a way of treating the symptoms [73]. They can temporarily stabilize or improve the cognitive functions and control disorders of the behavior [72].

Additionally, progress is being made in the field of gene therapy (in repairing the faulty DNA/gene/protein and attacking the disease at the source) and immunotherapy (in developing anti-amyloid and anti-tau agents) [74]. Immunotherapies targeting $\text{A}\beta$ deposits have been studied in rodent models. The response of amyloid burden to therapeutic intervention can be monitored due to advances in imaging of retinal $\text{A}\beta$ [75].

Although they vary in methodology, the animal studies collectively suggest that the retina is a tissue that may faithfully mirror pathological changes in the brain.

As the retina is a site enabling the monitoring of disease progression in response to medication, it is probable that future therapeutic intervention may be done through it. By exploiting the molecular delivery system through the optic nerve, the retina may be a crucial site of drug administration, especially in the absence of effective AD therapy [75].

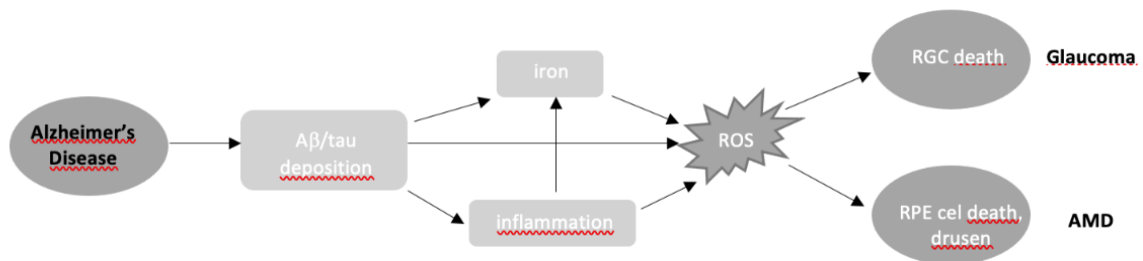
ALZHEIMER'S DISEASE IN COMPARISON TO OTHER AGE-RELATED DISEASES OF THE EYE

Alzheimer's Disease is often associated with other degenerative conditions, such as age-related macular degeneration (AMD) and glaucoma [76]. These conditions share common features both in terms of pathophysiological mechanisms and risk factors², such as smoking, hypertension, hypercholesterolemia, atherosclerosis, obesity, unhealthy diet [77]. Upon analysis, the pathology of said diseases seems overlapping: the hallmark of AMD is the accumulation of $\text{A}\beta$ and iron in drusen, while p-tau and $\text{A}\beta$ deposits are found in retina ganglion cells, the main cell type implicated in glaucoma [76].

Another potential link between the mentioned conditions is the role of inflammation in the disease progression. Inflammation is a prominent feature of brain tissue affected by AD. Due to incomplete activation of phagocytosed A β pro- and anti-inflammatory cytokines are being secreted, causing iron dyshomeostasis which potentially leads to ROS production and associated toxicity [76]. Similarly, inflammation as well as oxidative stress, accompany AMD and glaucomatous degeneration.

As much as AD shares many analogies with AMD and glaucoma, a definitive link between the diseases has not yet been confirmed. In AD and AMD the extracellular deposits do consist of largely similar aggregated proteins, however, the genetic background between the two seems to be different [77].

Pathogenesis of all three disorders, as well as their connections, remain the subject of undergoing studies.



REFERENCES

1. Alzheimer's Disease International (ADI), <https://www.alzint.org/>, Accessed 30 May 2023.
2. Romaus-Sanjurjo D, Regueiro U, López-López M, et al. Alzheimer's Disease Seen through the Eye: Ocular Alterations and Neurodegeneration. *International Journal of Molecular Sciences*, 2022, 23(5), 2486.
3. Chang LYL, Lowe J, Ardiles A, et al. Alzheimer's disease in the human eye. Clinical tests that identify ocular and visual information processing deficit as biomarkers. *Alzheimer's and Dementia*. 2014, 10(2), 251-261.
4. Zhang J, Shi L, Shen Y. The retina: A window in which to view the pathogenesis of Alzheimer's disease. *Aging Research Reviews*, 2022, 77.
5. Weiner MW, Veitch DP, Aisen PS, et al. The Alzheimer's disease neuroimaging initiative: A review of papers published since its inception. *Alzheimer's and Dementia*. 2012, 8(1 SUPPL.), S1-68.

6. Jiang J, Wang H, Li W, Cao X, Li C. Amyloid plaques in retina for diagnosis in Alzheimer's patients: A meta-analysis. *Frontiers in Aging Neuroscience*, 2016, 8, 267.
7. Koronyo-Hamaoui M, Koronyo Y, Ljubimov A V., et al. Identification of amyloid plaques in retinas from Alzheimer's patients and noninvasive in vivo optical imaging of retinal plaques in a mouse model. *Neuroimage*. 2011, 54(SUPPL. 1), S204-211.
8. Koronyo Y, Salumbides BC, Black KL, Koronyo-Hamaoui M. Alzheimer's disease in the retina: Imaging retinal A β plaques for early diagnosis and therapy assessment. *Neurodegenerative diseases*. 2012, 10(1-4), 285-293.
9. Örnek N, Dağ E, Örnek K. Corneal sensitivity and tear function in neurodegenerative diseases. *Current Eye Research*, 2015, 40(4), 423-428.
10. Singh A, Verma S. Use of ocular biomarkers as a potential tool for early diagnosis of Alzheimer's disease. *Indian Journal of Ophthalmology*. 2020, 68(4), 555-561.
11. Snyder PJ, Alber J, Alt C, et al. Retinal imaging in Alzheimer's and neurodegenerative diseases. *Alzheimer's and Dementia*. 2021, 17(1), 103-111.
12. Zhang Y, Wang Y, Shi C, Shen M, Lu F. Advances in retina imaging as potential biomarkers for early diagnosis of Alzheimer's disease. *Translational Neurodegeneration* 2021, 10(1).
13. Javaid FZ, Brenton J, Guo L, Cordeiro MF. Visual and ocular manifestations of Alzheimer's disease and their use as biomarkers for diagnosis and progression. *Frontiers in Neurology*, 2016, 19, 7, 5.
14. Liu B, Rasool S, Yang Z, et al. Amyloid-peptide vaccinations reduce β -amyloid plaques but exacerbate vascular deposition and inflammation in the retina of Alzheimer's transgenic mice. *American Journal of Pathology*. 2009, 175(5), 2099-2110.
15. Goldstein LE, Muffat JA, Cherny RA, et al. Cytosolic beta-amyloid deposition and supranuclear cataracts in lenses from people with Alzheimer's disease. *The Lancet*. 12;361(9365):1258-1265.
16. Mutlu U, Colijn JM, Ikram MA, et al. Association of Retinal Neurodegeneration on Optical Coherence Tomography with Dementia: A Population-Based Study. *JAMA Neurology*. 2018, 75(10), 1256-1263.
17. Prakasam A, Muthuswamy A, Ablonczy Z, et al. Differential accumulation of secreted A β PP metabolites in ocular fluids. *Journal of Alzheimer's Disease*. 2010, 20(4), 1243-1253.

18. Kwak DE, Ko T, Koh HS, et al. Alterations of aqueous humor A β levels in A β -infused and transgenic mouse models of Alzheimer disease. *PLoS One*. 2020, 15(1). e0227618.
19. Hart NJ, Koronyo Y, Black KL, Koronyo-Hamaoui M. Ocular indicators of Alzheimer's: exploring disease in the retina. *Acta Neuropathologica*. 2016, 132(6), 767-787.
20. Chowdhury UR, Madden BJ, Charlesworth MC, Fautsch MP. Proteome analysis of human aqueous humor. *Investigative Ophthalmology & Visual Science*. 2010, 51(10), 4921-4931.
21. Mancino R, Martucci A, Cesareo M, et al. Glaucoma and Alzheimer Disease: One Age-Related Neurodegenerative Disease of the Brain. *Current Neuropharmacology*. 2017, 16(7), 971-977.
22. Cappelli F, Caudano F, Marengo M, et al. Evaluating the correlation between Alzheimer's amyloid- β peptides and glaucoma in human aqueous humor. *Translational Vision Science & Technology*. 2020, 9(5), 1-5.
23. Ashok A, Singh N, Chaudhary S, et al. Retinal degeneration and Alzheimer's disease: An evolving link. *International Journal of Molecular Sciences*. 2020, 21(19), 1-17.
24. Bayer AU, Keller ON, Ferrari F, Maag KP. Association of Glaucoma With Neurodegenerative Diseases With Apoptotic Cell Death: Alzheimer's Disease and Parkinson's Disease. *American Journal of Ophthalmology*. 2002, 133(1):135-137.
25. Wostyn P, Audenaert K, De Deyn PP. Alzheimer's disease-related changes in diseases characterized by elevation of intracranial or intraocular pressure. *Clinical Neurology and Neurosurgery*. 2008, 110(2), 101-109.
26. Yoneda S, Hara H, Hirata A, Fukushima M, Inomata Y, Tanihara H. Vitreous fluid levels of β -amyloid(1-42) and tau in patients with retinal diseases. *Japanese Journal of Ophthalmology*. 2005, 49(2), 106-108.
27. Kremen WS, Panizzon MS, Elman JA, et al. Pupillary dilation responses as a midlife indicator of risk for Alzheimer's disease: association with Alzheimer's disease polygenic risk. *Neurobiology of Aging*. 2019, 83, 114-121.
28. Chougule PS, Najjar RP, Finkelstein MT, Kandiah N, Milea D. Light-induced pupillary responses in Alzheimer's disease. *Frontiers in Neurology*. 2019, 10, 360.
29. Craig LA, Hong NS, Kopp J, McDonald RJ. Selective lesion of medial septal cholinergic neurons followed by a mini-stroke impairs spatial learning in rats. *Experimental Brain Research*. 2009, 193(1), 29-42.

30. Shen J, Wu J. Nicotinic Cholinergic Mechanisms in Alzheimer's Disease. *International Review of Neurobiology*. 2015, 124, 275-292.
31. Fotiou DF, Brozou CG, Haidich AB, et al. Pupil reaction to light in Alzheimer's disease: evaluation of pupil size changes and mobility. *Aging Clinical And Experimental Research*. 2007, 19(5), 364-371.
32. Fotiou DF, Stergiou V, Tsiptsios D, Lithari C, Nakou M, Karlovasitou A. Cholinergic deficiency in Alzheimer's and Parkinson's disease: Evaluation with pupillometry. *International Journal of Psychophysiology*. 2009, 73(2), 143-149.
33. Frost S, Robinson L, Rowe CC, et al. Evaluation of Cholinergic Deficiency in Preclinical Alzheimer's Disease Using Pupillometry. *Journal Of Ophthalmology*. 2017, 2017:7935406.
34. Bittner DM, Wieseler I, Wilhelm H, Riepe MW, Müller NG. Repetitive pupil light reflex: Potential marker in alzheimer's disease? *Journal of Alzheimer's Disease*. 2014, 42(4), 1469-1477.
35. Ferrario E, Molaschi M, Villa L, et al. Is Videopupillography Useful in the Diagnosis of Alzheimer's Disease? *Neurology*, 1998, 50(3), 642-644.
36. Moncaster JA, Moir RD, Burton MA, et al. Alzheimer's disease amyloid- β pathology in the lens of the eye. *Experimental Eye Research*. 2022, 221, 108974.
37. Wormstone M.I, Wride M.A. The ocular lens: A classic model for development, physiology and disease. *Philosophical Transactions of the Royal Society B: Biological Sciences*. 2011, 366(1568), 1190-1192.
38. Tian T, Zhang B, Jia Y, Li Z. Promise and challenge: The lens model as a biomarker for early diagnosis of Alzheimer's disease. *Disease markers*. 2014, 2014, 826503.
39. Kerbage C, Sadowsky CH, Jennings D, et al. Alzheimer's disease diagnosis by detecting exogenous fluorescent signal of ligand bound to beta amyloid in the lens of human eye: An exploratory study. *Frontier in Neurology*, 2013, 27, 4, 62.
40. Bambo MP, Garcia-Martin E, Gutierrez-Ruiz F, et al. Analysis of optic disk color changes in Alzheimer's disease: A potential new biomarker. *Clinical Neurology and Neurosurgery*. 2015, 132, 68-73.
41. Podgorny PJ, Suchowersky O, Romanchuk KG, Feasby TE. Evidence for small fiber neuropathy in early Parkinson's disease. *Parkinsonism & Related Disorders*. 2016, 28, 94-99.
42. Bitirgen G, Akpınar Z, Malik RA, Ozkagnici A. Use of Corneal Confocal Microscopy

- to Detect Corneal Nerve Loss and Increased Dendritic Cells in Patients with Multiple Sclerosis. *JAMA Ophthalmology*, 2017,135(7),777-782.
43. Lee EJ, Kim TW, Lee DS, et al. Increased CSF tau level is correlated with decreased lamina cribrosa thickness. *Alzheimer's Research & Therapy*, 2016, 8, 6.
 44. Sun SW, Nishioka C, Labib W, Liang HF. Axonal terminals exposed to amyloid- β may not lead to pre-synaptic axonal damage. *Journal of Alzheimer's Disease*. 2015, 45(4), 1139-1148.
 45. Girard B, Berthoz A. From brainstem to cortex: Computational models of saccade generation circuitry. *Progress in Neurobiology*, 2005, 77(4), 215-251.
 46. Pierrot-Deseilligny C, Rivaud S, Gaymard B, Miiri R, Vermersch AI. Cortical Control of Saccades. *Annals Of Neurology*, 1995, 37(5), 557-567.
 47. Molitor RJ, Ko PC, Ally BA. Eye movements in Alzheimer's disease. *Journal of Alzheimer's Disease*. 2015, 44(1), 1-12.
 48. Yang Q, Wang T, Su N, Xiao S, Kapoula Z. Specific saccade deficits in patients with Alzheimer's disease at mild to moderate stage and in patients with amnesic mild cognitive impairment. *Age (Omaha)*. 2013, 35(4), 1287-1298.
 49. Yang Q, Wang T, Su N, Liu Y, Xiao S, Kapoula Z. Long Latency and High Variability in Accuracy-Speed of Prosaccades in Alzheimer's Disease at Mild to Moderate Stage. *Dementia and Geriatric Cognitive Disorders Extra*. 2011, 1(1), 318-329.
 50. Fletcher WA, Sharpe JA. Saccadic Eye Movement Dysfunction in Alzheimer's Disease.; 1986, 20(4), 464-471.
 51. Hotson JR, Steinke GW. Vertical and horizontal saccades in aging and dementia: Failure to inhibit anticipatory saccades. *Neuro-Ophthalmology*. 1988, 8(5), 267-273.
 52. Pratt J, Bekkering H, Abrams RA, Adam J. The Gap Effect for Spatially Oriented Responses. *Acta Psychologica*, 1999, 102(1), 1-12.
 53. Amieva H, Phillips LH, Della Sala S, Henry JD. Inhibitory functioning in Alzheimer's disease. *Brain*. 2004, 127(5), 949-964.
 54. Crawford TJ, Higham S, Renvoize T, et al. Inhibitory control of saccadic eye movements and cognitive impairment in Alzheimer's disease. *Biol Psychiatry*. 2005, 57(9), 1052-1060.
 55. Mosimann UP, Felblinger J, Ballinari P, Hess CW, Müri RM. Visual exploration behaviour during clock reading in Alzheimer's disease. *Brain*. 2004, 127(2), 431-438.
 56. Pierrot-Deseilligny C, Müri RM, Ploner CJ, Gaymard B, Demeret S, Rivaud-Pechoux

- S. Decisional role of the dorsolateral prefrontal cortex in ocular motor behaviour. *Brain*. 2003, 126(6), 1460-1473.
57. Kaufman LD, Pratt J, Levine B, Black SE. Antisaccades: A probe into the dorsolateral prefrontal cortex in Alzheimer's disease. A critical review. *Journal of Alzheimer's Disease*. 2010, 19(3), 781-793.
 58. Zaccara G, Gangemi PF, Muscas GC, et al. Smooth-Pursuit Eye Movements: Alterations in Alzheimer's Disease. *Journal of the neurological Sciences*, 1992, 112(1-2), 81-89.
 59. Fletcher WA, Sharpe JA. Smooth Pursuit Dysfunction in Alzheimer's Disease. *Neurology*, 1988, 38(2), 272-277.
 60. Lage C, López-García S, Bejanin A, et al. Distinctive Oculomotor Behaviors in Alzheimer's Disease and Frontotemporal Dementia. *Frontiers In Aging Neuroscience*. 2021, 4, 12, 603790.
 61. Prettyman R, Bitsios P, Szabadi E. Altered Pupillary Size and Darkness and Light Reflexes in Alzheimer's Disease. *Journal Of Neurology, Neurosurgery, And Psychiatry*. 1997, 62(6), 665-668.
 62. Fotiou F, Fountoulakis KN, Tsolaki M, Goulas A, Palikaras A. Changes in Pupil Reaction to Light in Alzheimer's Disease Patients: A Preliminary Report. *International Journal Of Psychophysiology : Official Journal Of The International Organization Of Psychophysiology*, 2000, 37(1), 111-120.
 63. Cormack FK, ToveeMartin, Ballard C. Contrast sensitivity and visual acuity in patients with Alzheimer's disease, *International Journal Of Geriatric Psychiatry*. 2000, 15(7), 614-620.
 64. Lee YT, Pai MC. Recognition of personally familiar scenes in patients with very mild alzheimer's disease: Effects of spatial frequency and luminance. *Journal of Alzheimer's Disease*. 2012, 29(2), 441-448.
 65. Risacher SL, WuDunn D, Pepin SM, et al. Visual contrast sensitivity in Alzheimer's disease, mild cognitive impairment, and older adults with cognitive complaints. *Neurobiology of Aging*. 2013, 34(4), 1133-1144.
 66. Passafiume D, Giacomo D Di, Giubilei F. Reading latency of words and nonwords in Alzheimer's patients, *Cortex*, 2000, 36(2), 293-298.
 67. Salamone G, Di Lorenzo C, Mosti S, et al. Color discrimination performance in patients with Aalzheimer's Disease. *Dementia and Geriatric Cognitive Disorders*. 2009, 27(6), 501-507.

68. Bateman R. Alzheimer's disease and other dementias: Advances in 2014. *Lancet Neurology*, 2015, 14(1), 4-6.
69. Millington RS, James-Galton M, Maia Da Silva MN, Plant GT, Bridge H. Lateralized occipital degeneration in posterior cortical atrophy predicts visual field deficits. *Neuroimage Clinical*, 2017, 14, 242-249.
70. Trick GL, Trick LR, Morris P, Wolf M. Visual Field Loss in Senile Dementia of the Alzheimer's Type, *Neurology*, 1995, 45(1), 68-74.
71. Gilmore GC, Wenk HE, Nay Lor LA, Koss E. Motion Perception and Alzheimer's Disease. *Journal Of Gerontology*, 1994, 49(2), P52-57.
72. Passeri E, Elkhoury K, Morsink M, et al. Alzheimer's Disease: Treatment Strategies and Their Limitations. *International Journal Of Molecular Sciences*. 2022, 23(22), 13954.
73. Breijyeh Z, Karaman R. Comprehensive Review on Alzheimer's Disease: Causes and Treatment. *Molecules*. 2020, 25(24), 5789.
74. Khan S, Barve KH, Kumar MS. Recent Advancements in Pathogenesis, Diagnostics and Treatment of Alzheimer's Disease. *Current Neuropharmacology*. 2020, 18(11), 1106-1125.
75. Hart NJ, Koronyo Y, Black KL, Koronyo-Hamaoui M. Ocular indicators of Alzheimer's: exploring disease in the retina. *Acta Neuropathologica*, 2016, 132(6), 767-787.
76. Ashok A, Singh N, Chaudhary S, et al. Retinal degeneration and alzheimer's disease: An evolving link. *International Journal of Molecular Sciences*. 2020, 21(19), 1-17.
77. Kaarniranta K, Salminen A, Haapasalo A, Soininen H, Hiltunen M. Age-related macular degeneration (AMD): Alzheimer's disease in the eye? *Journal of Alzheimer's Disease*. 2011, 24(4), 615-631.

DRUSEN IN OPHTHALMOLOGY

**Aleksandra Jany^{1,2}, Magdalena Urbaniak¹, Dagmara Pawelczyk-Sicińska³,
Magdalena Targońska³, Jan Gnus^{1,3}**

1. Wrocław Medical University
2. Students' Research Group of Ophthalmic Surgery
3. Regional Specialist Hospital in Wrocław, Research and Development Center

ABBREVIATION LIST

- AMD- age-related macular degeneration
- RPE- retinal pigment epithelium
- HAP- hydroxyapatite
- BrM- Bruch's membrane
- FA- fluorescence angiography
- SOCT- spectral optical coherence tomography
- OCT- optical coherence tomography
- BLD- basal laminar drusen
- FAF- fundus autofluorescence
- SDD- subretinal drusenoid deposit
- ODD- optic disc drusen
- AION- anterior ischaemic optic neuropathy
- DPED- drusenoid pigment epithelial detachment
- GA- geographic atrophy
- MNV- macular neovascularization
- CNV- choroidal neovascularization
- RD- retinal detachment
- MGPN- mesangial glomerulonephritis
- EZ- ellipsoid zone
- OCTA- optical coherence tomography angiography
- ICGA- indocyanine green angiography
- EPA- eicosapentaenoic acid

- DHA- docosahexaenoic acid
- UV- ultraviolet radiation
- AAO- American Academy of Ophthalmology

INTRODUCTION

Drusen are an important topic in the field of ophthalmology. Their role in the creation and development of various eye conditions such as age-related macular degeneration (AMD) is the subject of intensive scientific research. They are yellow or white accumulations of extracellular material that build up between Bruch's membrane and the retinal pigment epithelium. Typical location is posterior ocular poles around or within the central fovea under the basal lamina of the retinal pigment epithelium (RPE) [1,2,3]. They are associated with natural aging but depending on their size, number, location and type they may be related to an increased risk of developing specific diseases [4]. The aim of this study is to review information on drusen in ophthalmology focusing on the classification, pathogenesis and clinical significance. Studying drusen and understanding their impact on the organ of vision is crucial.

DEFINITION AND PATHOGENESIS

In 1855 Franciscus Donders described the yellow-white lesions as “*Colloidkugeln*” (colloidal ball). Based on their yellow and shiny appearance in ophthalmoscopy a year later Heinrich Müller referred to them as “*geode*”- a rock containing a crystal lined cavity [5, 6, 7].

Drusen consist of residual bodies of retinal sensory epithelial cells. These include lipofuscin, phagosomes, lipid and phospholipid waste products, accumulating as granules or vesicles. Lipids with cholesterol form a central core structure on which hydroxyapatite (HAP) spherules precipitate which promote the accumulation of proteins on their surface. There are some of the most common proteins involved in this process including complement proteins, amyloid-beta, apolipoproteins and vitronectin. Experimental studies indicate that Bruch's membrane (BrM) lipoprotein binding may be moderated by the plasma factor CFH H,197 and genetics indicate a role for CFH in the pathway of soft drusen biogenesis. Increased levels of zinc, an element responsible for normal retinal homeostasis are also detected in the druses. We can suspect that zinc is an early and key marker of drusen. Research into the development of a sensitive probe for zinc has the potential to understand the pathogenesis of drusen and may help in the early diagnosis of AMD. Due to the location of the drusen it is possible that they

deprive the RPE and photoreceptor cells of oxygen and nutrients. This leads finally to retinal degeneration and atrophy. Their number and size increase with age. They may not cause visual impairment but in most cases represent the first phase of non-neovascular AMD. Thick deposits can detach the RPE from Bruch's membrane. Druses tend to attract inflammatory and vasoactive factors that can lead to neovascularization and hemorrhage [2, 3, 4, 5, 8, 9].

Drusen are dynamically fused and spontaneously disappear in a way which suggests regulated processes. Between 20% and 34% of drusen disappear spontaneously in about 7 years [9].

Important factors contributing to the formation of drusen:

- cholesterol-related gene variants such as CETP, ABCA1, ABCG1, LIPC and APOE
- RPE dysfunction
- thickening of BrM
- choroidal capillary atherosclerosis
- older age
- female
- smoking
- higher body index
- inflammation
- impaired cholesterol metabolism
- family history
- complement dysregulation
- cellular debris generated by RPE degeneration
- increased sunlight exposure during young ages
- caucasian race
- cardiovascular diseases [5, 10, 11].

Some research suggests that increased physical activity and a mediterranean diet may have a protective effect [4].

CLASSIFICATION

The classification of drusen is based on size, consistency and histological characteristics present [4].

By **appearance** we can categorize them into:

- **Hard drusen**

Sharply demarcated, small, round, yellow foci, discrete lesions less than half the diameter of a venous vessel [2, 3, 4]. They are located inside or behind the retinal pigment epithelium and also termed “small drusen”. Unfortunately, it is still not known whether the small, hard drusen are direct precursors of the soft drusen, or whether the soft drusen are developing independently. Risk factors include higher age, shorter axial length, hyperopia and female sex. Theoretically, stretching Bruch's membrane in myopia can expand the pore size, reduce its thickness and promote increased flow through the membrane, thus reducing the formation of drusen. The Beaver Dam Eye Study found that a higher incidence of early AMD occurs in people with a larger area covered by small, hard drusen. They show hyperfluorescence in the form of window defects in the RPE on fluorescence angiography (FA) and have the character of small RPE elevations on spectral optical coherence tomography (SOCT) [12, 13].

- **Soft drusen**

Yellowish-white, shapeless and less well confined, biomechanically fragile, size is usually greater than the diameter of the venous vessel- ranging from 30 μm to over 1000 μm , with mound-like elevations with sloping sides and completed with “membranous debris”. They are usually classified in the category of large drusen with reflective and homogeneous “ground-glass” interiors inside BrM. Soft drusen shows polygonal areas of uniformly electron-dense material originally called “hard drusen breaking up” [2, 3, 4, 9]. They are made up of lipoproteins containing apolipoproteins B and E, which are secreted by the RPE in a physiological lipid recycling programme. They are the most frequent types of macular drusen and recognised as determining the progression of the disease [9].

- **Confluent drusen**

With a continuous transition between each other. Confluent soft drusen leads to drusenoid elevation of the RPE [3, 14].

Soft and confluent drusen are more likely to develop AMD than hard drusen.

By **size**:

- **Small drusen:** $<63 \mu\text{m}$

With a low risk of developing AMD

- **Median drusen:** 63- 125 μm
- **Large drusen:** >125 μm ,

With a significant risk of AMD. The size of 125 μm is approximately the diameter of a large venous vessel near the optic disc [2, 3, 4, 9, 13, 15].

Others:

- **Cuticular drusen:** 30 do 60 μm ,

Small, yellow, round, dot-like drusen and there are numerous. They are subretinal lesions located between the basement membrane of the RPE and the cytoplasm of the RPE cells. Their large number gives the appearance of “stars in the sky”. In optical coherence tomography (OCT) they have a spheroid or triangular shape. Originally called basal laminar drusen (BLD) [2, 3, 4, 9]. They are usually characterized by a central hypoautofluorescent lesion with a hyperautofluorescent border on the fundus autofluorescence (FAF). They tend to coalesce leading to a specific dispersed distribution. The deposits are hardly visible on physical examination and are easily visible on the arteriovenous phase of fluorescein angiography. Cutaneous drusen on OCT B-scans sometimes show triangular raised RPE-BL with the bases resting on Bruch's membrane giving a characteristic pattern called “saw teeth” [16].

- **Calcified drusen**

Shiny appearance is the result of secondary dystrophic calcification of hard or soft drusen. They have punctate reflectivity on OCT.

- **Subretinal drusenoid deposit (SDD)**

Called also reticular pseudodrusen. Together with soft drusen, they are the main risk factors for progression to end-stage atrophy and neovascularization which include significant loss of RPE and photoreceptors. Extracellular, space-filling, distinct from drusen section. In comparison to classical drusen, SDDs are located between the RPE and the sensory retina. In looks, they resemble soft druses, but never undergo spontaneous regression as can be seen in some cases of soft druses. They are usually lighter in color. In SOCT they take the form of deposits of granular hyperreflective material situated between the RPE layer and the ellipsoidal layer. They were previously called “reticular druses” because of the characteristic reticular image in FAF imaging [2, 3, 4, 9, 13, 15].

- **Optic disc drusen (ODD)**

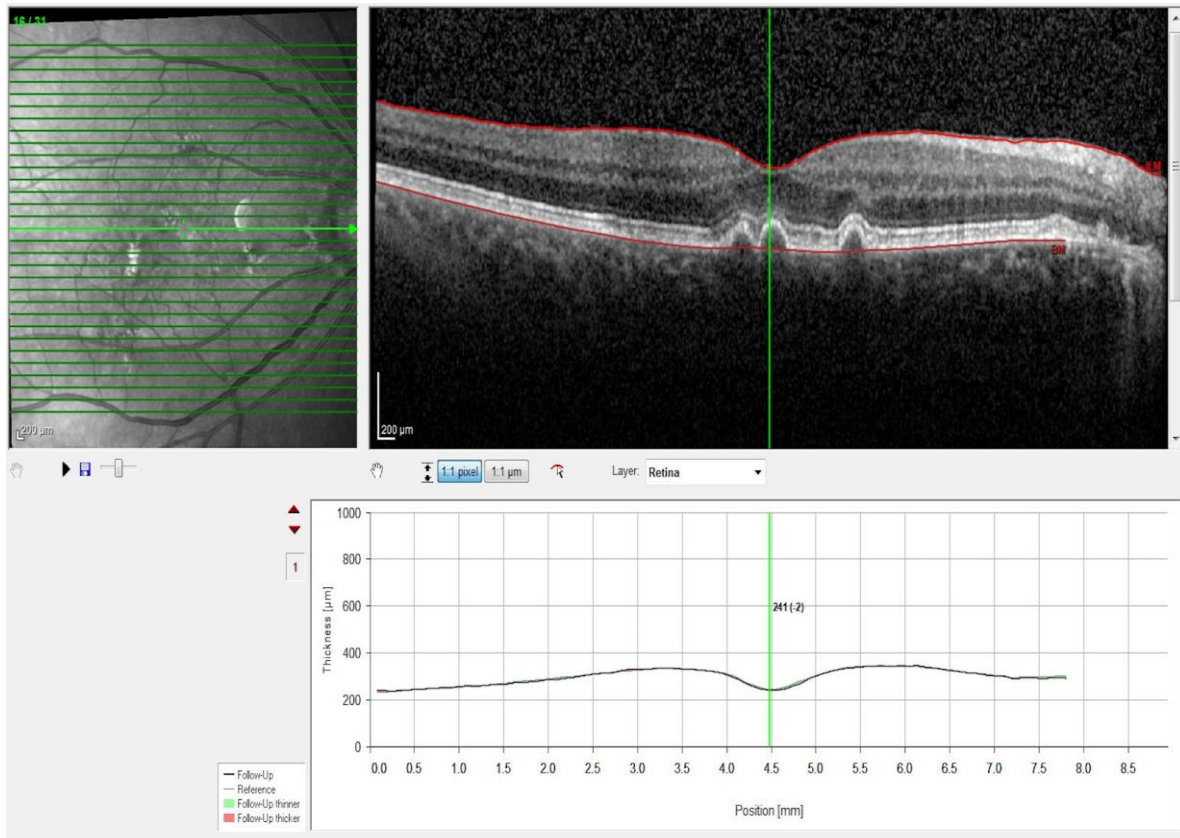
Cell-free, hyaline or colloid, often calcified deposits present in the

optic nerve head. Consist of amino acids, nucleic acids and mucopolysaccharides. These are circular, multilayered structures in the size range 5-1000 μm . They are situated in front of the lamina cribrosa in the optic nerve head and may present familial. They are usually bilateral [3, 17, 18]. Optic nerve drusen can be mistaken for oedema of the disc and is often a cause of diagnostic confusion. They can be seen occasionally and generally do not cause loss of visual acuity. More prevalent is visual field loss like enlarged blind spots or peripheral stenosis [19]. They can also lead to anterior ischaemic optic neuropathy (AION) and result in loss of vision. Currently, there are no therapy options to avoid or relieve the loss of vision caused by ODD [17]. On ophthalmoscopy, a small disc can be observed, with irregular borders and an abnormal vascular hollow [3].

Hard drusen are common and are the only type of drusen considered to be a normal age-related phenomenon. An increase of the number of drusen and their size increases the probability of progression to AMD. Localization in the macula or central retinal area is of more concern than in the peripheral retina. Soft drusen are typically located more in the central retina or macula making them more likely to progress to AMD [4]. Hard drusen $<63 \mu\text{m}$ in diameter are the most common type and without pigmentary lesions have a 0.4% five-year progression rate to advanced AMD [4, 5]. Intermediate drusen present in one eye with no pigmentary lesions have a 0.5% five-year progression rate, and in both eyes - 2.1%. Soft and large drusen present in one eye without pigmentary lesions have a 3.9% five-year progression rate; in both eyes- 13% [4].

DRUSENOID PIGMENT EPITHELIAL DETACHMENT (DPED)

DPED is caused by fusion of large areas of soft drusen. It is also a factor in the progression of AMD. Eyes with DPED have a high risk of progression to geographic atrophy (GA) [2, 15]. It is caused by drusen with $>350 \mu\text{m}$ base diameter. The primary RPE layer becomes thickened, hyperreflective lesions appear vertically above in the retina and the RPE-BL degrades leading to collapse of the deposits with total atrophy of the RPE and outer retina [9]. It is characterized by a quite well limited elevation of the RPE. It is defined that if the horizontal width of the DPED is wider than 2 disc diameters then progression to geographic atrophy (GA) or macular neovascularization (MNV) may develop within 2 years [20].



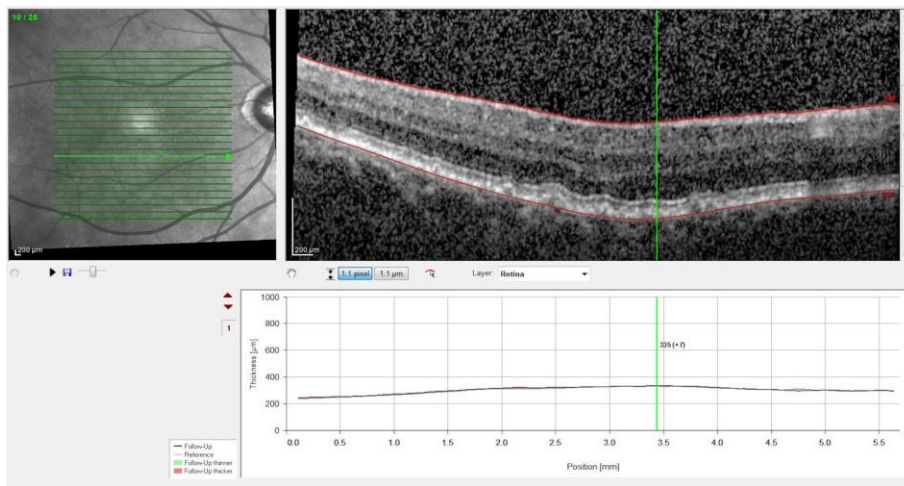
Photograph 1: OCT. DPED in the macular area in a 77-year-old female patient. Right eye.
Photograph by lek. Dagmara Paweńczyk-Sicińska

CLINICAL SIGNIFICANCE

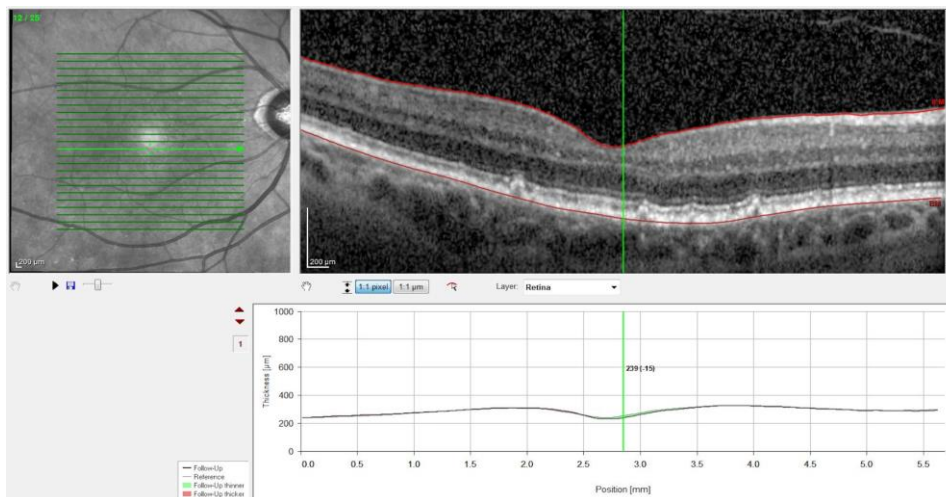
Drusen bodies are typical symptoms of AMD [4]. In the western world AMD is the most prevalent cause of permanent vision loss after the age of 65 [10]. Worldwide is the third most common cause of blindness after cataracts and glaucoma [21]. Some studies have indicated that AMD is associated with reduced quality of life. The most frequent serious consequence is choroidal neovascularization (CNV) in the center of the macula [22]. The predictive value has factors such as the type, number and location of the drusen. Other less common hereditary diseases should not be forgotten, such as Sorsby's fundus dystrophy, North Carolina macular dystrophy, Stargardt's disease and adult vitellio-retinal dystrophy. Drusen have also been associated with some systemic diseases such as Alport syndrome and dense deposits disease [4]. They may also be related with long-term retinal detachment (RD) and its successful surgery allows for their regression [23]. Cuticular drusen are quite often observed in patients with mesangial glomerulonephritis type 2 (MGN type 2) [13].

DIAGNOSIS

OCT - OCT is the gold standard in the diagnosis of drusen. It allows documentation of changes in the size of individual drusen, retinal atrophy and, most importantly, detection of intraretinal and subretinal fluid. The drusen are observed as elevations of the RPE in the form of nodules of different reflectivity located either on or in Bruch's membrane [24, 25, 26]. Intermediate reflexivity is exhibited by soft drusen and high reflexivity by hard drusen. The first ones additionally show a thickened Bruch's membrane. Some of the OCT changes observed may indicate an increased risk of disease progression. These include a large volume of drusen, migrating hyperreflective foci and heterogeneity of drusen in terms of reflectivity [24, 25, 27].

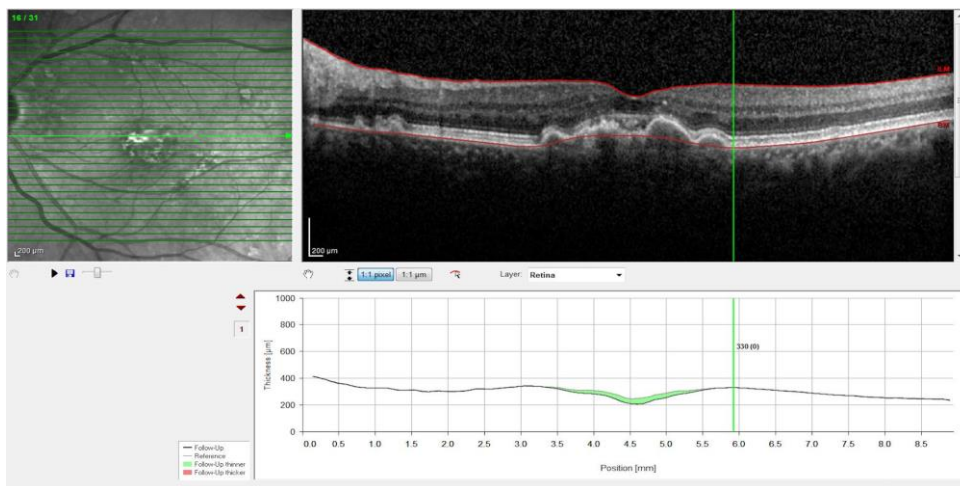


Photograph 2: OCT. Large and soft drusen in the macular area in a 78-year-old male patient. Right eye. Photograph by lek. Dagmara Pawełczyk-Sicińska



Photograph 3: OCT. Large and soft drusen in the macular area in a 78-year-old male patient. Right eye. Photograph by lek. Dagmara Pawełczyk-Sicińska

DPED and CNV are highly visible on OCT [24, 25]. In the case of DPED, elevation of the focal damaged RPE with a hyporeflective area above Bruch's membrane is observed [27]. The edges of the RPE are collapsed and the RPE in the area is folded [24, 25]. DPED can be seen as a vesicle, hemorrhage, RPE disruption and neovascularization. CNV in OCT is diagnosed depending on the type by different features. Distinguishing between elevation and disruption of the RPE layer with hyperreflective spaces under the retina through the presence of hyporeflective space under the neurosensory epithelium to neovascularization from the deep retinal capillary plexus. Advanced CNV is characterized by the presence of scarring [28]. Hyporeflective lesions corresponding to fluid spaces are also observed [27].



Photograph 4: OCT. DPED and CNV in the macular area in a 77-year-old female patient. Left eye. Photograph by lek. Dagmara Pawełczyk-Sicińska

Observation of small and raised foci located on the RPE indicates SDD. They are triangular in shape and penetrate the ellipsoid zone (EZ). It is possible that thinning of the outer retinal surface and loss of the EZ in the peak zone of deposition coexist [29].

Swept-source technology, thanks to imaging at greater depths, makes it possible to diagnose optic disc drusen [30].

It should be noted that OCT is the diagnostic standard for evaluating response to treatment.

FAF - This is the next basic examination in the diagnosis of drusen. The image can be varied. They are often visualized as a reduced central area of autofluorescence with a ring of increased autofluorescence around it.

A moderate, diffuse increase in FAF sharply bordered by a ring of decreased fluorescence is characteristic of DPED [31].

FA - Hard drusen in fluorescein angiography are observed in the early phase as hyperfluorescence of the fenestration cavity type with a normal choriocapillaris layer, while in the late phase the fluorescence decreases. Soft drusen in the first phase also show the same features. Fluorescence blockage is characteristic of large soft drusen. Diffuse drusen are described as a “stars in the sky” image.

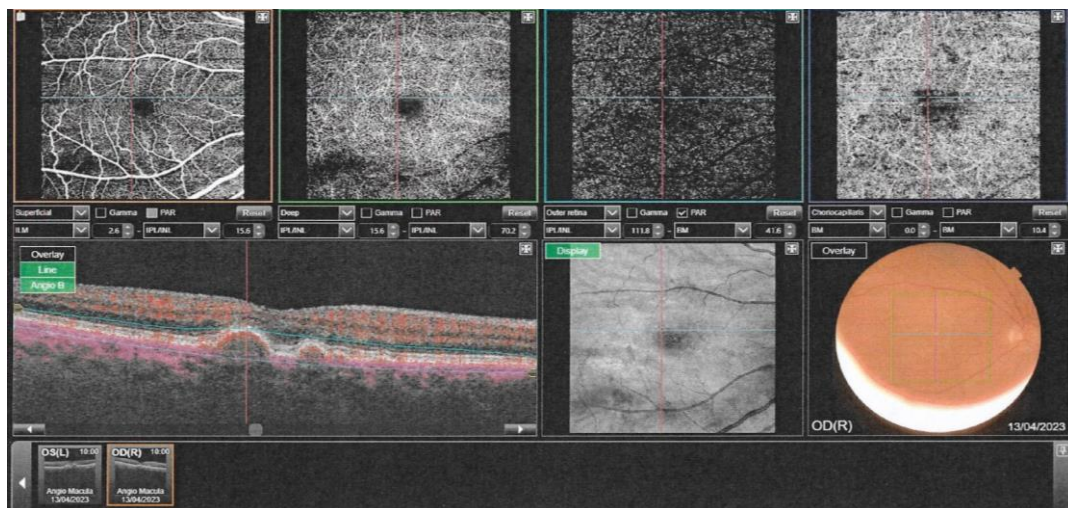
CNV is highly visible on fluorescein angiography. The classic form in the early phase is a well-demarcated area of hyperfluorescence with distinct coronal borders. In later phases, this area becomes enhanced and in the late phase the borders become blurred.

Observation of a circular or oval area of homogeneous fluorescence clearly demarcated suggests DPED. In the late phase, fluorescein stasis is observed in the area of detachment [32].

Optical coherence tomography angiography (OCTA) - OCTA provides an opportunity to evaluate inactive choroidal neovascularization. Attention is also focused on shaded areas on en-face images, indicative of nonperfusion zones [24, 25].

In the case of SDD, advanced choroidal nonperfusion zones can be seen, as well as a significant reduction in blood flow. So called “ghost vessels” are also described, in areas of reduced choriocapillaris density. Areas of early atrophy with co-occurrence of drusen indicate early changes on the outer surface of the retina [29].

Dark halo and changes in the deep retinal vessels indicate the presence of CNV. The image can take different forms depending on the type of CNV. Distinctions include “jellyfish”, “bundle”, “glomerular” or glomerular vascular pattern with adherent telangiectasias [24, 25].



Photograph 5: OCTA. DPED in the macular area in a 77-year-old female patient. Right eye. Photograph by lek. Dagmara Pawełczyk-Sicińska

Indocyanine angiography - Is an additional examination in the diagnosis of drusen. Performed in DPED, in which no neovascular membrane is present. The image of the drusen varies depending on its composition. This examination makes it possible to determine the boundaries of the neovascular membrane. It shows the vascular network of the classic neovascular membrane.

A hyperfluorescent halo is characteristic of DPED, while in indocyanine green angiography (ICGA), hypofluorescence surrounded by a hyperfluorescent halo indicates serous detachment of the pigment epithelium [33].

TREATMENT

Small drusen do not require treatment but should be observed regularly [34]. There have been trials of using laser photocoagulation that achieved regression of the drusen, but the risk of vision loss due to CNV or geographic atrophy was similar in the treated and untreated groups. It is not yet evident that reducing drusen can result in clinical benefits [23]. Research is proceeding on the effectiveness of blue-light filtering devices to avoid excessive oxidative stress that leads to the development of drusen. Supplementation with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) to compensate for omega 3 and 6 fatty acid deficiencies may have a beneficial effect on slowing lesion progression. More research is still needed to determine the effectiveness of statins and other lipid-lowering drugs. Quitting smoking can also reduce the accumulation of protein aggregates, increase autophagy and the antioxidant response. Treating diabetes, hypertension and obesity has positive effects by reducing the mechanisms of retinal vascular aging. According to recent evidence, there is a close correlation between the retina and the intestinal microbiota called the "intestinal-retina axis." Further research on the intestinal microbiota may contribute to achievements related to the treatment of drusen [35]. Definitely, regular eye examinations are necessary for proper monitoring of lesions and their treatment.

CONCLUSION

Unfortunately, we still do not understand the exact mechanisms of drusen formation, but it is sure that they are induced by age-related biochemical changes. Studies like Chesapeake Bay (USA), Rotterdam (USA), Beaver Dam (USA) and Blue Mountain Eye (Australia)

confirmed that the frequency of minimum one drusen in the fundus in older people is around 96 percent [8]. Therefore, the ability of different specialists to recognise the specific types of drusen is significant. Furthermore, it will allow a broader education on modifiable risk factors and a quicker response to the implementation of the necessary treatment to delay or avoid the onset of the relevant disease conditions associated with the presence of drusen. They should promote quitting smoking, eating a healthy diet and using sunglasses to avoid damage to the eyes from ultraviolet radiation (UV) [4]. The American Academy of Ophthalmology (AAO) suggests that all patients sixty-five years of age and older should have a comprehensive eye examination every one to two years, independently of any prior history of eye disease [12]. Understanding how deposits are formed can result in new methods of prevention and therapeutic treatment [9].

REFERENCES

1. Silvestri G., Williams M., McAuley C., Oakes K., Sillery E. et al.: Eye: Drusen prevalence and pigmentary changes in Caucasians aged 18–54 years, 2012, 26, 1357–1362.
2. Bowling B., Kański J., Szaflik J., Izdebska J.: Nabyte choroby plamki i schorzenia towarzyszące [w:] Okulistyka kliniczna. Bowling B., Kański J., Szaflik J., Izdebska J. (red.) Elsevier Urban & Partner, Wrocław, 2009, 669- 706.
3. Niżankowska H.: Choroby siatkówki [w:] Okulistyka. Podstawy kliniczne. Niżankowska H. (red.) PZWL, Warszawa, 2007, 379- 424.
4. VanDenLangenberg A., Carson M.: Drusen Bodies, 2023, PMID: 32644513, Bookshelf ID: NBK559087.
5. Zhang X., Sivaprasad S.doi: Eye: Drusen and pachydrusen: the definition, pathogenesis, and clinical significance, 2021, 35 (1), 121–133.
6. Müller H.: Graefe's Archive for Clinical and Experimental Ophthalmology: Anatomische Beiträge zur Ophthalmologie – Untersuchungen über die Glashäute des Auges, insbesondere die Glaslamelle der Chorioidea und ihre senilen Veränderungen, 1856, 2, 1–69.
7. Khan K., Mahroo O., Khan R., Mohamed M., McKibbin M. et al.: Progress in Retinal and Eye Research: Differentiating drusen: Drusen and drusen-like appearances associated with ageing, age-related macular degeneration, inherited eye disease and other pathological processes, 2016, 53, 70-106.

8. Lengyel I., Tufail A., Hosaini H., Luthert P., Bird A., et al.: Investigative Ophthalmology & Visual Science: Association of drusen deposition with choroidal intercapillary pillars in the aging human eye, 2004, 45, 2886-2892.
9. Curcio C.: Investigative Ophthalmology & Visual Science: Soft Drusen in Age-Related Macular Degeneration: Biology and Targeting Via the Oil Spill Strategies, 2018, 59 (4): 160–181.
10. Algvere P., Kvanta A., Seregard S.: Acta Ophthalmologica: Drusen maculopathy: a risk factor for visual deterioration, 2016, 94(5), 427-433.
11. Altay L., Subiras X., Lorés de Motta L., Schick T., Berghold A., et al.: Molecular Vision: Genetic and environmental risk factors for extramacular drusen, 2020, 26, 661-669.
12. Belmouhand M., Rothenbuehler S., Dabbah S., Bjerager J., Sander B., et al.: PLOS One: Small hard drusen and associated factors in early seniority, 2022, 17 (12): e0279279.
13. Gawęcki M.: Wszystkie druzy duże i małe. <https://www.mp.pl/okulistyka/ekspert/213875,wszystkie-druzy-duze-i-male> . Accessed 14 Jul 2023.
14. Święch- Zubilewicz J.: Diagnostyka różnicowa AMD. <https://www.edukacja.przegladokulistyczny.pl/diagnostyka-roznicowa-AMD>. Accessed 14 Jul 2023.
15. Despotovic I., Ferrara D.: Drusen [w:] Atlas of Retinal OCT: Optical Coherence Tomography. Goldman D., Waheed N., Duker J. (red) Elsevier, 2018, 16-23.
16. Fragiotta S., Fernández-Avellaneda P., Breazzano M., Scuderi G.: Clinical Ophthalmology: Clinical Manifestations of Cuticular Drusen: Current Perspectives, 2021, 15, 3877-3887.
17. Hamann S., Malmqvist L., Costello F.: Acta Ophthalmologica: Optic disc drusen: understanding an old problem from a new perspective, 2018, 96(7), 673-684.
18. Mariak Z., Obuchowska I.: Druzy tarczy nerwu wzrokowego. <https://www.mp.pl/pacjent/okulistyka/chorobyoczu/neurookulistykaizez/83032,druzy-tarczy-nerwu-wzrokowego> (accessed 14 Jul 2023).
19. Ahmed H., Khazaeni L.: Optic Disc Drusen, 2023, PMID: 35593854, Bookshelf ID: NBK580547.
20. Shijo T., Sakurada Y., Tanaka K., Miki A., Yoneyama S., et al.: International Journal of Molecular Sciences: Drusenoid Pigment Epithelial Detachment: Genetic and Clinical Characteristics, 2021, 22(8), 4074.
21. Bisant L.: Crusin' for Drusen. <https://www.reviewofoptometry.com/article/crusin-for-drusen>. Accessed 14 Jul 2023).

22. Virgili G., Michelessi M., Parodi M., Bacherini D., Evans J.: Cochrane Database of Systematic Reviews: Laser treatment of drusen to prevent progression to advanced age-related macular degeneration, 2015, 10, CD006537.
23. Raman R., Alam S., Delhiwala K., Biswas J.: Oman journal of ophthalmology: Large drusen in long-standing retinal detachment, 2018, 11(3), 272–273.
24. Niewysiękowe zwyrodnienie plamki związane z wiekiem [w:] OCT i OCTA w chorobach siatkówki. Ehlers J., Modi Y., Srivastava S., Kaiser P. (red.) Edra Urban & Partner, Wrocław, 2023: 111- 115.
25. Neowaskularne zwyrodnienie plamki związane z wiekiem [w:] OCT i OCTA w chorobach siatkówki. Ehlers J., Modi Y., Srivastava S., Kaiser P. (red.) Edra Urban & Partner, Wrocław, 2023, 121- 126.
26. Nabyte choroby plamki [w:] Kanski Okulistyka kliniczna. Bowling B., Szaflik J., Izdebska J. (red.) Edra Urban & Partner, Wrocław, 2017, 669- 706.
27. Michalska-Małecka K., Śpiewak D.: Optyczna koherentna tomografia komputerowa [w:] Biblioteka Okulisty Praktyka. Rejdak R., Rękas M. (red.) Via Medica, Gdańsk, 2022, 18- 26.
28. Michalska- Małecka K., Sierocka- Stępień J.: Badanie dna oka [w:] Biblioteka Okulisty Praktyka. Rejdak R., Rękas M. (red.) Via Medica, Gdańsk, 2022, 16- 18.
29. Druzoidalne podsiatkówkowe depozyty [w:] OCT i OCTA w chorobach siatkówki. Ehlers J., Modi Y., Srivastava S., Kaiser P. (red.) Edra Urban & Partner, Wrocław, 2023, 116- 120.
30. Obrzęk tarczy nerwu wzrokowego i neuropatie nerwu wzrokowego [w:] OCT i OCTA w chorobach siatkówki. Ehlers J., Modi Y., Srivastava S., Kaiser P. (red.) Edra Urban & Partner, Wrocław, 2023, 444- 449.
31. [31] Michalska- Małecka K., Wycisło- Gawron P.: Autofluorescencja [w:] Biblioteka Okulisty Praktyka. Rejdak R., Rękas M. (red.) Via Medica, Gdańsk, 2022, 27- 29.
32. Michalska- Małecka K., Wycisło- Gawron P.: Angiografia fluoresceinowa [w:] Biblioteka Okulisty Praktyka. Rejdak R., Rękas M. (red.) Via Medica, Gdańsk, 2022, 30- 34.
33. Michalska- Małecka K., Wycisło- Gawron P.: Angiografia indocyjaninowa [w:] Biblioteka Okulisty Praktyka. Rejdak R., Rękas M. (red.) Via Medica, Gdańsk, 2022, 34- 40.
34. Porter D., Gregori N.: What Are Drusen? <https://www.aao.org/eye-health/diseases/what-are-drusen>. Accessed 14 Jul 2023.

35. Garcia-Garcia J., Usategui-Martin R., Sanabria M., Fernandez-Perez E., Telleria J., et al.: Ophthalmic Research: Pathophysiology of Age-Related Macular Degeneration: Implications for Treatment, 2022, 65 (6), 615–636.

HERPES SIMPLEX INFECTION OF THE EYE

**Magdalena Urbaniak¹, Aleksandra Jany^{1,2}, Dagmara Pawełczyk-Sicińska³,
Magdalena Targońska³, Jan Gnus^{1,3}**

1. Wrocław Medical University
2. Students' Research Group of Ophthalmic Surgery
3. Regional Specialist Hospital in Wrocław, Research and Development Center

ABBREVIATION LIST

- HSV- *Herpes simplex virus*
- DNA- deoxyribonucleic acid
- PCR- polymerase chain reaction
- IOP- intraocular pressure
- ARN- Acute Retinal Necrosis
- VZV- *Varicella-Zoster virus*
- AUS- American Uveitis Society
- CMV- *Cytomegalovirus*
- RRD- rhegmatogenous retinal detachment
- PORN- progressive outer retinal necrosis

INTRODUCTION

Herpes simplex virus (HSV) is a common virus and infections caused by it are widespread [1, 2]. HSV is a deoxyribonucleic acid (DNA) virus that encodes more than 80 proteins. The HSV-1 subtype (occasionally HSV-2 as well) is responsible for causing inflammation localized on and around the eyeball. In the ocular area, HSV can be transmitted in infectious secretions from vesicles located on the hands, by venereal, droplet or during delivery [1, 2, 3, 4].

The site of reactivation of the virus can be in a remote area from the site of the original infection. HSV in primary infection localizes in mucosal epithelial cells and causes disease

symptoms. Characteristic symptoms of infection include translucent blisters filled with serous contents which rupture and turn into scabs within 48 h. In a further stage of infection, the virus localizes in the surrounding neurons and is integrated into the host's DNA. As a result of external factors such as immunosuppression, fever, stress, ultraviolet radiation, the virus passes from the latency phase and causes a secondary infection. There is also the phenomenon of subclinical reactivation when HSV is secreted by an infected patient despite the absence of clinical symptoms [2, 3]. It is estimated that after one episode, secondary infection will occur in 10% of people after 1 year and in 50% after 10 years. Hundreds of reactivations can occur over a patient's lifetime. Moreover, it has been proven that a higher risk of recurrence is associated with a higher number of previous episodes. Predisposing factors for the severe character of the disease with multiple reinfections include immunodeficiency or suppression, childhood, atypical eye disease, measles, malaria and malnutrition. On the other hand, inappropriate use of steroids can exacerbate the development of geographic ulceration [3]. HSV can occupy almost any part of the eyeball and the accessory visual structures. It causes various inflammatory conditions that often require medical intervention.

HERPETIC KERATITIS

Most symptomatic HSV infections involve inflammation of the corneal epithelium. The inflammation progresses from single punctate lesions to dendritic or geographic ulceration to necrotizing inflammation. Patients initially complain of eye pain, redness of the eye, tearing and a foreign body sensation. The inflammation causes neuronal death, resulting in reduced corneal sensation. This can lead to neurotrophic keratopathy and consequently to permanent corneal defects and perforation. Involvement of the corneal parenchyma results in scarring and ingrowth of blood vessels. All of the described changes can cause permanent damage to vision. Diagnosis of HPV infection should consist of a polymerase chain reaction (PCR) test [1, 3, 5, 6, 7, 8, 9]. There are several forms of herpetic keratitis:

Epithelial keratitis

Results from active viral replication and takes the form of dendritic or geographic keratitis. Symptoms are of mild to moderate severity, accompanied by photophobia, tearing, redness and corneal congestion. The inflammation begins with blurred vision accompanied by epithelial cell edema. There is exfoliation of the superficial layer of cells and the formation of a characteristic dendritic ulceration which may fuse together and form a larger geographic

ulceration. Corneal lesions stain with fluorescein and rose bengal. Active virus particles are present at the edges of the ulceration. This is followed by reduced corneal sensation due to neuronal destruction. Typically, there is mild subepithelial haze and increased intraocular pressure (IOP) which can persist for up to several weeks after the inflammation stops. Sometimes there is scarring which with further recurrences of the infection can cause visual impairment or loss of vision. Diagnosis can be made by clinical examination. Keratitis in the form of dendritic ulceration is most often able to heal on its own. The standard local treatment is to apply ointment with acyclovir 3% or ganciclovir 0.15% five times a day. With the treatment used, most ulcers heal within two weeks. Oral antiviral drugs are used in immunocompromised patients and those with marked disease on the surface of the eye. The treatment used then includes acyclovir 200-400 mg five times a day for 5-10 days. In severe cases, mechanical cleaning of the cornea is used. The epithelium should be removed with a 2 mm margin of healthy-looking tissue. With mechanical cleansing of the cornea, local antiviral treatment should be included. This procedure should not be performed with geographic ulceration [1, 3, 6, 7, 8, 9, 10].

Disciform keratitis

Disciform keratitis can occur as a result of infection of keratinocytes or corneal endothelium or as a result of a hypersensitivity reaction to virus antigens present in the cornea. Not all patients develop a dendritic ulceration. The disease is associated with gradually progressive blurred vision that may be associated with halo effects around light sources. Discomfort and redness of the eyeball are often present but of lower severity than in epithelial keratitis. Features of disciform keratitis include edema of the corneal stroma in the central zone with frequent edema of the epithelium, sometimes present at the periphery of the cornea. During examination corneal deposits located below the edema are observed and in severe cases folds of Descemet's membrane can be seen. Disciform keratitis like dendritic keratitis is accompanied by impaired corneal sensitivity and may have increased IOP. The accumulating deposits formed by complexes of virus antigens and host antibodies form a surrounding immune ring (Wessely's) in the stroma. After healing, the lesions often leave behind a fine ring of haze that is associated with thinning of the corneal parenchyma. Recurrent lesions can result in subepithelial scarring or the corneal stroma and the appearance of superficial and deep vascularization. This can lead to impaired visual acuity or loss of vision. Treatment initially includes local application of steroid drugs (like prednisolone 1% or dexamethasone 0.1%) and

antivirals, both four times a day. If the patient shows improvement, treatment can be switched to twice-daily use. Treatment should not be continued for more than four weeks. During therapy, IOP should be monitored. Continuation of treatment consists of administering 0.5% prednisolone once a day with a covering local antiviral drug. It is recommended to periodically try to quit the medication before the end of treatment [1, 3, 6, 8, 9, 10].

Stromal necrotic keratitis

This is a rare condition in which corneal parenchymal necrosis and melting occurs. This is likely to occur as a result of active viral replication or an advanced immune response. Commonly, profound interstitial opacification occurs, leading to impaired vision. Corneal deposits outside of necrotic foci and anterior uveitis are present. Corneal defects may develop. In stromal necrotic keratitis it is common to see scarring, vascularization and lipid deposition. Treatment consists of recovering epithelial defects through the use of artificial tear preparations without conservatives. Topical treatment is similar to that used in disciform keratitis with concomitant oral use of antiviral medications [1, 3, 8, 9].

Metaherpetic ulceration

The factor causing the appearance of metaherpetic ulceration is the abnormal recovery of the corneal epithelium. The condition occurs as a result of necrosis of the stroma which is caused by the presence of the virus and its toxic effects on the cells. Characteristic features are unhealed epithelial defects despite prolonged topical treatment and an opaque gray stroma beneath the epithelial defects. Treatment includes low doses of topical steroids and lubricants without preservatives [3, 9].

ACUTE RETINAL NECROSIS (ARN)

ARN is a relatively rare condition that leaves severe consequences in the form of extensive retinal destruction. HSV is responsible for causing ARN in young people and *Varicella Zoster Virus* (VZV) in older people [11].

The disease affects healthy people of all ages, twice as often as men than women. It has been observed that the symptoms of the disease can occur after previous herpes encephalitis, or in a few cases together with it and dermatitis herpetiformis. The progression of ARN is usually unilateral initially, and there may be changes in the severity of symptoms over time. Periorbital pain and occasionally visual field opacities are present. The active phase of the inflammation

lasts 4-6 weeks. If treatment is not initiated early enough there is a risk of involvement of the second eyeball. Later, there is a decline in visual acuity due to necrotizing retinitis, opacity of the vitreous body, sometimes optic neuritis.

Diagnosis of ARN based on the criteria of The American Uveitis Society (AUS):

- Visible granulomatous inflammation of the anterior uvea and vitreous body present. Scleritis and epitheliitis are also sometimes observed.
- Presence of peripheral necrosis in the form of one or more foci with deep well-demarcated white-yellow infiltrates with a tendency to merge. The necrosis involves the entire depth of the retina. Hemorrhages may occur on the retina but they are less visible than those occurring in *cytomegalovirus* (CMV)-induced inflammation. Acute lesions resolve within 6-12 weeks leaving necrotic lesions on the retina with clearly demarcated borders. The main cause of vision loss is a rhegmatogenous retinal detachment (RRD) secondary to the lesions present.
- The inflammation spreads peripherally, finally affecting the posterior pole, so that visual acuity remains good for a long time - inadequate for the severity of the disease. Sometimes inflammation of the optic nerve can occur.
- Vasculitis with obliteration is present, including arterioles. Hemorrhages into the vitreous body as a result of developing preretinal neovascularization are possible.
- The disease progresses rapidly if treatment is not included [12].

For diagnosis, a PCR test for HSV DNA is performed from material taken from the vitreous body and/or the aqueous humor.

Treatment consists of starting intravenous acyclovir as soon as possible at a dose of 10 mg/kg every 8 h for 10-14 days. This is followed by a switch to oral acyclovir therapy at a dose of 800 mg 5 times a day and lasts for 6 to 12 weeks. If the patient develops a recurrence, long-term treatment should then be initiated. It is possible to administer ganciclovir or foscarnet into the vitreous body which can improve the prognosis. When there is optic nerve involvement, it is recommended to administer steroids 24 hours after the initiation of antiviral treatment. Administration of medications can accelerate the regression of active lesions on the retina and reduce the risk of involvement of the other eye. Unfortunately, pharmacological treatment will not protect against retinal detachment. Currently, prophylactic laser photocoagulation around necrotic lesions is not used, a procedure that does not prevent retinal detachment. On the other hand, if RRD occurs, vitrectomy with silicone oil is performed.

The prognosis for people with ARN is relatively poor. After surviving, more than half

of patients have severely impaired visual acuity $<6/60$ due to optic nerve and retinal ischemia, retinal vasculitis, and as a result of RRD, which occurs in up to 70% of cases if treatment is not started within the first 1-2 months of the disease [6, 11, 12, 13, 14, 15].

The specific morphological variant of ARN is progressive outer retinal necrosis (PORN). It is a disease entity with a poor prognosis observed in patients with severe immunodeficiency. It is characterized by rapid involvement of the posterior pole and relatively little reaction from the retinal vessels. Treatment uses acyclovir generally and administered by intravitreal injection [12, 15, 16].

HERPES SIMPLEX ANTERIOR UVEITIS

Herpes simplex anterior uveitis most commonly affects patients with a positive history of HSV infection. It usually takes the form of combined keratitis and anterior uveitis (keratouveitis) or as isolated inflammation. It typically occupies one eye and in many cases takes the form of chronic granulomatous inflammation. Characteristically, the cells are equally distributed in the anterior chamber (“star-shaped” type) or arranged in an Arlt's triangle (they then occupy $\frac{1}{3}$ of the lower part of the cornea). During the inflammation, there is an uneven, fragmented atrophy of the pigment epithelium of the iris. In the infected eye, there may be pupil dilation and an increase in IOP which is caused by associated blepharitis (trabeculitis). If there are recurrences of the disease, they affect one and the same eye in most patients. In the course of diagnosis, attention should be paid to the possible difficulty of distinguishing between inflammation caused by HSV and CMV. Treatment consists of topical steroids (prednisolone acetate 1% four times daily) and cycloplegics. In combination with topical treatment, acyclovir (400 mg five times daily) or oral famciclovir is used. If there is an elevated IOP these should also be treated [1, 6, 12, 17, 18].

HERPES SIMPLEX CONJUNCTIVITIS

Herpes simplex conjunctivitis is a rare disease and is not epidemic, unlike inflammation caused by adenoviruses. It is most often caused by reactivation of HSV-1 in the ganglia near the eyeball or by primary infection with HSV-1 as a result of direct contact with an infected person. Conjunctivitis is manifested by a foreign body sensation under the eyelid, burning eyes and pain. Characteristically, there are numerous vesicles in the initial stage of the disease which rupture within 48 h and a scab forms in their place. In addition, it has other typical features of

viral conjunctivitis: redness, plentiful serous secretion, a papular reaction on the conjunctiva, and possible swelling and photophobia. When herpes simplex conjunctivitis is present, treatment should be implemented quickly to prevent the infection from spreading to the cornea [1, 6, 19, 20, 21].

The standard treatment is eye ointment with 3% acyclovir or ganciclovir in 0.15% eye gel [20, 22, 23].

HSV-2 causes herpetic conjunctivitis in newborns. Infection is associated with fetal passage through the birth canal during delivery, when the mother showed signs of primary HSV-2 infection especially in the second and third trimesters of pregnancy, or when there is recurrent infection and skin lesions found during delivery. Symptoms usually appear between the 5th and 7th day after birth [4].

Observable symptoms include the presence of a serous secretion, a papillary reaction of the conjunctiva and occasionally characteristic vesicles on the eyelids may appear. Infants are treated with topical acyclovir or in advanced cases generally. Often with herpetic conjunctivitis there is keratitis, oral ulcers and skin lesions. Despite treatment, permanent visual impairment often occurs [24].

HERPES SIMPLEX BLEPHARITIS

Herpetic lesions on the eyelids are relatively rare. The lesions appear as a result of primary infection or reactivation of the infection when the latent virus was in the trigeminal ganglion. The disease has a unilateral course. At first, patients complain of a sensation of itching or tingling of the skin which can last up to 24 hours. Later, transparent vesicles can be seen, which are filled with serous fluid. Within 48 hours, the vesicles rupture and transform into scabs. The course of the disease is usually mild. If herpetic lesions are observed on the eyelids or on the skin around the eye, acyclovir ointment should be applied 5 times a day or acyclovir orally. In untreated and uncomplicated patients, eyelid skin herpes passes on its own within a week. Antibiotics are used in patients with secondary bacterial superinfection [6, 25, 26, 27].

HERPES SIMPLEX SCLERITIS

Herpetic scleritis accounts for less than 10% of all episodes of scleritis. It is an acute, monocular inflammation, with pain and redness of the eyeball. It most commonly takes the form of diffuse anterior inflammation. It manifests as an inflammatory infiltrate occupying the

dermis of the sclera, present as an extensive flat elevation. Scleritis caused by HSV responds well to treatment with acyclovir. There have been cases of necrotizing scleritis or forms of prolonged inflammation [28, 29, 30]. With herpetic scleritis, vision loss was more frequently observed (34.3%) compared to idiopathic scleritis (11.5%) [28].

INFLAMMATORY GLAUCOMA

Secondary open-angle glaucoma occurs as a result of experiencing acute anterior uveitis caused by HSV. Acute trabeculitis leads to impaired outflow of aqueous fluid from the anterior chamber. This is caused by the edema of the trabecular meshwork and secondary pore reduction. As a result of scarring, outflow of the aqueous fluid is impaired, IOP increases and finally secondary glaucoma develops [31, 32]. Treatment consists of causal and conservative treatment of glaucoma secondary to HSV inflammation [33].

CONCLUSION

Infections of the eye and accessory visual structures caused by *Herpes simplex virus* are a current phenomenon in medical practice and often require specialized care and treatment. Despite the potential spontaneous curability of most of these diseases, antiviral treatment must often be implemented to prevent serious complications from spreading inflammation. Scarring, vascular ingrowth and accumulation of deposits are just some of the pathological conditions caused by HSV infection [3, 7].

The body's immune response itself also has serious consequences for the patient [3, 9]. Infection can be associated with serious complications in the form of impaired visual acuity or even complete loss of vision. It is HSV-1 that is considered the main infectious cause of blindness in developed countries [1, 3, 6].

This has consequences including reduced patient independence, social exclusion and impaired work functioning. Other complications of HSV infection include secondary infections, mainly as a result of bacterial superinfection, secondary glaucoma as a result of elevated IOP and steroid use. Corneal thinning can falsify the results of an applanation IOP test, which delays the diagnosis of developing intraocular hypertension and glaucoma. Steroid use can also lead to a complicated cataract. Another reason for it is ongoing inflammation. Complications also include iris atrophy caused by inflammation of the anterior uvea and cornea [3].

REFERENCES

1. Korda M., Wobszal P., Malinowska A.: Przegląd okulistyczny: Choroby oczu wywołane przez wirusa opryszczki zwykłej. <https://www.przegladokulistyczny.pl/2019> Accessed 14 Jul 2023.
2. Ludzkie herpeswirusy [w.] Mikrobiologia. Murray P., Rosenthal K., Pfaller M.. (red.) Edra Urban & Partner, Wrocław, 2018, 483-506.
3. Herpes simplex keratitis [w.] Kanski's Clinical Ophthalmology, A systematic approach, Salmon J.F. (red.) Elsevier, 2020, 218-224.
4. Nowakowska D., Wilczyński J.: Zakażenia i zarażenia [w.] Ginekologia i położnictwo tom 1, Bręborowicz G. (red.) Wydawnictwo lekarskie PZWL, 2016, 326-349.
5. Schoenberger S., Kim S., Thorne J., Mruthyunjaya P., Yeh S., et al.: Ophthalmology: Diagnosis and Treatment of Acute Retinal Necrosis: A Report by the American Academy of Ophthalmology, 2017, 124 (3), 382-392.
6. Kubicka-Trzaska A., Kozioł-Moszczyńska J., Kozicka K., Żuber-Łaskawiec K.: Opryszczkowe zapalenie gałki ocznej. <https://podyplomie.pl/okulistyka/31827,opryszczkowe-zapalenie-galki-ocznej> (accessed 14 Jul 2023).
7. Dobrowolski D.: Choroby rogówki [w.] Okulistyka. Grzybowski A. (red.) Edra Urban & Partner, Wrocław, 2018, 119-128.
8. Choroby rogówki [w.] Okulistyka Podstawy kliniczne. prof. dr hab. Hanna Niżanowska (red.) Wydawnictwo Lekarskie PZWL, Warszawa, 2007, s. 171-210
9. Rogówka [w.] Okulistyka Kliniczna, Kański J.J. (red.) Edra Urban & Partner, Wrocław, 2009, 278-287.
10. Lobo A., Agelidis A., Shukla D.: The Ocular Surface: Pathogenesis of herpes simplex keratitis: the host cell response and ocular surface sequelae to infection and inflammation, 2019, 17 (1), 40-49.
11. Zapalenie błony naczyniowej [w.] Okulistyka Kliniczna, Kański J.J. (red.) Edra Urban & Partner, Wrocław, 2009, 512-519.
12. Viral uveitis [w.] Kanski's Clinical Ophthalmology, A systematic approach, Salmon J.F. (red.) Elsevier, 2020, 465-473.
13. Tabela przeliczeniowa wartości ostrości wzroku. <https://www.mp.pl/okulistyka/praktyka/kalkulatory/105200,tabela-przeliczeniowa-wartosci-ostrosci-wzroku>. Accessed 14 Jul 2023.
14. Misiuk-Hojło M., Ruta M.: Ostra martwica siatkówki – diagnostyka i leczenie

- <https://podyplomie.pl/okulistyka/29690,ostra-martwica-siatkowki-diagnostyka-i-leczenie>. Accessed 14 Jul 2023).
15. Misiuk-Hojło M., Przeździecka-Dołyk J.: Choroby błony naczyniowej [w.] Okulistyka. Grzybowski A. (red.) Edra Urban & Partner, Wrocław, 2018, 135-146.
 16. Tripathy K., Farivari N., Law J., Bhat P., Bhagat N., et al.: Progressive Outer Retinal Necrosis. https://eyewiki.aao.org/Progressive_Outer_Retinal_Necrosis. Accessed 14 Jul 2023).
 17. Asif H., Feldman B., Gritz D., Read R., Palestine A., et al.: Herpes Simplex Uveitis. https://eyewiki.aao.org/Herpes_Simplex_Uveitis. Accessed 14 Jul 2023.
 18. Choroby błony naczyniowej [w.] Okulistyka Podstawy kliniczne. prof. dr hab. Hanna Niżanowska (red.) Wydawnictwo Lekarskie PZWL, Warszawa, 2007, 217-278.
 19. Prost M.: Opryszczkowe zapalenie spojówek. <https://www.mp.pl/pacjent/okulistyka/chorobyoczu/chorobyspojowki/83659,opryszczkowe-zapalenie-spojowek>, Accessed 14 Jul 2023.
 20. Sarnat-Kucharczyk M., Mrukwa-Kominek M.: Choroby spojówek [w.] Okulistyka. Grzybowski A. (red.) Edra Urban & Partner, Wrocław, 2018, 113-117.
 21. Choroby spojówek [w.] Okulistyka Podstawy kliniczne. prof. dr hab. Hanna Niżanowska (red.) Wydawnictwo Lekarskie PZWL, Warszawa, 2007, 145-170.
 22. Spojówki [w.] Okulistyka Kliniczna, Kański J.J. (red.) Edra Urban & Partner, Wrocław, 2009, 240-243.
 23. Viral conjunctivitis [w.] Kanski's Clinical Ophthalmology, A systematic approach, Salmon J.F. (red.) Elsevier, 2020, 177-180.
 24. Czaja-Drożdż M.: Choroby powierzchni oka [w.] Okulistyka dziecięca i zez. Hautz W., Loba P., Rękas M. (red.) Edra Urban & Partner, Wrocław, 2021, 265- 282.
 25. Januchowski P.: Czym jest opryszczka na oku? Leczenie, objawy i zapobieganie. <https://www.wokularach.pl/blog/czym-jest-opryszczka-na-okuleczenie-objawy-i-zapobieganie> (accessed 14 Jul 2023).
 26. Powieki [w.] Okulistyka Kliniczna, Kański J.J. (red.) Edra Urban & Partner, Wrocław, 2009, 133-135.
 27. Eyelids. Viral infections [w.] Kanski's Clinical Ophthalmology, A systematic approach, Salmon J.F. (red.) Elsevier, 2020, 68-70.
 28. Gonzalez-Gonzalez L., Molina-Prat N., Doctor P., Tauber J., Sainz de la Maza M., et al.: Ophthalmology: Clinical Features and Presentation of Infectious Scleritis from Herpes Viruses: A Report of 35 Cases, 2012, 119 (7), 1460-1464.

29. Bhat P., Jakobiec F., Kurbanyan K., Zhao T., Foster S.: American Journal of Ophthalmology: Chronic Herpes Simplex Scleritis: Characterization of 9 Cases of an Underrecognized Clinical Entity, 2009, 148 (5), 779-789.
30. Jurowski P., Wojciechowska K.: Choroby twardówki [w.] Okulistyka. Grzybowski A. (red.) Edra Urban & Partner, Wrocław, 2018, 129-134.
31. Jaskra wtórna otwartego kąta [w.] Okulistyka Podstawy kliniczne. prof. dr hab. Hanna Niżanowska (red.) Wydawnictwo Lekarskie PZWL, Warszawa, 2007, 350-356.
32. Inflammatory glaucoma [w.] Kanski's Clinical Ophthalmology, A systematic approach, Salmon J.F. (red.) Elsevier, 2020, 385-388.
33. Nowosielska A, Grabska-Liberek I., Terelak-Borys B., Jamrozy-Witkowska A., Wasyluk J., et al.: Farmakoterapia jaskry wtórnej. <https://www.czytelniamedyczna.pl/2764,farmakoterapia-jaskry-wtornej.html>. Accessed 14 Jul 2023.

A SHORT REVIEW OF INFLAMMATION PROCESS AND THERAPEUTIC CONCEPTS IN DIABETIC RETINOPATHY

Kinga Łysak¹, Agata Walulik², Michał Błaszkiwicz², Krzysztof Gomulka³

1. Medical University of Gdansk, Gdańsk
2. Student Scientific Group of Adult Allergology, Wrocław Medical University, Wrocław
3. Department of Internal Medicine, Pneumology and Allergology, Wrocław Medical University, Wrocław.

ABBREVIATION LIST

- AAO - American Academy of Ophthalmology
- AG - aminoguanidine
- AGEs - Advanced Glycation End Products
- ANG-2 - Angiopoietin-2
- BMI - body mass index
- CDC - central serous chorioretinopathy
- CEL - carboxyethyl-lysine
- CML - carboxymethyl-lysine
- CRT - central retinal thickness
- CW - continuous wave
- DARPs - designed ankyrin repeat proteins
- DM - diabetes mellitus
- DME - diabetic macular edema
- DR - diabetic retinopathy
- DRVS - Diabetic Retinopathy Vitrectomy Study
- ERM - epiretinal membrane
- FVP - fibrovascular proliferation
- Glo1 - glyoxalase 1
- HbA1c - haemoglobin A1c
- HIF-1 - hypoxia-induced factor 1
- HSP - heat shock proteins
- IRMA - intraretinal microvascular abnormalities

- JAK - Janus kinase
- JNK - c-Jun N-terminal kinases
- MAPKs - mitogen-activated protein kinases
- MG - methylglyoxal
- MOLD - methylglyoxal-lysine dimer
- nAMD - neovascular age-related macular degeneration
- NaMESys - nanostructured microemulsions system
- NPDR - nonproliferative diabetic retinopathy
- NVD - new vessels on the optic disc
- NVE - new vessels elsewhere
- PDR - proliferative diabetic retinopathy
- PDS - Port Delivery System
- PGF - placenta growth factor
- PI3-K - phosphoinositide 3-kinase
- PKC - protein kinase C
- PM - pyridoxamine
- PPV - pars plana vitrectomy
- PRP - Panretinal photocoagulation involves
- RPE - Retinal Pigment Epithelium
- RVO - nanostructured microemulsions system
- RVO - retinal vein occlusion
- SMPLT - subthreshold micropulse laser treatment
- STAT - signal transducer and activator of transcription
- TRD - tractional retinal detachment
- VEGF - vascular endothelial growth factor
- VEGFR - vascular endothelial growth factor receptor
- VMT - vitreo-macular traction
- WESDR - Wisconsin Epidemiologic Study of Diabetic Retinopathy

INTRODUCTION

Diabetic retinopathy is a chronic complication of diabetes mellitus that can lead to severe visual impairment and blindness [1]. It is the most common microvascular cause of new

cases of total blindness among adults aged 20-74 years [2]. Estimates indicate that about 366 million people in the world are affected by diabetes mellitus [3]. During the first 10 years of diabetes, almost all patients with type 1 diabetes and over 60% of patients with type 2 diabetes develop retinopathy. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy, 3.6% of patients with diabetes diagnosed at a younger age (type 1 diabetes) and 1.6% of patients with diabetes diagnosed at an older age (type 2 diabetes) were classified as blind. In the group of patients with type 1 diabetes, diabetic retinopathy was the cause of visual loss in 86% of cases. In the group of patients with diabetes that developed at an older age and often presented with other eye diseases, diabetic retinopathy was the cause of visual loss in one-third of cases [2].

The main risk factor for retinopathy is the duration of the disease [4]. Among participants in the WESDR study with diabetes diagnosed at a younger age, the 4-year incidence of proliferative retinopathy increased from 0% in the first 5 years to 27.9% after 13-14 years of diabetes duration. After 15 years of disease duration, the incidence of proliferative retinopathy remained stable [1]. The development of diabetic retinopathy also strongly correlates with greater hyperglycemia, glycated haemoglobin A1c and hypertension [5]. Additionally, body mass index and dyslipidemia are also potential predictors of DR development [5]. Since there are no therapies that can fight the onset of diabetic retinopathy, patients should be advised to control risk factors through optimal glycemic control and lifestyle modification [6].

CLASSIFICATION OF DIABETIC RETINOPATHY

Since Diabetic retinopathy was recognized as one of the most important complications of diabetes, there have been many attempts to classify the severity and stages of the disease [7]. The classic symptoms of DR are lipid deposits, micro-aneurysms, flame-shaped haemorrhages, cotton wool spots, venous dilation and beading, and intraretinal vascular abnormalities [8]. These symptoms are useful in the classification of DR into five stages no apparent DR, mild NPDR, moderate NPDR and severe NPDR and PDR. The AAO classification of DR allows for predicting the risk of progression and vision loss, as well as it could be a helpful tool for ophthalmologists in planning further treatment and predicting the progression of the disease [9].

Early stages of DR include non-proliferative diabetic retinopathy and pre-proliferative diabetic retinopathy. The symptoms of NPDR are any of the following: intraretinal haemorrhages (-20 in each quadrant), definite venous beading (in 2 quadrants), and intraretinal

microvascular abnormalities (in 1 quadrant). In both cases, changes may be present without clinical symptoms and require regular ophthalmic monitoring in patients with diabetes. Proliferative diabetic retinopathy is a severe stage of DR. The manifestations of PDR are the same as in non-proliferative DR and 1 or more of the following: neovascularization, which can be divided into two groups: new vessels on the optic disc and new vessels elsewhere and/or vitreous/preretinal haemorrhage [9, 10]. At each of the above stages of diabetic retinopathy, diabetic macular edema may develop. This term refers to the presence of vision-threatening changes in the macula [11]. In the most advanced stage of diabetic retinopathy, also the following can occur pre-retinal and vitreous haemorrhages which are a complication of neovascularization, fibrovascular proliferation, tractional retinal detachment and rubeosis iridis [12].

LASER THERAPY IN THE TREATMENT OF DIABETIC RETINOPATHY

The first research that led to the development of lasers dates back to the 19th and 20th centuries. Many physicists, including N. Bohr, M. Planck, A. Einstein studied the processes that occur in atoms under the influence of electromagnetic radiation. In 1960, Maiman built the first working ruby laser [13]. In the following years, new materials were used to create new laser designs. Thus, mainly ophthalmologists quickly became interested in using lasers to treat eye diseases such as diabetic retinopathy [14].

Lasers are divided based on various characteristics. In terms of ophthalmology, the most important division is based on the type of active medium used to produce the laser action. They are divided into gas, solid-state and semiconductor lasers. Another division of these devices also takes into account the mode of operation of the laser, and the wavelength of the electromagnetic radiation emitted by the laser. Lasers are categorized as continuous wave or pulsed lasers based on their mode of operation. CW lasers generate a constant stream of light, while pulsed lasers emit short bursts of laser pulses. Lasers emitting light of different wavelengths are used in various ophthalmic procedures. The most commonly used lasers emit light in the range of 532 nm (green) and 810 nm (infrared) [15].

Laser procedures are a very important part of modern ophthalmology and in many clinical situations are the treatment of choice. They can be divided, taking into account the place of their execution, into procedures within the protective apparatus of the eye, the anterior segment of the eye, and the posterior segment of the eye. Laser methods related to the treatment of diabetic retinopathy mainly concern the retina of the eye [16].

The most important lasers used in ophthalmology are argon lasers. They are useful in the treatment of retinal vascular disorders such as diabetic retinopathy and retinal vein occlusion. As well as YAG lasers, used in the treatment of posterior capsule opacification by creating holes in the lens capsule and excimer laser used in refractive surgery to correct vision problems such as myopia, hyperopia, and astigmatism [17].

PHOTOCOAGULATION

Photocoagulation is a thermal process in which the energy of light absorbed by pigments contained in tissues is converted into heat, causing protein denaturation. Laser photocoagulation is the primary method of treating many retinal diseases such as proliferative diabetic retinopathy, diabetic macular edema, retinal vein occlusion and retinal detachment [18]. The effectiveness of laser photocoagulation has been confirmed in various clinical studies. Therefore, this procedure is becoming increasingly used and the process of developing new methods is still ongoing. This procedure aims to achieve highly precise thermal effects („burns”) while minimizing damage to surrounding tissues [19].

Panretinal photocoagulation involves creating 1000-2000 coagulation spots in the peripheral part of the retina. Areas of retinal ischemia are destroyed, and permanent chorioretinal scars are formed. The regression of neovascularization resulting from these processes reduces the risk of vitreous and tractional retinal detachment, hemorrhages as well as the risk of developing diabetic maculopathy. The study Diabetic Retinopathy Study has shown that PRP reduces the risk of severe vision loss in patients with PDR or severe non-proliferative diabetic retinopathy by at least 50% compared to untreated eyes [20].

PDR is characterized by abnormal retinal vessels, often accompanied by leaking microaneurysms, hard and soft exudates („cotton wool spots”), intraretinal and preretinal haemorrhages, and extensive areas of retinal ischemia [21]. In such advanced stages of retinopathy, combined procedures are most commonly used: intravitreal anti-VEGF drug injections (vascular endothelial growth factor inhibitors) with panretinal photocoagulation [22].

Diabetic macular edema is mainly caused by leaking microaneurysms or capillaries that result in thickening or swelling of the central retina. The aim of focal laser photocoagulation is to treat these leaking microaneurysms, while grid laser photocoagulation targets diffuse capillary leakage. In the study of Early Treatment Diabetic Retinopathy, the risk of vision loss in patients with clinically significant DME was significantly reduced after focal laser photocoagulation [23].

In case of retinal tear or detachment, laser coagulation is performed to securely attach the retina to the RPE and choroid. In this procedure, laser spots are placed around the area of the tear. The most commonly used devices for this purpose are the indirect ophthalmoscope laser, endolaser, or transscleral laser [24].

SUBTHRESHOLD MICROPULSE LASER TREATMENT

Subthreshold micropulse laser treatment is an alternative method to conventional continuous-wave laser in the treatment of retinal and macular diseases such as diabetic macular edema and central serous chorioretinopathy [25].

In this method, by using minimal laser radiation intensity necessary to raise the temperature within the RPE but without exceeding the threshold beyond which protein denaturation occurs, the neurosensory retina can be spared [26].

This fact is particularly important when treating lesions near the fovea. The mechanism of action of SMPLT is to stimulate RPE for the production of HSP, thus modulate its metabolism and improve its function. According to the latest research on mice models, SMPLT restores the oxidant/antioxidant balance within the retinal tissue and, this way, modulates retinal cell apoptosis, counteracting the programmed cell death [27].

The analysis of the treatment of DME using a micropulse laser has shown effectiveness in both morphological and functional indicators. Subthreshold micropulse laser can be an option for treating patients who do not respond well enough to anti-VEGF therapy or are unable to comply with the principles of this treatment method. Much better visual acuity and a similar reduction of central retinal thickness are observed after SML compared to conventional lasers [28].

VITRECTOMY

In 1970, Robert Machemer performed the first pars plana vitrectomy on a patient with diabetes and non-resolving bleeding into the vitreous body in the course of proliferative diabetic retinopathy [29]. This surgical technique has undergone continuous evolution, but the goal of the procedure remained the same - removal of the vitreous body to restore the transparency of the optical media and release of retinal traction. Pars plana vitrectomy involves making up to 10,000 cuts per minute, which results in the removal of the vitreous body with minimal traction on the retina, reducing the risk of bleeding and iatrogenic holes [30].

Indications for vitrectomy in patients with diabetic retinopathy include vitreous haemorrhage, tractional retinal detachment, combined tractional and rhegmatogenous retinal detachment, neovascular glaucoma, diabetic macular edema, progressive fibrovascular proliferation and tractional macular detachment [31].

One of the most common indications for performing PPV is bleeding into the vitreous body. The main goal of the surgery is to restore the transparency of the optical media and improve visual function, as well as to create conditions for performing panretinal laser photocoagulation [32]. This procedure should be performed when the bleeding into the vitreous body is intense and prevents examination of the fundus of the eye, and it is associated with retinal detachment confirmed by ultrasound. In patients with type 1 diabetes, studies on PPV in diabetic retinopathy have shown a beneficial effect of early vitrectomy on the postoperative improvement of visual function. This relationship has not been confirmed in patients with type 2 diabetes [33].

Tractional retinal detachment is caused by the contraction of the fibrovascular membrane. It is also a common indication for PPV in patients with PDR. TRD involving the macula is an indication of early surgical intervention to avoid significant irreversible visual loss. Removal of the internal limiting membrane during the operation reduces the risk of epiretinal membrane formation [34].

In the case of diabetic macular edema, coexisting with vitreo-macular traction or epiretinal membrane, anti-VEGF treatment is not very effective. PPV is the preferred treatment. This method with the removal of the inner limiting membrane of the retina can improve retinal oxygenation and contribute to the reduction of DME [35].

Vitrectomy plays a crucial role in the treatment of advanced proliferative diabetic retinopathy. The indications for vitrectomy have expanded with the advancement of surgical tools and the preoperative use of anti-VEGF agents [36]. However, to achieve therapeutic success, a comprehensive patient assessment is important. Proper systemic control is necessary before surgical intervention. Preoperative anti-VEGF injections and panretinal photocoagulation should be considered to reduce the risk of intraoperative complications.

OTHER THERAPEUTICS

Although diabetic retinopathy is becoming an increasingly common complication of diabetes in the working-age population, therapeutic options are still limited and require further research [37]. It is crucial to search for novel therapeutic strategies for DR that will not only

provide better therapeutic effects but also show less invasiveness than the procedures currently used in treatment, e.g. photocoagulation. The latest therapeutic mechanisms such as PKC pathway inhibitors, hormone antagonists, VEGF antagonists and AGE pathway inhibitors are under exact investigation [38, 39, 40]. The following chapter will present the advances of selected VEGF and AGEs related therapies.

ANTI-VEGF BIOLOGICAL TREATMENT

Angiogenesis plays an important role in PDR development. One of the crucial molecules of complex pathological angiogenesis pathways is vascular endothelial growth factor described in 1983 by Senger [41]. All members of the VEGF family (VEGF - A, B, C, D, E and PGF) contain the core cysteine-knot structural domain, which binds with specific tyrosine kinase receptors [42]. Currently, the anti-VEGF molecules constitute a vital point in PDR and diabetic macular edema treatment [43].

Pegaptanib, 28-nucleotide RNA aptamer of 50 kDa RNA pegylated aptamer with high affinity to VEGF-A₁₆₅. The intravitreal injections of pegaptanib were discovered to effectively inhibit leukostasis, retinal neovascularization, and cellular hyperfiltration induced by VEGF [44]. Pegaptanib has the ability to inhibit pathological neovascularization while not affecting physiological revascularization. The recommended intravitreal injection is 0.3 mg once every six weeks [45].

Bevacizumab, a fully humanized immunoglobulin G1 molecule of 148 kDa binding VEGF-A isoforms. Bevacizumab can interact with hypoxia-induced factor 1, which consequently hinders its ability to stimulate VEGF production. The use of this drug for retinal diseases through intravitreal injection into the eye is still regarded as an "off-label" treatment [46].

Ranibizumab, a 48.3 kD monoclonal antibody, with an affinity to all isoforms of VEGFA. It can be delivered by a specific system called Ranibizumab Port Delivery System surgically implanted through an incision in the sclera and provides continuous release of the drug [47].

Aflibercept is a recombinant glycoprotein with a molecular weight of 115 kDa. It is composed of the Fc portion of human immunoglobulin IgG1, which is fused with the second extracellular domain of human VEGFR-1 and the third extracellular domain of human VEGFR-2. It exhibits affinity to VEGF-A, VEGF-B and PGF. Aflibercept works by blocking the binding of VEGF to VEGFR-1 and VEGFR-2 receptors through competitive inhibition. The

experimental findings indicate that aflibercept binding affinity to VEGF-A165 is approximately 100 times stronger than the one of ranibizumab and bevacizumab [48].

Conbercept - the complete human DNA sequence of 143 kDa generated by fusing extracellular domain 2 of VEGFR-1 with extracellular domains 3 and 4 of VEGFR-2, along with the Fc portion of human IgG1. It binds VEGF-A, VEGF-B and PGF having a relative affinity for VEGF-C [46]. Conbercept intravitreal injection treatment was found to be more effective than laser photocoagulation in improving the best corrected visual acuity of patients with diabetic macular edema [49].

Abicipar-pegol is categorized as a 34 kDa member of the designed ankyrin repeat proteins, which are a type of protein that can imitate antibodies [6]. It binds all VEGFA isoforms, but the intraocular half-life of this drug is longer than that of ranibizumab (more than 13 days compared to 7.2 days), which combined with its high affinity, makes it a potential anti-VEGF therapy that requires less frequent injections [50].

Faricimab also belongs to the DARPins family, the 150 kDa molecule has the ability to bind and neutralize both VEGF-A and Angiopoietin-2 independently and at the same time. That ability gives it a multitarget profile and presents promising opportunities for the treatment of exudative retinal diseases [46]. Faricimab was granted its initial approval in the United States in January 2022 for treating patients with neovascular (wet) age-related macular degeneration or diabetic macular edema. Additionally, it has been recently approved in Japan and is presently undergoing regulatory assessment in the European Union [51].

Sorafenib tosylate is a kinase II inhibitor that inhibits VEGFr. It blocks the phosphorylation of VEGFr by creating the non-functional hydrogen bonds in the ATP-binding site and changing its conformation [52]. According to current studies, there is a possibility to administrate Sorafenib topically at the eye surface using a nanostructured microemulsions system. It can avoid complications and side effects of repeating intravitreal injections [53].

There are two more of the newest anti-VEGF molecules, which are still under investigation. KSI-301 is an antibody biopolymer conjugate (consisting of 950 kDa KSI-301 and 800 kDa phosphorylcholine-based biopolymer), which could potentially resolve common problems due to its safety, efficacy, and exceptional biological durability of action. It is currently being tested in clinical trials as a potential treatment option for neovascular age-related macular degeneration, diabetic macular edema, and macular edema caused by retinal vein occlusion [46, 54]. OPT-302, which is a VEGF-C/D inhibitor, is currently being studied in a Phase 2b clinical trial for the treatment of exudative age-related macular degeneration. A Phase 3 clinical trial is also underway. Based on current results, this molecule has the

potential to enhance visual acuity beyond the standard of care and may result in a better quality of life and increased independence for patients. It is currently the only molecule in advanced stages of development with this potential [46, 55].

ADVANCED GLYCATION END PRODUCTS

Chronic hyperglycemia promotes the formation of excessive AGEs, molecules formed in the Maillard reaction - nonenzymatic interaction between macromolecules (proteins, lipids, and nucleic acids) and glucose or other saccharides [56,57].

The most important and known AGEs are carboxymethyl-lysine, carboxyethyl-lysine, pyrraline, pentosidine and methylglyoxal-lysine dimer [58, 59].

AGEs bind to their receptors on the cell surface, with RAGE being the most well-known among them. Four major AGE-RAGE pathways are identified that promote cellular responses involved in pathological processes in DR:

- 1) Ras-Rac-Cdc42;
- 2) mitogen-activated protein kinases, including p44/43, p38, c-Jun N-terminal kinases;
- 3) Janus kinase-signal transducer and activator of transcription;
- 4) phosphoinositide 3-kinase-Akt/PKB [56, 60, 61].

All of the above result in oxidative stress, inflammatory response, and endothelial dysfunction [61,62]. Novel therapies affecting AGEs mechanisms can be divided into 4 groups:

- 1) inhibitors of AGE formation;
- 2) breakers of preformed AGEs;
- 3) blockades of AGE–RAGE axis signaling;
- 4) inducers of intracellular glyoxalase, ubiquitin–proteasome, and autophagy pathways (Figure 1) [40].

They may be an attractive target to inhibit the development or progression of DR, which is the most common cause of vision loss among work-age patients with DM.

AGEs synthesis inhibitors are meant to prevent or reduce the formation by interfering with several glycation process stages. They may affect the early stages of AGEs synthesis by scavenging or trapping reactive sugar and protein intermediates or enter further processes by blocking certain enzymes involved in AGEs formation.

Aminoguanidine (Primagedine) is the first compound designed to inhibit AGEs formation and prototype therapeutic agent for the prevention of AGEs-related diseases [60, 63, 64]. AG works as a scavenger of α -oxoaldehydes such as glyoxal, methylglyoxal and 3-

deoxyglucosone which react with proteins and lead to AGEs synthesis [65]. The products of a modified reaction with AG inserted are 3-amino-1,2,4-triazines - inhibitors of inducible nitric oxide synthase.

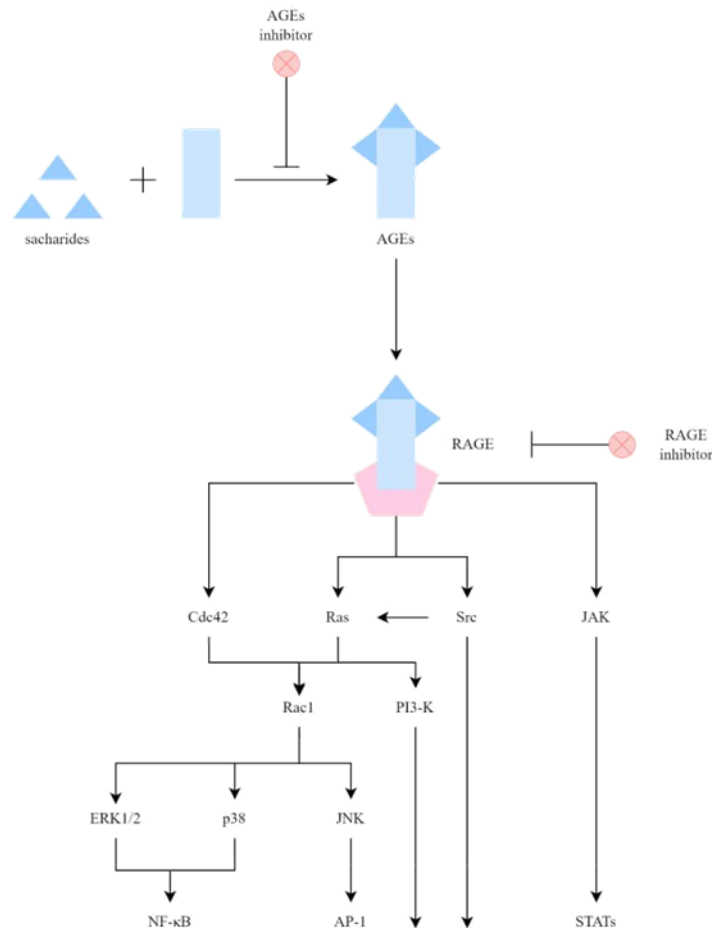


Figure 1. Action points of selected age-related drugs

Luo et al. in a study conducted on non-diabetic and STZ-induced diabetic rats - AG-treated and control group, has shown potential therapeutic effects of Primagedine. After 3 and 6 months of study extensive stainings of AGEs were detected in retinal blood vessels among diabetic rats, while there was no significant staining found in non-diabetic and AG-treated animals. After 6 months pericyte loss, capillary occlusion, and endothelial cell proliferation were found in the diabetic group. No AG-treated rats showed similar morphological changes [66].

Another AGEs inhibitor is pyridoxamine one of three natural forms of vitamin B6 [67]. There are three mechanisms that lead to the inhibition of AGEs formation:

- 1) the complexation of metal ions that catalyze the secondary reactions of protein glycation;

- 2) the scavenging of RCS;
- 3) ROS generated as byproducts of previous reactions [68, 69].

Research showed that pyridoxamine is an effective therapeutic agent in diabetic retinopathy. In the study of Stitt et al. PM treatment on STZ-induced diabetic Sprague-Dawley rats resulted in a reduction of acellular capillaries in the retina to a level not statistically different than that for non-diabetic and reduction of laminin levels in the vessel walls. PM also prevented CML formation in the retina during exposure to chronic hyperglycemia [70].

One of the compounds involved in the Maillard reaction is methylglyoxal which in the reaction with lysine, arginine or cysteine forms AGEs [71]. The enzyme associated with methylglyoxal metabolism is glyoxalase 1. The imbalance between the two of the above leads to the development of diabetic complications such as nephropathy, neuropathy and retinopathy [72]. The level of hyperglycemia defines the level of MG production, while its degradation depends on the activity of Glo1 activity [73]. Research on rodents has shown that boosting the glyoxalase system by overexpression may have promising results in the prevention of diabetes complications [73, 74, 75].

RAGE antagonists have been investigated as potential therapeutic agents in various diseases characterized by RAGE-mediated pathology, including DR. Extensive studies in rodents with inhibitors of RAGE have not shown any detrimental effects of RAGE inhibition. Based on the study, small-molecule inhibitors capable of targeting both the extracellular and intracellular domains of RAGE were developed. [76].

Azeliragon (also known as TTP488 or PF-04494700) is an orally bioavailable investigational drug that belongs to the class of RAGE antagonists [76]. It is currently being studied in phase 3 clinical trials for its potential therapeutic effects on Alzheimer's disease [77].

Ma et al. in the study of STZ-induced diabetic mice showed the positive effects of TTP488 on the reducing mechanical nociceptive threshold after 28 days. The readmission of azeliragon was needed thus the disappearance of the positive effect after 24 hours [78]. The above results suggest that regular intake of the drug could potentially provide a method of pharmacological treatment of complications resulting from chronic hyperglycemia.

DISCUSSION

Diabetic Retinopathy is not uncommon, a chronic complication, which can lead to severe impairments such as blindness. Although surgical treatment of proliferative diabetic retinopathy brings many benefits, it remains challenging even for the most experienced

vitreoretinal surgeons. Laser therapies have promising results, but the crucial point is to control diabetes progression. Patients with less deteriorated retina condition have better procedure outcomes. Further studies about biological anti-VEGF agents and the way of their administration are needed. Current reports point out the potential effectiveness and possible non-invasive treatment with fewer side effects of anti-VEGF molecules. Mainstay PDR therapies should focus on a complex approach to molecular pathways and other methods to develop the most optimal effects. It's important to note that while AGE synthesis inhibitors may hold promise in reducing AGE formation and related complications in vitro and in vivo in rodents research, further research is needed to understand their effectiveness and safety in DM complications.

REFERENCES

1. Ding J., Wong T. Y.: Current epidemiology of diabetic retinopathy and diabetic macular edema. *Current Diabetes Reports*, 2012, 12, (4), 346–354.
2. Fong D. S., Aiello L., Gardner T. W., King G. L., Blankenship G., et al.: Retinopathy in diabetes. *Diabetes Care*, 2004, 27(1), 84–87.
3. Wild S., Roglic G., Green A., Sicree R., and King H.: Global prevalence of diabetes. *Diabetes Care*, 2004, 27(5), 1047–1053.
4. Esteves J., Laranjeira A. F., Roggia M. F., Dalpizol M., Scocco C., et al.: Fatores de risco para retinopatia diabética. *Arquivos Brasileiros de Endocrinologia & amp Metabologia*, 2008, 52(3), 431–441.
5. Hirsch I. B.: Beyond Hemoglobin A1c-Need for Additional Markers of Risk for Diabetic Microvascular Complications - commentary., 2010, *JAMA* 303(22), 2291.
6. Hainsworth D. P., Bebu I., Aiello L. P., Sivitz W., Gubitosi-Klug R., et al.: Risk factors for retinopathy in type 1 diabetes: The DCCT/EDIC study. *Diabetes Care*, 2019, 42(5), 875–882.
7. Yang Z., Tan T.-E., Shao Y., Wong T. Y., Li X.: Classification of diabetic retinopathy: Past, present and future. *Frontiers in Endocrinology* 2022, 13.
8. Scanlon PH, Sallam A.: *A Practical Manual of Diabetic Retinopathy Management*. Wiley Blackwell, 2017.
9. Wong T. Y., Sun J., Kawasaki R., Ruamviboonsuk P., Gupta N., et al.: Guidelines on diabetic eye care. *Ophthalmology* 2018, 125(10), 1608–1622.

10. Wilkinson C., Ferris F. L., Klein R. E., Lee P. P., Agardh C. D., et al.: Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. *Ophthalmology*, 2003, 110(9), 1677–1682.
11. Antonetti D. A., Klein R., Gardner T. W.: Diabetic retinopathy. *New England Journal of Medicine*, 2012, 366(13), 1227–1239.
12. Fei Lee P., McMeel J. W., Schepens C. L., Field, R. A.: A new classification of diabetic retinopathy. *American Journal of Ophthalmology*, 1966, 62(2), 207–219.
13. Bożena Romanowska-Dixon. *Chirurgia Okulistyczna*. Wyd. Lekarskie PZWL, 2021.
14. Lock J. H., Fong K. C. S.: An update on retinal laser therapy. *Clinical and Experimental Optometry*, 2011, 94(1), 43–51.
15. No authors listed.: Photocoagulation treatment of proliferative diabetic retinopathy. Clinical application of Diabetic Retinopathy Study (DRS) findings, DRS Report Number 8. The Diabetic Retinopathy Study Research Group. *Ophthalmology* 1981, 88(7), 583–600.
16. Chhablani J., Roh Y. J., Jobling A. I., Fletcher E. L., Lek J. J., et al.: Restorative retinal laser therapy: Present state and future directions. *Survey of Ophthalmology*, 2018, 63(3), 307–328.
17. Shah A. M., Bressler N. M., Jampol L. M.: Does laser still have a role in the management of retinal vascular and neovascular diseases? *American Journal of Ophthalmology*, 2011, 152(3), 332–339.
18. Prskavec F., Fulmek R., Klemen C., and Stelzer N.: Veränderungen des Gesichtsfeldes und der Dunkeladaptation nach panretinaler Photokoagulation bei diabetischer Retinopathie. *Klinische Monatsblätter für Augenheilkunde*, 1986, 189(11), 385–387.
19. Royle P., Mistry H., Auguste P., et al.: The Landmark Trials: Diabetic Retinopathy Study and Early Treatment Diabetic Retinopathy Study. *NIHR Journals Library*, 2015.
20. No authors listed.: Comparison of the modified early treatment diabetic retinopathy study and mild macular grid laser photocoagulation strategies for diabetic macular edema. *Archives of Ophthalmology* 2007, 125(4), 469.
21. Alghadyan A. A.: Diabetic retinopathy – an update. *Saudi Journal of Ophthalmology* 2011, 25(2), 99–111.
22. Shah A. R., Gardner T. W.: Diabetic retinopathy: research to clinical practice. *Clinical Diabetes and Endocrinology*, 2017, 3(1).
23. Musat O., Cernat C., Labib M., Gheorghe A., Toma O., et al.: Diabetic macular edema. *Rom J Ophthalmol*, 2015, 59(3), 133–136.

24. Bloom S. M., Murphy S. F., Brier M. E.: Laser indirect ophthalmoscope photocoagulation and scleral depression for rhegmatogenous retinal detachment. *Retina*, 1995, 15(3), 224–232.
25. Dorin G.: Subthreshold and micropulse diode laser photocoagulation. *Seminars in Ophthalmology*, 2003, 18(3), 147–153.
26. Gawęcki M.: Micropulse laser treatment of retinal diseases. *Journal of Clinical Medicine*, 2019, 8(2), 242.
27. de Cilla S., Vezzola D., Farruggio S., Vujosevic S., Clemente N., et al.: The subthreshold micropulse laser treatment of the retina restores the oxidant/antioxidant balance and counteracts programmed forms of cell death in the mice eyes. *Acta Ophthalmologica*, 2018, 97(4), 559–567.
28. Frizziero L., Calciati A., Mideni G., Torresin T., Parrozzani R., et al.: Subthreshold micropulse laser modulates retinal neuroinflammatory biomarkers in diabetic macular edema. *Journal of Clinical Medicine*, 2021, 10(14), 3134.
29. Annan J. E., Carvounis P. E.: Current management of vitreous hemorrhage due to proliferative diabetic retinopathy. *International Ophthalmology Clinics*, 2014, 54(2), 141–153.
30. Bansal R., Dogra M., Chawla R., Kumar A.: Pars plana vitrectomy in uveitis in the era of microincision vitreous surgery. *Indian Journal of Ophthalmology*, 2020, 68(9), 1844.
31. Cruz-Inigo Y. J., Acaba L. A., Berrocal M. H.: Surgical management of retinal diseases: Proliferative diabetic retinopathy and traction retinal detachment., *Developments in ophthalmology*, 2014, 54, 196–203.
32. Mathis A., Pagot V., Malecaze F.: Hémorragies intra-vitréennes: attitudes thérapeutiques, vitrectomie. *Diabète & métabolisme*, 1993, 19(5), 436–440.
33. The Diabetic Retinopathy Vitrectomy Study Research Group.: Early vitrectomy for severe vitreous hemorrhage in diabetic retinopathy. two-year results of a randomized trial. *diabetic retinopathy vitrectomy study report 2. the diabetic retinopathy vitrectomy study research group. Archives of Ophthalmology*, 1985, 103(11), 1644–1652.
34. Stewart M., Browning D., Landers, M.: Current management of diabetic tractional retinal detachments. *Indian Journal of Ophthalmology*, 2018, 66(12), 1751.
35. Joussen A. M., Joeres S.: Benefits and limitations in vitreoretinal surgery for proliferative diabetic retinopathy and macular edema. In *Developments in Ophthalmology*, 2007, 69–87.

36. Mahmoud T., Oellers P.: Surgery for proliferative diabetic retinopathy: New tips and tricks. *Journal of Ophthalmic and Vision Research*, 2016, 11(1), 93.
37. Tan T.-E., Wong T. Y.: Diabetic retinopathy: Looking forward to 2030. *Frontiers in Endocrinology*, 2023, 13.
38. Frank R. N.: Potential new medical therapies for diabetic retinopathy: protein kinase c inhibitors. *American Journal of Ophthalmology*, 2002, 133(5), 693–698.
39. Stitt A. W., Curtis T. M., Chen M., Medina R. J., McKay G. J., et al.: The progress in understanding and treatment of diabetic retinopathy. *Progress in Retinal and Eye Research*, 2016, 51, 156–186.
40. Shen C.-Y., Lu C.-H., Wu C.-H., Li K.-J., Kuo Y.-M, et al.: The development of maillard reaction, and advanced glycation end product (AGE)-receptor for AGE (RAGE) signaling inhibitors as novel therapeutic strategies for patients with AGE-related diseases. *Molecules*, 2020, 25(23), 5591.
41. Melincovici C. S., Boşca A. B., Şuşman S., Mărginean M., Mişu C. et al.: Vascular endothelial growth factor (VEGF) - key factor in normal and pathological angiogenesis. *Romanian journal of morphology and embryology*, 2018, 59(2), 455–467.
42. Eldrid C., Zloh M., Fotinou C., Yelland T., Yu L., Mota F., et al.: VEGFA, b, c: Implications of the c-terminal sequence variations for the interaction with neuropilins. *Biomolecules*, 2022, 12(3), 372.
43. Madjedi K., Pereira A., Ballios B. G., Arjmand P., Kertes P. J., et al.: Switching between anti-VEGF agents in the management of refractory diabetic macular edema: A systematic review. *Survey of Ophthalmology*, 2022, 67(5), 1364–1372.
44. Mirshovkatovna, N.N., Faridovich, K.F., Tolibovich, S.T.: Use of anti-vegf drugs in diabetic retinopathy (literature review). *International Scientific Research Journal*, 2022, 3.
45. Amadio M., Govoni S., Pascale A.: Targeting VEGF in eye neovascularization: What's new? *Pharmacological Research*, 2016, 103, 253–269.
46. Arrigo A., Aragona E., Bandello F.: VEGF-targeting drugs for the treatment of retinal neovascularization in diabetic retinopathy. *Annals of Medicine*, 2022, 54(1), 1089–1111.
47. Chen E. R., Kaiser P. K.: Therapeutic potential of the ranibizumab port delivery system in the treatment of AMD: Evidence to Date. *Clinical Ophthalmology*, 2020, 14, 1349–1355.

48. Cai S., Yang Q., Li X., Zhang Y.: The efficacy and safety of aflibercept and conbercept in diabetic macular edema. *Drug Design, Development and Therapy*, 2018, 12, 3471–3483.
49. Liu K., Wang H., He W., Ye J., Song Y., et al.: Intravitreal conbercept for diabetic macular oedema: 2-year results from a randomised controlled trial and open-label extension study. *British Journal of Ophthalmology*, 2021, 106(10), 1436–1443.
50. Moisseiev E., Loewenstein A.: Abicipar pegol—a novel anti-VEGF therapy with a long duration of action. *Eye*, 2019, 34(4), 605–606.
51. Shirley M.: Faricimab: First approval. *Drugs*, 2022, 82(7), 825–830.
52. Dave V., Sharma R., Gupta C., Sur S.: Folic acid modified gold nano-particle for targeted delivery of sorafenib tosylate towards the treatment of diabetic retinopathy. *Colloids and Surfaces B: Biointerface*, 2020, 194.
53. Santonocito M., Zappulla C., Viola S., Rosa L. R. L., Solfato E., et al.: Assessment of a new nanostructured microemulsion system for ocular delivery of sorafenib to posterior segment of the eye. *International Journal of Molecular Sciences*, 2021, 22(9), 4404.
54. Chandrasekaran P. R., Madanagopalan V.: KSI-301: antibody bio-polymer conjugate in retinal disorders. *Therapeutic Advances in Ophthalmology*, 2021, 13.
55. Khanani A.M.: OPT-302 VEGF-C/D ”trap” molecule for AMD promising in Phase 2b, moves to Phase 3. *Modern Retina*, 2022, 2.
56. Singh R., Barden A., Mori T., Beilin, L.: Advanced glycation end-products: a review. *Diabetologia*, 2001, 44(2), 129–146.
57. Perrone A., Giovino A., Benny J., Martinelli F.: Advanced glycation end products (AGEs): Biochemistry, signaling, analytical methods, and epigenetic effects. *Oxidative Medicine and Cellular Longevity*, 2020, 1–18.
58. Safi S. Z., Qvist R., Kumar S., Batumalaie K., Ismail I. S. B.: Molecular mechanisms of diabetic retinopathy, general preventive strategies, and novel therapeutic targets. *BioMed Research International*, 2014, 1–18.
59. Stitt A.W.: The maillard reaction in eye diseases. *Annals of the New York Academy of Sciences*, 2005, 1043(1), 582–597.
60. Zong H., War M., Stitt A. W.: AGEs, RAGE, and diabetic retinopathy. *Current Diabetes Reports*, 2011, 11(4), 244–252.
61. Zeng C., Li Y., Ma J., Niu L., Tay, F. R.: Clinical/translational aspects of advanced glycation end-products. *Trends in Endocrinology and Metabolism*, 2019, 30(12), 959–973.

62. Oshitari T.: Advanced glycation end-products and diabetic neuropathy of the retina. *International Journal of Molecular Sciences*, 2023, 24(3), 2927.
63. Holstad M., Jansson L., Sandler S.: Inhibition of nitric oxide formation by aminoguanidine: An attempt to prevent insulin-dependent diabetes mellitus. *General Pharmacology: The Vascular System*, 1997, 29(5), 697–700.
64. Brouwers O., Niessen P. M., Haenen G., Miyata T., Brownlee M., et al.: Hyperglycaemia-induced impairment of endothelium-dependent vasorelaxation in rat mesenteric arteries is mediated by intracellular methylglyoxal levels in a pathway dependent on oxidative stress. *Diabetologia*, 2010, 53(5), 989–1000.
65. Thornalley P. J.: Use of aminoguanidine (pimagedine) to prevent the formation of advanced glycation endproducts. *Archives of Biochemistry and Biophysics*, 2003, 419(1), 31–40.
66. Luo D., Fan Y., Xu X.: The effects of aminoguanidine on retinopathy in STZ-induced diabetic rats. *Bioorganic & Medicinal Chemistry Letters*, 2012, 22(13), 4386–4390.
67. Voziyani P. A., Hudson B. G.: Pyridoxamine: The many virtues of a maillard reaction inhibitor. *Annals of the New York Academy of Sciences*, 2005, 1043(1), 807–816..
68. Ramis R., Ortega-Castro J., Caballero C., Casasnovas R., Cerrillo A., et al.: How does pyridoxamine inhibit the formation of advanced glycation end products? the role of its primary antioxidant activity. *Antioxidants*, 2019, 8(9), 344.
69. Metz T. O., Alderson N. L., Thorpe S. R., Baynes J. W.: Pyridoxamine, an inhibitor of advanced glycation and lipoxidation reactions: a novel therapy for treatment of diabetic complications. *Archives of Biochemistry and Biophysics*, 2003, 419(1), 41–49.
70. Stitt A., Gardiner T. A., Anderson N. L., Canning P., Frizzell N., et al.: The AGE inhibitor pyridoxamine inhibits development of retinopathy in experimental diabetes. *Diabetes*, 2002, 51(9), 2826–2832.
71. Hanssen N. M., Stehouwer C. D., Schalkwijk C. G.: Methylglyoxal stress, the glyoxalase system, and diabetic chronic kidney disease. *Current Opinion in Nephrology and Hypertension*, 2019, 28(1), 26–33.
72. Rabbani N., Thornalley P. J.: Glyoxalase in diabetes, obesity and related disorders. *Seminars in Cell Developmental Biology*, 2011, 22(3), 309–317.
73. Giacco F., Du X., D’Agati V. D., Milne R., Sui G., et al.: Knockdown of glyoxalase 1 mimics diabetic nephropathy in nondiabetic mice. *Diabetes*, 2013, 63(1), 291–299.
74. Brouwers O., Niessen P. M., Haenen G., Miyata T., Brownlee M., et al.: Hyperglycaemia-induced impairment of endothelium-dependent vasorelaxation in rat

mesenteric arteries is mediated by intracellular methylglyoxal levels in a pathway dependent on oxidative stress. *Diabetologia*, 2010, 53(5), 989–1000.

75. Brouwers O., Vos-Houben J., Niessen P., Miyata T., Nieuwenhoven F., et al.: Mild oxidative damage in the diabetic rat heart is attenuated by glyoxalase-1 overexpression. *International Journal of Molecular Sciences*, 2013, 14(8), 15724–15739.
76. Hudson B. I., Lippman M. E.: Targeting RAGE signaling in inflammatory disease. *Annual Review of Medicine*, 2018, 69(1), 349–364.
77. Reddy V. P., Aryal P., Soni P.: RAGE inhibitors in neurodegenerative diseases. *Biomedicines*, 2023, 11(4), 1131.
78. Ma S., Nakamura Y., Hisaoka-Nakashima K., Morioka N.: Blockade of receptor for advanced glycation end-products with azeliragon ameliorates streptozotocin-induced diabetic neuropathy. *Neurochemistry International*, 2023, 163, 105470.

NON-IMAGING DIAGNOSIS OF INFECTIVE ENDOCARDITIS - CHALLENGES AND GUIDELINES

Katarzyna Jania

Medical University of Warsaw

INTRODUCTION

Infective endocarditis (IE) is an infection that affects the endothelium of the heart. Although the incidence of this illness is relatively low, ranging from 3 to 10 cases per 100,000 of the population, its mortality rate within 30 days can be severe, reaching up to 30% [1,2]. Typically, IE is induced by bacteria, with *Staphylococcus aureus* being the predominant causative agent. Fungal infections also do occur, although they are somewhat less common [3]. The disease predominantly affects individuals with pre-existing structural heart conditions and is increasingly prevalent among those who have been in contact with healthcare facilities, particularly those with intravascular prosthetic devices or materials [4].

Due to its nonspecific symptoms, changing epidemiology and diverse clinical presentation, diagnosing IE remains challenging, despite ongoing improvements in disease management [4,5]. At the time of writing, there are several readily available diagnostic methods that can be helpful in IE diagnostics. Those include imaging techniques such as echocardiography, computed tomography (CT), magnetic resonance imaging (MRI) and nuclear imaging [6]. Additionally, one can also leverage microbiological diagnosis, relying on performing blood culture tests. While these methods provide a reasonable degree of certainty in detecting IE, statistically speaking, their diagnostic ability is not fully satisfactory [7].

PURPOSE

Given the existing challenges in diagnosing IE and the limited availability of comprehensive diagnostic approaches, this paper aims to provide a focused review of IE diagnostic methods, with a particular emphasis on non-imaging techniques. The objective is to establish a set of practical guidelines for effective disease detection. The reason for prioritizing non-imaging diagnostics is twofold. Firstly, these methods demonstrate a superior ability to

identify pathogens [5,7]. Secondly, they are more readily accessible in various healthcare settings, encompassing blood cultures, serological tests and clinical evaluation. These factors have influenced the decision to narrow the scope of this work to this specific area, in order to provide more concise and actionable conclusions.

METHODS USED

Taking into account the low incidence rate of IE, the absence of broad randomized trials and limited number of meta-analyses available, this paper relies on a comprehensive review of existing literature for findings. To identify the most relevant and reliable evidence, an extensive literature search was conducted using databases such as PubMed. The search was performed for articles published between January 1st, 2010, and May 30th, 2023, with a specific focus on non-imaging IE diagnostics. In order to provide an accurate view, publications were selected based on their citation rates and currency to ensure the inclusion of the most up-to-date knowledge on the topic of IE.

DISCUSSION

Diagnosis

Infective endocarditis (IE) can manifest in various forms, including acute infections, as well as subacute or chronic diseases characterized by nonspecific symptoms, which pose challenges in accurately diagnosing the condition. The most common presenting symptoms observable in approximately 80-90% of patients include fever, night sweats, fatigue as well as weight and appetite loss [3,8]. Additionally, the majority of patients exhibit heart murmurs [8]. Embolic complications are observed in about 25% of patients and these can manifest in various organs such as the brain, lung, or spleen [3]. Vascular and immunological phenomena, such as splinter hemorrhages, Roth spots, and glomerulonephritis, may also occur, although less frequently [9].

Laboratory findings

Elevated levels of inflammatory and immunological indicators may increase the probability, yet do not unequivocally confirm the presence of infective endocarditis. These biomarkers are not included in the main diagnostic criteria because they can be altered in other pathological states of function, e.g., sepsis or myocarditis [10]. The indicators which may also

point to sepsis or IE are the levels of leucocytosis/leucopenia, the number of immature white cell forms, procalcitonin and CRP concentration, ESR and markers of end-organ dysfunction (lactatemia, elevated bilirubin, thrombocytopenia and changes in the serum creatinine concentration) [11].

Microbiological diagnosis

Blood culture-positive infective endocarditis

Blood cultures are the standard test for determining the etiology of infective endocarditis [12]. Positive blood culture results are crucial for identifying the typical microorganisms causing the disease. To perform the test, it is necessary to collect three blood samples, each 10 ml in volume, from different venipuncture sites at 30-minute intervals. The first and last samples should be drawn at least 1 hour apart [13]. These samples should be incubated under both aerobic and anaerobic conditions [14]. It is important to collect the blood samples before administering antibiotics [12].

To minimize the risk of contamination and ensure accurate result interpretation, it is recommended to obtain blood samples from peripheral veins rather than central venous catheters. All procedures should follow aseptic non-touch techniques.

Extending the incubation time for difficult-to-cultivate microorganisms is generally not recommended, as current culture systems contain specialized media that facilitate growth. For incubating microorganisms like *Candida*, HACEK organisms and *Brucella*, a 5-day period is typically sufficient [12].

After identifying the microorganisms, blood culture tests should be repeated after a 48-72 hour period to assess treatment effectiveness. The initial assessment of the samples is based on the Gram staining method. For identifying atypical or fastidious organisms, longer investigation periods may be necessary [15]. However, the process can be expedited by using rapid bacteria identification procedures based on peptide spectra obtained by matrix-assisted laser desorption ionization time-of-flight mass spectrometry [15]. While interpreting the results it ought to be remembered that a single positive blood culture cannot with certainty identify the exact pathogen causing the IE [12].

Blood culture-negative infective endocarditis

Negative blood culture test results for infective endocarditis present a significant diagnostic and therapeutic challenge. When no microorganism can be grown using the commonly utilized blood culture method, it indicates a negative result. This situation occurs in approximately 2-40% of investigated cases [12]. Several factors can contribute to a negative

test result, such as alternative etiology of the infection (e.g., fungi or fastidious bacteria) and previous antibiotic administration. If antibiotics have been administered, they ought to be stopped so that the blood cultures may be taken during an antibiotic-free period. The recommended time for this is approximately 7-10 days [12].

The most common causes of negative blood cultures in cases of IE are *C. burnetii* and *Bartonella* species [12]. In order to identify the microorganism, systematic serological testing can be employed for *Aspergillus spp.*, *Bartonella spp.*, *Brucella spp.*, *Coxiella burnetii*, *Legionella pneumophila* and *Mycoplasma pneumoniae* [16].

PCR (polymerase chain reaction) and real-time PCR are more sensitive and specific than blood and tissue cultures for detecting microorganisms associated with infective endocarditis [17]. These tests can detect a broader range of microorganisms. However, due to their high cost, PCR tests are not commonly used for diagnostic purposes.

Specific PCR tests can confirm the presence of *Tropheryma whipplei*, *Bartonella spp.*, *Candida spp.* and *Aspergillus spp.* in cases of IE [16]. Common causative organisms of IE include *Streptococcus gallolyticus*, *Streptococcus mitis*, *Enterococci*, *Staphylococcus aureus*, *Escherichia coli* and fastidious bacteria [18]. If patients undergo valve surgery for endocarditis, PCR analysis of valve tissue can identify the infecting organism in most cases. Broad-range PCR of whole blood is not recommended due to its very low sensitivity. A negative PCR result may be due to various factors, such as poor performance of the PCR test or incorrect material provided for the test [17].

If microbiological test results turn out to be negative, it is still necessary to perform additional tests for antinuclear antibodies, anti-DNA antibodies, rheumatoid factor, as well as antiphospholipid syndrome and anti-B2-glycoprotein antibodies [12].

Microbiological diagnostic algorithm in suspected infective endocarditis

When suspecting infective endocarditis, the diagnostic scope needs to be expanded to include blood cultures and systemic serological testing for *Coxiella burnetii*, *Bartonella henselae*, *Bartonella quintana*, *Legionella pneumophila*, *Brucella spp.* and *Mycoplasma spp.*, as well as testing for *Aspergillus spp.* [3]. In cases where the serological test results are negative, a blood PCR test should be conducted for *Staphylococcus aureus*, *Tropheryma whipplei*, fungi, *Escherichia coli*, *Streptococcus gallolyticus*, *Streptococcus mitis* and *Enterococcus* [12]. If the PCR test results are negative, additional serological tests for antiphospholipid syndrome, antinuclear antibodies, anti-pork antibodies, and rheumatoid factor need to be performed [19]. Comparing the fast broad-range 16S rDNA PCR/sequencing test to Gram stain and culture, the former exhibits superior sensitivity in identifying the underlying bacterial pathogen in both

native and prosthetic valve endocarditis [20]. However, if the test results are positive, a specific PCR test should be conducted to confirm the validity of the findings.

Histological diagnosis

Histopathological examination remains one of the gold standards for the diagnosis of infective endocarditis. It is performed following the surgical removal of cardiac valves or embolic fragments to diagnose infective endocarditis [18]. Under the microscope, the histopathological findings vary depending on the causative pathogen. Endocarditis caused by *Staphylococcus aureus* often presents as acute inflammation with extensive neutrophilic infiltration, large colonies and tissue destruction. In cases involving less virulent bacteria, the healing process can be observed, including fibrin deposition and the presence of mononuclear inflammatory cells [21]. Chronic inflammation is seen in endocarditis caused by *Bartonella* species, *Coxiella burnetii*, or *Tropheryma whippelii*. Macrophages may be observed in cases of *Tropheryma whippelii* and *Coxiella burnetii* infections. Fungal etiology of IE may show a widely spread fungal mass around the vegetation site without visible infiltration of inflammatory cells [22].

Hematoxylin and eosin staining methods can visualize basophils and eosinophils but may not always identify the specific pathogen. Therefore, a panel of stains is used, including Gram stain and Grocott-Gomori methenamine silver stain. Tissue Gram stain is employed to recognize bacteria on cardiac valves. Additional stains such as Warthin-Starry stain (for *Bartonella*), Ziehl-Neelsen stain (for *Mycobacterium*), periodic acid-Schiff stain (PAS, for *Tropheryma whippelii*), and organism-specific immunohistochemical stains are used to facilitate identification [12]. Histopathology is also necessary for ANCA-induced infective endocarditis [23].

Diagnostic criteria & clinical features

The clinical recognition of infective endocarditis relies on the application of the modified Duke criteria [3]. These criteria encompass clinical, echocardiographic and biological findings, as well as the results of blood cultures and serologies [4]. The overall sensitivity of the modified Duke criteria is 80%; however, the sensitivity is notably lower in cases of prosthetic valve endocarditis or implantable electronic device infections [3]. To enhance the sensitivity of the modified Duke criteria, imaging modalities such as cardiac/whole-body CT

scan, cerebral MRI, 18F-FDG Positron emission tomography (PET) and radiolabeled leukocyte single-photon emission computed tomography (SPECT) can be utilized [24].

The modified Duke criteria confirm the diagnosis of IE when the pathological and clinical criteria meet 2 major criteria, or 1 major and 3 minor criteria, or 5 minor criteria [4,24]. The presence of IE may be ruled out in cases where a firm alternate diagnosis is proposed, symptoms disappear after 4 days of antibiotic therapy, there is no pathological evidence of IE during surgery or autopsy after the use of antibiotics for up to 4 days, or when none of the criteria are met [3].

CONCLUSION

The objective of this paper was to conduct a comprehensive review of non-imaging diagnostic methods for infective endocarditis and provide a thorough overview of the guiding principles for disease detection. A wide range of literature and existing studies has been analyzed to derive clear and actionable recommendations for IE detection. The findings underscore the significance of blood cultures and present a step-by-step diagnostic algorithm for cases involving suspected infective endocarditis.

It is important to acknowledge that the analytical approach employed in this study has certain limitations, as it relies solely on existing publications. The lack of proprietary research diminishes the strength of the conclusions and should be addressed in future investigations. Furthermore, new publications should explore the synergies between imaging and non-imaging diagnostic methods to assess how their combined utilization can enhance patient outcomes.

REFERENCES

1. Mostaghim AS, Lo HYA, Khardori N. A retrospective epidemiologic study to define risk factors, microbiology, and clinical outcomes of infective endocarditis in a large tertiary-care teaching hospital. *SAGE Open Medicine*, 2017, 13;5:2050312117741772
2. Iung B. Endocardite infectieuse. *Épidémiologie, physiopathologie et anatomopathologie* [Infective endocarditis. Epidemiology, pathophysiology and histopathology]. *La Presse Médicale*, 2019, 48(5), 513-521.
3. Rajani R, Klein JL. Infective endocarditis: A contemporary update. *Journal of Clinical Medicine (Lond)*. 2020, 20(1), 31-35.
4. Holland TL, Baddour LM, Bayer AS, Hoen B, Miro JM, Fowler VG Jr. Infective endocarditis. *Nature Reviews Disease Primers*, 2016, 1(2), 16059.

5. Cahill TJ, Baddour LM, Habib G, Hoen B, Salaun E, Pettersson GB, Schäfers HJ, Prendergast BD. Challenges in Infective Endocarditis. *Journal of the American College of Cardiology*, 2017, 24, 69(3), 325-344.
6. Hubers SA, DeSimone DC, Gersh BJ, Anavekar NS. Infective Endocarditis: A Contemporary Review. *Mayo Clinic Proceedings*, 2020, 95(5), 982-997.
7. Khaledi M, Sameni F, Afkhami H, Hemmati J, Asareh Zadegan Dezfuli A, Sanae MJ, Validi M. Infective endocarditis by HACEK: a review. *Journal of Cardiothoracic Surgery*. 2022, 19, 17(1), 185.
8. Yakut K, Ecevit Z, Tokel NK, Varan B, Ozkan M. Infective Endocarditis in Childhood: a Single-Center Experience of 18 Years. *Brazilian Journal of Cardiovascular Surgery*. 2021, 1, 36(2), 172-182.
9. Ruddy SM, Bergstrom R, Tivakaran VS. Roth Spots. *StatPearls*. Treasure Island (FL): StatPearls Publishing; 2023, 29494053, <https://www.ncbi.nlm.nih.gov/books/NBK482446/>, Accessed 30 May 2023.
10. Covino M, De Vita A, d'Aiello A, Ravenna SE, Ruggio A, et al. New Clinical Prediction Rule for Infective Endocarditis in Emergency Department Patients With Fever: Definition and First Validation of the CREED Score. *Journal of the American Heart Association*, 2023, 2, 12(9), e027650.
11. Yu CW, Juan LI, Hsu SC, Chen CK, Wu CW, Lee CC, Wu JY. Role of procalcitonin in the diagnosis of infective endocarditis: a meta-analysis. *American Journal of Emergency Medicine*, 2013, 31(6), 935-941.
12. Liesman RM, Pritt BS, Maleszewski JJ, Patel R. Laboratory Diagnosis of Infective Endocarditis. *The Journal of Clinical Microbiology*, 2017, 55(9), 2599-2608.
13. Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Tleyjeh IM, et al.; American Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and Stroke Council. Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications: A Scientific Statement for Healthcare Professionals From the American Heart Association. *Circulation*. 2015, 13, 132(15), 1435-1486.
14. Kamde SP, Anjankar A. Pathogenesis, Diagnosis, Antimicrobial Therapy, and Management of Infective Endocarditis, and Its Complications. *Cureus*. 2022, 15, 14(9), e29182.

15. La Scola B, Raoult D. Direct identification of bacteria in positive blood culture bottles by matrix-assisted laser desorption ionisation time-of-flight mass spectrometry. *PLoS One*. 2009, 25, 4(11), e8041.
16. Şimşek-Yavuz S, Akar AR, Aydoğdu S, Berzeg-Deniz D, Demir H, Hazirolan et al. Consensus Report on Diagnosis, Treatment and Prevention of Infective Endocarditis by Turkish Society of Cardiovascular Surgery (TSCVS), Turkish Society of Clinical Microbiology and Infectious Diseases (KLIMIK), Turkish Society of Cardiology (TSC), Turkish Society of Nuclear Medicine (TSNM), Turkish Society of Radiology (TSR), Turkish Dental Association (TDA) and Federation of Turkish Pathology Societies (TURKPATH) Cardiovascular System Study Group. *Türk Göğüs Kalp Damar Cerrahisi Dergisi*. 2020, 23, 28(1), 2-42.
17. Faraji R, Behjati-Ardakani M, Moshtaghioun SM, Kalantar SM, Namayandeh SM, Soltani M, Emami M, Zandi H, Firoozabadi AD, Kazeminasab M, Ahmadi N, Sarebanhassanabadi M. The diagnosis of microorganism involved in infective endocarditis (IE) by polymerase chain reaction (PCR) and real-time PCR: A systematic review. *Kaohsiung Journal of Medical Sciences*. 2018, 34(2), 71-78.
18. Gauduchon V, Chalabreysse L, Etienne J, Célarde M, Benito Y, Lepidi H, Thivolet-Béjui F, Vandenesch F. Molecular diagnosis of infective endocarditis by PCR amplification and direct sequencing of DNA from valve tissue. *Journal of Clinical Microbiology*, 2003, 41(2), 763-766.
19. Schirone L, Iaccarino A, Saade W, D'Abramo M, De Bellis A, Frati G, Sciarretta S, Mestres CA, Greco E. Cerebrovascular Complications and Infective Endocarditis: Impact of Available Evidence on Clinical Outcome. *BioMed Research International*, 2018, 30, 2018, 4109358
20. Miller RJ, Chow B, Pillai D, Church D. Development and evaluation of a novel fast broad-range 16S ribosomal DNA PCR and sequencing assay for diagnosis of bacterial infective endocarditis: multi-year experience in a large Canadian healthcare zone and a literature review. *BMC Infectious Diseases*. 2016, 12, 16, 146.
21. Tong SY, Davis JS, Eichenberger E, Holland TL, Fowler VG Jr. *Staphylococcus aureus* infections: epidemiology, pathophysiology, clinical manifestations, and management. *Clinical Microbiology Reviews*. 2015, 28(3), 603-661.
22. Yuan SM. Fungal Endocarditis. *Brazilian Journal of Cardiovascular Surgery*. 2016, 31(3), 252-255.

23. Shi XD, Li WY, Shao X, Qu LM, Jiang ZY. Infective endocarditis mimicking ANCA-associated vasculitis: does it require immunosuppressive therapy?: A case report and literature review. *Medicine (Baltimore)*. 2020, 17, 99(29), e21358.
24. Pecoraro AJK, Herbst PG, Pienaar C, Taljaard J, Prozesky H, Janson J, Doubell AF. Modified Duke/European Society of Cardiology 2015 clinical criteria for infective endocarditis: time for an update? *Open Heart*. 2022, 9(1), e001856.

REVIEW OF SELECTED IMMUNOLOGICAL ASPECTS OF PLANT-BASED DIETS

Adam Szwed¹, Krzysztof Gomulka²

1. Student Scientific Group of Adult Allergology, Wrocław Medical University, Wrocław, Poland
2. Department of Internal Medicine, Pneumology and Allergology, Wrocław Medical University, Wrocław, Poland

ABBREVIATION LIST

- PBD – plant-based diet
- PBF – plant-based food
- PBMS – plant-based milk substitute

INTRODUCTION

As plant-based diet (PBD) continues to maintain considerable popularity worldwide, being one of the most prominent dietary models, more efforts are put into studying its impact on human health [1].

Plant-based diets are often referred to as vegan, as in veganism which is a practice and philosophy associated with abstaining from animal-derived products not only in diet but also in other areas of consumption including clothing or entertainment [2, 3].

Therefore, in this article, only the term ‘plant-based’ will be used meaning a dietary model which relies on plant-based foods (PBFs including fruits, vegetables, whole grains, legumes, nuts, and seeds) while excluding animal foods such as red meat, fish, poultry, dairy, and eggs. This model differs from traditional omnivorous diets and presents novel solutions and challenges that researchers are actively exploring in conjunction with the advancements in medical and dietary sciences.

This article aims to review selected immunological aspects of plant-based dietary models, including their role in supporting the immune system, their impact on asthma, and the allergenicity of plant-based milk substitutes. The health outcomes discussed in this article related to PBDs should not be interpreted as achievable solely through complete adherence to

plant-based diets but rather as a result of specific dietary features that usually constitute PBDs, such as increased or decreased intake of certain food products.

PLANT-BASED FOODS AS NATURAL IMMUNE BOOSTERS

Plant-based diets promote high intakes of fruits and vegetables. The nutrients present in PBFs are long known to play a significant role in maintaining the function of the immune system [4,5].

Vitamin C (L-ascorbic acid) is a crucial micronutrient with antioxidant properties that benefits the immune system. It is found in various sources such as citrus fruits, strawberries, potatoes, kiwi, tangerine, red capsicum, tomato juice, broccoli, and mango. Vitamin C supports the innate and adaptive immune systems by maintaining the function of the epithelium and protecting the skin from oxidative stress. It also enhances the activity of phagocytes, which is important in the elimination of microorganisms. Additionally, vitamin C aids in the differentiation and multiplication of type B and T lymphocytes. Insufficient vitamin C can lead to weakened immunity and increased susceptibility to infections [4, 5].

Vitamin A, known as an anti-inflammatory agent, supports immune function and protects the integrity of epithelial tissues. It is found in plant sources like carrots, pumpkins, papaya, and mangoes. Vitamin A is crucial for both innate and adaptive immunity, aiding in the development of immune cells and enhancing the cellular and humoral immune responses. A deficiency of vitamin A can impair the immune system's ability to respond to infections and compromise mucosal barrier function [6].

Vitamin E, specifically alpha-tocopherol, is a fat-soluble antioxidant that plays a vital role in regulating immune function. It is abundant in plant oils like sunflower, corn, soybean and walnut, as well as in vegetables such as spinach, red pepper, avocado, mango, pumpkin, and kale. Vitamin E helps protect immune cells and regulates inflammatory mediators, thereby modulating the function of T cells. Adequate vitamin E intake strengthens the immune system, reducing the risk of infections, especially in older individuals [7, 8].

Vitamin B6 is essential for the production of red blood cells and immune system cells. It is found in PBFs such as oats, bananas, wheat germ, soybeans, and peanuts. Vitamin B6 facilitates neurotransmitter synthesis, including serotonin, and supports normal brain function. It also enhances the immune response by promoting antibody production, lymphocyte growth, and communication among cytokines and chemokines. These vitamins play crucial roles in

supporting the immune system and can be obtained from a variety of PBFs, contributing to overall health and well-being.

PLANT-BASED DIETS AND ASTHMA

Asthma is a chronic pulmonary disease involving airway inflammation, remodeling, and airways hyperresponsiveness associated with IgE-mediated response to environmental factors [10, 11]. Diets that prioritize the consumption of fruits, vegetables, and whole grains, while reducing the intake of high-fat meats and dairy products, have demonstrated an association with a lower likelihood of asthma. A 2015 case-control study conducted on Peruvian children with asthma reported decreased asthma risk with higher consumption of fruits, vegetables, legumes, cereals, pasta, rice, and potatoes, as well as reduced intake of meat. Additionally, a similar dietary pattern has been observed to lead to a reduction in the lifetime diagnosis of asthma among children [12,13,14].

Systemic inflammation is known to have a negative impact on clinical outcomes in patients suffering from asthma. Diets centered on plant-based products are recognized as reducing levels of inflammation-mediating molecules while activating anti-inflammatory agents. Unsaturated fatty acids and antioxidants present in PBFs are observed to attenuate inflammation and conditions driven by a systemic inflammatory response and contribute to improvements in FEV₁ (forced expiratory volume in the first second) and FVC (forced vital capacity) [15,16,17]. Nonetheless, further research including more case-control studies is needed to deepen the understanding of the association between dietary patterns and asthma symptoms.

ALLERGENICITY OF PLANT-BASED MILK SUBSTITUTES

Plant-based milk substitutes (PBMS) are water-soluble extracts from oil seeds, nuts, legumes, and cereal that are presented as an alternative for bovine and other mammalian milk, aimed at consumers following PBD. Among other reasons for considering them as an option, such as problems of diets rich in cholesterol, changing lifestyles towards veganism, and negative environmental impacts of dairy production, it also implied that PBMS is suitable for individuals suffering from lactose intolerance and cow's milk protein allergy [18]. However, a recent study conducted by Vojdani et al. indicates that these products are not without risk of allergic reaction. The researchers examined 500 patients' sera for IgE, IgG, and IgA antibodies

against different kinds of mammalian milk and PBMS (including almond, soy, and coconut-based products). Most of the samples that presented increased IgE-mediated reactivity to cow's milk were observed to be highly reactive with goat's milk (79%), sheep's milk (71%), and camel's milk (58%) but also with PBMS made from almond (67%) and soy (63%), however only 29% presented increased reactivity against coconut milk. Individuals with immunological reactivity to cow milk protein, while reported to have an increased risk of experiencing immunological reactivity to goat, sheep, or camel milk, presented no statistically significant likelihood of immunological reactivity to almond, soy, or coconut milk substitutes. Despite PBMS being acknowledged as viable alternatives to mammalian milks with lower allergic reactivity, a limited number of individuals were found to potentially exhibit strong allergies to these products. Notably, among the three tested products, the coconut milk substitute demonstrated the lowest allergenic and antigenic properties. For accurate identification of milks to be avoided in cases of true cow's milk allergy, the most effective approach would involve precise testing of IgE, IgG, and IgA antibodies in the blood [19].

CONCLUSIONS

Plant-based diets remain a subject of interest for both consumers and researchers, warranting further investigation into their health outcomes. However, the existing literature on the effects of fully restrictive PBDs on the immune system is limited, highlighting the need for additional research to expand our understanding in this area. Given the potential health benefits associated with plant-based diets, it is crucial to rely on evidence-based dietary models to maintain a healthy and balanced diet that fulfills all necessary nutrient requirements [20].

REFERENCES

1. Kamiński M., Skonieczna-Żydecka K., Nowak J.K., Stachowska E. Global and local diet popularity rankings, their secular trends, and seasonal variation in Google Trends data. *Nutrition*, 2020, 79-80, 110759,
2. Dutkiewicz J., Dickstein J. The Ism in Veganism: The Case for a Minimal Practice-based Definition. *Food Ethics*, 2021, 6(2), 1-19.
3. Ostfeld R.J.: Definition of a plant-based diet and overview of this special issue. *Journal of Geriatric Cardiology*, 2017, 14(5), 315.
4. García-Closas R., Berenguer A., Tormo M.J., et al. Dietary sources of vitamin C, vitamin E and specific carotenoids in Spain. *British Journal of Nutrition*, 2004, 91(6),

- 1005-1011.
5. Carr A.C., Maggini S.: Vitamin C and Immune Function. *Nutrients*. 2017, 3, 9(11), 1211.
6. Stephensen C.B. Vitamin A, infection, and immune function. *Annual review of nutrition*, 2001, 21(1), 167-192.
7. Schneider C.. Chemistry and biology of vitamin E. *Molecular nutrition & food research*, 2005, 49(1), 7-30.
8. Lewis E.D., Meydani S.N., Wu D., 2019. Regulatory role of vitamin E in the immune system and inflammation. *Journal of the International Union of Biochemistry and Molecular Biology life*, 2019, 71(4), 487-494.
9. Stover P.J., Field M.S. Vitamin B-6. *Advances in Nutrition*, 2015, 6(1), 132-133.
10. Tota M., Łacwik J., Laska J., et al. The Role of Eosinophil-Derived Neurotoxin and Vascular Endothelial Growth Factor in the Pathogenesis of Eosinophilic Asthma. *Cells*, 2023, 12(9), 1326.
11. Sinyor B., Concepcion Perez L.: Pathophysiology Of Asthma [In:] StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK551579/> Accessed 30 May 2023.
12. Rice J.L., Romero K.M., Galvez Davila R.M. et al. Association between adherence to the Mediterranean diet and asthma in Peruvian children. *Lung*, 2015, 193, 893-899.
13. Guglani L., Joseph C.L. Asthma and diet: could food be thy medicine?. *Indian Pediatrics*, 2015, 52, 21-22.
14. Lv N., Xiao L., Ma J., Dietary pattern and asthma: a systematic review and meta-analysis. *Journal of Asthma and Allergy*, 2014, 12(7), 105-121.
15. Schwingshackl L., Hoffmann G. Mediterranean dietary pattern, inflammation and endothelial function: a systematic review and meta-analysis of intervention trials. *Nutrition, Metabolism and Cardiovascular Diseases*, 2014, 24(9), 929-939.
16. Widmer R.J., Flammer A.J., Lerman L.O., Lerman A. The Mediterranean diet, its components, and cardiovascular disease. *The American Journal of Medicine*, 2015, 128(3), 229-238.
17. Schünemann H.J., Grant B.J., Freudenheim J.L. et al. The relation of serum levels of antioxidant vitamins C and E, retinol and carotenoids with pulmonary function in the general population. *American journal of respiratory and critical care medicine*, 2001, 163(5), 1246-1255.

18. Rasika D.M., Vidanarachchi J.K., Rocha R.S., et al. Plant-based milk substitutes as emerging probiotic carriers. *Current Opinion in Food Science*, 2021, 38, 8-20.
19. Vojdani A., Turnpaugh C., Vojdani E. Immune reactivity against a variety of mammalian milks and plant-based milk substitutes. *Journal of Dairy Research*, 2018, 85(3), 358-365.
20. Fehér A., Gazdecki M., Véha M., et al. A Comprehensive Review of the Benefits of and the Barriers to the Switch to a Plant-Based Diet. *Sustainability*, 2020, 12(10), 4136.

ROBOTIC VERSUS LAPAROSCOPIC APPROACH IN BARIATRIC SURGERY

Maja Mielczarek¹, Jan Sroczyński², Paulina Wójcik¹

1. Medicine, Faculty of Medicine, Wrocław Medical University,
2. Medicine, Faculty of Health and Medical Sciences, Kazimierz Pułaski University of Technology and Humanities in Radom

ABBREVIATION LIST

- WHO- World Health Organization
- BMI- Body Mass Index
- BPD- Biliopancreatic diversion
- DS- Duodenal switch
- VBG- Vertical banded gastroplasty
- RYGB- Roux-en-Y gastric bypass
- LVSG- Laparoscopic vertical sleeve gastrectomy
- MGB-OAGBP- Mini gastric bypass, one gastric bypass anastomosis
- LAGB- Laparoscopic adjustable gastric banding

INTRODUCTION

Obesity is a multifactorial disease that affects almost 60% of adults and one in three children in WHO European Region [1]. Its prevalence has significantly grown for the last 50 years and it has become an immensely important problem [2]. It is associated with multiple comorbidities such as hypertension, diabetes type 2, fatty liver disease and obstructive sleep apnea, which lead to decrease in life expectancy and its quality [1,3]. According to recent evaluations it is suggested to be the fourth most common risk factor for non communicable diseases in the Region [1]. It also increases a risk for multiple types of cancer [2].

Patients with obesity require individualized treatment. Bariatric surgery is one of the types of long term obesity treatment that has proven to be very effective. History of bariatric surgery dates back to 1950s and 1960s for managing severe hyperlipidemia [4].

Back then they were based on small bowel resection with anastomosis and associated

with high morbidity, mortality and failure rates [2].

Indications for metabolic surgery according to the American Society for Metabolic and Bariatric Surgery are BMI 30-34.9kg/m² with obesity-related comorbidities and a patient not being able to achieve substantial weight loss and comorbidities improvement with nonsurgical methods. Patients are recommended to be above the age of 18 and not older than 65. They shouldn't have psychiatric disorders and cognitive impairments in order to properly understand the consequences of the surgery and follow the recommendations after. Other contradictions are alcoholism, drug abuse and endocrine disorders [3]. According to studies comparing different bariatric procedures and no surgery, in terms of cost-effectiveness for patients with morbid obesity, surgery proved to be a significantly better option [5].

TYPES OF BARIATRIC SURGERY

There are various types of bariatric surgery that can be categorized as restrictive, malabsorptive and mixed.

Malabsorptive surgeries are based on bypassing a portion of the small intestine in order to limit absorption of nutrients [6]. They consist of surgeries such as biliopancreatic diversion (BPD) and duodenal switch (DS) [2]. They are very effective in achieving long-term weight loss. However, malabsorptive procedures aren't commonly chosen due to its technical complexity and significant complications following the surgery such as protein malnutrition or nutrient and vitamin deficiencies [7]. They are often reserved for patients with super morbid obesity (BMI>50) or severe metabolic disease [8].

Restrictive procedures reduce the size of the stomach, minimizing the portions of food that a patient can eat and feel full [6]. First restrictive surgeries were partial horizontal gastric division with greater curvature conduit. Alas due to dilatation of the gastric chamber and outlet they resulted in poor weight loss. Later a more successful method was introduced, called a vertical banded gastroplasty (VBG) [2]. It is based on dividing the stomach vertically creating a small proximal pouch and a small outlet channel. When the food is delivered to the proximal pouch of the stomach it distends its wall and stimulates the vagus nerve to send a signal of satiety to the hypothalamus regulating appetite [9]. Although promising, with time it also turned out to have serious side effects such as weight regain, band erosion, dysphagia and inability to tolerate solid foods [2]. Currently the most commonly performed in Europe, being considered a gold standard is Roux-en-Y Gastric Bypass (RYGB). It is especially beneficial for patients with gastroesophageal reflux and T2DM [6]. It has several mechanisms of action

including nutrient restriction, hormonal and neuronal manipulation [2]. Roux-en-Y anastomosis prevents bile reflux, commonly experienced with different anastomosis configurations like Billroth II. During the procedure, a small pouch (15-30ml) is anastomosed to distal jejunum to bypass the bilio-pancreatic secretions. Average excessive weight loss is reported to be 55-60% in addition to reductions and remissions of type 2 diabetes, hypertension and dyslipidemia [8].

In the United States however, RYGB was recently overtaken by a new method-laparoscopic vertical sleeve gastrectomy (LVSG). It has been rapidly growing in popularity, in spite of absence of proven long-term efficacy [3]. The number of LVSG grew from 17,8% in 2011 to 61,4% of all bariatric procedures performed in 2018. LVSG is based on removing 70-80% of the stomach to lower its capacity and achieve satiety earlier and reduce food intake. It is also proven to have several hormonal effects. It decreases production of ghrelin, which is responsible for increasing hunger and inhibiting insulin production [10]. It is believed to increase the production of glucagon-like-peptide-1, peptide YY and pancreatic polypeptide that leads to decreased hunger and calorie intake. Average long-term excess weight loss is estimated to be around 60% [10]. The major superiority of LVSG over RYGB is the technical simplicity and palatability to patients [3]. The operative time is significantly shorter making it safer for high-risk patients [11].

Mini gastric bypass or one gastric bypass anastomosis (MGB-OAGBP) is another rising technique, now being the most commonly performed bariatric procedure in the world [3]. It is a relatively short and effective surgery with great long-term weight loss results and patient satisfaction [12]. MGB is technically simpler and reversible compared to RYGB. It combines the merits of SG and RYGB with creating one omega-loop gastro-jejunal anastomosis [13]. Nevertheless there are multiple controversies as to whether MGB should be a recommended procedure. Some studies suggest that the omega mounting predisposes to bile reflux in the gastric bag that leads to ulcers and higher risk of protein and lipid malabsorption [3]. Surgical technique should be chosen depending on the goal of the treatment, cardiovascular risk, experience of the operating team and digestive, esophagogastric pathology [6]. We can also divide bariatric surgeries into primary and revisional. Revisional surgeries play an important role in management of weight regain and complications of primary procedures [14].

LAPAROSCOPY IN BARIATRIC SURGERY

Laparoscopic approaches were introduced to bariatrics only in the last 5 years of the 20th century. Years from 1998 to 2003 are believed to be the time of The Bariatric Revolution

in the United States [4]. They are believed to be one of the most technically challenging laparoscopic procedures that require advanced skills like suturing [15]. Qualifications like that are measurably hard to acquire during residency training. Studies suggest that it takes at least 75 to 100 cases for the surgeon to obtain proper skills to perform Roux-en-Y gastric bypass [15]. The difficulty in minimally invasive surgery is the hand-eye coordination within the two dimensional view, when there is no depth perception. This problem was solved with the invention of the 3D cameras that provide better depth perception, and improve accuracy, making procedures safer and easier for the operator [16].

Laparoscopy has undoubtedly transformed the field of bariatric surgery with better outcomes, lesser invasiveness and postoperative complications. It has gained huge popularity with the introduction of a laparoscopic adjustable gastric banding procedure (LAGB) in 1994 [4].

LAGB has the lowest perioperative risk compared to other bariatric procedures and it is reversible. Although effective it also has a high number of reoperations [17].

The same year as LAGB, the first laparoscopic RYGB was performed. However revolutionary, because of the complexity of the procedure it took several years for it to be implemented in the common practice [4].

Laparoscopic approach's major advantages are decrease in wound related complications and incisional hernias. Patients experience less pain, better recovery, fewer respiratory complications and their stay at the hospital is shorter [4]. However there are some limitations to laparoscopic surgeries, which can be amplified when operating obese patients. Those include space challenges, caused by increased liver size, intra-abdominal fat and thick abdominal wall. In these conditions it is challenging to handle manual instruments used in laparoscopy. Obesity is a risk factor that can also lead to difficulties during anesthesia [18].

According to some studies, with the advance of the surgical techniques, the risk associated with laparoscopic bariatric procedures can be compared to those of laparoscopic cholecystectomies or hysterectomies, which are some of the most basic surgeries. However there is a group of patients that are susceptible to a more complicated course of this treatment. People who have a history of extensive abdominal surgeries or revision have significantly higher risk of morbidity and mortality. For this reason, many surgeons, even with great experience, are reluctant to operate on these patients [19].

In the same study it is suggested that patients with these risk factors should not be denied access to bariatric surgery. It is proposed that for very complex, highly selected patients staging laparoscopy can be a key to proper decision making process and surgical planning [19].

ROBOTIC BARIATRIC SURGERY

The concept of robotic surgery has existed since the late 1970s. This technology has been evolving rapidly ever since, leading to invention of the da Vinci robot, which currently is the most commonly used robotic system worldwide [20]. Robotic-assisted surgery was first introduced to bariatrics in 1999 [18]. Major technological superiorities of robotic surgery over laparoscopy are 3-dimensional interface, tremor filtration, improved wrist motion freedom, motion scaling and improved ergonomics. The 3D stereotactic vision and 7 degrees of freedom of instruments gives the operator the ability to dissect in narrow spaces and enables him to perform accurate intracorporeal suturing [21]. Improved visualization and manipulation of tissue enables the main surgeon to be less dependent on surgical assistants [22]. Better ergonomics deals with problems such as prolonged operative times with unnatural body postures and positioning of the trocars associated with laparoscopic surgery. Robotic surgery allows neutral posture and comfortable seating [22].

A research comparing groups of muscles activated during both of those approaches using electromyography proved that operating on a laparoscopic platform is associated with higher muscle activation in multiple muscle groups [23]. Another advantages of a robotic approach are shorter hospital stay, lower levels of postoperative pain and faster recovery [18]. Robotic surgery itself is not associated with any specific surgery-related complications. Difficulties usually arise due to equipment malfunctioning or inadequate surgical skills [22]. Robotic platform in RYGB enables a completely hand-sewn gastrojejunostomy and jejunajejunostomy. It also leads to lower anastomotic stricture rates [18]. However, many surgeons, despite the possible benefits of robotic surgery, still prefer the classic laparoscopic approach because of its proven clinical benefits, no requirement of a complex setup and smaller cost [24]. As with most of the new technologies, robotic procedures are significantly more expensive than traditional laparoscopy [3]. Higher cost and lack of haptic feedback are major impediments to robotic surgery becoming a standard procedure, especially in general surgery [20]. Docking the device and hand sewing anastomosis can also result in longer operative time than traditional laparoscopy.

CONCLUSION

Both laparoscopy and robotic surgery have been evolving and improving in the field of bariatrics over the years, making bariatric procedures significantly safer, easier and resulting in

lower levels of complications. The studies comparing these techniques in bariatric surgery are sadly still inconclusive. [24] The evidence supporting the superiority of robotic bariatric surgery has not been well documented yet, but it is suggested that robotic technology can shorten the learning curve of RYGB. The current data also confirms non-inferiority of robotic approach [18].

REFERENCES

1. WHO European Regional Obesity Report 2022. <https://apps.who.int/iris/bitstream/handle/10665/353747/9789289057738-eng.pdf>, Accessed 30 May 2023.
2. Phillips B., Shikora S. The history of metabolic and bariatric surgery: Development of standards for patient safety and efficacy, *Metabolism*, 2018, 79, 97–107.
3. Lueasma J., Fernando J., Cantarero I., et al. Surgical Treatment of Obesity. Special Mention to Roux-en-Y Gastric Bypass and Vertical Gastrectomy, *Frontiers in Endocrinology*, 2022, 31;13:867838.
4. Schirmer B., Watts S. Laparoscopic bariatric surgery, *Surgical Endoscopy*, 2006, 20, 450-455.
5. Alsumali A., Egualé T., Bairdain S., Smnaliev M. Cost-Effectiveness Analysis of Bariatric Surgery for Morbid Obesity, *Obesity Surgery*, 2018, 28(8), 2203-2214.
6. Pineda E., Sanchez-Romero L., Brown M., et al. Forecasting Future Trends in Obesity Across Europe: The Value of Improving Surveillance, *Obesity Facts*, 2018, 11(5), 360-371.
7. Mason R. Duodenal Switch for Morbid Obesity. Is it Safe?, *Advances in Surgery*, 2013, 47, 153-176.
8. Lim C., Jahansouza C., Abraham A., et al. The future of the Roux-en-y gastric bypass., *Expert Review of Gastroenterology & Hepatology*, 2016, 10(7), 777-784.
9. Doherty C. Vertical Banded Gastroplasty, *Surgical Clinics of North America*, 2001, 81(5), 1097-1112.
10. Climaco K., Ahnfeldt E. Laparoscopic Vertical Sleeve Gastrectomy, *Surgical Clinics of North America*, 2021, 101(2), 177-188.
11. Chung A., Thompson R., Overby D., et al. Sleeve Gastrectomy: Surgical Tips, *Journal of Laparoendoscopic & Advanced Surgical Techniques*, 2018, 28(8), 930-937.
12. Ruthledge R., Kular K., Manchanda N. The Mini-Gastric Bypass Original Technique, *International Journal of Surgery*, 2018, 61, 38-41.

13. Wang F., Yan W., Yan M., Song M., Outcomes of Mini vs Roux-en-Y gastric bypass: A meta-analysis and systematic review, *International Journal of Surgery*, 2018, 56, 7-14.
14. Fulton C., Sheppard C., Birch D., Karmali S., de Gara C. A comparison of revisional and primary bariatric surgery, *Canadian Journal of Surgery*, 2017, 60(3), 205-211.
15. Curet M. Bariatric Surgery, *The American Journal of Surgery*, 2011, 201(2), 266-268.
16. Padin E., Santos R., Fernandez S., et al. Impact of Three-Dimensional Laparoscopy in a Bariatric Surgery, *Obesity Surgery*, 2017, 27(10), 2552-2556.
17. Beitner M., Kurian M. Laparoscopic adjustable gastric banding, *Abdominal Radiology*, 2012, 37(5), 687-689.
18. Jung M., Hagen M., Buchs N. et al. Robotic bariatric surgery: A general review of the current status, *The International Journal of Medical Robotics and Computer Assisted Surgery*, 2017, 13(4).
19. Sudlow A., Roux., Hardwick R., Pournaras D. The role of staging laparoscopy in complex bariatric surgery, *Clinical Obesity*, 2021, 11, 4.
20. Leal Ghezzi T., Campos Corleta O. 30 Years of Robotic Surgery, *World Journal of Surgery*, 2016, 40(10), 2550-2557.
21. Dreifuss N., Mangano A., Hassan C., Masrur M. Robotic Revisional Bariatric Surgery: A High-Volume Center Experience, *Obesity Surgery*, 2021, 31, 1656-1663.
22. Jara R., Guerron A., Portenier D. Complications of Robotic Surgery, *Surgical Clinics of North America*, 2020, 100(2):461-468.
23. Rodriguez Z., Zihni A., Ohu I. et al. Ergonomic analysis of laparoscopic and robotic surgical task performance at various experience levels, *Surgical Endoscopy*, 2018, 33(6), 1938-1943.
24. Toro J., Lin E., Patel A. Review of robotics in foregut and bariatric surgery, *Surgical Endoscopy*, 2014, 29(1), 1-8.

LAPAROSCOPIC GROIN HERNIA REPAIR

Maja Mielczarek¹, Julia Wodniakowska¹, Paulina Wójcik¹, Jan Sroczyński²

1. Medicine, Faculty of Medicine, Wrocław Medical University,
2. Medicine, Faculty of Health and Medical Sciences, Kazimierz Pułaski University of Technology and Humanities in Radom

ABBREVIATION LIST

- TAPP- Transabdominal Preperitoneal Procedure
- TEP- Total Extraperitoneal Procedure
- SILS- Single Incision Laparoscopic Surgery
- IPOM- Intraperitoneal Onlay Mesh Repair

INTRODUCTION

Groin hernia is one of the most common surgical diseases caused by a defect in the abdominal wall [1]. It is one of the most common reasons for a patient's admission to a surgical ward. Around 20 million patients are operated annually for groin hernias [2]. Estimated lifetime risk of a groin hernia is around 27% for men and 3% for women [3]. They can be divided into femoral and inguinal hernias. Inguinal hernia is an opening in the myofascial plain of oblique and transversus abdominis muscle. Inguinal hernias can be either direct or non-direct [4]. Groin hernias can be asymptomatic or present with pain in the groin area, feeling of burning, gurgling or aching that can worsen with prolonged physical activity [5]. They usually present as a reversible lump in the inguinal area [6]. Hernias can lead to serious complications such as strangulation, intestinal obstruction and infarction [7].

GROIN HERNIA REPAIR

Groin hernia repair is one of the most basic and frequent surgical procedures. There are multiple techniques and approaches for this surgery that have been evolving for years [8]. Procedures vary in terms of complications, recurrence rates and postoperative pain [4]. The operations are based on closing the defect in the abdominal wall by suturing or with addition of

a mesh [3]. They can be performed with an open or laparoscopic approach. Indications for the surgery involve all symptomatic hernias, however in some cases of asymptomatic or minimally bothersome hernias can be left under observation [4].

First attempt at laparoscopic hernia repair was taken in Germany in 1979, using a transabdominal clip adaptation of hernia edges [9].

TRANSABDOMINAL PREPERITONEAL PROCEDURE (TAPP)

Transabdominal Preperitoneal Procedure is a laparoscopic groin hernia repair technique introduced and reported in 1991 by Aregui [8]. An initially complex surgery was further developed and standardized, currently being a procedure possible to be performed even by surgical trainees [10]. During this procedure, hernia is repaired fully intraperitoneally which provides a panoramic view of the myopectineal orifice and a possibility to detect unsuspected collateral hernia [11]. On the contrary to Total Extraperitoneal Procedure (TEP) in which the peritoneal cavity is not fully entered, TAPP has no major technical or operative space constraints [11]. Another major benefit of the TAPP procedure is the possibility to perform bilateral hernia repair during one operation [4]. TAPP approach is characterized by minimal tissue trauma, rapid recovery and quick return to work of the patients [12]. Operation is based on incising the peritoneum from cephalad to the inguinal floor, dissecting the hernia defect and placing a mesh covering the direct, indirect and femoral spaces [8]. Before placing the working ports, it is necessary to evaluate the anatomical findings on both sides, regardless of the preoperative findings [13]. Careful initial dissection of the peritoneum gives the operator a proper view of the area of repair and contains of the sac. It is also very important to remember and be careful operating around the areas called a “Triangle of Doom” and “Triangle of Pain”. In the “Triangle of Doom” it is possible to injure epigastric vessels, which can be a very dangerous complication. “Triangle of Pain” on the other hand contains cutaneous nerves [13]. Other postoperative complications that can occur are scrotal swelling, urinary retention, surgical site infection and mesh infection. Nevertheless they are significantly less common and serious than in open surgeries [4]. According to meta-analysis TAPP is associated with less chronic inguinal pain than open Lichtenstein method [14]. There are also notably less recurrences after TAPP in comparison to the traditional open approach [4]. Most important disadvantages of TAPP and other laparoscopic repairs over open approach are prolonged operative time and steep learning curve [12].

TOTAL EXTRAPERITONEAL PROCEDURE TEP

Extraperitoneal approaches for laparoscopic groin hernia repair were also invented in early 1990s in order to avoid complications associated with entering peritoneal cavity. First performed procedure was the Stoppa repair based on laparoscopically inserting a preperitoneal prosthetic mesh [8]. Total Extraperitoneal Procedure was first performed by Duluq in 1992 [15]. It is a technically challenging technique due to the complexity of the anatomical location and limited space [16]. The success of the surgery depends on multiple factors including correct dissection, hernia characteristics, surgeon's skills and patient's anatomy [16]. In TEP technique, preperitoneal space is entered with a CO₂-supported trocar or a balloon dissector. The mesh is placed flat on the peritoneum beyond the anterior superior iliac spine [9]. There is no evidence against or for fixing the mesh in terms of recurrence frequency, but some studies point out that fixing them can lead to higher amounts of complications [15]. The biggest importance during TEP is a proper technical use of the fascial structures by the surgeon. The quality of the dissection also depends on the condition of the tissue in the working area [16]. It can be performed under general or spinal anesthesia. The foremost advantage of TEP over TAPP is not entering the peritoneal cavity with a risk of injuring meticulous nerves, vessels and intestines [17]. It also reduces the risk of post-site hernia and postoperative adhesion [16]. TEP is believed to enable shorter recovery time and hospital stay as well as less postoperative pain [15]. An often encountered problem in TEP is the leakage of CO₂ into the peritoneal cavity which compresses the space and limits visualization in the operating site. [9] In some cases, when the peritoneum is violated during the surgery it is recommended to convert the procedure into TAPP [4]. TEP can also be found more challenging in patients after previous lower abdominal laparotomy and in cases of previous extraperitoneal surgeries, totally excluded [9]. Standardized technique is described to be very similar to TAPP, however the learning curve in TEP seems to be longer [16].

SINGLE INCISION LAPAROSCOPIC SURGERY SILS

Single Incision Laparoscopic Surgery is a relatively new surgical technique currently growing in popularity. It is accepted to be even less invasive than conventional laparoscopy [18].

Single port access's major benefit is a possibility of a "scarless surgery" and better

aesthetic results. Both TEP and TAPP approaches can be performed with SILS modification [19]. Apart from being superior in cosmetic area, some studies prove that SILS can be safely performed on hernias that are irreducible or incarcerated, which is traditionally considered a contraindication for laparoscopic surgery. First SILS TEP procedure was performed in 2008 [20]. Trans-umbilical single-incision TAPP (SILS TAPP) however was first reported 2 years later in 2010 by Rahman and John [18]. SILS approach is still being evaluated but so far shows no major intra- or postoperative comorbidities and higher recurrence rate, showing much potential in future trends for treating inguinal hernias [18].

INTRAPERITONEAL ONLAY MESH REPAIR IPOM

Another possible approach for laparoscopic inguinal hernia repair is an Intraperitoneal Onlay Mesh Repair IPOM procedure. In this technique a mesh is sutured directly on the peritoneum from the intraperitoneal space. It can be especially beneficial for patients who have previously undergone abdominal surgeries like prostatectomy resulting in adhesions [21]. When scarring, peritoneal defect or fibrosis are present on the abdominal wall in the proximity of the internal inguinal ring TAPP or TEP can be difficult to perform and IPOM can be a good alternative [22]. Several studies prove that IPOM is a feasible, safe and effective survey for recurrent and bilateral inguinal hernias [23]. It has shown to be faster and easier than other laparoscopic approaches like TAPP and TEP [24]. It is suggested that IPOM could be a suitable option for young males and heavy duty workers [23]. However there are also researches that claim that this method should be avoided due to causing chronic neuropathic pain [22].

ROBOTIC INGUINAL HERNIA REPAIR

Robotic hernia repair is becoming more popular and being used by skilled surgeons around the world. During an operation, the surgeon sits at the console and directs the robotic arms to perform the procedure. The robot enables making precise, controlled, small, 1-2 cm incisions, with their prior visualization. In addition, the robot directly and seamlessly translates the surgeon's natural hand, wrist and finger movements from the controls to the surgical instruments inside the patient. Furthermore, the robotic system used for this purpose allows for the procedure to be performed in 10x magnification, increased maneuverability, three-dimensional views, enhanced endowrist dexterity and a shorter learning curve [25,26]. There

is still a lack of multicenter randomized controlled trials comparing robotic, open, and laparoscopic techniques. However, it is emphasized that robotic hernia repair is a safe and efficient technique with a short learning curve. Moreover, studies indicate a lower rate of complications and a lower rate of readmissions compared to the laparoscopic and open surgery methods, respectively [27]. Additionally, robot-assisted inguinal hernia repair appears to result in reduced trauma to the body, less scarring, less postoperative pain, and also a lower risk of nerve damage and the development of chronic pain [28,29,30,31]. However, not all studies conducted so far confirm this analysis [27]. In contrast, the robotic approach is thought to be connected with longer operative time and longer room time compared to the laparoscopic approach [28]. Moreover, the biggest disadvantage of performing robotic surgery at this point is the cost. This makes this technique not yet widely used in the world. However, it seems to be only a matter of time.

CONCLUSIONS

Groin hernia repair is a commonly performed surgical procedure that can be done using an open or laparoscopic approach. Both the TAPP and TEP procedures have their advantages and disadvantages, and the choice of the appropriate method depends on the surgeon's preferences, experience, and the individual anatomy of the patient. Both techniques carry a risk of complications, including postoperative pain, surgical site infection, bleeding, and hernia recurrence. TEP (video-assisted method) results in less severe pain and fewer intra-abdominal complications and is technically easier to perform [32].

On the other hand, TAPP (laparoscopic method) provides better visualization and anatomical assessment, as well as greater standardization of equipment among laparoscopic instrument manufacturers, but it comes with higher costs [32,33].

A major advantage of TAPP is minimal tissue trauma, rapid recovery, and quick return to work for patients [12].

According to meta-analysis, TAPP is associated with a lower risk of chronic inguinal pain compared to the traditional Lichtenstein method [14].

Currently, laparoscopic TAPP with the use of a biological mesh appears to be the most promising technique in adults [34].

However, advanced modern operative techniques, including both TAPP and TEP, may raise concerns about previously unknown long-term consequences [35].

REFERENCES

1. Shakil A., Aparicio K., Barta E., Munez K., Inguinal Hernias: Diagnosis and Management, American Family Physician, 2020, 102(8), 487-492.
2. HerniaSurge Group, International guidelines for groin hernia management, Hernia 2018, 22, 1, 1-165.
3. Smith S., Khoja A., Jacobsen J., et al, Mesh versus non-mesh repair of groin hernias: a rapid review, ANZ Journal of Surgery, 2022, 92(10), 2400-2763.
4. Hammoud M., Gerken J., StatPearls, Inguinal Hernia, 2022, <https://www.ncbi.nlm.nih.gov/books/NBK513332/>, Accessed 30 May 2023.
5. LeBlanc K., LeBlanc L., LeBlanc K.A., Inguinal hernias: diagnosis and management, American Family Physician, 2013, 87, 12, 844-848
6. O'Rourke M., O'Rourke T., Inguinal hernia: aetiology, diagnosis, post-repair pain and compensation, ANZ Journal of Surgery, 2011, 82(4), 201-206
7. Purkayastha S., Chow A., Athanasiou T., Darzi A., Inguinal hernia, BMJ Clinical Evidence, 2008, 16, 2008:0412.
8. Crawford D., Phillips E. Laparoscopic Repair and Groin Hernia Surgery, Surgical Clinics of North America, 1998, 78(6), 1047-1062.
9. Leibl B., Jager C., Kraft B., Kraft K., Schwarz J., et al., Laparoscopic hernia repair-TAPP or/and TEP?, Langenbeck's Archives of Surgery, 2005, 390, 2.
10. Bittner R., Die evidenzbasierte TAPP-Technik [Evidence-based TAPP technique], Die Chirurgie, 2017, 88(4), 281-287.
11. Aiolfi A., Cavalli M., Del Ferraro S., Manfredini L., Lombardo F. et al. Total extraperitoneal (TEP) versus laparoscopic transabdominal preperitoneal (TAPP) hernioplasty: systematic review and trial sequential analysis of randomized controlled trials., Hernia, 2021, 25(5), 1147–1157.
12. Ahmad S., Aslam R., Ifitkhar M., et al. Early Outcomes of Laparoscopic Transabdominal Preperitoneal TAPP Repair, Cureus, 2023, 15, 2.
13. Lotz J. Inguinal Hernia- The Practicalities of TAPP Repair, Acta Chirurgica Belgica, 2009, 109, 2.
14. Scheuermann U., Niebisch S., Lyros O., Jansen-Winkeln B., Gockel I. Transabdominal Preperitoneal (TAPP) versus Lichtenstein operation for primary inguinal hernia repair – A systematic review and meta-analysis of randomized controlled trials, BMC Surgery, 2017, 17, 1.

15. Łomnicki J, Leszko A., Kuliś D., Szura M., Folia Medica Cracoviensa, Current treatment of the inguinal hernia- the role of the totally extraperitoneal (TEP) hernia repair, 2018, 58(3), 103-114.
16. Zhou X., Luo J., Huang H., Wang Y., Zhang H. Totally Extraperitoneal Herniorrhaphy (TEP): Lessons Learned from Anatomical Observations, Minimally Invasive Surgery, 2021, 2021, 5524986.
17. Huang L., Kang Y., Do TEP and TAPP have similar effect on postoperative pain?, Hernia, 2021, 25(5):1401-1402.
18. Chen Q., Chen K., Huang D., Pan Y., Yan J., et al., Trans-umbilical single-incision laparoscopic trans-abdominal pre-peritoneal hernioplasty of inguinal hernia by self-made glove port., Medicine (Baltimore), 2020, 21, 99, 34.
19. Yussra Y., Sutton P., Kosai N., Razman J., Mishra R., et al, Single incision laparoscopic surgery (SILS) inguinal hernia repair - recent clinical experiences of this novel technique, Clinical Therapeutics, 2013, 164(5), 425-428.
20. Ye Q., Chen Y., Zhan X., Zhu J., The Superior Inguinal Ligament Approach of Single Incision Laparoscopic Surgery for Total Extraperitoneal Inguinal Hernia Repair, Journal of Laparoendoscopic & Advanced Surgical Techniques, 2017, 27(12), 1290–1292.
21. Ohuchi M., Inaki N., Nagakari K., Kohama S., Sakamoto K., Ishizaki Y., Surgical Procedures and Results of Modified Intraperitoneal Onlay Mesh Repair for Inguinal Hernia After Radical Prostatectomy, Journal of Laparoendoscopic & Advanced Surgical Techniques, 2020, 30(11), 1189-1193.
22. Hanada K., Narita M., Goto K., Okada H., Okura K. et al. Chronic inguinal pain after laparoscopic intraperitoneal onlay mesh (IPOM) repair for inguinal hernia treated successfully with laparoscopic selective neurectomy: A case report., International Journal of Surgery Case Reports, 2017, 38, 172–175.
23. Catani M., De Milito R., Pietroletti R., Chiaretti M., Spaziani E., et al. Is there a place for intraperitoneal onlay mesh repair (IPOM) of inguinal hernia among laparoscopic techniques? Hepatogastroenterology, 2004, 51(59), 1387-1392.
24. Catani M., De Milito R., Materia A., Chiaretti M., Spaziani E., et al., Ernioplastica inguinale laparoscopica "IPOM" con Dual-Mesh [Laparoscopic inguinal hernia repair "IPOM" with Dual-Mesh]., Annali Italiani di Chirurgia, 2003, 74(1), 53-60.

25. Aiolfi A, Cavalli M, Micheletto G. et al. Robotic inguinal hernia repair: is technology taking over? Systematic review and meta-analysis. *Hernia*, 2019, 23, 509–519.
26. Pirolla E., Patriota G., Pirolla F. et al., Inguinal repair via robotic assisted technique: literature review. *Arquivos Brasileiros de Cirurgia Digestiva*, 2018, 31, 1408.
27. Qabbani A., Aboumarzouk O., ElBakry T., Al-Ansari A., Elakkad M., Robotic inguinal hernia repair: systematic review and meta-analysis, *ANZ Journal of Surgery*, 2021 91(11), 2277-2287.
28. Waite K., Herman M., Doyle P. Comparison of robotic versus laparoscopic transabdominal preperitoneal (TAPP) inguinal hernia repair, *Journal of Robotic Surgery*, 2016, 10(3), 239-244.
29. Cunha-E-Silva J., Oliveira F., Ayres A., Iglesias A. Conventional inguinal hernia repair with self-fixating mesh versus totally extraperitoneal laparoscopic repair with polypropylene mesh: early postoperative results, *Revista de Colegio Brasileiro de Cirurgioes*, 2017, 44(3), 238-244.
30. Iraniha A., Peloquin J. Long-term quality of life and outcomes following robotic assisted TAPP inguinal hernia repair, *Journal of Robotic Surgery*, 2018, 12(2), 261-269.
31. Kleidari B., Mahmoudieh M., Yaribakht M., Homaei Z., Mesh fixation in TAPP laparoscopic hernia repair: introduction of a new method in a prospective randomized trial., *Surgical Endoscopy* , 2014, 28(2), 531-536.
32. Nguyen H. Laparoscopic inguinal herniorrhaphy. In: Cameron J, Cameron A. *Current Surgical Therapy*. Philadelphia: Elsevier Saunders, 2014: 1325-1334
33. Mongelli F., Ferrario di Tor Vajana A., FitzGerald M., Cafarotti S., Lucchelli M., et al, Open and Laparoscopic Inguinal Hernia Surgery: A Cost Analysis., *Journal of Laparoendoscopic and Advanced Surgical Techniques*, 2019, 29, 608–613.
34. Yasukawa D., Aisu Y., Hori T. Crucial anatomy and technical cues for laparoscopic transabdominal preperitoneal repair: advanced manipulation for groin hernias in adults, *World Journal of Gastrointestinal Surgery*, 2020, 12, 307–325.
35. Kane E., Leduc M., Schlosser K., Parentela N., Wilson D. et al., Comparison of peritoneal closure versus non-closure in laparoscopic trans-abdominal preperitoneal inguinal hernia repair with coated mesh., *Surgical Endoscopy*, 2018, 32, 627–637.

CURRENT APPROACH IN POSTOPERATIVE MANAGEMENT OF PATIENTS AFTER BARIATRIC SURGERY- AN OVERVIEW OF GUIDELINES

Maria Greniuk¹, Maria Łuszcz², Paula Hauzer¹, Jakub Cisek¹, Mateusz Mierniczek¹, Michał Łabuda¹, Przemysław Kubicki¹

1. Wrocław Medical University
2. Medical College Jan Kochanowski University of Kielce

ABBREVIATION LIST

- WHO - World Health Organization
- BMI - Body Mass Index
- WHR – Waist - Hip Ratio
- ASMBS - American Society for Metabolic and Bariatric Surgery
- IFSO - International Federation for the Surgery of Obesity and Metabolic Disorders
- NIH - National Institutes of Health
- ADA - American Diabetes Association
- ERABS - Enhanced Recovery After Bariatric Surgery
- LoE - Level of Evidence
- PONV - Postoperative nausea and vomiting
- LMWH - Low molecular weight heparin
- LOS - Length of Stay

INTRODUCTION

Obesity is a complex medical condition characterized by excessive accumulation of body fat that poses a threat to a person's health. Obesity is commonly measured by the body mass index (BMI), which is calculated by dividing a person's weight in kilograms by the square of his or her height in meters [1].

According to the World Health Organization (WHO), overweight is defined as a BMI $>25 \text{ kg/m}^2$ and obesity as a BMI $30 > \text{kg/m}^2$ [1].

Table 1 Body mass index

Weight status	BMI
Underweight	Below 18.5
Normal range	18.5-24.9
Overweight	25.0-29.9
Obese class I	30.0-34.9
Obese class II	35.0-39.9
Obese class III	Above 40.0

Another indicator used in practice is the WHR (waist-hip ratio), which is a simple measure of central obesity, or excessive fat accumulation in the abdominal region. In determining WHR, we measure the narrowest point at the waist and the widest point at the hips, and then divide the waist circumference by the hip circumference. The resulting WHR for women should not exceed 0.8; while for men it should not exceed 0.9 [2].

EPIDEMIOLOGY

In 2016, according to WHO [3], 1,900 million people worldwide were overweight and more than 650 million people were obese. In addition, most of the world's human population lives in countries where overweight and obesity have caused more deaths than poverty and underweight. Therefore, due to the rapid increase in the number of obese people, and the prevalence worldwide, obesity has been called the pandemic of the 21st century. In addition, epidemiological studies have shown an association of increasing body weight with increased risk of morbidity, decreased quality of life and decreased life expectancy [4]. Obesity is associated with a higher incidence [1] of:

- cardiovascular disease,
- cancer (breast, endometrial, ovarian, cervical, colon, rectal, kidney),
- type 2 diabetes,
- chronic renal failure,
- venous thromboembolism,
- arthritis,
- back pain,

- polycystic ovarian syndrome,
- sleep apnea,
- social and psychological problems.

Therefore, it is important to treat obesity as soon as possible.

TREATMENT METHODS

Patient care [5] should begin with a comprehensive assessment and the development of an individualized weight control plan. It is also important to create an environment that is aware of and supportive of the patient's goal of gradual weight loss. The next step should be lifestyle modification, including the introduction of a balanced diet, physical activity, adequate sleep and avoidance of excessive stress. Pharmacotherapy of obesity is also possible for patients with a BMI ≥ 30 kg/m² or ≥ 27 kg/m² with type 2 diabetes, hypertension or dyslipidemia. The final step in therapy is bariatric surgery. Treatment of obesity should not be limited to only one method. An individualized approach to each patient, in addition to a non-pharmacological approach, may require pharmacological and surgical treatment [5].

SURGICAL TREATMENT

Bariatric surgery is an important and integral part of the overall treatment of patients with morbid obesity. It has been found to be the most effective treatment [5]. Therefore, a multispecialty team of experts has created guidelines for the surgical treatment of obesity. Bariatric surgery is indicated for patients aged 18-60 years who meet the following criteria:

- BMI ≥ 40 kg/m²
- BMI 35-40 kg/m² with comorbidities such as metabolic disorders (type 2 diabetes mellitus), cardiorespiratory diseases, severe (advanced) joint disease, psychological problems related to obesity, dyslipidemia, obstructive sleep apnea. These diseases must be obesity-dependent, that is, the disorder is expected to improve after surgically induced weight loss.
- BMI 30-35 kg/m² indications for surgical treatment are determined individually depending on the type of comorbidities.

In contrast, patients over the age of 60 are qualified for surgical treatment after individual consideration of the advantages of such treatment and the risk of complications [6].

Weight reduction and a decrease in BMI below the value required for surgery according to the above criteria is not a contraindication to surgical treatment, as the highest documented BMI value in the past is taken into account. Contraindications to bariatric surgery include incurable diseases that lead to cachexia and are life-threatening in the short term, lack of cooperation from the patient, and inability to participate in long-term post-operative care (e.g., mental disorders, active alcohol or drug addiction, severe mental retardation).

Bariatric surgeries can be divided into 3 groups: restrictive - limiting the volume of food intake, e.g. sleeve gastrectomy which is the most common surgery performed, exclusionary - e.g. biliary-pancreatic exclusion and restrictive-exclusionary, e.g. gastrointestinal bypass and biliary-pancreatic exclusion with duodenal switch [6].

Morbid obesity is a lifelong condition. Therefore, bariatric surgery does not guarantee 100% treatment success. Studies have shown that some patients have failed to achieve weight loss after surgery, and in some cases have experienced re-growth [7]. A prerequisite for the effectiveness of surgical treatment of obesity is a permanent change in eating habits. Nutritional treatment after bariatric surgery consists of many stages and, regardless of the method of surgery used, involves a significant reduction in the energy value of the diet and changes in the type, consistency and size of meals [8]. Therefore, proper long-term and multispecialty postoperative care is necessary to maintain satisfactory treatment results. This includes, among other things, post-operative follow-up with assessment of metabolic and nutritional status, and explaining to the patient the nutritional changes that are necessary after surgery as well as in later life. However, in Poland, there are no clear guidelines explaining what such control and changes in eating habits after surgery should look like, so in our work we want to analyze the recommendations available in Poland, as well as internationally.

GUIDELINES FOR POSTOPERATIVE CARE OF PATIENTS AFTER BARIATRIC SURGERY

Although no uniform dietary guidelines have yet been developed in Poland after various types of bariatric surgery, recommendations on dietary principles are in use. In 2010, dietary recommendations were created at the University of Nevada with the collaboration of the American Dietetic Association for patients after bariatric surgery [9].

After surgery, the patient should receive intravenous rehydration fluids. Calorie-free fluids without sugar, caffeine or intense sweeteners, such as water or weak tea, are usually added within 1-2 days after surgery. These fluids should be consumed in small sips (15-30 ml)

in an amount tolerated by the body. Fluid intake should be about 1500-1900 ml/day. On the 3rd-7th day after surgery, the fluid supply can be increased to 1900 ml/day, taken at a rate of about 100 ml every hour [10].

Start introducing nutritional beverages (such as skimmed milk, soy milk, skimmed natural yogurt, vegetable juices, blended soups, broth). Protein powder should be added to nutritional fluids, but not more than 20 g per serving. During this period it is also necessary to introduce supplementation with vitamin and mineral preparations in the amount of 1 tablet twice a day [9].

From the 2nd from the 3rd week after surgery, the amount of recommended neutral fluids per day is maintained at up to 1,900 ml, while nutritional fluids should be replaced with solid, soft, moist, ground, low-fat, high-protein foods such as eggs, fish, poultry, lean meat, low-fat granular cheese, cooked beans. During this period, 4-6 meals of $\frac{1}{4}$ cup should be consumed and the daily serving of protein should be 60g. In week 4-6, it is recommended to gradually expand the diet by introducing cooked soft vegetables, soft peeled or canned fruits without added sugar. If the patient tolerates well, one soft solid meal should be included. Continue the supply of neutral fluids up to 1,900 ml per day, increase the volume of previously recommended meal amounts to $\frac{1}{2}$ cup, and take in 60-80 g of protein per day. It is important that at this stage fluids are given 30 min before or 30-60 min after the meal which is associated with minimizing the risk of early postprandial hypoglycemia, the so-called dumping syndrome (vomiting, bloating, diarrhea, dizziness, palpitations) [11].

Week 7 and beyond is the time for a gradual transition from a mushy diet to a solids diet. The daily menu should adjust the caloric value of the diet according to age, weight and height. Meals should be well balanced to consist of lean meat, fruits, vegetables and whole grain products. Three 1 cup meals and two snacks per day are advisable. On the other hand, according to dietary recommendations developed by the Department of General Surgery of the Jagiellonian University in Krakow and the Department of General and Transplant Surgery of the Warsaw Medical University, the total volume of ground food consumed during the day should not exceed 500 g and a single meal should not exceed 100-150 grams. The previously recommended amount and times of inert fluid intake are maintained. Raw fruits and vegetables high in dietary fiber should be avoided or eaten grated or well-cooked. A summary of foreign recommendations can be observed in table number 2.

A nutritional pyramid for bariatric surgery patients has been created, with mineral and vitamin supplementation, adequate fluid intake and daily physical activity at its base. The first level of the pyramid includes high-protein and low-fat products. At the second level, the authors

suggest low-energy products and vegetable fats (vegetables, fruits with low carbohydrate content). The third level of the pyramid contains starchy foods, while on the last level they find products that patients should avoid such as high-energy items containing saturated fat, cholesterol and sugars [12].

Table 2. nutritional guidelines in the early postoperative period

Period	Dietary Recommendations
Days 1-2	• Clear fluids (without carbohydrates and caffeine) • Gradually increase fluid intake to approximately 1500 ml per day
Days 3-7	• Fluids: Approximately 1500-1900 ml per day • Gradually introduce nutrient-rich beverages (skim milk, soy milk, low-fat plain yogurt, broth, vegetable juices, cream soups) • Whey protein or isolated soy protein (up to 20 g protein per serving) • Supplementation with vitamin and mineral supplements (1 tablet twice a day)
Week 2-3	• Fluids: Approximately 1500-1900 ml per day • Gradually replace fluids with soft, moist, ground low-fat, high-protein food items (eggs, fish, poultry, lean meat, low-fat cottage cheese, cooked beans) • Protein intake: 60 g per day • Consume 3-6 meals (meal volume around 1/4 cup)
Week 4-6	• Introduce cooked, soft vegetables and soft and/or peeled or canned fruits (without added sugar) • Include one solid meal/food item with a consistent texture • Consume 3-6 meals (meal volume around 1/2 cup) • Protein intake: 60-80 g per day • Fluids: Approximately 1500-1900 ml per day • Consume fluids 30 minutes before or 30-60 minutes after a meal
Week 7+	• Adjust the energy value of the diet according to the patient's growth, body weight, and age • Balanced meals (lean meat, dairy, fruits, vegetables, and whole-grain products) • Avoid raw fibrous fruits and vegetables (celery, corn, artichokes, pineapples, oranges) • Consume 5-6 meals (meal volume around 1 cup) • Clear fluids: Approximately 1500-1900 ml per day • Consume fluids 30 minutes before or 30-60 minutes after a meal

In 2022, ASMBS/IFSO guidelines on indications for metabolic and bariatric surgery emerged [13]. They replaced an official statement developed 30 years ago by the National Institutes of Health (NIH). The American Society for Metabolic and Bariatric Surgery

(ASMBS) has become the newest association of bariatric surgeons and integrated health care professionals in the United States. The International Federation for Surgery of Obesity and Metabolic Disorders (IFSO) currently represents 72 national societies and associations from around the world [8]. In 2016, a group of 45 medical societies led by the American Diabetes Association (ADA) presented a joint position statement recommending metabolic surgery as a possible management for patients with type 2 diabetes and a BMI in the range of 30-35 whose diabetes has not been sufficiently regulated despite optimal treatment. In 2022, The ADA developed "Standards of Medical Care in Diabetes - 2022," in which it also recommended the above recommendations for bariatric surgery [14].

Most useful for guiding post-operative care are the Enhanced Recovery After Bariatric Surgery (ERABS) guidelines, which were first published in 2016 and updated in 2022 [15]. A review article comparing the differences between the 2022 and 2016 guidelines has the potential to form a global consortium for bariatric research [16]. This work highlights the methodology for developing the ERABS guidelines and how research can be improved. The classification of recommendations highlighting the level of evidence (LoE) is extremely valuable. According to the researchers, the low level of evidence (LoE) remained low for postoperative care in terms of postoperative analgesia and postoperative oxygen therapy. Low LoE, which changed to high LoE, was reported for postoperative nausea and vomiting (PONV) and thromboprophylaxis. A moderate LoE, which remained moderate, was noted for early postoperative feeding. High LoE, which remained high, concerned postoperative analgesia, thromboprophylaxis, and postoperative oxygenation. The authors of the study emphasized that the description of the assessment was well graded, but there was no mention of what criteria were used to arrive at the assessment score [16]. The main postoperative guidelines considered in ERABS are discussed below.

Postoperative nausea and vomiting (PONV) occurs at a rate of 8-92%. ERABS recommends prevention of PONV [17], with a polypharmacologic approach preferred over monotherapy. A reduction in the incidence of PONV has been reported with the use of antiemetics, opioid analgesics and fluid infusions [18]. Thromboprophylaxis occurs after bariatric surgery in about 0.1-0.5% and in most cases after the patient is discharged home [19]. Multimodal thromboprophylaxis using chemoprophylaxis, mechanical aids and patient mobilization is suggested. Chemoprophylaxis with low-molecular-weight heparin (LMWH) after surgery and discharge home is considered effective. However, there is insufficient evidence to recommend a specific dose and duration of LMWH treatment [20].

An article published in *Surgical Endoscopy* 2020 examined the reduction in opioid use after implementing enhanced recovery after bariatric surgery (ERABS). According to ERABS, multimodal analgesia provides the most effective results in pain management, allowing lower doses of each drug to be administered. An important factor in ERABS is the objective assessment of pain intensity using contemporary graded rating scales [21]. Early postoperative mobilization is another key element for better postoperative recovery in ERABS. It is recommended in obese patients undergoing bariatric surgery [22]. The recommended time was at least 4 hours in the first 24 hours after surgery and was significantly associated with lower rates of postoperative complications and shorter length of stay (LOS) [23]. Early re-feeding has been reported in ERABS and appears to be particularly associated with earlier recovery of bowel function, faster wound healing, fewer infections and a lower risk of postoperative complications [24]. Compared to the conventional approach, ERABS reduces the length of hospital stay, which also reduces hospitalization costs. ERABS does not increase the risk of serious postoperative complications, reoperations and hospital readmissions. Unfortunately, the importance of contributions to international guidelines is not always matched by their implementation in different medical centers. ERABS results vary from medical center to medical center, and results are inconsistent.

In Italy, medical experts have leaned into this problem. The Italian Society for Surgery of Obesity and Metabolic Diseases and the Italian Society for Anesthesiology, Analgesia, Resuscitation and Intensive Care have joined to create an official statement on ERABS [25]. Another laparoscopic center developed its own implementation of the ERABS protocol [26]. The results were positive. The median length of hospital stay (LOS) was four days in the placebo group compared to two days in the group where the ERABS protocol was implemented ($p < .0001$). There were no significant differences in rates of postoperative complications, readmissions and mortality [26].

These examples demonstrate the importance not only of the guidelines themselves, but also of the cooperation of medical centers in establishing the highest possible level of service, care and protocol implementation.

CONCLUSIONS

There is no consensus on the postoperative management of patients after bariatric surgery. The purpose of this study was to collect and summarize different approaches to this topic. There are several recommendations in Polish and international guidelines that are often

repeated. The repeated guidelines concern basic examinations. It is recommended to attend follow-up visits to mainly assess the effects of weight reduction and to monitor the occurrence of postoperative complications [27]. It is important to assess the extent of microscopic deficiencies including vitamins. For this purpose, a blood count laboratory test is recommended [27]. A lipidogram and glycemic measurement should also be performed to monitor the course of obesity-induced diseases. The goal here is the gradual resolution of hypercholesterolemia and diabetes, where the criteria for diabetes remission should be in accordance with the guidelines of international diabetes societies (complete remission, partial remission, long-term remission) [13].

The most recent guidelines that address this topic were developed in 2022. ASMBS/IFSO guidelines introduced the recommendation of bariatric surgery as a way to treat type II diabetes and with a BMI in the range of 30-35, in which diabetes has not been sufficiently regulated despite optimal treatment [13]. An important management that should be implemented is also the assessment of the patient's diet, mentioned many times, and educating the patient about it. If we look at the management to prevent postoperative complications, they are primarily discussed in international recommendations. The most helpful here are the ERABS guidelines updated in 2022. It is important to place special emphasis on thromboprophylaxis during postoperative care. It is recommended to continue anticoagulant treatment for a minimum of 7 days after surgery, preferably with low molecular weight heparin. Early mobilization of the patient is important, preferably for 4h already within the first 24 hours after surgery [20], [23]. To control nausea and vomiting, according to the indications, polypharmacotherapy consisting of antiemetics, opioids and infusions is most beneficial [18]. The anesthesia used during surgery should be multimodal. This gives the most favorable results in reducing postoperative pain. Contemporary graded scales are recommended for its objective assessment [21]. Multimodal analgesia also reduces the length of postoperative hospital stay without increasing the risk of postoperative complications. Finally, one of the main recommendations should be the center's own postoperative patient assessment system, developed at each center based on the center's own outcomes and capabilities. There are centers that keep such records and share their results [25], [26].

Centers that perform bariatric surgery should keep records of patient outcomes and implement national and international management guidelines based on this. Such management brings the highest benefit to the patient as well as the medical center. We hope that our attention to the problem of the lack of clear-cut guidelines for the postoperative care of bariatric patients

will contribute to the establishment of a consensus on this issue and to the publication of guidelines in accordance with international standards.

REFERENCES

1. World Health Organization: The challenge of obesity in the WHO European Region and the strategies for response. <https://apps.who.int/iris/bitstream/handle/10665/326533/9789289014083-eng.pdf?sequence=1&isAllowed=y> Accessed: 15 Jul 2023.
2. Wąsowski M., Walicka M., Marcinkowska-Suchowierska E.: Otyłość - definicja, epidemiologia, patogeneza. *Postępy Nauk Medycznych*, 2013, 26(4), 301-306.
3. Gargallo Vaamonde J., Álvarez-Món M. A.: Obesity and overweight. *Medicine - Programa de Formación Médica Continuada Acreditado*, 2020, 13(14), 767–776.
4. Peeters A., Barendregt J. J., Willekens F., Mackenbach J. P., Abdullah Al Mamun A. et al.: Obesity in adulthood and its consequences for life expectancy: a life-table analysis. *Annals of Internal Medicine*, 2003, 138(1), 24–32.
5. Gossmann M., Butsch W. S., Jastreboff A. M.: Treating the Chronic Disease of Obesity. *Medical Clinics of North America*, 2021, 105(6), 983-1016.
6. Tarnowski W., Jaworski P.: Operacje bariatryczne w praktyce. *Gastroenterologia Kliniczna*, 2018, 10(3), 93-101.
7. Fred M., Hainer V., Basdevant A. et al.: Wytyczne europejskie w zakresie chirurgicznego leczenia otyłości olbrzymiej. *Endokrynologia, Otyłość i Zaburzenia Przemiany Materii*, 2009, 5 (3), 99–108.
8. Jastrzębska-Mierzyńska M., Ostrowska L., Wasiluk D., Konarzewska-Duchnowska E.: Dietetic recommendations after bariatric procedures in the light of the new guidelines regarding metabolic and bariatric surgery. *Roczniki Państwowego Zakładu Higieny*, 2015, 66(1), 13-19.
9. Kulick D., Hark L., Deen D.: The bariatric surgery patient: a growing role for registered dietitians. *Journal of the American Dietetic Association*, 2010, 110(4), 593–599.
10. Healthcare Improvement Scotland: Guidance on the use of surgery to aid weight reduction for people with morbid obesity. https://www.healthcareimprovementscotland.org/our_work/technologies_and_medicines/mta_resources/appraisal_46.aspx (15 Jul 2023).
11. Fujioka K.: Follow-up of nutritional and metabolic problems after bariatric surgery. *Diabetes Care*, 2005, 28(2), 481–484.

12. Moizé V. L., Pi-Sunyer X., Mochari H., Vidal J.: Nutritional pyramid for post-gastric bypass patients. *Obesity Surgery*, 2010, 20(8), 1133–1141.
13. Eisenberg D., Shikora S., Aarts E. et al.: 2022 American Society for Metabolic and Bariatric Surgery (ASMBS) and International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO): Indications for Metabolic and Bariatric Surgery. *Surgery for Obesity and Related Diseases*, 2022, 18(12), 1345–1356.
14. Rubino F., Nathan D. M., Eckel R. H. et al.: Metabolic Surgery in the Treatment Algorithm for Type 2 Diabetes: A Joint Statement by International Diabetes Organizations. *Diabetes Care*, 2016, 39(6), 861–877.
15. Stenberg E., Dos Reis Falcao L. F., O’Kane M. et al.: Guidelines for Perioperative Care in Bariatric Surgery: Enhanced Recovery After Surgery (ERAS) Society Recommendations: A 2021 Update. *World journal of surgery*, 2022, 46(4), 729–751.
16. Torensma B., Hisham M., Eldawlatly A. A., Hany M.: Differences Between the 2016 and 2022 Editions of the Enhanced Recovery After Bariatric Surgery (ERABS) Guidelines: Call to Action of FAIR Data and the Creation of a Global Consortium of Bariatric Care and Research. *Obesity Surgery*, 2022 , 32(8), 2753–2763.
17. Thorell A., MacCormick A. D., Awad S. et al.: Guidelines for Perioperative Care in Bariatric Surgery: Enhanced Recovery After Surgery (ERAS) Society Recommendations. *World journal of surgery*, 2016, 40(9), 2065–2083.
18. Carron M., Safaee Fakhr B., Iepariello G., Foletto M.: Perioperative care of the obese patient. *British Journal of Surgery*, 2020, 107(2), 39–55.
19. Mechanick J. I., Apovian C., Brethauer S. et al.: Clinical practice guidelines for the perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures – 2019 update: cosponsored by American Association of Clinical Endocrinologists/American College of Endocrinology, The Obesity Society, American Society for Metabolic & Bariatric Surgery, Obesity Medicine Association, and American Society of Anesthesiologists. *Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists*, 2020, 16(2), 175–247.
20. Gambhir S., Inaba C. S., Alizadeh R. F. et al.: Venous thromboembolism risk for the contemporary bariatric surgeon. *Surgical Endoscopy*, 2020, 34(8), 3521–3526.
21. Ma P., Lloyd A., McGrath M. et al.: Reduction of opioid use after implementation of enhanced recovery after bariatric surgery (ERABS). *Surgical Endoscopy*, 2020, 34(5), 2184–2190.

22. Geubbels N., Evren I., Acherman Y. I. Z. et al.: Randomized clinical trial of an enhanced recovery after surgery programme versus conventional care in laparoscopic Roux-en-Y gastric bypass surgery. *British journal of surgery Open*, 2019, 3(3), 274–281.
23. Małczak P., Wysocki M., Twardowska H. et al.: Impact of Adherence to the ERAS® Protocol on Short-term Outcomes after Bariatric Surgery. *Obesity Surgery*, 2020, 30(4), 1498–1505.
24. Ljungqvist O., Scott M., Fearon K. C.: Enhanced Recovery After Surgery. *Journal of the American Medical Association surgery*, 2017, 152(3), 292.
25. Marinari G., Foletto M., Nagliati C. et al.: Enhanced recovery after bariatric surgery: an Italian consensus statement. *Surgical endoscopy*, 2022, 36(10), 7171–7186.
26. Navarro-Martínez S., Sebastián-Tomás J. C., Ares J. A. D. et al.: Enhanced recovery after bariatric surgery (ERABS) protocol implementation in a laparoscopic center. *Minimally Invasive Therapy & Allied Technologies*, 2022, 31(2), 269–275.
27. Budzyński A., Major P., Głuszek S., i wsp.: Polskie rekomendacje w zakresie chirurgii bariatrycznej i metabolicznej. *Medycyna Praktyczna. Chirurgia*, 2016, 6, 13-25.

INTERLEUKIN 23 AND ITS ROLE IN INFLAMMATORY BOWEL DISEASE

Aleksandra Korta¹, Julia Kula¹, Krzysztof Gomulka²

1. Student Scientific Group of Adult Allergology, Wrocław Medical University, Wrocław, Poland.

Head: Krzysztof Gomulka MD, PhD

2. Clinical Department of Internal Medicine, Pneumology and Allergology, Wrocław Medical University, Wrocław, Poland.

INTRODUCTION

The gastrointestinal tract is a crucial component of the immune system, as it maintains immune homeostasis by balancing tolerance to various antigens, including commensal bacteria, food antigens, and the body's own antigens in the gut [1]. Additionally, it protects the body against harmful pathogens that can cause infections and diseases.

However, when the balance of the gastrointestinal tract is disturbed, it can lead to inflammatory bowel disease (IBD) [1]. IBD is a chronic inflammatory disorder that has two primary clinical forms: Crohn's disease (CD) and ulcerative colitis (UC) [2,3]. These disorders lead to lifelong relapsing and remitting phases [4,5] and are characterized by uncontrolled innate and adaptive immune responses that result in mucosal inflammation [6]. While the exact cause of IBD is not yet fully understood, murine studies have provided some insight into its pathogenesis.

Several factors can contribute to the development of IBD, including genes, the immune system, and environmental factors. For instance, studies suggest that individuals with specific genetic variations may be more susceptible to developing IBD. Similarly, environmental factors such as diet, smoking, and exposure to certain infections have also been linked to the development of IBD [7-11].

Pathogenesis of inflammatory bowel disease - key factors

- Genetic susceptibility
 - NOD2,
 - IL-23 receptor,

- ATG16L1,
- LRRK2,
- others,
- Environmental factors
 - smoking,
 - stress,
 - medicaments,
 - infections,
 - diet,
 - lifestyle,
 - others,
- Gut microbiome
 - *Lactobacillus*,
 - *Escherichia coli*,
 - *Bifidobacterium*,
 - others,
- Immunology
 - dysregulation of immune system,
 - defects in epithelial barrier function,
 - overactive immune response to autophagy,
 - fluctuations in lymphocyte counts,
 - variable cytokine levels.

Despite numerous studies, there is still much to learn about the pathogenesis, diagnosis, and treatment of IBD. However, ongoing research in this field provides hope for better understanding and management of this debilitating disease. IL-23 has been identified as a contributing factor in the development of autoimmune inflammatory diseases, such as IBD and cancer. In this review, we will explore the complex and multifaceted role of the proinflammatory cytokine IL-23 in the pathogenesis of inflammatory bowel disease (IBD).

BIOLOGICAL ROLE OF THE IL-23

Research has identified cytokine networks that are important for treating IBD. Innate immune cells generate a cytokine called IL-12, which comprises four types: IL-12, IL-23, IL-

27, and IL-35. Antigen-presenting cells produce IL-12, IL-23, and IL-27, while regulatory T and B cells produce IL-35 [12, 13]. IL-27 and IL-35 are inhibitory, while IL-12 and IL-23 are pro-inflammatory [14]. Family members IL-12 and IL-23 differ in their subunit compositions. IL-23 is composed of an IL-12p40 subunit complexed with a unique IL-23p19 via a disulfide bond, while IL-12 consists of a 12p40 subunit complexed with an IL-12p35 subunit [15]. Interleukin-23 (IL-23) is known to interact with two receptor chains: the specific IL-23 receptor and IL-12R β 1. IL-23 is involved in the development, differentiation, and proliferation of Th17 cells, as well as innate immune cells such as $\gamma\delta$ T cells, natural killer T (NKT) cells, and innate lymphoid cells (ILCs) [16, 17].

IL-12 cytokines help regulate cellular pathways and maintain intestinal homeostasis. They activate proinflammatory responses to protect against infection and inhibit uncontrolled immune responses that cause autoimmune disorders. IL-23 is a crucial mediator in tissue damage, and dysregulation of IL-23 and its receptor signaling is strongly implicated in inflammatory disorders [12,18,19].

IL-23 carries out its biological functions by binding to a particular receptor complex that is highly expressed on the surface of activated CD4⁺ T cells [20], group 3 innate lymphoid cells (ILCs) [21], and $\gamma\delta$ T cells [22]. It is also found at lower levels on intestinal epithelial cells [23], monocytes, and macrophages [24], neutrophils [25], natural killer (NK) cells, and invariant NKT cells [26].

THE IL-23-Th17 AXIS

IL-23 stimulates the growth and maintenance of Th17 cells in the innate immune system. However, it does not initiate Th17 differentiation or IL-17A production from naïve CD4⁺ T cells by itself, as these cells do not express the IL-23R [20].

Nevertheless, IL-23 appears to contribute to the ongoing survival and growth of Th17 cells [27].

CD4⁺ T cells lacking the IL-23 receptor can develop into Th17 cells through signals from antigen-presenting cells and cytokines like IL-6, IL-21, and TGF- β . As a result, there is a reciprocal regulation of the signature transcription factors ROR γ t and Forkhead box P3 (FoxP3), along with an elevation in the expression of IL-23 receptor. IL-23 signaling plays a crucial role in supporting the survival and expansion of Th17 cells, which produce IL-17 and IL-22. These effects are mediated through the corresponding IL-23 receptor. However, certain

variants in IL-23R that offer protection against autoimmune diseases diminish this effect. When reactivated, Th17 cells can undergo a transition to a Th1-like phenotype characterized by the expression of T-bet and the production of the inflammatory cytokine IFN- γ , especially in the presence of elevated levels of IL-23/IL-12 [28].

IL-23 influences both innate and adaptive immune cells in diverse manners, ultimately leading to intestinal inflammation. It facilitates the generation and persistence of Th17 cells, resulting in the production of cytokines like IL-17, IFN γ , IL-22, and granulocyte-macrophage colony-stimulating factor (GM-CSF) [29, 30].

GM-CSF, in turn, promotes the accumulation of granulocyte-monocyte progenitors (GMPs) and activated eosinophils in the intestine. IL-23 also stops the formation of regulatory T cells and encourages group 3 innate lymphoid cells (ILC3s) to produce cytokines, such as IL-17, IL-22, and GM-CSF.

IL-23 IN INFLAMMATORY BOWEL DISEASE

IL-23 is a critical factor in the development of autoimmune diseases, including psoriatic skin inflammation, experimental autoimmune encephalomyelitis, and inflammatory bowel disease (IBD) [14,20,31].

It controls the production and activation of various immune cells in the gut, such as natural killer cells (NK), T helper 17 cells, intraepithelial lymphocytes (IEL), and innate lymphoid cells (ILCs) [32].

Regarding inflammatory bowel disease, serum IL-23 levels are a better indicator of severe IBD than other inflammatory biomarkers, such as fecal calprotectin (FCal), CRP, and albumin [33,34].

This is significant because IBD is a chronic and often debilitating condition that affects millions of people worldwide. Research suggests that the serum level of IL-23 is an indicator of prognosis in IBD patients and positively correlated with disease duration. Based on a recent study, it was found that samples from patients with CD displayed notable expression levels of IL-17, IL-23, and IL-32 mRNA when compared to non-IBD samples. In contrast, UC specimens did not show such expression [35].

During both acute and chronic colitis elevated levels of IL-23, IL-23R and IFN γ in colon mucosa were observed [36].

TREATMENT

IL-23 and IL-12 are cytokines that promote inflammation and stimulate naive CD4⁺ precursor T cells to differentiate into T-helper 1 and T-helper 17 cells. These cells are involved in the development and progression of various autoimmune and inflammatory diseases, including inflammatory bowel disease (IBD) [37]. However, recent research shows that blocking these cytokines can be a promising treatment for IBD.

The IL-23 and IL-12 pathways are closely related to each other, both in terms of their structure and function. They share the same cytokine subunit (p40) and a subunit of their receptors (IL-12R β 1), which suggests a potential overlap in their biological activities [40]. Therefore, targeting either of these cytokines can potentially affect the other. There are currently three generations of treatments targeting IL-23 for IBD, both in use and in development [33,41].

The first generation of treatment targets anti-IL-12p40, which inhibits IL-23 rather than blocking IL-12. It was primarily represented by ustekinumab. This fully human monoclonal antibody specifically targets the p40 subunit of IL-12 and IL-23 [42], and has been approved for inducing and maintaining clinical responses, as well as achieving remission in patients with moderate-to-severe Crohn's disease who have previously failed anti-TNF- α therapy [43]. Another representative of the first-generation treatment is briakinumab, which is another type of anti-p40 antibody [38].

Moreover, there have been findings indicating that apilimod can effectively hinder the nuclear accumulation of c-Rel [39].

This transcription factor plays a crucial role in governing the expression of the IL-12/23 p40 subunit, the IL-23p19 subunit, and the IL-12p35 subunit [36,40-42].

The second generation - selective anti-IL-23 therapies, which focus on IL-23p19, have exhibited encouraging outcomes. Brazikumab, guselkumab, mirikizumab, and risankizumab are four different second-generation anti-IL-23 therapies that have been evaluated in clinical trials for IBD treatment [43-48].

The latest advancement in treatment options involves a category of small molecule inhibitors known as the third generation. These inhibitors focus on targeting signaling molecules that are activated after IL-23R, specifically Janus kinase inhibitors like tofacitinib, filgotinib, and upadacitinib. The JAK/STAT pathway plays a significant role in the

pathogenesis of IBD, and therefore, JAK inhibitors are currently under development as a new category of small-molecule drugs [49].

CONCLUSIONS

The cytokine networks that contribute to the development of inflammatory bowel disease (IBD) exhibit a high degree of complexity. As shown above, the cytokine IL-23 plays a crucial role in the development of IBD by interacting with key parts of the intestinal tissue, such as epithelial cells, the gut microbiome, pathogens and immune cells. A lot of environmental factors, including diet, microbiome, and genetic factors, can impact how IL-23 contributes to inflammatory diseases.

Research has indicated that IL-23 has a significant impact on mucosal immunity and is particularly vital in sustaining and increasing the Th17 lineage. This is accomplished through a positive feedback loop that enhances levels of IL-17, ROR γ t, TNF, IL-1, and IL-6. The mechanisms by which IL-23 drives chronic IBD remain a matter of debate, including the relative importance of Th1/Th17 cells, ILC3s, and myeloid cells, as well as the cytokines IFN γ , IL-22, and IL-17A in colitogenesis. The identification of the IL-23/IL-17 axis has offered fresh perspectives on the pathogenesis of chronic inflammatory disorders such as IBD.

In the future, therapeutic strategies focused on inhibiting IL-23 may hold particular significance in the treatment of patients with IBD. Further exploration of molecular and clinical factors that impact the response to these medications could help in the identification of patients who are most likely to derive benefits from them.

REFERENCES

1. Ahluwalia B., Magnusson M. K., Öhman L.: Mucosal Immune System of the Gastrointestinal Tract: Maintaining Balance between the Good and the Bad. *Scandinavian Journal of Gastroenterology*, 2017, 52(11), 1185–1193.
2. Uhlig H.H., Powrie F.: Translating Immunology into Therapeutic Concepts for Inflammatory Bowel Disease. *Annual Review of Immunology*, 2018, 36(1), 755–781.
3. Kaser A., Zeissig S., Blumberg R. S.: Inflammatory Bowel Disease. *Annual Review of Immunology*, 2010, 28(1), 573–621.
4. Gomollón F., Dignass A., Annese V., Tilg H., Van Assche G., et al.: On behalf of ECCO. 3rd European Evidence-Based Consensus on the Diagnosis and Management of

- Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. Journal of the European Crohn's and Colitis Organisation, 2017, 11(1), 3–25.
5. Wallace K. L.: Immunopathology of Inflammatory Bowel Disease. World Journal of Gastroenterology, 2014, 20(1), 6.
 6. Xavier R. J., Podolsky D. K.: Unravelling the Pathogenesis of Inflammatory Bowel Disease. Nature. 2007, 448 (7152), 427–434.
 7. Xu X.-R.: Dysregulation of Mucosal Immune Response in Pathogenesis of Inflammatory Bowel Disease. World Journal of Gastroenterology, 2014, 20(12), 3255.
 8. De Souza H. S. P., Fiocchi C.: Immunopathogenesis of IBD: Current State of the Art. Nature Reviews Gastroenterology & Hepatology, 2016, 13(1), 13–27.
 9. Swidsinski A., Ladhoff A., Pernthaler A., Swidsinski S., Loening-Baucke V., et al. Mucosal Flora in Inflammatory Bowel Disease. Gastroenterology, 2002, 122(1), 44–54.
 10. Zhang Y.-Z.: Inflammatory Bowel Disease: Pathogenesis. World Journal of Gastroenterology, 2014, 20(1), 91.
 11. Schirbel A., Fiocchi C.: Inflammatory Bowel Disease: Established and Evolving Considerations on Its Etiopathogenesis and Therapy: IBD Etiopathogenesis and Therapy, The Journal of Digestive Diseases. 2010, 11(5), 266–276.
 12. Collison L. W., Workman C. J., Kuo T. T., Boyd K., Wang Y., et al.: The Inhibitory Cytokine IL-35 Contributes to Regulatory T-Cell Function. Nature. 2007, 450(7169), 566–569.
 13. Wang R.-X., Yu C.-R., Dambuza I. M., et al.: Interleukin-35 Induces Regulatory B Cells That Suppress Autoimmune Disease. Nature Medicine, 2014, 20(6), 633–641.
 14. Jefremow A., Neurath M. F.: All Are Equal, Some Are More Equal: Targeting IL 12 and 23 in IBD – A Clinical Perspective. ImmunoTargets and Therapy, 2020, 9, 289–297.
 15. Kastelein R. A., Hunter C. A., Cua D. J.: Discovery and Biology of IL-23 and IL-27: Related but Functionally Distinct Regulators of Inflammation. Annual Review of Immunology, 2007, 25(1), 221–242.
 16. Yoshiga Y., Goto D., Segawa S. et al.: Invariant NKT Cells Produce IL-17 through IL-23-Dependent and -Independent Pathways with Potential Modulation of Th17 Response in Collagen-Induced Arthritis. International Journal of Molecular Medicine, 2008, 22(3), 369–374.

17. Lee J. S., Tato C. M. et al.: Interleukin-23-Independent IL-17 Production Regulates Intestinal Epithelial Permeability. *Immunity*, 2015, 43 (4), 727–738.
18. Hunter C. A.: New IL-12-Family Members: IL-23 and IL-27, Cytokines with Divergent Functions. *Nat. Rev. Immunol.* 2005, 5 (7), 521–531.
19. Trinchieri G., Pflanz S., Kastelein R. A.: The IL-12 Family of Heterodimeric Cytokines. *Immunity*. 2003, 19(5), 641–644.
20. Oppmann B., Lesley R., Blom B., et al. Novel P19 Protein Engages IL-12p40 to Form a Cytokine, IL-23, with Biological Activities Similar as Well as Distinct from IL-12. *Immunity*. 2000, 13(5), 715–725.
21. Eken A., Singh AK, Treuting PM, Oukka M.: IL-23R⁺ innate lymphoid cells induce colitis via interleukin-22-dependent mechanism. *Mucosal Immunology*, 2014, 7, 143–154.
22. Sutton CE, Lalor SJ, Sweeney CM, et al.: Interleukin-1 and IL-23 induce innate IL-17 production from gammadelta T cells, amplifying Th17 responses and autoimmunity. *Immunity*, 2009, 31, 331–341.
23. Aden K., Rehman A., Falk-Paulsen M., et al.: Epithelial IL-23r signaling licenses protective IL-22 responses in intestinal inflammation. *Cell Reports*, 2016, 16, 2208–2218.
24. Sun R., Hedl M., Abraham C.: IL23 induces IL23R recycling and amplifies innate receptor-induced signalling and cytokines in human macrophages, and the IBD-protective IL23R R381Q variant modulates these outcomes. *Gut*, 2020, 69, 264–273.
25. Zindl CL, Lai JF, Lee YK, et al.: IL-22-producing neutrophils contribute to antimicrobial defense and restitution of colonic epithelial integrity during colitis. *Proceedings of the National Academy of Sciences of the United States of America*, 2013, 110, 12768–12773.
26. Rachitskaya AV, Hansen AM, Horai R, et al.: Cutting edge: Nkt cells constitutively express IL-23 receptor and ROR γ and rapidly produce IL-17 upon receptor ligation in an IL-6-independent fashion. *Journal of Immunology*, 2008, 180, 5167–71.26.
27. Veldhoen M., Hocking R. J., Atkins C. J., et al. TGF β in the Context of an Inflammatory Cytokine Milieu Supports De Novo Differentiation of IL-17-Producing T Cells. *Immunity*, 2006, 24(2), 179–189.
28. Sewell G. W., Kaser A.: Interleukin-23 in the Pathogenesis of Inflammatory Bowel

- Disease and Implications for Therapeutic Intervention. *The Journal of Crohn's and Colitis*, 2022, 16 (Supplement_2), ii3–ii19.
29. Liang S. C., Tan X.-Y., Luxenberg D. P. et al.: Interleukin (IL)-22 and IL-17 Are Coexpressed by Th17 Cells and Cooperatively Enhance Expression of Antimicrobial Peptides. *Journal of Experimental Medicine*, 2006, 203(10), 2271–2279.
 30. Schmitt H., Neurath M. F., Atreya R.: Role of the IL23/IL17 Pathway in Crohn's Disease. *Frontiers in Immunology*. 2021, 12, 622934..
 31. Croxford A. L., Mair F., Becher B.: IL-23: One Cytokine in Control of Autoimmunity: HIGHLIGHTS. *European Journal Of Immunology*, 2012, 42(9), 2263–2273.
 32. Neurath M. F.: IL-23 in Inflammatory Bowel Diseases and Colon Cancer. *Cytokine & Growth Factor Reviews*. 2019, 45, 1–8.
 33. McDonald B. D., Dyer E. C., Rubin D. T.: IL-23 Monoclonal Antibodies for IBD: So Many, So Different? *Journal of the European Crohn's and Colitis Organisation*. 2022, 16 (Supplement_2), ii42–ii53.
 34. Deepak P., Loftus E. V.: Ustekinumab in Treatment of Crohn's Disease: Design, Development, and Potential Place in Therapy. *Drug Design, Development and Therapy*. 2016, 10, 3685–3698.
 35. Engel T., Yung D. E., Ma C., et al. Effectiveness and Safety of Ustekinumab for Crohn's Disease; Systematic Review and Pooled Analysis of Real-World Evidence. *Digestive and Liver Disease*, 2019, 51 (9), 1232–1240.
 36. Carmody R. J., Ruan Q., Liou H.-C., Chen Y. H.: Essential Roles of C-Rel in TLR-Induced IL-23 P19 Gene Expression in Dendritic Cells. *Journal of Immunol (Baltimore Md) 1950*. 2007, 178(1), 186–191.
 37. Moschen A. R., Tilg H., Raine T.: IL-12, IL-23 and IL-17 in IBD: Immunobiology and Therapeutic Targeting. *Nature Reviews Gastroenterology & Hepatology*, 2019, 16(3), 185–196.
 38. Panaccione R., Sandborn W. J., Gordon G. L., Lee S. D., Safdi A. et al.: Briakinumab for Treatment of Crohn's Disease: Results of a Randomized Trial. *Inflammatory Bowel Diseases*, 2015, 21(6), 1329–1340.
 39. Wada Y., Cardinale I., Khatcherian A., Chu J., Kantor A. B. et al.: Apilimod Inhibits the Production of IL-12 and IL-23 and Reduces Dendritic Cell Infiltration in Psoriasis. *PloS One*. 2012, 7(4), e35069.
 40. Grumont R. Hochrein H. O'Keeffe M. et al.: C-Rel Regulates Interleukin 12 P70

- Expression in CD8(+) Dendritic Cells by Specifically Inducing P35 Gene Transcription. *Journal of Experimental Medicine*, 2001, 194(8), 1021–1032.
41. Mason N., Aliberti J., Caamano J.C., et al. Cutting Edge: Identification of c-Rel-Dependent and -Independent Pathways of IL-12 Production during Infectious and Inflammatory Stimuli. *Journal of immunology (Baltimore, Md)* 1950. 2002, 168(6), 2590–2594.
 42. Sanjabi S., Hoffmann A., Liou H. C., et al. Selective Requirement for C-Rel during IL-12 P40 Gene Induction in Macrophages. *Proceedings of the National Academy of Sciences of the United States of America*, 2000, 97(23), 12705–12710.
 43. Sands B. E. Chen J. Feagan B. G. et al.: Efficacy and Safety of MEDI2070, an Antibody Against Interleukin 23, in Patients With Moderate to Severe Crohn's Disease: A Phase 2a Study. *Gastroenterology*, 2017, 153(1), 77-86.e6.
 44. Feagan B. G. Sandborn W. J. D'Haens G. et al. Induction Therapy with the Selective Interleukin-23 Inhibitor Risankizumab in Patients with Moderate-to-Severe Crohn's Disease: A Randomised, Double-Blind, Placebo-Controlled Phase 2 Study. *Lancet London England*, 2017, 389(10080), 1699–1709.
 45. Sandborn W. J., Ferrante M., Bhandari B. R. et al.: 882 - Efficacy and Safety of Anti-Interleukin-23 Therapy with Mirikizumab (LY3074828) in Patients with Moderate-To-Severe Ulcerative Colitis in a Phase 2 Study. *Gastroenterology*. 2018, 154(6), S-1360-S-1361.
 46. D'Haens G. G. R., Sandborn W. J., Ferrante M., et al. OP38 Maintenance Treatment with Mirikizumab, a P19-Directed IL-23 Antibody: 52-Week Results in Patients with Moderately-to-Severely Active Ulcerative Colitis. *Journal of the European Crohn's and Colitis Organisation*. 2019, 13 (Supplement_1), S026–S027..
 47. Sands B. E., Sandborn W. J., Peyrin-Biroulet L., et al. 1003 – Efficacy and Safety of Mirikizumab (LY3074828) in a Phase 2 Study of Patients with Crohn's Disease. *Gastroenterology*. 2019, 156(6), S-216.
 48. Baker K. F., Isaacs J. D.: Novel Therapies for Immune-Mediated Inflammatory Diseases: What Can We Learn from Their Use in Rheumatoid Arthritis, Spondyloarthritis, Systemic Lupus Erythematosus, Psoriasis, Crohn's Disease and Ulcerative Colitis? *Annals of the Rheumatic Diseases*, 2018, 77(2), 175–187.
 49. Soendergaard C., Bergenheim F. H., Bjerrum J. T., Nielsen, O. H.: Targeting JAK-STAT Signal Transduction in IBD. *Pharmacology & Therapeutics*, 2018, 192, 100–111.

THE ANTIBIOTIC RESISTANCE CRISIS

**Laura Więcko, Marzena Jargilo, Łukasz Dylewicz, Kacper Solarz,
Jakub Bętkowski**

Faculty of Medicine in Katowice, Medical University of Silesia, Poland

INTRODUCTION

Antimicrobial agents such as antibiotics are key tools for bacterial infections, but they are becoming less effective. The antibiotics can kill or inhibit the growth of microorganisms. Many decades after antibiotics were introduced into pharmacotherapy, bacterial infections have again become a major threat. Alarming levels of resistance have been observed in countries of all income levels, resulting in common diseases becoming incurable and medical treatments that are supposed to save lives are becoming increasingly dangerous and complicated [1,2]. The antibiotic resistance crisis is related to the overuse as well as inappropriate application of these drugs. Unfortunately, new drugs are not being introduced due to reduced economic incentives and difficult regulatory requirements.

The Centers for Disease Control and Prevention (CDC) has developed a classification of bacteria with reference to their pathogenicity. It should be added that there are bacteria resistant to many antibiotics and infections associated with them are responsible for a huge clinical and financial burden on the health care system, patients and their families [3].

HISTORY

The first known use of antibiotics occurred in ancient China more than 2,500 years ago. The treatment of bacterial infections in ancient Egypt, Greece and China is well documented. We know that ancient civilizations used molds and plants to treat infections [1,3].

The first well-known antibiotic called Salvarsan, was developed and marketed as a drug against syphilis in 1910. The creator of the revolutionary drug was Paul Ehrlich, who performed 606 tests of the drug's effects on rabbits with syphilis (the alternate name of Salvarsan is compound 606).

A significant downside of the introduced drug was its frequent and dangerous side effects [4, 5].

The discovery of penicillin (a product of the fungus *Penicilium*) by Sir Alexander Fleming in 1928 launched the golden age of natural antibiotics [1, 4]. The drug is often described as a "child of war, as numerous research and observations were conducted during World War II, before its development [1, 3]. Antibiotics were first prescribed to treat severe infections in the 1940s. The discovery of penicillin was extremely groundbreaking, because it saved millions of lives, but resistance to these antibiotics quickly emerged. New beta-lactam antibiotics were introduced in response to a global problem in the treatment of infections. Unfortunately, the first case of methicillin-resistant *Staphylococcus aureus* (MRSA) was identified in the same decade- in the United Kingdom in 1962 and in the United States in 1968 [3]. Researchers looked for other therapeutic solutions that would not be associated with resistance. Cases of vancomycin resistance were noted in coagulase-negative staphylococci in 1979 and 1983. A gradual decline in discovery due to the depletion of potential drug sources and the development of antibiotics, as well as the evolution of drug resistance in many human pathogens, has led to the current antimicrobial resistance crisis [3,4].

CAUSES

As early as 1945, Sir Alexander Fleming raised the alarm regarding antibiotic overuse when he warned that the “public will demand [the drug and] ... then will begin an era ... of abuses.” [3]. The misuse and overuse of antibiotics is a major factor contributing to the development of antibiotic resistance. Bacteria can gain antibiotic resistance through spontaneous mutations on its own, or gain it from another relative or non-relative bacteria through the process of conjugation. This process relies on the temporary union of two bacteria or unicellular organisms for the exchange of genetic material, which are called plasmids. Overprescription and the misuse of the antibiotics include taking antibiotics without a prescription, not completing the full course of antibiotics, using leftover antibiotics from previous treatments, or using antibiotics for viral infections, which they are ineffective against. These actions contribute to formation of new genes of the bacteria that had contact with the antibiotic.

Another cause of the rising antibiotic resistance is the use of antibiotics in agriculture. Intensive animal production involves giving livestock animals large quantities of antibiotics to promote growth and prevent infection. The resistant bacteria from agricultural environments

may be transmitted to humans, in whom they cause disease that cannot be treated by conventional antibiotics [6].

Lack of new antibiotics also contributes to the antibiotic growth resistance upcoming crisis. Over the years there has been a decline in the development of new antibiotics. Despite increasing rates of antibiotic resistance, pharmaceutical companies are reluctant to develop new antibiotics due to scientific, regulatory, and financial barriers [7]. As a result, the available arsenal of antibiotics has become limited, allowing bacteria to develop resistance faster than new drugs can be developed.

Addressing antibiotic resistance requires a multi-faceted approach, including promoting appropriate and responsible use of antibiotics, promoting the development of new antibiotics and alternative therapies and raising awareness among healthcare providers and the general public about the importance of combating antibiotic resistance.

ANTIBIOTIC RESISTANCE BACTERIAL INFECTIONS

Methicillin-Resistant *Staphylococcus Aureus*

MRSA has been spread worldwide as the most threatening antibiotic-resistant bacteria. It is resistant to penicillin-like beta-lactam antibiotics [8]. It can also be resistant to drugs such as glycopeptides (e.g., vancomycin and teicoplanin), linezolid, tigecycline, daptomycin, and more modern drugs for example ceftaroline and ceftobiprole. The biggest concern arises that even though this bacteria becomes resistant due to bacterial mutation it can be also resistant to linezolid and glycopeptide antibiotics. However data shows that MRSA the rise of infections is decreasing in some areas because of the precautions taken by hospitals which include aggressive preventive hygiene.

Vancomycin-Resistant Enterococci

VRE is a concerning threat. It is developing resistance to many common antibiotics [8]. Enterococci cause illness to mostly patients in hospitals [8, 9]. The infections are often caused by *Enterococcus faecium* and less frequently by *Enterococcus faecalis*. [10]. Antibiotics which are used against VRE are linezolid and quinupristin/dalfopristin, but the use of daptomycin and tigecycline needs to be further researched [10]. VRE has developed an extremely big interest in developing new drugs that could have bactericidal activity against VRE, such as oritavancin [10].

Drug-Resistant *Streptococcus pneumoniae*

S. pneumoniae is a common respiratory pathogen which can cause serious infections [9]. It is known to be the major cause of bacterial pneumonia and meningitis, and also bloodstream, ear, and sinus infections [9, 10]. The majority of these cases and deaths occur among the elderly [9]. *S. pneumoniae* has developed resistance to drugs in the penicillin class and erythromycins, such as amoxicillin and azithromycin [9]. The new version of pneumococcal conjugate vaccine (PCV13), protects against 13 strains of the bacteria including infections caused by the most resistant pneumococcus strains.

Drug-Resistant *Mycobacterium Tuberculosis*

Drug-resistant *M. tuberculosis* infections are a serious threat [8, 10]. *M. tuberculosis* is spread through the air [9]. Infections caused by this bacterium are mostly present in the lungs but they can occur anywhere. The major factor causing TB drug resistance are the incompleteness of treatment of the bacteria. Usually TB infections are treatable first-line drugs: isoniazid or rifampicin. Extensively drug-resistant TB (XDR-TB) is resistant to most TB drugs, including isoniazid and rifampicin, any fluoroquinolones, and any the second-line injectable drugs amikacin, kanamycin, and capreomycin [9].

Carbapenem-Resistant Enterobacteriaceae (CRE)

Carbapenem-resistant Enterobacteriaceae (CRE) are a group of bacteria that is resistant to “all” available treatments. Even to carbapenems [8, 9, 10]. An enzyme New Delhi metallo-beta-lactamase (NDM-1) is present in some gram-negative Enterobacteriaceae bacteria such as *Escherichia coli* and *K. pneumoniae* that makes them resistant

MDR *Pseudomonas Aeruginosa*

P. aeruginosa is a common cause of pneumonia and bloodstream, urinary tract, and surgical-site infections. Some strains of MDR *P. aeruginosa* are found to be resistant to nearly all antibiotics, including aminoglycosides, cephalosporins, fluoroquinolones, and carbapenems [9].

MDR *Acinetobacter*

Acinetobacter causes pneumonia or bloodstream infections, most dangerously in critically ill patients on mechanical ventilation.[9] Some *Acinetobacter* species have become resistant to all or nearly all antibiotics, including carbapenems.

ESBL-Producing Enterobacteriaceae

Extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae carry a broad-spectrum beta-lactamase enzyme that enables them to become resistant to a wide variety of penicillin and cephalosporin antibiotics [9]. Some ESBL-producing Enterobacteriaceae are resistant to nearly all antibiotics in the penicillin and cephalosporin categories [9]. In these cases, the treatment option is an carbapenem antibiotic.

Drug-resistant *Neisseria gonorrhoeae*

Drug-resistant forms of *N. gonorrhoeae*, which cause the sexually transmitted disease gonorrhea,. The characterization of Gonorrhea is discharge and inflammation of the urethra, cervix, pharynx, or rectum [9, 10]. If drug-resistant *N. gonorrhoeae* becomes more widespread, it can cause additional cases of pelvic inflammatory disease, epididymitis, human immunodeficiency virus infections. Cephalosporin-resistant *N. gonorrhoeae* is often resistant to antibiotics, such as fluoroquinolones, tetracyclines, and penicillins [9, 11]. Infections caused by these bacteria can then fail to be treated [9]. Treatment guidelines recommend ceftriaxone, plus either azithromycin or doxycycline, as the first-line treatment for gonorrhea [10].

CONCLUSION

In conclusion: Antibiotic Resistance is a huge medical problem worldwide. It does not mean that we should stop using drugs as antibiotics, because in a lot of situation they are saving patients life. On the other hand commonly antibiotics are used unjustifiably, what provides to spreading of the antibiotic resistance. Antibiotics should be used only in justified moments to save patients health and life.

REFERENCES

1. Kourkouta, L. History of Antibiotics. Sumerianz Journal of Medical and Healthcare, 2018, 1(2), 51-54.
2. No time to wait: securing the future from drug-resistant infections report to the secretary-general of the united nations, April 2019
3. Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. Pharmacy and therapeutics. 2015, 40(4), 277-283.
4. Hutchings M.I., Truman A.W., Wilkinson B. Antibiotics: past, present and future, Current Opinion in Microbiology, 2019, 51, 72-80.

5. Kubicki J. History of the syphilis, Puls Uczelni 2013, 7(3), 37-39.
6. Khachatourians G.G.. Agricultural use of antibiotics and the evolution and transfer of antibiotic-resistant bacteria. Canadian Medical Association Journal, 1998, 159(9), 1129-1136.
7. Dutescu IA, Hillier SA. Encouraging the Development of New Antibiotics: Are Financial Incentives the Right Way Forward? A Systematic Review and Case Study. Infection and Drug Resistance, 2021, 5(14), 415-434.
8. Sengupta S., Chattopadhyay MK., Grossart HP. The multifaceted roles of antibiotics and antibiotic resistance in nature. Frontiers in Microbiology. 2013, 4(47).
9. Centers for Disease Control and Prevention, Office of Infectious Disease Antibiotic resistance threats in the United States, 2013. Apr, 2013. Available at: <http://www.cdc.gov/drugresistance/threat-report-2013>. Accessed 28 January 2015.
10. Gross M. Antibiotics in crisis. Current Biology, 2013, 23(24), R1063–R1065.
11. Rossolini GM, Arena F, Pecile P, Pollini S. Update on the antibiotic resistance crisis. The Journal of Clinical Pharmacology. 2014, 18, 56–60.

CURRENT AND FUTURE ROLE OF AI IN MEDICINE

Łukasz Dylewicz¹, Jakub Bętkowski¹, Jakub Rudzki¹, Zuzanna Kata², Laura Więcko¹, Kacper Solarz¹, Justyna Talaska¹

1. Faculty of Medicine in Katowice, Medical University of Silesia, Poland
2. Faculty of Dentistry in Zabrze, Medical University of Silesia, Poland

ABBREVIATION LIST

- HIPAA- Health Insurance Portability and Accountability Act
- GDPR- General Data Protection Regulation
- FDA- Food and Drug Administration

INTRODUCTION

Artificial intelligence (AI) is a rapidly advancing field of computer science that focuses on creating machines that can learn, reason, and perform tasks that typically require human intelligence. AI has the potential to transform various aspects of our lives, from healthcare and education to transportation and entertainment. While there are concerns about the ethical and social implications of AI, many experts believe that it could lead to significant advancements in technology and revolutionize the way we live and work. Artificial intelligence (AI) is a type of computer technology that allows machines to learn from data and perform tasks that typically require human intelligence. At its core, AI uses algorithms and statistical models to analyze data and identify patterns. These patterns can then be used to make predictions or take actions based on the data. For example, a simple AI system could be trained to recognize images of cats. The system would be fed thousands of images of cats and non-cats, and over time, it can learn how to identify the key features that distinguish a cat from other objects. Once trained, the system could then be used to recognize cats in new images that it has never seen before [1]. The story of AI dates back to ancient times, where Greek myths portrayed intelligent machines created by gods. However, it wasn't until the 20th century that the concept of artificial intelligence really took off. In the 1950s, computer scientists began to explore the idea of creating machines that could think and reason like us, humans. They started by developing

programs that could perform simple tasks, like solving mathematical problems and playing games. In the 1980s and 1990s, there was a surge of interest in AI, with many companies and governments investing in research and development. However, progress was slow, and many of the early AI systems were limited by their lack of computing power and the inability to handle large amounts of data [2].

It wasn't until the 21st century, with the advent of big data, cloud computing, and deep learning algorithms, that AI really began to take off. Today, AI systems are used in a wide range of applications, from image recognition and natural language processing to self-driving cars and virtual assistants. While there is still much to be learned about the potential of AI, many experts believe that it has the potential to revolutionize the way we live and work. Some even predict that AI, one day can be better than human intelligence, leading to a new era of technological advancements, discoveries and possibilities.

APPLICATIONS OF AI IN MEDICINE

Artificial intelligence (AI) and related technologies are widely used in various fields and disciplines, including medicine. AI is being effectively utilized in healthcare facilities such as hospitals and clinical laboratories. AI is also an integral part of scientific research [3].

The following are medical-related ventures which use artificial intelligence on a daily basis:

- a. Drug design - AI technology in healthcare can help pharmaceutical companies speed up the drug discovery and design process. Designing new medications with the support of AI is based on monitoring the interactions of 3D models of molecules and target sites like receptors, enzymes that can represent a possible therapy [4]. This is achieved through the application of deep learning based on knowledge of the behavior of molecules. In 2018, research was launched to find existing and safe drugs that could be redesigned to treat the Ebola virus.
- b. Two medicines were successfully found by using AI that could significantly reduce the virulence of the Ebola virus. The analysis presented, which usually takes months or years, was done in one day. Most experts believe that these tools will become more crucial in the future. AI and machine learning could help develop drug therapies that are faster, cheaper and more effective [5].
- c. Diagnostics and prevention of disease - The analysis of a patient's condition involves assessing the severity and progression of the disease. The goal is to improve the

accuracy of treatment as well as disease prognosis. To ensure reproducibility, disease status is assessed using clear, verbalized observations. ANN- artificial neural network is used in clinical diagnostics, in the the functioning of radiographs, magnetic resonance imaging, computed tomography, ultrasonography, and analysis of waveforms, electrocardiogram (ECG), electroencephalograms (EEG). We can use successively AI-based systems in pathologic diagnosis. Automated analysis of histological slides is possible with special scanners which can obtain and store slides in the form of digital images. The aforementioned computer techniques have found proven application in breast pathology and also in dermatopathology [7]. It is immensely important to combine deep learning with pathologist's diagnostics, because it allows the human error rate to be reduced by about 85% [5]. Based on the use of automated information systems, doctors can more easily provide optimal patient care by reducing diagnostic and therapeutic errors [4,6].

- d. Health monitoring- applications for patients and physicians - Patients these days can monitor their health using AI-enabled tools. We have access to easy-to-use wearables and fitness gadgets. These devices using AI allow 24/7 collection, analysis of health data and most importantly providing information to the user- patient [3]. Well-known and widely used Heart360 application for monitoring cardiac patients. Heart360 allows patients to document parameters relevant to their condition. Patients can collect and record data, set goals and track their progress. An app has also been created to observe the progress of patients taking antidepressant therapy [5].

BENEFITS OF ARTIFICIAL INTELLIGENCE IN MEDICINE

Artificial intelligence (AI) is based on mathematical algorithms that allow to imitate the thinking process and has the significant potential to improve healthcare and revolutionize the medical industry by reducing the need for human interaction and increasing productivity through automatization. AI is one of the best decision-making assistant today by delivering real-time data analysis and collecting important information and identifying options. Nowadays there are many research that demonstrates the powerful and impactful potential, benefits, and challenges of AI [8,9].

Most of innovations in healthcare sector is based on AI. The amount of processed information is too large for human being which increased accuracy, reduces the risk of errors, and saves time. AI can be used to automate tasks, calculate risk, forecast and predicting

outcomes, diagnose, patient monitoring and create individualized treatment plans. Artificial intelligence can speed up the development of therapies but also help medical staff in more careful and considered decision-making process. Currently, AI is commonly used in radiology or as a virtual assistant that enables patients to better control their care, which is positively evaluated [8,10,11,12].

AI is improving surgery by offering high-precision surgical robots that are used for example in orthopedic and maxillofacial surgery. Da Vinci surgical robots are currently becoming more and more popular. Surgery based on AI have enabled remote work for the surgeon, but still this type of surgery must be monitored by human via video pictures and communication systems. AI allows newer approaches and less invasive surgical techniques and real-time consultations with more experienced surgeons [10,12,13].

Artificial intelligence also supports mental health by sentiment analysis and creating virtual assistants for patients. The computer provides detailed information about the patient's emotional and psychological state, interpreting and reacting to verbal expressions of human emotions, detecting suicidal thoughts and risk [10].

WHICH MEDICAL SPECIALTIES WILL USE AI THE MOST ON A DAILY BASIS?

Currently AI may seem the most beneficial for medical specialties with large amount of image-based data, like radiology, ophthalmology, neurology, cardiology, and dermatology. Basing on the FDA Artificial Intelligence and Machine Learning (AI/ML)-Enabled Medical Devices, there are currently 523 approved software and devices of which the majority are radiology-related. Rapid growth of aforesaid technology will, without doubt, bring solutions to many other medical fields [14]. In this paragraph we would like to concisely describe some medical fields where AI can be used on a daily basis in the future.

Radiology is a medical field dedicated to making diagnosis or further recommendations based on imaging studies like MRI, CT, RTG. 393 AI/ML devices has been already approved by FDA in radiology field. [14] These software and devices can differentiate normal image from pathology thanks to machine learning and analyzing many radiologic images. Sometimes, to meet work demand, radiologist must analyze one image every 3-4 seconds during work shift leading to fatigue and potential diagnostic errors. In this case AI can provide preliminarily analyzed radiological images with marked pathologies [15]. For instance, a meta-analysis with 11 papers included, done by Adamou A. et al. showed that ASPECTS artificial intelligence software performed comparably or better than radiology specialists in

detecting early stroke from CT scans [16]. Good performance is also observed in oncology-related imaging. Among other things, AI performs well in diagnosing lung neoplasms, metastatic nodules and brain cancers, even with their types [17,18]. Yet there is still room for an improvement. Generally in radiology, AI and ML can significantly improve workflow, efficacy [20].

Another field with promising AI results is cardiology. There are 61 AI-related devices approved by FDA right now, which is the second largest number among other approved AI/ML devices [14]. As well as in previous paragraph, the mode of action of AI in cardiology is the same as in radiology – based on image studies. In this case mainly echocardiography images which is ultrasound study of heart. There are many studies showing that AI performs well in diagnosing cardiomyopathies – problems with heart which may cause disorder in pumping blood, ECG analysis [20,21]. These test are done on a daily basis in cardiology field. Like in a radiology case, pathology marking or automatic analysis may reduce the burden of workload.

Dermatology is another promising field in which AI can be implemented in the future. Melanoma is one of the most malignant cancers which diagnosis is often delayed resulting in poor outcome. In this case AI can be used to analyze birthmarks. There is no FDA approved software or device in dermatology field at this moment, but there are already studies according to this topic. Some of them show that the efficacy of diagnosing melanomas by AI is comparable with the specialists [22].

These were just three examples of how AI can notably improve efficacy and efficiency of medical specialists work. This technology is still in development but is it alacritous, so we can expect major changes in the medical fields in the future.

POSSIBLE THREATS OF AI USE IN MEDICINE

The use of artificial intelligence (AI) in medicine has a great potential to revolutionize healthcare by improving diagnosis, treatment, and patient outcomes as mentioned previously. Nevertheless, there are also risks and threats associated with the implementation of the AI in medicine, the most significant of which is patient harm. Other risks include the risk of bias and increased health inequalities, lack of transparency and trust, and vulnerability to hacking and data privacy breaches [23].

Patient harm due to AI errors may include a missed diagnosis of life-threatening conditions or a false diagnosis and lead to inadequate treatment and incorrect scheduling or

prioritisation of intervention. These AI errors can be caused by noise and artifacts in input data, which can emerge during any diagnostic scanning process [23,24]. Errors can also occur due to data shift between AI training data and the real-world data, such as when using machines from different manufactures, resulting in loss of accuracy [23].

Another critical consideration when implementing AI in medicine is the threat of hacking and data privacy breaches. Health service data are the most sensitive information that can be owned by an individual about another [25]. Ai systems rely on access to large amounts of personal and sensitive data and if this data is not adequately secured, it can result in identity theft or fraud [26]. As the data is prone to cyberattacks, it can lead to contamination by malicious data and sabotage resulting in biased data [27].

The risk of bias is another significant concern. In the global population, some patients are more susceptible to certain diseases than others due to their genes, ethnic group, geographical location, occupation, and many other factors. As AI systems are trained on data from historical datasets, they may be incomplete and prejudiced towards smaller ethnic groups, resulting in wrong diagnoses. For example, clinicians may incorrectly discount the diagnosis of myocardial infarction in women because these patients are more likely to present with atypical symptoms. Thus, an AI algorithm that learns from historical electronic health record data may not recommend testing for cardiac ischemia for women [28].

These are just three of the many threats that come with implementing AI in medicine. Many other factors need to be considered and addressed before doctors can fully rely on AI to diagnose patients and avoid causing any harm to the patient.

DIFFICULTIES OF IMPLEMENTATION ARTIFICIAL INTELLIGENCE IN HOSPITALS

1. Data quality and interoperability: The success of AI in healthcare largely depends on the availability and quality of data. Hospitals may face challenges in integrating data from different sources, ensuring data privacy and security, and making sure that the data is accurate, complete, and relevant [29].
2. Cost: Implementing AI in hospitals can be expensive, requiring investments in hardware, software, and personnel. Hospitals may need to justify the cost of AI implementation by demonstrating the potential benefits, such as improved patient outcomes, reduced costs, and increased efficiency [30].

3. Integration with existing systems: Hospitals may have legacy systems that are difficult to integrate with new AI systems. It is important to ensure that the new AI systems are compatible with existing systems and that they can be seamlessly integrated into the hospital's workflow [30].
4. Resistance to change: Healthcare professionals may be resistant to new technologies and processes, which can slow down the adoption of AI in hospitals. It is important to involve healthcare professionals in the implementation process and provide them with training and support to help them adapt to the new technology [30,31].
5. Regulatory compliance: AI in healthcare is subject to regulatory requirements, such as HIPAA, GDPR, and FDA regulations.[32] Hospitals must ensure that their AI systems are compliant with these regulations and that they maintain patient privacy and security [31].
6. Ethical considerations: AI in healthcare raises ethical concerns, such as bias, fairness, and transparency. Hospitals must ensure that their AI systems are designed and implemented in an ethical and responsible manner [29,33].

Overall, implementing AI in hospitals requires careful planning, collaboration, and a commitment to overcoming the challenges that arise during the process. By addressing these challenges proactively, hospitals can realize the potential benefits of AI in healthcare, such as improved patient outcomes, reduced costs, and increased efficiency.

REFERENCES

1. Diaz M. What is AI? Everything to know about artificial intelligence, <https://www.zdnet.com/article/what-is-ai-heres-everything-you-need-to-know-about-artificial-intelligence/> Accessed 21 April 2023.
2. Rockwell Anyoha. The History of Artificial Intelligence. <https://sitn.hms.harvard.edu/flash/2017/history-artificial-intelligence/> Accessed 28 August 2017
3. Kaur E., Bans A., Okereke Eze U, Singh J., Artificial intelligence in healthcare: a prospective approach anveshan: Multidisciplinary Journal of Geeta University, 2023, <https://www.geetauniversity.edu.in/wp-content/uploads/2023/03/ARTIFICIAL-INTELLIGENCE-IN-HEALTHCARE.pdf> Accessed 21 April 2023
4. Shaheen M.Y. Applications of Artificial Intelligence (AI) in healthcare: A review. ScienceOpen 2021. file:///C:/Users/User/Downloads/Applications%20of%20Artificial%20Intelligence%20(AI)%20in%20healthcare%20A%20review.pdf, Accessed 21 April 2023.

5. Kostić E.J., Pavlović D.A., Živković M.D. Applications of artificial intelligence in medicine and pharmacy - ethical aspects. *Acta Medica Medianae*, 2019, 58(3), 128-137.
6. Suh H.J., Son J., Kang K. Application of Artificial Intelligence in the Practice of Medicine. *Applied Sciences*, 2022, 12, 4649.
7. Ahmad Z., Rahim S., Zubair M., Abdul-Ghafar J.: Artificial intelligence (AI) in medicine, current applications and future role with special emphasis on its potential and promise in pathology: present and future impact, obstacles including costs and acceptance among pathologists, practical and philosophical considerations. A comprehensive review; *Diagnostic Pathology*, 2021, 16(1), 24.
8. Yeasmin S. Benefits of Artificial Intelligence in Medicine. *BMC Diagnostic Pathology*, 2021, 16,24.
9. Hamet P, Tremblay J. Artificial intelligence in medicine. *Metabolism*. 2017, 69S, S36-S40.
10. Shaheen MY. AI in Healthcare: medical and socio-economic benefits and challenges. *ScienceOpen Preprints*, 2021. <https://www.scienceopen.com/hosted-document?doi=10.14293/S2199-1006.1.SOR-PPRQNI1.v1> Accessed 21 April 2023.
11. Vearrier L, Derse AR, Basford JB, Larkin GL, Moskop JC. Artificial Intelligence in Emergency Medicine: Benefits, Risks, and Recommendations. *The Journal of Emergency Medicine*, 2022, 62(4), 492-499.
12. Iroda A, Diyora A. Artificial intelligence in medicine: benefits and drawbacks. *British View*. 2021, 6(1), 55-59.
13. Makhni EC, Makhni S, Ramkumar PN. Artificial Intelligence for the Orthopaedic Surgeon: An Overview of Potential Benefits, Limitations, and Clinical Applications. *Journal of The American Academy of Orthopaedic Surgeons*. 2021, 29(6), 235-243.
14. Health C for D and R. Artificial Intelligence and Machine Learning (AI/ML)-Enabled Medical Devices. FDA. 2022. <https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-aiml-enabled-medical-devices>. Accessed 21 May 2023.
15. Hosny A, Parmar C, Quackenbush J, Schwartz LH, Aerts HJWL. Artificial intelligence in radiology. *Nature Reviews Cancer*. 2018, 18(8), 500-510.
16. Adamou A, Beltsios ET, Bania A, et al. Artificial intelligence-driven ASPECTS for the detection of early stroke changes in non-contrast CT: a systematic review and meta-analysis. *Journal of Neurointerventional Surgery*. 2022, 15, jnis-2022-019447.

17. Jena B, Saxena S, Nayak GK, et al. Brain Tumor Characterization Using Radiogenomics in Artificial Intelligence Framework. *Cancers*. 2022, 14(16), 4052.
18. Binczyk F, Prazuch W, Bozek P, Polanska J. Radiomics and artificial intelligence in lung cancer screening. *Translational Lung Cancer Research*. 2021, 10(2), 1186-1199.
19. van Leeuwen KG, de Rooij M, Schalekamp S, van Ginneken B, Rutten MJCM. How does artificial intelligence in radiology improve efficiency and health outcomes? *Pediatric Radiology*. 2022, 52(11), 2087-2093.
20. Grün D, Rudolph F, Gumpfer N, et al. Identifying Heart Failure in ECG Data With Artificial Intelligence - A Meta-Analysis. *Frontiers in Digital Health*. 2021, 25, 2, 584555.
21. Lopez-Jimenez F, Attia Z, Arruda-Olson AM, et al. Artificial Intelligence in Cardiology: Present and Future. *Mayo Clinic Proceedings*. 2020, 95(5), 1015-1039.
22. Hogarty DT, Su JC, Phan K, et al. Artificial Intelligence in Dermatology—Where We Are and the Way to the Future: A Review. *American Journal of Clinical Dermatology*. 2020, 21(1), 41-47.
23. Artificial Intelligence in Healthcare: Applications, Risks, and Ethical and Societal Impacts. European Parliament. Directorate General for Parliamentary Research Services, 2022. [https://www.europarl.europa.eu/RegData/etudes/STUD/2022/729512/EPRS_STU\(2022\)729512_EN.pdf](https://www.europarl.europa.eu/RegData/etudes/STUD/2022/729512/EPRS_STU(2022)729512_EN.pdf), Accessed 21 May 2023.
24. Goyal B, Dogra A, Agrawal S, Sohi B. S. Noise Issues Prevailing in Various Types of Medical Images. *Biomedical and Pharmacology Journal*, 2018, 11(3).
25. Sunarti, S., Fadzlul Rahman, F., Naufal, M., Risky, M., Febriyanto, K., Masnina, R. (2021). Artificial intelligence in healthcare: opportunities and risk for future. *Gaceta Sanitaria*, 2021, 35, S67–S70.
26. King, M.R. The Future of AI in Medicine: A Perspective from a Chatbot. *Annals of Biomedical Engineering*, 2023, 51, 291–295.
27. Chinzei, K., Shimizu, A., Mori, K., Harada, K., Takeda, H., Hashizume, M., ... Mitsuishi, M. Regulatory Science on AI-based Medical Devices and Systems. *Advanced Biomedical Engineering*, 2018, 7(0), 118–123.
28. Vokinger K. N., Gasser U. Regulating AI in medicine in the United States and Europe. *Nature Machine Intelligence*, 2012, 3(9), 738–739.
29. Jiang F., Jiang Y., Zhi H. , Dong Y., Li H., et al.: Artificial intelligence In Healthcare: past, present and future. *Stroke and Vascular Neurology* 2017, 2(4), 230-243.

30. Davenport T. , Kalakota R.: The potential for artificial intelligence In Healthcare . Future Healthcare Journal, 2019, 6(2), 94–98.
31. Peterson L., Larson I., Nygren J., Nilsena P., Neher M., et al.: Challenges to implementing artificial intelligence in healthcare: a qualitative interview study with healthcare leaders in Sweden BMC Health Services Research volume 2022, 22(850), 143-144.
32. Forcier M. Gallois H. , Mullan S. , Joly Y.: Integrating artificial intelligence into health care through data access: can the GDPR act as a beacon for policymakers? The Journal of Law and the Biosciences, 2019, 6(1), 317–335.
33. Farhud D., Zokaei S.: Ethical Issues of Artificial Intelligence in Medicine and Healthcare. Iranian Journal of Public Health, 2021, 50(11), 217-226.

ENDOMETRIOSIS – WHAT WE SHOULD KNOW

Anita Froń, Urszula Tokarczyk, Karol Zagórski

Wroclaw Medical University

ABBREVIATION LIST

- ACOG - American College of Obstetricians and Gynecologists
- CNGOF - Collège National des Gynécologues et Obstétriciens Français
- DIE - deep infiltrating endometriosis
- ESHRE - European Society of Human Reproduction and Embryology
- GnRH - gonadotropin-releasing hormone
- LUNA - laparoscopic uterine nerve ablation
- MRI - magnetic resonance imaging
- qRT-PCR - quantitative reverse transcription polymerase chain reaction
- TAHBSO - hysterectomy with bilateral salpingo-oophorectomy

INTRODUCTION

Endometriosis, a complex and chronic gynecological condition, poses significant challenges for both patients and medical professionals. Characterized by the abnormal growth of endometrial tissue outside the uterus, endometriosis affects millions of women worldwide, causing local inflammation, debilitating pain, fertility issues, and a host of other symptoms. Managing this enigmatic condition requires a multidimensional approach, encompassing accurate diagnosis, personalized treatment plans, and comprehensive care that addresses the physical, emotional, and social aspects of the disease [1,2].

Endometriosis is the second most common gynecological condition in reproductive-age women, affecting 5-30% of the population. It is estimated that endometriosis affects about 190 million women worldwide. The percentages among infertile women and women with chronic pelvic pain can approach 50% and 30%, respectively. The condition is most prevalent between the ages of 25 and 40. Nonetheless, epidemiological studies indicate an increase in endometriosis prevalence among adolescents (2-5%) and postmenopausal women (3-6%).

There have been isolated cases of endometriosis-like symptoms in men undergoing hormone treatment for prostate cancer [2–4].

Endometriosis can be superficial, affecting the peritoneum of the pelvic organs and abdominal wall, including the diaphragm, or the surface of the ovary, which can create ovarian cysts (endometriomas). Deep infiltrating endometriosis (DIE) occurs when endometriosis spreads beyond the peritoneum and invades the bladder, intestinal wall, and structures surrounding the uterus. It usually manifests itself as a singular nodule in the vesicouterine fold or in the lowest 20 cm of the intestine [5].

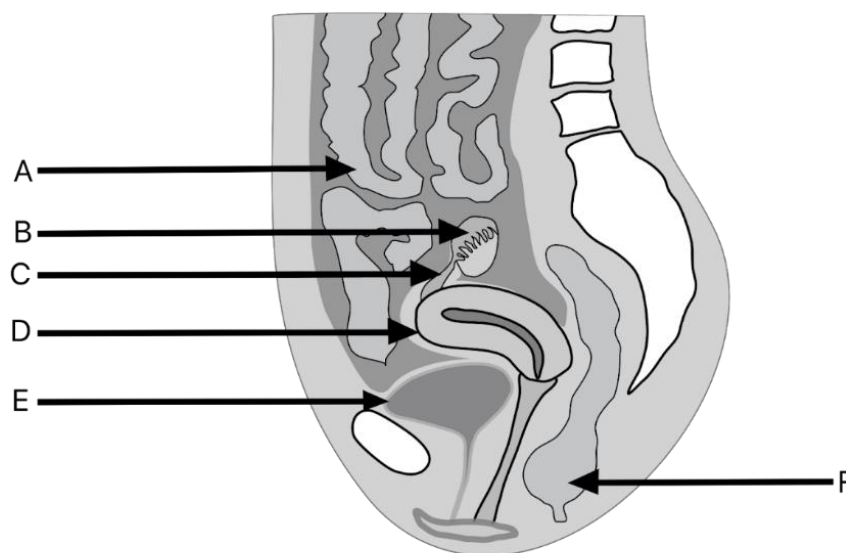


Figure 1. The most frequently observed endometriosis foci locations.
A - intestine, B - ovary, C - fallopian tube, D - uterine wall, E - bladder, F - rectum
Source: own work

The most important risk factors for endometriosis are prolonged estrogen exposure from early menarche to late menopause and a shorter menstrual cycle length [6]. Endometriosis is classified into the following stages [7]:

- **Stage1.**

Endometriosis areas that grow outside the uterus are few and shallow, measuring no more than 5 mm in diameter. The tubes may be involved in avascular adhesions, but the fimbriae are free. Although the ovaries may have vascular adhesion, there is no ovarian fixation.

- **Stage2.**

The implants are more deeply embedded. Ovarian involvement might manifest as a cyst

or a surface area larger than 5 cm. The ovaries are fixed to the broad ligament and have regions of endometriosis larger than 5 mm in diameter.

- **Stage3.**

Adhesions surround the tubal fimbriae. Implants covering the bowels and uterus have been fixed.

- **Stage4.**

Implants in the bladder and appendix. Adhesions link the bowels, uterus and uterosacral ligaments.

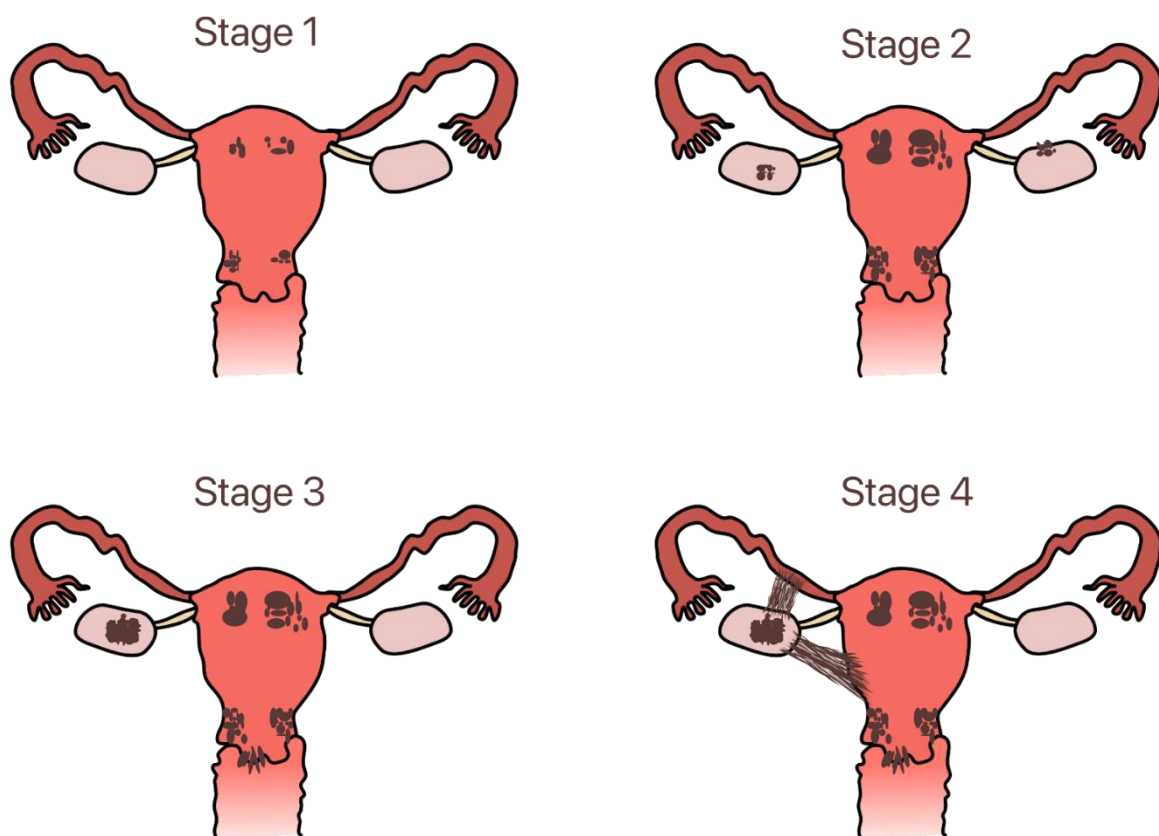


Figure 2. Stages of endometriosis, Source: own work

The pathophysiology of the condition is still unknown, but several theories of etiopathogenesis for the disease have been proposed so far. The most significant of these is the nearly 100-year-old theory of implantation. The concept is based on the observation of retrograde menstruation, where endometrial cells escape through the fallopian tubes into the peritoneal cavity. When the woman's immune system is unable to remove these cells, they primarily implant in the organs of the pelvis minor. However, it is acknowledged that the

implantation theory is probably no longer applicable [8]. There are other different hypotheses, such as Endometrial Stem Cell Recruitment Theory, Bone Marrow-Derived Stem Cell Theory, Immune Dysregulation, Hormonal Imbalance, etc. [9].

DIAGNOSTICS

Even highly trained experts face challenges when diagnosing endometriosis. The fundamental issue is the presence of non-specific symptoms such as persistent pain that appears at different points in the menstrual cycle, as well as unrelated to it, tiredness, bloating, constipation, diarrhea and discomfort during sexual activity (dyspareunia) [1]. It is common for the above symptoms to be ignored by both patients and doctors. One of the contributing causes is likely a lack of understanding of the disease by healthcare practitioners [1]. Painful menstruation is frequently considered as a physiological symptom that does not require diagnostic implementation, a variant of the standard. Many times, it is assumed that these individuals exaggerate the symptoms or suffer from conditions of a psychosomatic nature, which consequently leads to referral to gastroenterologists or even psychiatrists [10]. Another issue could be an inaccurate gynecological examination and the examining physician's lack of experience [11]. The clinical examination cannot detect minor and superficial alterations [12]. Transvaginal ultrasound appears to be an adequate diagnostic tool. Although, the accuracy of diagnosis is dependent on the sonographer's competence. Ultrasonography has a reported sensitivity and specificity of >85% in the detection of endometriosis. This does not, however, imply that all alterations will be seen in the imaging, because ultrasonographic investigations are ineffective for diagnosing sigmoid endometriosis [13,14]. MRI provides information about areas that are not visible on ultrasound, although, it is limited in its sensitivity for detecting the depth of lesion invasion [13].

Until recently, laparoscopy was considered the "gold standard" for detecting endometriosis. It confirms the presence of the disease and its spread. The aggressiveness of the lesions can be assessed via tissue biopsies and pathological examination. Another issue is that diagnostic laparoscopy is often avoided and delayed, particularly in younger women, because endometriosis severity is difficult to estimate, and surgery might be unexpectedly challenging [1,12,15]. Therefore, according to the most recent guidelines, laparoscopy is now only recommended for patients who have negative imaging results [16].

Another concern is that no particular biomarker for endometriosis has been established so far. Ca125 levels can indeed be raised in endometriosis, but they can also be associated with

ovarian cancer, peritoneal irritation due to infection, pregnancy, or even menstruation. Therefore, this biomarker is limited to its use in diagnosing endometriosis in patients with chronic pelvic pain as well as to evaluating treatment response [17,18].

A breakthrough in diagnostics came with the patenting of the EndoRNA qRT-PCR test.

The aim of the test is to determine the mRNA level of the FUT4 gene relative to the mRNA level of a reference gene encoding 3-phosphoglyceraldehyde dehydrogenase. FUT4 expression is significantly elevated in endometrial cells of patients with endometriosis. The test is done during the secretory phase of the menstrual cycle using an aspiration biopsy of the endometrium. EndoRNA testing is performed by quantitative RT-PCR (qRT-PCR). The sensitivity of the test is 94.12%, and the specificity of the test is 89.29% [19–21].

TREATMENT

Treatment of endometriosis depends on the individual case, the severity of the disease and the symptoms. The goals of endometriosis treatment are to eliminate pain, reduce the growth and removal of endometrial foci as well as enable pregnancy [2].

Pharmacological treatment

The major available drugs for the treatment of endometriosis belong to several groups: estrogens-progestins (oral contraceptives), progestins, GnRH agonists and GnRH antagonists [22].

Oral contraceptives and progestins are commonly used as first-line pharmacological therapy for symptomatic endometriosis. They have a hyperprogestogenic effect helping reduce inflammation, induce atrophy of endometriotic tissue, and limit retrograde menstruation. Studies have shown that the majority of women with endometriosis-related pelvic pain benefit from estrogen-progestin combinations and experience a significant improvement in their quality of life. However, some women may not respond to this treatment, possibly due to progesterone resistance. In addition, they induce side effects such as unexpected bleeding, breast soreness, nausea, headaches, and mood fluctuations [22,23]

Different modalities of delivering estrogen-progestin therapy, such as oral, vaginal, or transdermal administration, can be tailored to individual preferences to improve compliance and adherence. Contraceptives also offer the advantage of maintaining cyclic uterine bleeding, which some women consider important. If dysmenorrhea persists with cyclic usage, continuous administration of estrogen-progestins can be considered [22].

GnRH analogs, including both agonists and antagonists, are used when first-line therapies are not effective in managing endometriosis-associated pain. GnRH agonists create a hypoestrogenic state, effectively reducing symptoms, but their use is limited by side effects such as vasomotor symptoms, genital hypotrophy and mood swings. They also result in a negative calcium balance, which increases the risk of osteopenia. Because of the androgenic effects, this class of medicines is not recommended for long-term treatment [22,23].

In addition to the aforementioned drugs, anti-inflammatory medications are often prescribed as adjuncts. These medications are effective in alleviating primary dysmenorrhea, but patients need to be mindful of potential adverse effects, including the risk of gastric ulcers, cardiovascular events, and acute renal failure [23].

Surgical treatment

Surgical treatment aims to reduce endometriosis-associated pain and restore normal anatomy. All applicable guidelines recommend laparoscopic surgery over laparotomy for chronic pain and infertility because of the shorter hospitalization, less pain, and better cosmetic results [16,24–31]. To date, robotic surgery is not included as an option in the recommendations, although it has been proven that robotic-assisted laparoscopy yields similar outcomes [13]. Operative laparoscopy with excision or ablation reduces endometriosis-associated pain, generally with no preference for different techniques [24,29] but ESHRE (European Society of Human Reproduction and Embryology) presents weak recommendations for considering excision [16]. Ovarian endometriomas can be excised, especially if they cause pain or if there is a concern for malignancy. Surgical treatment includes cystectomy, drainage, coagulation, and CO₂ laser vaporization. In terms of recurrence of dysmenorrhoea, dyspareunia, cyst recurrences, and the need for additional surgical procedures, laparoscopic cystectomy of endometriomas measuring more than 3 cm is superior to drainage and ablation with electrocoagulation. Simple drainage has limited therapeutic effect because the recurrence rate is 80-100% and is hence no longer practiced [28,29]. Only ESHRE [16] and CNGOF (Collège National des Gynécologues et Obstétriciens Français) [24] address laser vaporization in endometrioma treatment due to similar recurrence rates beyond the first year after surgery. According to ACOG (American College of Obstetricians and Gynecologists), the cyst wall should be removed to acquire a histology sample, especially in women who have never had endometriosis, in order to rule out the minimal chance of malignancy [32]. To avoid ovarian damage during surgery for ovarian endometrioma, special precautions should be taken. Cystectomy, or ablation can decrease ovarian reserve, which has a detrimental impact on

fertility. Women with recurring or bilateral endometriomas are at a higher risk.

Prior to ovarian surgery, Anti-Mullerian Hormone levels must be measured. Oocyte freezing should be considered by young women prior to endometrioma surgery [33]. Women with DIE should be assigned to tertiary care centers for a comprehensive surgical approach [34]. For endometriosis-related pain, most standards recommend the removal of deep, infiltrating endometriosis nodules. This procedure is associated with significant intraoperative and postoperative complications, which include leaks from anastomosis, fistulas, rectal dysfunction, and bladder atony caused by surgical alteration of the hypogastric plexus (splanchnic nerves) [16,24,35].

In patients who have completed their family planning and have not responded to more conservative therapies, laparoscopic hysterectomy with concomitant removal of endometriotic lesions may be considered. It is not clearly defined whether hysterectomy with bilateral salpingo-oophorectomy (TAHBSO) or ovarian preservation should be preferred [16,24–31]. TAHBSO lowers the risk of pain recurrence and reoperation; however, maintaining healthy ovaries preserves hormonal function. Even such an extensive procedure does not remove the risk of a recurrence of symptoms. Pain persistence is observed in approximately 15% of patients, and 5% can develop new symptoms [36]. Laparoscopic uterine nerve ablation (LUNA) is a procedure that involves the destruction of uterine nerve fibers that exit the uterus through the uterosacral ligament in order to reduce uterine pain in women with refractory dysmenorrhea. However, it appears that it is ineffective as a supplement to standard laparoscopic surgery for endometriosis because it offers no meaningful advantage over surgery alone [37]. The interruption of the sympathetic innervation of the uterus at the level of the superior hypogastric plexus is referred to as presacral neurectomy. It is a complex procedure that has a considerable risk of bleeding from the venous plexus. Hematoma, constipation, and urinary dysfunction are some of the possible side effects of presacral neurectomy. However, as an addition to traditional laparoscopic surgery, it may be effective for the treatment of endometriosis-related midline pain [38]. The latest guidelines do not recommend preoperative hormone treatment to improve the outcome of surgery for pain [16,24], thus it can be considered as a postoperative additional treatment in secondary prevention [16,24,26,30].

Alternative treatment options

The literature draws attention to proper diet in the prevention and treatment of endometriosis. Trans fat, palmitic acid, and red meat consumption are linked to a higher incidence of endometriosis, whereas monounsaturated fats and omega-3 polyunsaturated fatty

acids, plant-based meals, particularly fiber, antioxidants, and vitamin D, may be beneficial for both prevention and therapy [39,40]. Acupuncture and electrotherapy are also thought to be beneficial in the treatment of pain related to endometriosis [41].

PSYCHOLOGICAL ASPECT

In addition to physical symptoms, women with endometriosis experience a variety of psychological difficulties. This disease negatively affects the overall quality of life. Chronic pain, unpredictable symptoms, and the impact on everyday activities can all lead to emotional distress [42]. Endometriosis can cause physical alterations such as bloating, weight fluctuations, and surgical scars. These changes might have an impact on one's physique and self-esteem, resulting in feelings of insecurity or a negative body image [43]. Some patients may unfortunately experience disparagement and be accused of exaggerating or fabricating their symptoms during medical visits [42].

Endometriosis pain can interfere with sexual intimacy and relationships. Fear of pain during intercourse, decreased libido as a result of medication or hormonal imbalances, and reproductive issues can all strain personal relationships and communication [44].

Endometriosis especially causes difficulties with work and social life when pain, fatigue and absenteeism are not understood by the surrounding community [45].

Seeking help from medical specialists, therapists, support groups, or family members is critical for dealing with the psychological components of endometriosis [46].

In order to increase the detection rate of endometriosis and public awareness of the disease, educational campaigns should be introduced, preferably among young people [47,48].

DISCUSSION

Endometriosis is a highly complex condition that requires a multifaceted approach. The first issues occur during the diagnosis stage, often resulting in significant delays. The primary challenges include a lack of specific markers, standardized diagnostic criteria, and clinicians' typically contemptuous attitude toward patients with unclear symptoms. Another issue lies in the lack of understanding of the disease, its inconsistent picture, and the common belief that painful menstruation is the norm.

There are also many concerns regarding the treatment of endometriosis. Oral contraceptives, gestagens, antiestrogens, and gonadoliberein analogues suppress symptoms and

slow down the disease process but do not eliminate endometriosis outbreaks. Pharmacotherapy has a long duration and has several adverse effects that patients may continue to experience even after completing the treatment. Surgical treatment of endometriosis, however, is frequently linked with numerous complications as well as insufficient excision of the foci, which promotes recurrence. Furthermore, removing ovarian endometrial cysts reduces ovarian reserve, which can result in infertility in the patient. Chronic pain and associated symptoms can significantly limit daily activities, exclude patients from social and professional life, and decrease patients' well-being.

It is therefore essential to enhance public awareness—among doctors, patients, and their families—in order to improve the process of diagnosis, treatment, and adequate care for women affected with endometriosis.

REFERENCES

1. Chapron C., Marcellin L., Borghese B., Santulli P.: Rethinking mechanisms, diagnosis and management of endometriosis. *Nature Reviews Endocrinology*, 2019, 15, 666–682.
2. Horne A.W., Missmer S.A.: Pathophysiology, diagnosis, and management of endometriosis. *BMJ (Clinical Research Ed)*, 2022, 379.
3. Smolarz B., Szyłło K. and Romanowicz H.: Endometriosis: Epidemiology, Classification, Pathogenesis, Treatment and Genetics (Review of Literature). *International Journal of Molecular Sciences*, 2021, 22, 10554.
4. Basta A., Brucka A., Górski J. et al.: The statement of polish society's experts group concerning diagnostics and methods of endometriosis treatment. *Ginekologia Polska*, 2012, 83, 871–876.
5. Van den Bosch T., Van Schoubroeck D.: Ultrasound diagnosis of endometriosis and adenomyosis: State of the art. *Best Practice & Research Clinical Obstetrics & Gynaecology*, 2018, 51, 16–24.
6. Blass I., Sahar T., Shraibman A. et al.: Revisiting the Risk Factors for Endometriosis: A Machine Learning Approach. *Journal of Personalized Medicine*, 2022, 7, 12(7), 1114.
7. Kistner R.W., Siegler A.M., Behrman S.J.: Suggested Classification for Endometriosis: Relationship to Infertility. *Fertility and Sterility*, 1977, 28, 1008–1010.
8. Amro B., Aristondo M.E.R., Alsuwaidi S. et al.: New Understanding of Diagnosis, Treatment and Prevention of Endometriosis. *International Journal of Environmental Research and Public Health*, 2022, 31, 19(11), 6725.

9. Lamceva J., Uljanovs R., Strumfa I.: The Main Theories on the Pathogenesis of Endometriosis. *International Journal of Molecular Sciences*, 2023, 24(5), 4254.
10. Barcz E.: Najczęstsze błędy w diagnostyce i leczeniu endometriozy. *Ginekologia po Dyplomie*, 2016, 06. <https://podyplomie.pl/ginekologia/22712,najczestsze-bledy-w-diagnostyce-i-leczeniu-endometriozy>, Accessed 30 June 2023.
11. Bazot M., Daraï E.: Diagnosis of deep endometriosis: clinical examination, ultrasonography, magnetic resonance imaging, and other techniques. *Fertility and Sterility*, 2017, 108, 886–894.
12. Koninckx P.R., Fernandes R., Ussia A., Schindler L., Wattiez A., et al.: Pathogenesis Based Diagnosis and Treatment of Endometriosis. *Frontiers in Endocrinology*, 2021, 25, 12, 745548.
13. Nezhat C., Li A., Falik R. et al.: Bowel endometriosis: diagnosis and management. *American Journal of Obstetrics and Gynecology*, 2018, 218, 549–562.
14. Koninckx P.R., Ussia A., Adamyan L., et al. Deep endometriosis: definition, diagnosis, and treatment. *Fertility and Sterility*, 2012, 98, 564–571.
15. Rolla E.: Endometriosis: advances and controversies in classification, pathogenesis, diagnosis, and treatment. *F1000Research*, 2019, 8, 529.
16. Becker C.M., Bokor A., Heikinheimo O. et al.: ESHRE guideline: endometriosis. *Human Reproduction Open*, 2022, 26, 2022(20), hoac009.
17. Falcone T., Flyckt-Rebecca R.: Clinical Management of Endometriosis. *Obstetrics and Gynecology*, 2018, 131, 557–571.
18. Muyldermans M., Cornillie F.J., Koninckx P.R.: CA125 and endometriosis. *Human Reproduction Update*, 1995, 1, 173–187.
19. Żeberkiewicz M., Hyc A., Iwan A., Zwierzchowska A., Ścieżyńska A. et al.: Expression of Fucosyltransferase 4 (FUT4) mRNA Is Increased in Endometrium from Women with Endometriosis. *Journal of Clinical Medicine*, 2022, 11, 23, 11(19), 5606.
20. EndoRNA nowy nieinwazyjny test w kierunku endometriozy • oznaczanie poziomu ekspresji genu FUT4 • VeritaMed Warszawa • Centrum. <https://veritamed.com/aktualnosc/2172/EndoRNA-nowy-nieinwazyjny-test-w-kierunku-endometriozy>, Accessed 30 June 2023.
21. Przelomowy test na endometriozę, badanie i diagnostyka. InviMed. <https://www.invimed.pl/przelomowy-test-na-endometrioze>, Accessed 30 June 2023.
22. Barbara G., Buggio L., Facchin F., Vercellini P.: Medical Treatment for Endometriosis: Tolerability, Quality of Life and Adherence. *Frontiers in Global Women's Health*,

- 2021, 27, 2, 729601.
23. França P.R. de C., Lontra A.C.P., Fernandes P.D.: Endometriosis: A Disease with Few Direct Treatment Options. *Molecules*, 2022, 23, 27(13), 4034.
 24. Collinet P., Fritel X., Revel-Delhom C. et al.: Management of endometriosis: CNGOF/HAS clinical practice guidelines - Short version. *Journal of Gynecology Obstetrics and Human Reproduction*, 2018, 47, 265–274.
 25. Ulrich U., Buchweitz O., Greb R. et al.: National German Guideline (S2k): Guideline for the Diagnosis and Treatment of Endometriosis: Long Version - AWMF Registry No. 015-045. *Geburtshilfe Und Frauenheilkunde*, 2014, 74, 1104–1118.
 26. Leyland N., Casper R., Laberge P. et al.: Endometriosis: Diagnosis and Management. *Journal of Obstetrics and Gynaecology Canada*, 2010, 32, S1–S3.
 27. Practice bulletin no. 114: management of endometriosis. *Obstetrics and Gynecology*, 2010, 116, 223–236.
 28. Endometriosis and infertility: a committee opinion. *Fertility and Sterility*, 2012, 98, 591–598.
 29. Treatment of pelvic pain associated with endometriosis: a committee opinion. *Fertility and Sterility*, 2014, 101, 927–35.
 30. Diagnosis and management of endometriosis: summary of NICE guidance. *BMJ (Clinical Research Ed)*, 2017, 358, j4227.
 31. Johnson N.P., Hummelshoj L.: Consensus on current management of endometriosis. *Human Reproduction (Oxford, England)*, 2013, 28, 1552–1568.
 32. Kalaitzopoulos D.R., Mitsopoulou A., Iliopoulou S.M., Daniilidis A., Samartzis E.P. et al.: Association between endometriosis and gynecological cancers: a critical review of the literature. *Archives of Gynecology and Obstetrics*, 2020, 301, 355–367.
 33. Carrillo L., Seidman D.S., Cittadini E., Meirow D.: The role of fertility preservation in patients with endometriosis. *Journal of Assisted Reproduction and Genetics*, 2016, 33, 317–323.
 34. Kodaman P.H.: Current strategies for endometriosis management. *Obstetrics and Gynecology Clinics of North America*, 2015, 42, 87–101.
 35. Soto E., Luu T.H., Liu X. et al.: Laparoscopy vs. Robotic Surgery for Endometriosis (LAROSE): a multicenter, randomized, controlled trial. *Fertility and Sterility*, 2017, 107, 996-1002.e3.

36. Vercellini P., Barbara G., Abbiati A. et al.: Repetitive surgery for recurrent symptomatic endometriosis: what to do? *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, 2009, 146, 15–21.
37. Proctor M., Latthe P., Farquhar C., Khan K., Johnson N.: Surgical interruption of pelvic nerve pathways for primary and secondary dysmenorrhoea. *The Cochrane Database of Systematic Reviews*, 2005, 19, 2005(4), CD001896.
38. Miller L.E., Bhattacharyya R., Miller V.M.: Clinical Utility of Presacral Neurectomy as an Adjunct to Conservative Endometriosis Surgery: Systematic Review and Meta-Analysis of Controlled Studies. *Scientific Reports*, 2020, 10. 6901.
39. Barnard N.D., Holtz D.N., Schmidt N. et al.: Nutrition in the prevention and treatment of endometriosis: A review. *Frontiers in Nutrition*, 2023, 10. 17, 10, 1089891.
40. Marcinkowska A., Górnicka M.: The Role of Dietary Fats in the Development and Treatment of Endometriosis. *Life*, 2023, 13, 654.
41. Kalaitzopoulos D.R., Samartzis N., Kolovos G.N. et al.: Treatment of endometriosis: a review with comparison of 8 guidelines. *BMC Women's Health*, 2021, 21, 397.
42. Psychiatry.org - How Endometriosis, a Common, Painful Condition Many Women Face, Can Impact Mental Health. <https://www.psychiatry.org/news-room/apa-blogs/how-endometriosis-can-impact-mental-health> Accessed 30 June 2023.
43. Melis I., Litta P., Nappi L., Agus M., Melis G.B. et al.: Sexual Function in Women with Deep Endometriosis: Correlation with Quality of Life, Intensity of Pain, Depression, Anxiety, and Body Image. *International Journal of Sexual Health*, 2015, 27, 175–185.
44. Privitera G., O'Brien K., Misajon R.A., Lin C.Y.: Endometriosis Symptomatology, Dyspareunia, and Sexual Distress Are Related to Avoidance of Sex and Negative Impacts on the Sex Lives of Women with Endometriosis. *International Journal of Environmental Research and Public Health*, 2023, 14, 20(4), 3362.
45. Corte L. Della, Di Filippo C. et al.: The Burden of Endometriosis on Women's Lifespan: A Narrative Overview on Quality of Life and Psychosocial Wellbeing. *International Journal of Environmental Research and Public Health*, 2020, 17, 1–17.
46. Young K., Fisher J., Kirkman M.: Women's experiences of endometriosis: a systematic review and synthesis of qualitative research. *The Journal of Family Planning and Reproductive Health Care*, 2015, 41, 225–234.
47. Bush D., Brick E., East M.C., Johnson N.: Endometriosis education in schools: A New Zealand model examining the impact of an education program in schools on early recognition of symptoms suggesting endometriosis. *The Australian & New Zealand*

Journal of Obstetrics & Gynaecology, 2017, 57, 452–457.

48. Elrahim A.H.A., Abdelnaem S.A., Abuzaid O.N., Allah M.F.H.: Educational Intervention and Referral for Early Detection of Endometriosis among Technical Secondary Schools Students. Egyptian Nursing Journal, 2023, 19, 141.

ENDOMETRIOSIS – WHAT WE SHOULD KNOW

Anita Froń, Urszula Tokarczyk, Karol Zagórski

Wroclaw Medical University

ABBREVIATION LIST

- ACOG - American College of Obstetricians and Gynecologists
- CNGOF - Collège National des Gynécologues et Obstétriciens Français
- DIE - deep infiltrating endometriosis
- ESHRE - European Society of Human Reproduction and Embryology
- GnRH - gonadotropin-releasing hormone
- LUNA - laparoscopic uterine nerve ablation
- MRI - magnetic resonance imaging
- qRT-PCR - quantitative reverse transcription polymerase chain reaction
- TAHBSO - hysterectomy with bilateral salpingo-oophorectomy

INTRODUCTION

Endometriosis, a complex and chronic gynecological condition, poses significant challenges for both patients and medical professionals. Characterized by the abnormal growth of endometrial tissue outside the uterus, endometriosis affects millions of women worldwide, causing local inflammation, debilitating pain, fertility issues, and a host of other symptoms. Managing this enigmatic condition requires a multidimensional approach, encompassing accurate diagnosis, personalized treatment plans, and comprehensive care that addresses the physical, emotional, and social aspects of the disease [1,2].

Endometriosis is the second most common gynecological condition in reproductive-age women, affecting 5-30% of the population. It is estimated that endometriosis affects about 190 million women worldwide. The percentages among infertile women and women with chronic pelvic pain can approach 50% and 30%, respectively. The condition is most prevalent between the ages of 25 and 40. Nonetheless, epidemiological studies indicate an increase in endometriosis prevalence among adolescents (2-5%) and postmenopausal women (3-6%).

There have been isolated cases of endometriosis-like symptoms in men undergoing hormone treatment for prostate cancer [2–4].

Endometriosis can be superficial, affecting the peritoneum of the pelvic organs and abdominal wall, including the diaphragm, or the surface of the ovary, which can create ovarian cysts (endometriomas). Deep infiltrating endometriosis (DIE) occurs when endometriosis spreads beyond the peritoneum and invades the bladder, intestinal wall, and structures surrounding the uterus. It usually manifests itself as a singular nodule in the vesicouterine fold or in the lowest 20 cm of the intestine [5].

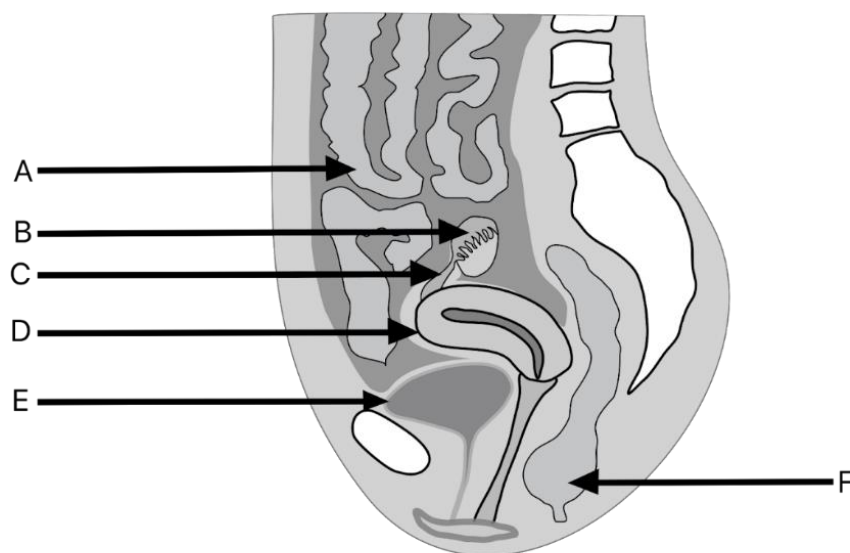


Figure 1. The most frequently observed endometriosis foci locations.
A - intestine, B - ovary, C - fallopian tube, D - uterine wall, E - bladder, F - rectum
Source: own work

The most important risk factors for endometriosis are prolonged estrogen exposure from early menarche to late menopause and a shorter menstrual cycle length [6]. Endometriosis is classified into the following stages [7]:

- **Stage 1.**

Endometriosis areas that grow outside the uterus are few and shallow, measuring no more than 5 mm in diameter. The tubes may be involved in avascular adhesions, but the fimbriae are free. Although the ovaries may have vascular adhesion, there is no ovarian fixation.

- **Stage 2.**

The implants are more deeply embedded. Ovarian involvement might manifest as a cyst or a surface area larger than 5 cm. The ovaries are fixed to the broad ligament and have regions of endometriosis larger than 5 mm in diameter.

- **Stage 3.**

Adhesions surround the tubal fimbriae. Implants covering the bowels and uterus have been fixed.

- **Stage 4.**

Implants in the bladder and appendix. Adhesions link the bowels, uterus and uterosacral ligaments.

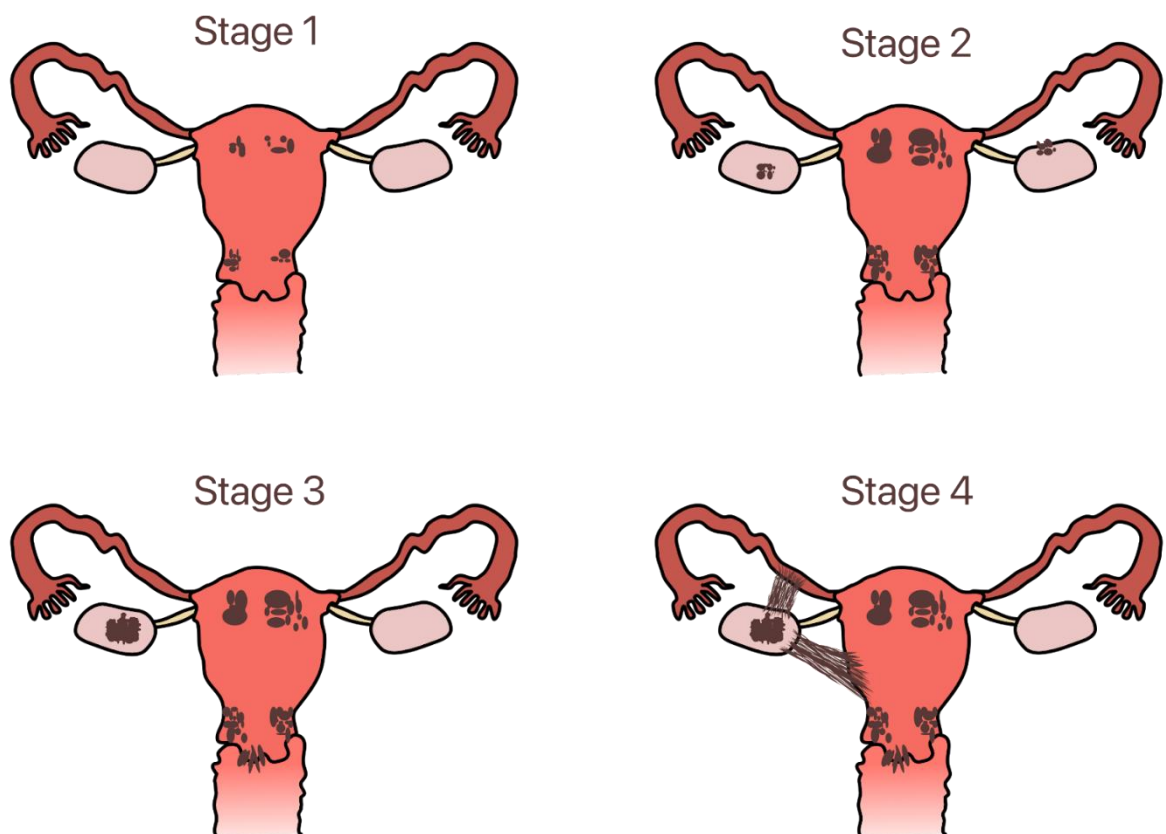


Figure 2. Stages of endometriosis, Source: own work

The pathophysiology of the condition is still unknown, but several theories of etiopathogenesis for the disease have been proposed so far. The most significant of these is the nearly 100-year-old theory of implantation. The concept is based on the observation of retrograde menstruation, where endometrial cells escape through the fallopian tubes into the peritoneal cavity. When the woman's immune system is unable to remove these cells, they primarily implant in the organs of the pelvis minor. However, it is acknowledged that the

implantation theory is probably no longer applicable [8]. There are other different hypotheses, such as Endometrial Stem Cell Recruitment Theory, Bone Marrow-Derived Stem Cell Theory, Immune Dysregulation, Hormonal Imbalance, etc. [9].

DIAGNOSTICS

Even highly trained experts face challenges when diagnosing endometriosis. The fundamental issue is the presence of non-specific symptoms such as persistent pain that appears at different points in the menstrual cycle, as well as unrelated to it, tiredness, bloating, constipation, diarrhea and discomfort during sexual activity (dyspareunia) [1]. It is common for the above symptoms to be ignored by both patients and doctors. One of the contributing causes is likely a lack of understanding of the disease by healthcare practitioners [1]. Painful menstruation is frequently considered as a physiological symptom that does not require diagnostic implementation, a variant of the standard. Many times, it is assumed that these individuals exaggerate the symptoms or suffer from conditions of a psychosomatic nature, which consequently leads to referral to gastroenterologists or even psychiatrists [10]. Another issue could be an inaccurate gynecological examination and the examining physician's lack of experience [11]. The clinical examination cannot detect minor and superficial alterations [12]. Transvaginal ultrasound appears to be an adequate diagnostic tool. Although, the accuracy of diagnosis is dependent on the sonographer's competence. Ultrasonography has a reported sensitivity and specificity of >85% in the detection of endometriosis. This does not, however, imply that all alterations will be seen in the imaging, because ultrasonographic investigations are ineffective for diagnosing sigmoid endometriosis [13,14]. MRI provides information about areas that are not visible on ultrasound, although, it is limited in its sensitivity for detecting the depth of lesion invasion [13].

Until recently, laparoscopy was considered the "gold standard" for detecting endometriosis. It confirms the presence of the disease and its spread. The aggressiveness of the lesions can be assessed via tissue biopsies and pathological examination. Another issue is that diagnostic laparoscopy is often avoided and delayed, particularly in younger women, because endometriosis severity is difficult to estimate, and surgery might be unexpectedly challenging [1,12,15]. Therefore, according to the most recent guidelines, laparoscopy is now only recommended for patients who have negative imaging results [16].

Another concern is that no particular biomarker for endometriosis has been established so far. Ca125 levels can indeed be raised in endometriosis, but they can also be associated with

ovarian cancer, peritoneal irritation due to infection, pregnancy, or even menstruation. Therefore, this biomarker is limited to its use in diagnosing endometriosis in patients with chronic pelvic pain as well as to evaluating treatment response [17,18].

A breakthrough in diagnostics came with the patenting of the EndoRNA qRT-PCR test.

The aim of the test is to determine the mRNA level of the FUT4 gene relative to the mRNA level of a reference gene encoding 3-phosphoglycerate dehydrogenase. FUT4 expression is significantly elevated in endometrial cells of patients with endometriosis. The test is done during the secretory phase of the menstrual cycle using an aspiration biopsy of the endometrium. EndoRNA testing is performed by quantitative RT-PCR (qRT-PCR). The sensitivity of the test is 94.12%, and the specificity of the test is 89.29% [19–21].

TREATMENT

Treatment of endometriosis depends on the individual case, the severity of the disease and the symptoms. The goals of endometriosis treatment are to eliminate pain, reduce the growth and removal of endometrial foci as well as enable pregnancy [2].

Pharmacological treatment

The major available drugs for the treatment of endometriosis belong to several groups: estrogens-progestins (oral contraceptives), progestins, GnRH agonists and GnRH antagonists [22].

Oral contraceptives and progestins are commonly used as first-line pharmacological therapy for symptomatic endometriosis. They have a hyperprogestogenic effect helping reduce inflammation, induce atrophy of endometriotic tissue, and limit retrograde menstruation. Studies have shown that the majority of women with endometriosis-related pelvic pain benefit from estrogen-progestin combinations and experience a significant improvement in their quality of life. However, some women may not respond to this treatment, possibly due to progesterone resistance. In addition, they induce side effects such as unexpected bleeding, breast soreness, nausea, headaches, and mood fluctuations [22,23]

Different modalities of delivering estrogen-progestin therapy, such as oral, vaginal, or transdermal administration, can be tailored to individual preferences to improve compliance and adherence. Contraceptives also offer the advantage of maintaining cyclic uterine bleeding, which some women consider important. If dysmenorrhea persists with cyclic usage, continuous administration of estrogen-progestins can be considered [22].

GnRH analogs, including both agonists and antagonists, are used when first-line therapies are not effective in managing endometriosis-associated pain. GnRH agonists create a hypoestrogenic state, effectively reducing symptoms, but their use is limited by side effects such as vasomotor symptoms, genital hypotrophy and mood swings. They also result in a negative calcium balance, which increases the risk of osteopenia. Because of the androgenic effects, this class of medicines is not recommended for long-term treatment [22,23].

In addition to the aforementioned drugs, anti-inflammatory medications are often prescribed as adjuncts. These medications are effective in alleviating primary dysmenorrhea, but patients need to be mindful of potential adverse effects, including the risk of gastric ulcers, cardiovascular events, and acute renal failure [23].

Surgical treatment

Surgical treatment aims to reduce endometriosis-associated pain and restore normal anatomy. All applicable guidelines recommend laparoscopic surgery over laparotomy for chronic pain and infertility because of the shorter hospitalization, less pain, and better cosmetic results [16,24–31]. To date, robotic surgery is not included as an option in the recommendations, although it has been proven that robotic-assisted laparoscopy yields similar outcomes [13]. Operative laparoscopy with excision or ablation reduces endometriosis-associated pain, generally with no preference for different techniques [24,29] but ESHRE (European Society of Human Reproduction and Embryology) presents weak recommendations for considering excision [16]. Ovarian endometriomas can be excised, especially if they cause pain or if there is a concern for malignancy. Surgical treatment includes cystectomy, drainage, coagulation, and CO₂ laser vaporization. In terms of recurrence of dysmenorrhoea, dyspareunia, cyst recurrences, and the need for additional surgical procedures, laparoscopic cystectomy of endometriomas measuring more than 3 cm is superior to drainage and ablation with electrocoagulation. Simple drainage has limited therapeutic effect because the recurrence rate is 80-100% and is hence no longer practiced [28,29]. Only ESHRE [16] and CNGOF (Collège National des Gynécologues et Obstétriciens Français) [24] address laser vaporization in endometrioma treatment due to similar recurrence rates beyond the first year after surgery. According to ACOG (American College of Obstetricians and Gynecologists), the cyst wall should be removed to acquire a histology sample, especially in women who have never had endometriosis, in order to rule out the minimal chance of malignancy [32]. To avoid ovarian damage during surgery for ovarian endometrioma, special precautions should be taken. Cystectomy, or ablation can decrease ovarian reserve, which has a detrimental impact on

fertility. Women with recurring or bilateral endometriomas are at a higher risk.

Prior to ovarian surgery, Anti-Mullerian Hormone levels must be measured. Oocyte freezing should be considered by young women prior to endometrioma surgery [33]. Women with DIE should be assigned to tertiary care centers for a comprehensive surgical approach [34]. For endometriosis-related pain, most standards recommend the removal of deep, infiltrating endometriosis nodules. This procedure is associated with significant intraoperative and postoperative complications, which include leaks from anastomosis, fistulas, rectal dysfunction, and bladder atony caused by surgical alteration of the hypogastric plexus (splanchnic nerves) [16,24,35].

In patients who have completed their family planning and have not responded to more conservative therapies, laparoscopic hysterectomy with concomitant removal of endometriotic lesions may be considered. It is not clearly defined whether hysterectomy with bilateral salpingo-oophorectomy (TAHBSO) or ovarian preservation should be preferred [16,24–31]. TAHBSO lowers the risk of pain recurrence and reoperation; however, maintaining healthy ovaries preserves hormonal function. Even such an extensive procedure does not remove the risk of a recurrence of symptoms. Pain persistence is observed in approximately 15% of patients, and 5% can develop new symptoms [36]. Laparoscopic uterine nerve ablation (LUNA) is a procedure that involves the destruction of uterine nerve fibers that exit the uterus through the uterosacral ligament in order to reduce uterine pain in women with refractory dysmenorrhea. However, it appears that it is ineffective as a supplement to standard laparoscopic surgery for endometriosis because it offers no meaningful advantage over surgery alone [37]. The interruption of the sympathetic innervation of the uterus at the level of the superior hypogastric plexus is referred to as presacral neurectomy. It is a complex procedure that has a considerable risk of bleeding from the venous plexus. Hematoma, constipation, and urinary dysfunction are some of the possible side effects of presacral neurectomy. However, as an addition to traditional laparoscopic surgery, it may be effective for the treatment of endometriosis-related midline pain [38]. The latest guidelines do not recommend preoperative hormone treatment to improve the outcome of surgery for pain [16,24], thus it can be considered as a postoperative additional treatment in secondary prevention [16,24,26,30].

Alternative treatment options

The literature draws attention to proper diet in the prevention and treatment of endometriosis. Trans fat, palmitic acid, and red meat consumption are linked to a higher incidence of endometriosis, whereas monounsaturated fats and omega-3 polyunsaturated fatty

acids, plant-based meals, particularly fiber, antioxidants, and vitamin D, may be beneficial for both prevention and therapy [39,40]. Acupuncture and electrotherapy are also thought to be beneficial in the treatment of pain related to endometriosis [41].

PSYCHOLOGICAL ASPECT

In addition to physical symptoms, women with endometriosis experience a variety of psychological difficulties. This disease negatively affects the overall quality of life. Chronic pain, unpredictable symptoms, and the impact on everyday activities can all lead to emotional distress [42]. Endometriosis can cause physical alterations such as bloating, weight fluctuations, and surgical scars. These changes might have an impact on one's physique and self-esteem, resulting in feelings of insecurity or a negative body image [43]. Some patients may unfortunately experience disparagement and be accused of exaggerating or fabricating their symptoms during medical visits [42].

Endometriosis pain can interfere with sexual intimacy and relationships. Fear of pain during intercourse, decreased libido as a result of medication or hormonal imbalances, and reproductive issues can all strain personal relationships and communication [44].

Endometriosis especially causes difficulties with work and social life when pain, fatigue and absenteeism are not understood by the surrounding community [45].

Seeking help from medical specialists, therapists, support groups, or family members is critical for dealing with the psychological components of endometriosis [46].

In order to increase the detection rate of endometriosis and public awareness of the disease, educational campaigns should be introduced, preferably among young people [47,48].

DISCUSSION

Endometriosis is a highly complex condition that requires a multifaceted approach. The first issues occur during the diagnosis stage, often resulting in significant delays. The primary challenges include a lack of specific markers, standardized diagnostic criteria, and clinicians' typically contemptuous attitude toward patients with unclear symptoms. Another issue lies in the lack of understanding of the disease, its inconsistent picture, and the common belief that painful menstruation is the norm.

There are also many concerns regarding the treatment of endometriosis. Oral contraceptives, gestagens, antiestrogens, and gonadoliberein analogues suppress symptoms and

slow down the disease process but do not eliminate endometriosis outbreaks. Pharmacotherapy has a long duration and has several adverse effects that patients may continue to experience even after completing the treatment. Surgical treatment of endometriosis, however, is frequently linked with numerous complications as well as insufficient excision of the foci, which promotes recurrence. Furthermore, removing ovarian endometrial cysts reduces ovarian reserve, which can result in infertility in the patient. Chronic pain and associated symptoms can significantly limit daily activities, exclude patients from social and professional life, and decrease patients' well-being.

It is therefore essential to enhance public awareness—among doctors, patients, and their families—in order to improve the process of diagnosis, treatment, and adequate care for women affected with endometriosis.

REFERENCES

1. Chapron C., Marcellin L., Borghese B., Santulli P.: Rethinking mechanisms, diagnosis and management of endometriosis. *Nature Reviews Endocrinology*, 2019, 15, 666–682.
2. Horne A.W., Missmer S.A.: Pathophysiology, diagnosis, and management of endometriosis. *BMJ (Clinical Research Ed)*, 2022, 379.
3. Smolarz B., Szyłło K. and Romanowicz H.: Endometriosis: Epidemiology, Classification, Pathogenesis, Treatment and Genetics (Review of Literature). *International Journal of Molecular Sciences*, 2021, 22, 10554.
4. Basta A., Brucka A., Górski J. et al.: The statement of polish society's experts group concerning diagnostics and methods of endometriosis treatment. *Ginekologia Polska*, 2012, 83, 871–876.
5. Van den Bosch T., Van Schoubroeck D.: Ultrasound diagnosis of endometriosis and adenomyosis: State of the art. *Best Practice & Research Clinical Obstetrics & Gynaecology*, 2018, 51, 16–24.
6. Blass I., Sahar T., Shraibman A. et al.: Revisiting the Risk Factors for Endometriosis: A Machine Learning Approach. *Journal of Personalized Medicine*, 2022, 7, 12(7), 1114.
7. Kistner R.W., Siegler A.M., Behrman S.J.: Suggested Classification for Endometriosis: Relationship to Infertility. *Fertility and Sterility*, 1977, 28, 1008–1010.
8. Amro B., Aristondo M.E.R., Alsuwaidi S. et al.: New Understanding of Diagnosis, Treatment and Prevention of Endometriosis. *International Journal of Environmental Research and Public Health*, 2022, 31, 19(11), 6725.

9. Lamceva J., Uljanovs R., Strumfa I.: The Main Theories on the Pathogenesis of Endometriosis. *International Journal of Molecular Sciences*, 2023, 24(5), 4254.
10. Barcz E.: Najczęstsze błędy w diagnostyce i leczeniu endometriozy. *Ginekologia po Dyplomie*, 2016, 06. <https://podyplomie.pl/ginekologia/22712,najczestsze-bledy-w-diagnostyce-i-leczeniu-endometriozy>, Accessed 30 June 2023.
11. Bazot M., Daraï E.: Diagnosis of deep endometriosis: clinical examination, ultrasonography, magnetic resonance imaging, and other techniques. *Fertility and Sterility*, 2017, 108, 886–894.
12. Koninckx P.R., Fernandes R., Ussia A., Schindler L., Wattiez A., et al.: Pathogenesis Based Diagnosis and Treatment of Endometriosis. *Frontiers in Endocrinology*, 2021, 25, 12, 745548.
13. Nezhat C., Li A., Falik R. et al.: Bowel endometriosis: diagnosis and management. *American Journal of Obstetrics and Gynecology*, 2018, 218, 549–562.
14. Koninckx P.R., Ussia A., Adamyan L., et al. Deep endometriosis: definition, diagnosis, and treatment. *Fertility and Sterility*, 2012, 98, 564–571.
15. Rolla E.: Endometriosis: advances and controversies in classification, pathogenesis, diagnosis, and treatment. *F1000Research*, 2019, 8, 529.
16. Becker C.M., Bokor A., Heikinheimo O. et al.: ESHRE guideline: endometriosis. *Human Reproduction Open*, 2022, 26, 2022(20), hoac009.
17. Falcone T., Flyckt-Rebecca R.: Clinical Management of Endometriosis. *Obstetrics and Gynecology*, 2018, 131, 557–571.
18. Muyldermans M., Cornillie F.J., Koninckx P.R.: CA125 and endometriosis. *Human Reproduction Update*, 1995, 1, 173–187.
19. Żeberkiewicz M., Hyc A., Iwan A., Zwierzchowska A., Ścieżyńska A. et al.: Expression of Fucosyltransferase 4 (FUT4) mRNA Is Increased in Endometrium from Women with Endometriosis. *Journal of Clinical Medicine*, 2022, 11, 23, 11(19), 5606.
20. EndoRNA nowy nieinwazyjny test w kierunku endometriozy • oznaczanie poziomu ekspresji genu FUT4 • VeritaMed Warszawa • Centrum. <https://veritamed.com/aktualnosc/2172/EndoRNA-nowy-nieinwazyjny-test-w-kierunku-endometriozy>, Accessed 30 June 2023.
21. Przelomowy test na endometriozę, badanie i diagnostyka. InviMed. <https://www.invimed.pl/przelomowy-test-na-endometrioze>, Accessed 30 June 2023.
22. Barbara G., Buggio L., Facchin F., Vercellini P.: Medical Treatment for Endometriosis: Tolerability, Quality of Life and Adherence. *Frontiers in Global Women's Health*,

- 2021, 27, 2, 729601.
23. França P.R. de C., Lontra A.C.P., Fernandes P.D.: Endometriosis: A Disease with Few Direct Treatment Options. *Molecules*, 2022, 23, 27(13), 4034.
 24. Collinet P., Fritel X., Revel-Delhom C. et al.: Management of endometriosis: CNGOF/HAS clinical practice guidelines - Short version. *Journal of Gynecology Obstetrics and Human Reproduction*, 2018, 47, 265–274.
 25. Ulrich U., Buchweitz O., Greb R. et al.: National German Guideline (S2k): Guideline for the Diagnosis and Treatment of Endometriosis: Long Version - AWMF Registry No. 015-045. *Geburtshilfe Und Frauenheilkunde*, 2014, 74, 1104–1118.
 26. Leyland N., Casper R., Laberge P. et al.: Endometriosis: Diagnosis and Management. *Journal of Obstetrics and Gynaecology Canada*, 2010, 32, S1–S3.
 27. Practice bulletin no. 114: management of endometriosis. *Obstetrics and Gynecology*, 2010, 116, 223–236.
 28. Endometriosis and infertility: a committee opinion. *Fertility and Sterility*, 2012, 98, 591–598.
 29. Treatment of pelvic pain associated with endometriosis: a committee opinion. *Fertility and Sterility*, 2014, 101, 927–35.
 30. Diagnosis and management of endometriosis: summary of NICE guidance. *BMJ (Clinical Research Ed)*, 2017, 358, j4227.
 31. Johnson N.P., Hummelshoj L.: Consensus on current management of endometriosis. *Human Reproduction (Oxford, England)*, 2013, 28, 1552–1568.
 32. Kalaitzopoulos D.R., Mitsopoulou A., Iliopoulou S.M., Daniilidis A., Samartzis E.P. et al.: Association between endometriosis and gynecological cancers: a critical review of the literature. *Archives of Gynecology and Obstetrics*, 2020, 301, 355–367.
 33. Carrillo L., Seidman D.S., Cittadini E., Meirow D.: The role of fertility preservation in patients with endometriosis. *Journal of Assisted Reproduction and Genetics*, 2016, 33, 317–323.
 34. Kodaman P.H.: Current strategies for endometriosis management. *Obstetrics and Gynecology Clinics of North America*, 2015, 42, 87–101.
 35. Soto E., Luu T.H., Liu X. et al.: Laparoscopy vs. Robotic Surgery for Endometriosis (LAROSE): a multicenter, randomized, controlled trial. *Fertility and Sterility*, 2017, 107, 996-1002.e3.

36. Vercellini P., Barbara G., Abbiati A. et al.: Repetitive surgery for recurrent symptomatic endometriosis: what to do? *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, 2009, 146, 15–21.
37. Proctor M., Latthe P., Farquhar C., Khan K., Johnson N.: Surgical interruption of pelvic nerve pathways for primary and secondary dysmenorrhoea. *The Cochrane Database of Systematic Reviews*, 2005, 19, 2005(4), CD001896.
38. Miller L.E., Bhattacharyya R., Miller V.M.: Clinical Utility of Presacral Neurectomy as an Adjunct to Conservative Endometriosis Surgery: Systematic Review and Meta-Analysis of Controlled Studies. *Scientific Reports*, 2020, 10. 6901.
39. Barnard N.D., Holtz D.N., Schmidt N. et al.: Nutrition in the prevention and treatment of endometriosis: A review. *Frontiers in Nutrition*, 2023, 10. 17, 10, 1089891.
40. Marcinkowska A., Górnicka M.: The Role of Dietary Fats in the Development and Treatment of Endometriosis. *Life*, 2023, 13, 654.
41. Kalaitzopoulos D.R., Samartzis N., Kolovos G.N. et al.: Treatment of endometriosis: a review with comparison of 8 guidelines. *BMC Women's Health*, 2021, 21, 397.
42. Psychiatry.org - How Endometriosis, a Common, Painful Condition Many Women Face, Can Impact Mental Health. <https://www.psychiatry.org/news-room/apa-blogs/how-endometriosis-can-impact-mental-health> Accessed 30 June 2023.
43. Melis I., Litta P., Nappi L., Agus M., Melis G.B. et al.: Sexual Function in Women with Deep Endometriosis: Correlation with Quality of Life, Intensity of Pain, Depression, Anxiety, and Body Image. *International Journal of Sexual Health*, 2015, 27, 175–185.
44. Privitera G., O'Brien K., Misajon R.A., Lin C.Y.: Endometriosis Symptomatology, Dyspareunia, and Sexual Distress Are Related to Avoidance of Sex and Negative Impacts on the Sex Lives of Women with Endometriosis. *International Journal of Environmental Research and Public Health*, 2023, 14, 20(4), 3362.
45. Corte L. Della, Di Filippo C. et al.: The Burden of Endometriosis on Women's Lifespan: A Narrative Overview on Quality of Life and Psychosocial Wellbeing. *International Journal of Environmental Research and Public Health*, 2020, 17, 1–17.
46. Young K., Fisher J., Kirkman M.: Women's experiences of endometriosis: a systematic review and synthesis of qualitative research. *The Journal of Family Planning and Reproductive Health Care*, 2015, 41, 225–234.
47. Bush D., Brick E., East M.C., Johnson N.: Endometriosis education in schools: A New Zealand model examining the impact of an education program in schools on early recognition of symptoms suggesting endometriosis. *The Australian & New Zealand*

Journal of Obstetrics & Gynaecology, 2017, 57, 452–457.

48. Elrahim A.H.A., Abdelnaem S.A., Abuzaid O.N., Allah M.F.H.: Educational Intervention and Referral for Early Detection of Endometriosis among Technical Secondary Schools Students. Egyptian Nursing Journal, 2023, 19, 141.

JUVENILE IDIOPATHIC ARTHRITIS - THE LATEST PERSPECTIVE ON THE CURRENT STATE OF KNOWLEDGE

Agata Boczar , Patryk Dryja

Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a chronic, inflammatory musculoskeletal disease that affects children before the age of 16. It is the most common inflammatory arthritis in this age group [1, 2].

The presentation of JIA is diverse and has an impact on prognosis, while the etiology remains largely unexplained [3].

EPIDEMIOLOGY

According to estimates, JIA occurs with a frequency ranging from 2.6 to 13.9 per 100,000 children, with a prevalence of 64 to 113.4 per 100,000 worldwide. In Poland, the incidence rate is approximately 6 per 100,000 children. Females are more susceptible to JIA, with an incidence rate nearly twice as high as in males (1.5-2:1) [4].

CLASSIFICATION AND DIAGNOSTIC CRITERIA

The classification of juvenile idiopathic arthritis is based on the criteria established by the International League of Associations for Rheumatology (ILAR). The following subtypes are distinguished:

- Systemic-onset juvenile idiopathic arthritis (sJIA) o Oligoarticular juvenile idiopathic arthritis (oJIA)
- Polyarticular juvenile idiopathic arthritis without rheumatoid factor (RF-) (pJIA-RF-)
- Polyarticular juvenile idiopathic arthritis with rheumatoid factor (RF+) (pJIA-RF+)

- Psoriatic juvenile idiopathic arthritis (psJIA) o Enthesitis-related juvenile idiopathic arthritis (ERA)
- Undifferentiated juvenile idiopathic arthritis [2].

To establish a diagnosis, it is necessary to meet the ILAR criteria:

- The disease must begin before the age of 16.
- Clinical symptoms should persist for at least 6 weeks.
- Other causes of joint inflammation should be excluded based on the exclusion criteria.

This includes considering infectious arthritis, reactive arthritis, allergic arthritis, toxic arthritis, growth-related disorders, other inflammatory connective tissue diseases, arthropathies associated with blood disorders and metabolic diseases, non-inflammatory systemic connective tissue diseases, arthropathies in immunological disorders, psychogenic arthralgia, and fibromyalgia [3].

CLINICAL PRESENTATION

The course of juvenile idiopathic arthritis (JIA) is primarily characterized by joint inflammation, which manifests as swelling, effusion, pain, and limited range of motion. The inflammatory changes initially occur in the synovial membrane of the joint and gradually spread to surrounding tissues, tendon insertions, muscles, tendon sheaths, and bone attachments [3].

As a result of inflammation, the synovial membrane transforms into an actively immunologic tissue with cellular infiltrates. In children who develop the disease early, developmental disturbances such as growth retardation and asymmetric bone growth disorders may be observed [5].

The most commonly affected joints in the course of JIA are the knees asymmetrically, as well as the hand joints symmetrically. Involvement of the hip joints and temporomandibular joints is a poor prognostic factor. With disease progression, morning stiffness, characteristic of JIA, appears [6].

In addition to joint symptoms, other manifestations such as fever, salmon-pink rash, hepatosplenomegaly, lymphadenopathy, pericarditis, pleuritis, and abdominal pain can be observed, mainly in the systemic form of JIA [7].

Early onset of the disease is associated with a higher likelihood of systemic involvement and complications such as amyloidosis and uveitis. In adult patients, JIA most commonly presents with a clinical picture consistent with the previous disease course, with intermittent

disease exacerbations [2, 3].

DIAGNOSIS

In the diagnosis of juvenile idiopathic arthritis (JIA), obtaining a patient's medical history and assessing family history are important to guide the diagnostic process. To monitor the patient's health status and quality of life, the Childhood Health Assessment Questionnaire (CHAQ) and visual analog scale (VAS) are utilized. The CHAQ is completed by the physician, while the VAS is used by the patient to self-assess their overall well-being. The following diagnostic methods are employed:

- Laboratory tests for monitoring the activity of the inflammatory process: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and complete blood count (CBC)
- Imaging studies: ultrasound (USG), magnetic resonance imaging (MRI), and radiography (X-ray) to visualize affected joints and internal organs
- Immunological markers: rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) antibodies, and antinuclear antibodies (ANA) [2,3].

In addition to the confirming criteria for juvenile idiopathic arthritis, the diagnosis is also based on the exclusion of other conditions such as bacterial, viral, fungal, mycoplasma, and Lyme arthritis, reactive arthritis, arthritis associated with hematologic and other systemic diseases, as well as psychogenic factors [1, 8].

TREATMENT

The primary goal of treating juvenile idiopathic arthritis (JIA) is to rapidly reduce the inflammatory and immunologic activity of the disease and slow down the progression of functional impairment in the musculoskeletal system [8].

Pharmacological therapy is used to initiate and maintain disease remission. The following medications are available for the treatment of JIA:

- symptomatic drugs,
- corticosteroids,
- immunoglobulins,
- non-biologic disease-modifying antirheumatic drugs (DMARDs),
- biologic agents [4].

In the early stages of the disease, symptomatic treatment is employed. Nonsteroidal anti-inflammatory drugs (NSAIDs) are administered to alleviate pain, swelling, and inflammation until a definitive diagnosis is established. Once diagnosed, non-biologic DMARDs such as methotrexate, cyclosporine A, sulfasalazine, chloroquine, cyclophosphamide, leflunomide, and azathioprine should be initiated as soon as possible [1, 8]. Corticosteroids play a significant role in treatment and can be administered intravenously, orally, intra-articularly, or periarticularly to exert anti-inflammatory and anti-edematous effects [9]. Biologic agents are used in patients with advanced disease who do not respond to non-biologic therapy. They can also be administered in cases of difficult-to-treat disease flare-ups or when patients are intolerant to methotrexate, corticosteroids, and cytotoxic drugs [10]. Available biologic agents include interleukin-1 (IL-1) blockers, anti-IL-6 agents, abatacept (a T-cell activation blocker), and rituximab (an anti-CD20 monoclonal antibody) [1, 11]. Currently, clinical trials are being conducted to evaluate the effectiveness of new molecules that may play a significant role in the treatment of JIA. Some of these include:

- Ustekinumab: This is a blocker of interleukin-12 (IL-12) and interleukin-23 (IL-23). Clinical studies are assessing the efficacy of this medication in symptom relief and disease progression prevention.
- IL-23 blockers: Research also focuses on IL-23 inhibitors, which are important factors in inflammatory processes. Their potential effectiveness in inhibiting JIA progression is being evaluated.
- Tofacitinib: This is an oral medication that acts as a Janus kinase (JAK) inhibitor and also blocks signal transduction and activators of transcription (STAT). Clinical trials of this medication are assessing its effectiveness in controlling inflammation and reducing JIA symptoms [2, 8].

In addition to pharmacological treatment, interdisciplinary cooperation and holistic care are essential for JIA patients. Physiotherapists and rehabilitation specialists may recommend various exercises, both active (performed independently by the patient) and passive (performed with the assistance of a physiotherapist), to improve range of motion, muscle strength, and joint function [12, 13].

Physical therapy may also include specific strengthening exercises targeting the muscles surrounding affected joints, which can contribute to better joint support and stability. Hydrotherapy can also be beneficial, as exercises performed in water provide pain relief, reduce joint stress, and improve range of motion [10, 12].

Psychological support for patients is also crucial in the treatment of JIA. Psychologists can assist in coping with stress, depression, or anxiety related to the chronic condition. Additionally, learning relaxation techniques and cognitive-behavioral therapy may be employed to improve the quality of life for patients [10, 13].

SUMMARY

Juvenile idiopathic arthritis (JIA) is a chronic inflammatory musculoskeletal disease that occurs in children before the age of 16. There are different types of JIA, and the diagnosis is based on ILAR criteria. The main symptoms include joint inflammation, leading to swelling, pain, and limited mobility. Diagnosis relies on laboratory and imaging tests, as well as the exclusion of other causes of joint inflammation. The treatment of JIA aims to reduce the inflammatory and immunologic activity of the disease and prevent long-term complications. Pharmacotherapy includes symptomatic drugs, corticosteroids, immunoglobulins, non-biologic disease-modifying antirheumatic drugs (DMARDs), and biologic agents such as interleukin-1 (IL-1) blockers, anti-IL-6 agents, abatacept, and rituximab. Clinical trials are ongoing to evaluate new molecules, including ustekinumab, IL-23 blockers, and tofacitinib. Collaborating with physiotherapists and rehabilitation specialists is an important part of the treatment. Active and passive exercises, muscle strengthening, hydrotherapy, and psychological support are integral components of non-pharmacological approaches to reduce pain and prevent long-term complications. Comprehensive patient care also encompasses holistic and psychological aspects. Further research is still needed to find more effective therapies for JIA and improve patients' quality of life.

REFERENCES

1. Smolewska E., Żuber Z., Aktualne cele, możliwości i perspektywy leczenia młodzieńczego idiopatycznego zapalenia stawów w Polsce i na świecie, Forum Reumatologiczne 2016, 2(1), 14–20.
2. Smolewska E., Żuber Z. Zalecenia ACR 2019 leczenia młodzieńczego idiopatycznego zapalenia stawów a możliwości terapii w warunkach polskich, Forum Reumatologiczne. 2020, 6(3), 105-112.
3. Smolewska E, Opoka- Winiarska V, Żuber Z. Młodzieńcze idiopatyczne zapalenie stawów [w:] Reumatologia wieku rozwojowego. Kompendium. Smolewska E. (red.), Wyd. PZWL, Warszawa, 2019: 127–138.

4. Żuber Z., Młodzieńcze idiopatyczne zapalenie stawów, *Pediatrica po Dyplomie*, 2012, 16(2), 23-32.
5. Kędzia A., Obara-Moszyńska M., Rabska-Pietrzak B. i wsp. Efekty leczenia ludzkim rekombinowanym hormonem wzrostu dzieci niskorosłych z młodzieńczym idiopatycznym zapaleniem stawów – opis trzech przypadków, *Endokrynologia Pediatryczna (Suplementy)*, 2008, 7(7), 77.
6. Kaminiarczyk D., Adamczak K., Niedziela M., Czynniki prozapalne u dzieci z młodzieńczym idiopatycznym zapaleniem stawów, *Reumatologia* 2010, 48(1), 62–65.
7. Rutkowska-Sak L, Gietka P. Juvenile idiopathic arthritis. *Reumatologia/Rheumatology Supplements*. 2016, supl. 1, 76-79.
8. Webb K., Wedderburn L.R. Advances in the treatment of polyarticular juvenile idiopathic arthritis. *Current Opinion in Rheumatology*. 2015, 27(5), 505–510.
9. Dąbkowska K., Wojdas M., Winsz-Szczotka K., Młodzieńcze idiopatyczne zapalenie stawów - postępowanie diagnostyczno-terapeutyczne, <https://www.ptfarm.pl/en/wydawnictwa/czasopisma/farmacja-polska/103/-/27902>. Accessed 28 June 2023.
10. Mazur P., Kabała K., Rozensztrauch A. Wpływ biologicznego leczenia młodzieńczego idiopatycznego zapalenie stawów na funkcjonowanie rodziny, *Współczesne Pielęgniarstwo i Ochrona Zdrowia*, 2020, 9(1–4), 3-8.
11. Lista leków refundowanych obwieszczenia Ministra Zdrowia, <http://www.mz.gov.pl/leki/refundacja/lista-lekow-refundowanych-obwieszczenia-ministra-zdrowia/> (data pobrania 28.06.2023) Accessed 28 June 2023.
12. Smolewska E., Niepełnosprawność dzieci i młodzieży chorych na młodzieńcze idiopatyczne zapalenie stawów, *Niepełnosprawność – zagadnienia, problemy, rozwiązania*. 2021, 3, 5-18.
13. Cepuch G, Kruszecka-Krówka A. Wybrane problemy zdrowotne dziecka z młodzieńczym idiopatycznym zapaleniem stawów – koncepcja opieki pielęgniarskiej. *Pielęgniarstwo i Zdrowie Publiczne*, 2020, 10(4), 269–276.

Nosocomial infections as a serious problem in the healthcare sector

Zuzanna Kata¹, Jakub Rudzki², Laura Więcko², Łukasz Dylewicz², Kacper Solarz², Jakub Bętkowski², Justyna Talaska²

1. Medical University of Silesia, Faculty of Dental Medicine
2. Medical University of Silesia, Faculty of Medicine

INTRODUCTION

Hospital-acquired infections are associated with patients under medical care. This type of infection occurs all over the world. In developed countries, 7% of hospitalized patients are affected by nosocomial infections, while in developing countries it is 10% of all patients [1]. According to the World Health Organization, healthcare-associated infections (HAIs) cause around 40,000 deaths per year [2].

The definition of a nosocomial infection refers to an infection occurring within 48 hours of hospital admission, 3 days after discharge or 30 days after surgery. Moreover, infection must be acquired by the patient in the hospital- the patient was admitted for another reason [3]. This group of infections also includes occupational infections among medical personnel [1]. The spread of infections among hospitalized patients is associated with reduced patient immunity, an increasing variety of medical procedures and invasive techniques that promote the transmission of microorganisms in the hospital environment [4, 5]. Patients hospitalized in intensive care units (ICUs), burn units, those undergoing organ transplants and newborns are particularly vulnerable to this type of infection. The Extended Prevalence of Infection in Intensive Care (EPIC II) estimates from research that the proportion of infected patients in intensive care units infected may be as high as 51% [1].

The most common hospital-acquired infections include:

- surgical wound infections
- urinary tract infections
- lower respiratory tract infections.

Hospital-acquired infections cause serious complications of the underlying disease leading to disability and even death. The condition is associated with prolonged hospital stays, which is a problem not only for the patient, but also for healthcare units - the cost of services

provided increases, moreover, patients who have been infected in the hospital often demand compensation [1, 4]. The frequency of hospital-acquired infections is heavily influenced by the overuse of antibiotics, resulting in an increasing number of bacterial strains with high levels of drug resistance. Due to the growing problem of hospital-acquired infections, medical facilities should focus on monitoring and recording the current epidemiological situation, conducting reliable microbiological diagnostics and controlling the treatment of infections with antibiotics [2].

EPIDEMIOLOGY OF NOSOCOMIAL INFECTIONS

When it comes to healthcare related problems, nosocomial infections are big, if not one of the biggest problems. One in every ten patients will acquire a nosocomial infection [6]. There are many risk factors which can predispose to this type of infection. We can divide them into few categories:

1. Related to underlying medical status e.g. advanced age, malnutrition, alcoholism, diabetes
2. Related to acute disease process e.g. trauma or surgery
3. Related to invasive procedures e.g. surgical drains
4. Related to treatment e.g. blood transfusion or immunosuppressive treatments [7].

Because of these risk factors patients can develop nosocomial infection such as pneumonia which is the most common type of healthcare-associated infections [8]. One of the risk factors is also length of stay [6]. This factor shows us that patients who are most likely to acquire a nosocomial infection, are the ICU patients (19,2% of all healthcare-associated infections) [9]. Studies show that nosocomial infections are more common in developing countries (prevalence of 15,5% most of which occur as ventilator-associated pneumonia) than e.g. in Africa and the western Pacific region where the infections were recorded poorly [10].

CAUSES OF NOSOCOMIAL INFECTIONS

We can point out several possible causes of nosocomial infections. The understanding of these sources is crucial for implementing effective and adequate prevention strategies which will help us face this challenge. The key factor that contribute to the occurrence of nosocomial infections is transmission of pathogens such as bacteria, viruses and fungal parasites [11]. Bacterial pathogens are the most common in nosocomial infections, which occur within

healthcare settings. Some of these bacteria are normally present in the patient's natural flora and cause infection only when the patient's immune system becomes compromised. *Acinetobacter* is a genus of pathogenic bacteria commonly responsible for infections in intensive care units (ICUs). It is typically found in soil and water and accounts for approximately 80% of reported infections [11]. *Bacteroides fragilis* is a commensal bacterium that resides in the intestinal tract and colon. It can cause infections when it combines with other bacteria. *Clostridium difficile* is another bacterium that causes inflammation of the colon, leading to antibiotic-associated diarrhea and colitis. This occurs when the beneficial bacteria in the colon are eliminated along with the pathogenic bacteria. *C. difficile* is transmitted from an infected patient to others through healthcare staff with improperly cleansed hands. *Enterobacteriaceae*, specifically carbapenem-resistant strains, can cause infections when they travel from the gut to other parts of the body. *Enterobacteriaceae* includes species such as *Klebsiella* and *Escherichia coli*. Their high resistance to carbapenem antibiotics makes them difficult to combat. Methicillin-resistant *Staphylococcus aureus* (MRSA) is transmitted through direct contact, open wounds, and contaminated hands. It can cause sepsis, pneumonia, and surgical site infections by spreading from organs or the bloodstream. MRSA exhibits high resistance to antibiotics known as beta-lactams. Apart from bacteria, viruses also play a significant role in the occurrence of nosocomial infections. According to regular monitoring, approximately 5% of all nosocomial infections are attributed to viral causes [11]. These viruses can be transmitted through various routes, including hand-to-mouth contact, respiratory droplets, and the fecal-oral route. Viral infections, such as hepatitis, pose a chronic disease risk in healthcare settings, affecting both patients and healthcare workers. Hepatitis B and C viruses are commonly transmitted through unsafe injection practices, leading to the potential spread of infection. In addition to hepatitis viruses, other common viruses associated with nosocomial infections include influenza, HIV, rotavirus, and herpes simplex virus [11].

Fungal parasites can act as opportunistic pathogens and contribute to nosocomial infections, particularly in individuals with compromised immune systems. *Aspergillus* species can cause infections through environmental contamination, while *Candida albicans* and *Cryptococcus neoformans* are also responsible for infections during hospital stays. *Candida* infections stem from the patient's own microbial flora, while *Aspergillus* infections occur when individuals inhale fungal spores from contaminated air during construction or renovation of healthcare facilities [11].

Nevertheless, there are also factors that result from the hospital environment such as patients with compromised immune system and invasive procedures [12].

The Covid-19 pandemic additionally draws our attention to poor hand hygiene, crowded healthcare settings [13].

The infections that occur the most are: urinary tract infections (UTIs), surgical site infections (SSIs), lower respiratory tract infections, bloodstream infections (BSIs), gastrointestinal infections, skin and soft tissue infections [13].

NOSOCOMIAL INFECTIONS CONSEQUENCES

The consequences of nosocomial infections (NI), also known as healthcare-associated infections can vary depending on several factors, including the type of infection, the patient's overall health, and the effectiveness of infection control measures in place. Some potential consequences of nosocomial infections include increased morbidity and mortality, growing antibiotic resistance, financial burden on the healthcare system, nosocomial outbreaks and many others. In this monograph we will focus on 3 aspects of NIs.

As briefly mentioned above nosocomial infections lead to increased morbidity and mortality. In the United States they are the sixth leading cause of death surpassing the combined deaths from human immunodeficiency virus/AIDS, cancer, and traffic accidents [14]. The estimated mortalities associated with nosocomial bloodstream infections and pneumonia are 23.8% to 50% and 14.8% to 71% (overall), or 16.3% to 35% and 6.8% to 30% (attributable), respectively [15]. One more statistic worth taking into consideration is, that of 2 million annual antibiotic-resistant infections 23 thousand patients die.

One of the contributing factors to such high mortality rates is the growing antibiotic resistance of bacteria. NIs are caused by bacteria, fungi, viruses, and parasites. In the middle-east they are most commonly caused by coagulase-negative staphylococci, methicillin-resistant *Staphylococcus aureus*, enterococci and the most dangerous out of all vancomycin-resistant enterococcus [16]. Nosocomial infections may result in spreading of these deadly pathogens as outbreaks happen on certain departments in hospitals.

The last aspect of NIs is the economic aspect. The estimated average costs of these infections are \$558 to \$593 for each urinary tract infection, \$2,734 for each surgical site infection, \$3,061 to \$40,000 for each bloodstream infection, and \$4,947 for each pneumonia [15]. In 2010 it was estimated that the annual hospital costs of HAIs in the USA to be between US\$28 billion and 45 billion per year [17].

These effects of Nosocomial infections may lead to a conclusion that more focus should go towards preventing NIs, to negate the severe health and economic effects.

HOW TO PREVENT NOSOCOMIAL INFECTIONS

Considering all the previous facts about nosocomial infections prevention is a vital element when it comes to nosocomial infections. Hand hygiene is one of the parts of prevention. It's a quick, easy way to prevent spreading the infection. Study from Kampf G. shows that washing hands only with water and soap is not enough to get rid of bacterial flora. On the other hand, using hand sanitizer is very effective form of prevention. Just 30 seconds of rubbing hands with sanitizer is capable of wiping hand's bacterial flora almost entirely [18]. For instance at Geneva University Hospital, the rate of nosocomial infections was reduced by over 40% thanks to hand disinfection [19].

It's well known that microorganisms are able to survive on many different surfaces. That's why another important factor of prevention is sanitizing surfaces and used equipment. It should be done with special care and with proper chemicals or UV light. Different pathogens can withstand different disinfection methods so it's important to pay special attention to this fact. For instance, *C. difficile* bacteria are resistant to alcohol-based liquids, but are sensitive to hydrogen peroxide based substances [20]. Obviously, patients with highly infectious diseases should be isolated in separated rooms. Especially when some immunodeficient patients are present because of their susceptibility for infectious diseases. Use of sterile equipment also helps in nosocomial infections prevention. It's important to remember about responsible antimicrobial treatment as it helps fighting and preventing of developing antibiotic resistant bacteria which then may spread among patients and cause serious problem.

SUMMARY

Nosocomial infections are caused by different microorganisms and can lead to serious consequences for patients. Factors like poor hand hygiene, contaminated equipment, and antibiotic resistance contribute to their spread. Nosocomial infections result in extended hospital stays, higher medical costs, complications, and even death. Preventive measures include proper handwashing, using protective gear, sterilizing equipment, maintaining cleanliness, following infection control guidelines, and raising awareness among healthcare workers, patients, and visitors. Nosocomial infections, also called healthcare-associated infections (HAIs), are a significant concern in hospitals and other healthcare settings. They occur when patients get infected during their stay and are not present when they arrive. These infections can take different forms, such as respiratory or urinary tract infections, surgical site

infections, or bloodstream infections. They are caused by various germs like bacteria, viruses, and fungi. The chances of getting nosocomial infections vary, depending on where you are, the type of healthcare facility, and the people being treated. Certain individuals, like older adults, those with weak immune systems, or those with invasive medical devices, are more at risk. Several factors contribute to the spread of nosocomial infections. These include not washing hands properly, using contaminated equipment, not sterilizing or cleaning things correctly, having crowded spaces, poor ventilation, and long hospital stays. Another concern is the rise of germs that are resistant to antibiotics. Nosocomial infections have serious consequences. They lead to longer hospital stays, higher medical expenses, complications, patient discomfort, disability, and even death. Additionally, these infections contribute to the problem of germs becoming resistant to antibiotics, which is a major global health issue.

Preventing nosocomial infections requires a comprehensive approach. Everyone involved needs to wash their hands regularly and correctly. Healthcare workers should wear protective gear, and equipment should be properly sterilized. It is crucial to keep the environment clean, follow infection control guidelines, and promote awareness among healthcare workers, patients, and visitors.

In conclusion, nosocomial infections are a significant concern in healthcare settings. Understanding how they spread and the consequences they can have is crucial for everyone involved. By taking simple yet effective preventive measures like washing hands, using protective gear, sterilizing equipment, maintaining cleanliness, following guidelines, and raising awareness, we can reduce the incidence of nosocomial infections, improve patient safety, and save lives.

REFERENCES

1. Khan H., Baig F., Mehboob R.. (2017). Nosocomial infections: Epidemiology, prevention, control and surveillance. *Asian Pacific Journal of Tropical Biomedicine*. 2017, 7, 478-482.
2. Lemiech-Mirowska, E., Kiersnowska, Z. M., Michałkiewicz, M. et al. Nosocomial infections as one of the most important problems of healthcare system. *Annals of Agricultural and Environmental Medicine*, 2021, 28(3), 361-366.
3. Inweregbu K., BSc FRCA and others, Nosocomial infections, *Continuing Education in Anaesthesia Critical Care & Pain*, 2005, 5(1), 14–17.
4. Wasilewski, P. Zakażenia szpitalne - nierozwiązany problem w lecznictwie zamkniętym. *Kontrola Państwowa*, 2018, 63, 6 (383), 75–88.

5. Girard, R.; Perraud, M.; Herriot, H. E.; Prüss, A.; Savey, A.; Tikhomirov, E.; Thuriaux, M.; Vanhems, P.; Bernard, U. C. Prevention of Hospital Acquired Infections. A Practical Guide (2nd ed.). Geneva, Switzerland : World Health Organization, 2002.
6. Inweregbu, BSc FRCA and others, Nosocomial infections, Continuing Education in Anaesthesia Critical Care & Pain, 2005, 5(1), 14–17.
7. Freeman J., McGowan J.E., Risk Factors for Nosocomial Infection, The Journal of Infectious Diseases, 1978, 138(6), 811–819.
8. Sikora A, Zahra F. Nosocomial Infections, 2023, <https://www.ncbi.nlm.nih.gov/books/NBK559312/>. Accessed 26 June 2023.
9. Vincent JL, Bihari DJ, Suter PM, Bruining HA, White J, Nicolas-Chanoin MH, Wolff M, Spencer RC, Hemmer M. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee. JAMA. 1995, 274(8), 639-644.
10. Allegranzi B, Bagheri Nejad S, Combescure C, Graafmans W, Attar H, Donaldson L, Pittet D. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. Lancet. 2011, 377(9761), 228-241.
11. Khan HA, Baig FK, Mehboob R. Nosocomial infections: Epidemiology, prevention, control and surveillance. Asian Pacific Journal of Tropical Biomedicine. 2017, 7(5), 478-482.
12. Sikora A, Zahra F., Nosocomial Infections, – StatPearls – NCBI. <https://www.ncbi.nlm.nih.gov/books/NBK559312/>, Accessed 26 June 2023.
13. Abdullah M., 5 Most Common Hospital Acquired Infections (HAIs), Published 28.01.202, <https://inivos.com/blog/5-most-common-hospital-acquired-infections-hais/> Accessed 26 June 2023.
14. Liu JY, Dickter JK. Nosocomial Infections: A History of Hospital-Acquired Infections. Gastrointestinal Endoscopy Clinics of North America. 2020, 30(4), 637-652.
15. Jarvis WR. Selected aspects of the socioeconomic impact of nosocomial infections: morbidity, mortality, cost, and prevention. Infection Control & Hospital Epidemiology, 1996, 17(8), 552-557.
16. Nimer NA. Nosocomial Infection and Antibiotic-Resistant Threat in the Middle East. Infection and Drug Resistance, 2022, 25(15), 631-639.

17. Stone PW. Economic burden of healthcare-associated infections: an American perspective. *Expert Review of Pharmacoeconomics & Outcomes Research*, 2009, 9(5), 417-422.
 18. Kampf G, Löffler H, Gastmeier P. Hand hygiene for the prevention of nosocomial infections. *Deutsches Ärzteblatt International*. 2009, 106(40), 649-655.
 19. Pittet D, Hugonnet S, Harbarth S, et al. Effectiveness of a hospital-wide programme to improve compliance with hand hygiene. *The Lancet*. 2000, 356(9238), 1307-1312.
- Marco JD. Prevention and Control Strategies for Nosocomial Infections. <https://www.chthealthcare.com/blog/nosocomial-infections>. Accessed 26 June 2023.

**SELECTED PROBLEMS
IN PSYCHIATRY**

**SELECTED PROBLEMS
IN PSYCHIATRY**

OXIDATIVE STRESS AND INFLAMMATION - COMMON PATHOGENESIS OF CELIAC DISEASE AND DEPRESSIVE DISORDER

**Joanna Mikulska¹, Diana Pietrzak¹, Paweł Rękawek¹, Krystian Siudaj¹,
Łucja Walczak-Nowicka²**

1. Student Science Club of Toxicology, Faculty of Pharmacy, Medical University of Lublin
2. Chair and Department of Toxicology, Faculty of Pharmacy, Medical University of Lublin,

ABBREVIATION LIST

- CAT- catalase
- GPx- glutathione peroxidase
- GRd- reductase glutathione
- GST- glutathione S-transferase
- HSP- heat shock proteins
- IL- interleukin
- INF- interferon
- iNOS- inducible nitric oxide synthase
- MDA- malondialdehyde
- NO- nitric oxide
- RNS- reactive nitrogen species
- ROS- reactive oxygen species
- sIL-2R- soluble interleukin-2 receptors
- SOD- superoxide dismutase
- TGF- transforming growth factor
- Th- T helper cells
- TNF- tumor necrosis factor

INTRODUCTION

Celiac disease belongs to autoimmune diseases of the small intestine [1,2]. In its course there is damage to enterocytes caused by gliadin (a peptide derived from gluten). Significantly, the disease is accompanied by chronic inflammation. It is one of the most common autoimmune diseases (incidence 0.5-1%). Increasingly, mood disorders, in particular depressive disorder are also being observed among patients with Celiac disease. This is a disease whose incidence is increasing every year [3–5]. Typical depressive symptoms can include sadness, irritability, decreased interest in pleasurable activities, feelings of guilt or worthlessness, lack of energy, poor concentration or suicidal thoughts. It is worth noting that this is a disease with a complex pathogenesis. The mechanisms include oxidative stress [6–8]. It may negatively affect brain function and neuronal plasticity. As a result of increased oxidative stress, many pro-inflammatory factors and signaling pathways are activated. The cytokines released in the course of the inflammatory response, could affect changes in neurotransmitters, levels of growth factors, e.g., neurotrophic brain-derived factor, and influence the modulation of environmental and genetic factors that may contribute to the development of depression.

Proper diet is a pivotal source of antioxidants, while physical activity offers many health benefits as well [9]. Recent findings have evidenced that both of the mentioned are combined with oxidative stress. Diet and physical factors have debatable roles in modulating oxidative stress [10]. Since endothelium and oxidative stress play significant role in cardiovascular and metabolic diseases, dietary and physical factors could have implications on prevention of the diseases.

Recent reports indicate that nutrients also play a role in the pathogenesis of mental illness [11]. Diet has been shown to be a significant contributor to depressive symptoms. The elimination or excess of some components of the diet can exacerbate these symptoms. One such ingredient is gluten. There are increasing reports of gluten's role in regulating mood and exacerbating depressive symptoms [12–14]. Moreover, there are an increasing number of studies that have found Celiac disease to be present in patients with depression and vice versa [15–17]. The link between Celiac disease and depression is still not fully understood. Studies have shown that a significant percentage of people with Celiac disease have depressive symptoms [18]. This may be related to impaired intestinal absorption and atrophy of the intestinal villi. This is a reaction of the immune system to the gluten found in some cereals. A gluten intake by patients with Celiac disease can result in production of antibodies which can cause changes in the central nervous system. Moreover, impaired absorption of amino acids

and their metabolites, like serotonin, can result in mood disorders [19]. Undoubtedly, the common denominator of both diseases is the presence of oxidative stress and inflammation.

Oxidative stress might be described as an imbalance between antioxidant defense system potential and the surplus of the reactive oxygen species (ROS) [20]. Crucial reasons of described state are pathological states incl. diseases. Excessive oxidative stress consequently contributes to inflammation. Devastating potential of any oxidizing molecules may cause a cascade of chemical processes which affect lipids (peroxidation), proteins (aggregation) carbohydrates and DNA which lead us into potential mutations [21,22]. Defence mechanisms protecting the integrity of structures against free radicals can be divided into: physical (appropriate structural organization of cells, which allows isolation of places where reactions occur with the production of radicals as by-products), non-enzymatic (ceruloplasmin, transferrin, polyamides, transition metal ions, metal sequester, metallothioneins) and enzymatic (superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), reductase glutathione (GRd), glutathione S-transferase (GST) and secretory phospholipase A2) and protein (reactions involving heat shock proteins (HSP) – chaperones and proteases) [23].

The co-occurrence of depressive disorder and Celiac disease is still under scientific investigation. Understanding the common mechanisms of both disorders may be crucial in treating such patients. Therefore, the aim of this study was to evaluate the role of oxidative stress and inflammation in the pathogenesis of Celiac disease and depressive disorder.

ROLE OF OXIDATIVE STRESS AND INFLAMMATION IN CELIAC DISEASE

A key role in the pathogenesis of the Celiac disease has innate immunity, but also cytokines such as interleukin (IL)-15 and interferon (INF)- α [24]. Another study also demonstrated the role of IL-8 and tumor necrosis factor (TNF)- α through a mechanism involving nuclear factor- $\kappa\beta$ [25]. It is worth noting that IFN- γ is the predominant cytokine in the damaged intestinal mucosa in Celiac disease [26]. Cytokines from IL-12, IL-23 and IL-27 can also increase in response to an increase in IFN- γ . However, this effect in Celiac disease is not well understood. It has only been observed in other inflammatory bowel conditions. Elevated levels of other cytokines such as IL-4, IL-5, IL-6, IL-10, TNF- α and transforming growth factor (TGF)- β have also been observed [27–29]. It has been suggested that cytokines can redirect signaling through various activating transcription factor (STAT) pathways [26]. Another study also observed an increase in INF- γ , IL-1 β , TNF- α , IL-6 and IL-8, and also T helper cells (Th)-2 cytokines such as IL-4 and IL-10 [30]. In addition, in one study,

a significant increase in mRNA of TNF- α , INF- γ , IL-8 was observed after gluten provocation [31]. In another study after gluten provocation, IL-2 was the earliest and most significant cytokine (preceded the onset of symptoms) [32]. One study found that gluten increased nitric oxide (NO), which was involved in the regulation of pro-inflammatory cytokines, particularly IL-1 β [33]. Cytokines have also been shown to play an important role in enterocyte proliferation and migration through their effects on cadherin and catenin [34]. It is worth noting that especially genetically determined "low" expression of IL-10, may be a key element in the onset of the disease in patients predisposed to the development of Celiac disease [35]. As for IL-15, it has been shown to be overexpressed in patients with untreated Celiac disease (in the lamina propria and intestinal epithelium). In the case of IL-21, biopsies from patients with Celiac disease on a gluten-free diet have been shown to overexpress it after *in vitro* provocation with gluten peptides [36]. Recently, the involvement of Th17 cells in the development of the disease has also been established since significantly higher expression of IL-17A was found in these patients [37]. One study estimated that with a one-unit increase in serum IL-1, the risk of Celiac disease increases by 1.13 times, while with a one-unit increase in IL-8, the risk of the disease increases by 0.004 times. On the other hand, an increase in serum IL-6 by one unit reduces the risk of the disease by 15% [38].

Diet including gluten can exacerbate vascular oxidative stress, inflammation and accelerate atherosclerosis [39,40]. Gluten feeding has shown to elevate the rate of superoxide and nitrotyrosine production in the aortic root lesion. When it comes to Celiac disease sufferers, a diet rich in gluten induces the massive surplus of ROS, which induce the cascade of oxidative reactions [41]. The current data states that the antioxidative potential measured by intestinal mucosa and body fluids is remarkably lower in newly diagnosed Celiac disease patients than in healthy cohorts. A gluten-free diet is usually compared with clinical improvement, the disappearance of serological markers specific for the Celiac disease, and regeneration of the small intestinal mucosa. This should be accompanied by noticeable improvement in the oxidative/antioxidant balance. In addition, it has been shown that gluten can induce intracellular oxidative imbalance in patients with Celiac disease [39]. Increased levels of lipid peroxidation products and an impaired oxidized/reduced glutathione ratio, as well as a reduced number of protein-bound sulfhydryl groups were observed in these patients. Another study observed that inducible nitric oxide synthase (iNOS) is constitutively expressed in human duodenal enterocytes and is increased in patients with untreated Celiac disease [42]. Adherence to a gluten-free diet partially reduced iNOS expression. Significantly, one study found that an increase in the rate of ROS production, assessed in peripheral blood, is in close correlation with

the severity of intestinal damage in celiac patients [43]. Furthermore, elevated levels of oxidative stress due to glutathione depletion are also considered to be present in these patients [44].

Moreover, Celiac disease is caused by chronic intolerance to different gluten peptides, like gliadin. Gliadin peptides can affect intestinal villi. Some of them (especially P31-43) accumulate in lysosomes and lead to increased levels of free radicals [45,46]. It is worthy noted that, the 33-residue gliadin peptide, α 2-gliadin 57-89 has been implicated as a source of gluten-mediated immunogenicity (strong stimulator of T lymphocytes) [47]. Gliadin peptides induce an adaptive response that proceeds through their binding to HLA-DQ2 or -DQ8 antigen-presenting cells and subsequent stimulation of cells.

Another study also showed that gliadin induces oxidative/nitrosative stress, mitochondrial dysfunction and damages cellular biomolecules in intestinal cells [48]. Gliadin-induced oxidative stress was also observed in *Caenorhabditis elegans* [49]. Oxidative stress plays an important role in gliadin toxicity. Gluten exposure can disturb oxidative balance, increase production of ROS, reactive nitrogen species (RNS) and lipid peroxidation products. Peptide accumulation in lysosomes can cause increased production of ROS. Consequently, it leads to the formation of permanent changes in DNA. Oxidative stress occurs when there is enhanced production of ROS and RNS relative to antioxidant defenses [50]. It may also be relevant that gliadin induces cellular oxidative stress, DNA damage and stimulates apoptosis in intestinal cells [51]. Another study observed that levels of lipid peroxidation, SOD and CAT enzyme activities were higher in samples from patients with Celiac disease, as well as those following a gluten-free diet, compared to controls [52]. Gliadin derived from gluten has also been shown to negatively effect on NrF, which is associated with antioxidant defense [48].

Dietary components, contained in gluten-free diet, like polyphenols, fatty acids, and carotenoids may have an important role in the modulation of intestinal chronic inflammation [45,53]. The association between gluten-free diet and inflammation is broadly studied now [54]. In addition, it was shown that in people without Celiac disease, it was observed that a gluten-free diet increased inflammation.

Moreover, gluten is a factor that induces oxidative stress in Celiac disease, but there are also causes independent of the diet (xenobiotics, endogenous compounds). Gluten-free diet seems to be an important factor in reducing the levels of gliadins and the amount of ROS [45,50,53]. Compliance with a gluten-free diet in Celiac disease is enough to decrease the production of ROS and mediators of oxidative stress. Interestingly, some studies [50] indicate that oxidative changes in gut cells are maintained even after adhering to a gluten-free diet. It

has also been mentioned that patients with Celiac disease on gluten-free diet have duodenal damage despite the clinical improvement, as evidenced by elevated levels of IFN- γ . Some of the proinflammatory cytokines persisted even for 2 years despite the disappearance of specific antibodies. Another study also observed that all markers of oxidative DNA damage were higher in celiac patients compared to controls, regardless of diet [55].

ROLE OF THE OXIDATIVE STRESS AND INFLAMMATION IN DEPRESSIVE DISORDER

Another entity in which oxidative stress and inflammation may play a role in pathogenesis is depressive disorder. The cytokine theory of depressive disorder posits that increased activity of T lymphocytes, monocytes, macrophages can be observed in depression [8,56]. This is confirmed by the increase in pro-inflammatory cytokines (IL-1 β , IL-2, IL-4, IL-6, TNF- α , INF- γ). Some of the studies indicate that depression is also associated with increased acute phase proteins (haptoglobin, α 1-antitrypsin, acid α 1-glycoprotein, C-reactive protein). Pro-inflammatory cytokines (especially IL-1 β , TNF- α and IFN- γ) have a meaningful impact on functioning of the serotonergic system and the hypothalamic-pituitary-adrenal axis [57,58]. They also take part in the communication between the immune system and the neurotransmitter system and the endocrine system. The link between depressive disorder and inflammation is also indicated by the cessation of depressive symptoms (anxiety, memory impairment, decreased libido, mood swings) when pro-inflammatory cytokine levels are normal [59]. Multiple inflammatory markers have been evaluated in depressive disorder.

Of particular note in the pathogenesis of depressive disorder is IL-6. It was shown that elevated levels of this interleukin were observed in depressed patients and could be associated with sleep disorders [60]. It was also noted that IL-6 levels were associated with impaired concentration and attention among people with depression [61]. It is thought that it may activate the hypothalamic-pituitary-adrenal axis or affect neurotransmitter metabolism [62]. On the other hand, IL-1 β variants have been associated with reduced function in the amygdala and anterior cingulate cortex [63]. These abnormalities have been linked to manifestation of depressive symptoms. It was also shown that IL-1 β was a potent stimulus for astrocytes [64]. IL-1 β induced mRNA and protein for both TNF- α and IL-6. Elevated levels of IL-8 were also observed in many studies [65,66]. It is worth noting that this interleukin is involved in neutrophil activation and chemotaxis, which may be important in inflammatory reactions in the central nervous system [67]. IL-17A similarly to Celiac disease may also be relevant to

depressive disorder. It is thought that levels of this interleukin may be associated with treatment resistance in patients with depression [68].

Elevated levels were observed: IL-6, TNF- α and soluble interleukin-2 receptors (sIL-2R) in serum from depressed patients [69]. In contrast, another study found that higher TNF- α levels could predict lack of response to escitalopram treatment and that changes in sIL-2R levels during treatment were different in responders and non-responders [70]. Additionally, higher levels of IL-4 and IL-13 (Th2) and significantly lower measurements of IL-2 and IFN- γ (Th1) cytokines were observed among patients with depressive disorder. In another study, it was observed that after treatment lasting 12 weeks, the levels of the following cytokines decreased in patients with depressive disorder [71]. IL-1Ra, IL-5, IL-6, IL-8, IL-10, granulocyte colony stimulating factor; IFN- γ and TNF- α were significantly reduced. Significantly, recent findings have shown that TNF- α and IL-1 play a role in regulating synaptic plasticity [72]. Similar observations regarding dysregulation of the immune system in depression were made in another study [73]. Patients with depressive disorder showed that IL-6 levels and TNF- α , TGF- β 1 production and IFN- γ /IL-4 ratio were significantly higher, while IFN- γ , IL-2 and IL-4 were significantly lower compared to the control group.

It is noteworthy that in one study, higher levels of autoantibodies such as antinuclear (ANA), thyroid gland (TGA) and parietal cell (PCA) antibodies were observed among depressed patients [74]. Importantly, depression could accompany several other autoimmune diseases, such as multiple sclerosis and diabetes type 1 [75,76]. Moreover, depressive disorder usually co-occurs with inflammatory diseases. Indeed, psychological stress can lead to activation of the immune system and inflammatory processes in the body [59,77–79]. Catecholamines released under stress act on α and β -adrenergic receptors to stimulate the production of pro-inflammatory cytokines [78].

Disrupted antioxidant defenses have been found repeatedly in depressed individuals in studies [7,80,81]. In one, a decrease in ceruloplasmin levels, elevated malondialdehyde (MDA) levels and reduced SOD levels were observed in people with depressive disorder compared to control [82]. Also, one study observed elevated MDA levels in patients before treatment depression, but also reduced CAT, GSH-Px, and NO [83]. Similar observations have also been made in other studies [84,85]. Another study among a group of female patients with depressive disorder also showed a significant link between the presence of this disorder and oxidative stress [86]. Elevated levels of: GRd, SOD, and conjugated dienes were observed among these females, as well as decreased levels of: GPX1, GSH. It was also reported that increased activity of both SOD, and CAT could be an indicator of acute depressive episodes [87]. Noteworthy is the fact

that ROS are also produced as byproducts of monoamine oxidase activity, which is necessary for the inactivation of the monoaminergic neurotransmitters serotonin, dopamine, norepinephrine and epinephrine [88]. Excess ROS adversely affects the cytoarchitecture of neurons and the function of various biological molecules, including lipids, nucleic acids and proteins. It is noteworthy that, as in the case of Celiac disease, the NrF transcription factor also plays a role. It was observed that knockout mice for this gene showed depressive symptoms [89]. Another study also observed that MDA levels were significantly higher in the depressive disorder group than in the control group [90]. In contrast, SOD and Nrf2 levels were significantly lower in these patients. In addition, another study observed a correlation between oxidative stress indices and inflammatory process in depressive disorder [91]. Similar observations were made by *Sarandol A. et al.* SOD levels were shown to be significantly correlated with the severity of depressive symptoms [92]. Furthermore, increased production of ROS and depletion of antioxidant defense mechanisms are thought to be responsible for the altered brain structure in depressed patients [93]. In addition, it is suggested that the brain is more susceptible to damage from increased ROS than any other organ in the body (a major consumer of oxygen and rich in oxidizable lipids) [7,94]. It is worth noting that oxidative stress itself can result in altered neuronal function and also affect neurotransmission and overall brain activity [95].

SUMMARY

Elevated levels of pro-inflammatory cytokines are found in both depressed and celiac patients (especially $\text{INF-}\gamma$ and $\text{TNF-}\alpha$). Notably, IL-8 and IL-6 play a role in both conditions and is thought to be strongly associated with severity of anxiety and depressive symptoms. The high levels of oxidative stress in Celiac disease may therefore be due to IL-8 released by microglia in response to ongoing inflammation. Other cytokines such as: IL-17A, IL-1 β are also not insignificant here. Abnormal NrF2 levels are also observed, which is undoubtedly associated with increased oxidative stress in both disease entities. It is worth noting that excessive oxidative stress and antibody production in Celiac disease can cause damage to the central nervous system, which may also contribute to the co-occurrence of depression. Significantly, when pro-inflammatory cytokine levels are normal, the depressed patient's condition improves. Therefore, excessive cytokine hypersecretion in the course of Celiac disease and chronic inflammation may exacerbate depressive symptoms. Meanwhile, a gluten-free diet that reduces oxidative stress and inflammation can significantly improve the quality

of life of patients with co-occurring Celiac disease and depressive disorder. These processes, particularly the hyperactivation of the immune system, are thought to contribute to autoimmune disease, as exemplified by the co-occurrence of depressive disorder and type 1 diabetes or the occurrence of autoantibodies in depressed patients. However, much research is still needed in this direction to more precisely define the mechanisms causing the increased levels.

REFERENCES

1. Posner E.B., Haseeb M. Celiac Disease. In StatPearls, StatPearls Publishing: Treasure Island (FL), <https://www.ncbi.nlm.nih.gov/books/NBK441900/>. Accessed 27 June 2023.
2. Parzanese I., Qehajaj D., Patrinicola F. et.al. Celiac Disease: From Pathophysiology to Treatment. World Journal of Gastrointestinal Pathophysiology, 2017, 8, 27–38.
3. Karrouri R., Hammani Z., Benjelloun R., Otheman Y. Major Depressive Disorder: Validated Treatments and Future Challenges. World Journal of Clinical Cases, 2021, 9, 9350–9367.
4. Chand S.P., Arif, H. Depression. In StatPearls, StatPearls Publishing: Treasure Island (FL), <https://www.ncbi.nlm.nih.gov/books/NBK430847/> . Accessed 27 June 2023.
5. Bains N., Abdijadid S. Major Depressive Disorder. In StatPearls, StatPearls Publishing: Treasure Island (FL), <https://www.ncbi.nlm.nih.gov/books/NBK559078/> Accessed 27 June 2023.
6. Michel T.M., Pülschen D. Thome J. The Role of Oxidative Stress in Depressive Disorders. Current Pharmaceutical Design 2012, 18, 5890–5899.
7. Bhatt S., Nagappa A.N., Patil C.R. Role of Oxidative Stress in Depression. Drug Discov Today 2020, 25, 1270–1276.
8. Felger J.C., Lotrich F.E. Inflammatory Cytokines in Depression: Neurobiological Mechanisms and Therapeutic Implications. Neuroscience 2013, 246, 199–229.
9. Man A.W.C., Li H., Xia N. Impact of Lifestyles (Diet and Exercise) on Vascular Health: Oxidative Stress and Endothelial Function. Oxidative Medicine and Cellular Longevity 2020, 2020, 1496462.
10. Jiang S., Liu H., Li C. Dietary Regulation of Oxidative Stress in Chronic Metabolic Diseases. Foods 2021, 10, 1854.
11. Firth J., Gangwisch J.E., Borsini A. et al. Food and Mood: How Do Diet and Nutrition Affect Mental Wellbeing? BMJ 2020, 369, m2382.

12. Peters, S.L., Biesiekierski, J.R., Yelland, G.W. et al. Randomised Clinical Trial: Gluten May Cause Depression in Subjects with Non-Coeliac Gluten Sensitivity – an Exploratory Clinical Study. *Alimentary Pharmacology & Therapeutics* 2014, 39, 1104–1112.
13. Aranburu, E., Matias, S., Simón E. et.al. Gluten and FODMAPs Relationship with Mental Disorders: Systematic Review. *Nutrients* 2021, 13, 1894.
14. Karakula-Juchnowicz, H., Rog, J., Juchnowicz, D. et.al. The Study Evaluating the Effect of Probiotic Supplementation on the Mental Status, Inflammation, and Intestinal Barrier in Major Depressive Disorder Patients Using Gluten-Free or Gluten-Containing Diet (SANGUT Study): A 12-Week, Randomized, Double-Blind, and Placebo-Controlled Clinical Study Protocol. *Nutrition Journal* 2019, 18, 50.
15. Häuser, W., Janke, K.-H., Klump, B. et al. Anxiety and Depression in Adult Patients with Celiac Disease on a Gluten-Free Diet. *World Journal of Gastroenterology* 2010, 16, 2780–2787.
16. Jackson J.R., Eaton W.W., Cascella, N.G. et al. Neurologic and Psychiatric Manifestations of Celiac Disease and Gluten Sensitivity. *Psychiatric Quarterly* 2012, 83, 91–102.
17. Clappison, E., Hadjivassiliou, M., Zis, P. Psychiatric Manifestations of Coeliac Disease, a Systematic Review and Meta-Analysis. *Nutrients* 2020, 12, 142.
18. Pikulicka, A., Pacek, K., Piekarska, M., Kasperski, R., Jedlina, K. et.al. Depression Development in Patients with Celiac Disease. *Journal of Education, Health and Sport* 2023, 13, 19–24.
19. Sommer, F., Bäckhed, F. The Gut Microbiota — Masters of Host Development and Physiology. *Nature Reviews Microbiology* 2013, 11, 227–238.
20. Sies, H. Oxidative Stress: Concept and Some Practical Aspects. *Antioxidants (Basel)* 2020, 9, 852.
21. Pizzino, G., Irrera, N., Cucinotta, M. et.al. Oxidative Stress: Harms and Benefits for Human Health. *Oxidative Medicine and Cellular Longevity* 2017, 2017, 8416763.
22. Kulbacka, J., Saczko, J., Chwiłkowska, A. Stres Oksydacyjny w Procesach Uszkodzenia Komórek. *Polski Merkuriusz Lekarski* 2009, 27, 44–47.
23. Correia, A.S., Cardoso, A., Vale, N. Oxidative Stress in Depression: The Link with the Stress Response, Neuroinflammation, Serotonin, Neurogenesis and Synaptic Plasticity. *Antioxidants (Basel)* 2023, 12, 470.

24. Caio, G., Volta, U., Sapone, A. et.al. Celiac Disease: A Comprehensive Current Review. *BMC Medicine* 2019, 17, 142.
25. Jelínková, L., Tucková, L., Cinová, J. et al. Gliadin Stimulates Human Monocytes to Production of IL-8 and TNF-Alpha through a Mechanism Involving NF-KappaB. *FEBS Lett* 2004, 571, 81–85.
26. Garrote, J.A., Gómez-González, E., Bernardo, D. et al. Celiac Disease Pathogenesis: The Proinflammatory Cytokine Network. *Journal of Pediatric Gastroenterology and Nutrition* 2008, 47, S27.
27. Nilsen, E.M., Lundin, K.E., Krajci, P. et.al. Gluten Specific, HLA-DQ Restricted T Cells from Coeliac Mucosa Produce Cytokines with Th1 or Th0 Profile Dominated by Interferon Gamma. *Gut* 1995, 37, 766–776.
28. Forsberg, G., Hernell, O., Melgar, S., et.al. Paradoxical Coexpression of Proinflammatory and Down-Regulatory Cytokines in Intestinal T Cells in Childhood Celiac Disease. *Gastroenterology* 2002, 123, 667–678.
29. LeÓN, F., SÁnchez, L., Camarero, C., Roy, G. Cytokine Production by Intestinal Intraepithelial Lymphocyte Subsets in Celiac Disease. *Digestive Diseases and Sciences* 2005, 50, 593–600.
30. Manavalan, J.S., Hernandez, L., Shah, J.G., et.al. Serum Cytokine Elevations in Celiac Disease: Association with Disease Presentation. *Human Immunology* 2010, 71, 50–57.
31. Brottveit, M., Beitnes, A., Tollefsen, S., et.al. Mucosal Cytokine Response After Short-Term Gluten Challenge in Celiac Disease and Non-Celiac Gluten Sensitivity. *Official journal of the American College of Gastroenterology | ACG* 2013, 108, 842.
32. Goel, G., Tye-Din, J.A., Qiao, S.-W et.al. Cytokine Release and Gastrointestinal Symptoms after Gluten Challenge in Celiac Disease. *Science Advances* 2019, 5, eaaw7756.
33. Beckett, C.G., Dell’Olio, D., Shidrawi, R.G., et al. Gluten-Induced Nitric Oxide and pro-Inflammatory Cytokine Release by Cultured Coeliac Small Intestinal Biopsies. *European Journal of Gastroenterology & Hepatology* 1999, 11, 529–535.
34. Perry, I., Tselepis, C., Hoyland, J., et.al. Reduced Cadherin/Catenin Complex Expression in Celiac Disease Can Be Reproduced in Vitro by Cytokine Stimulation. *Laboratory Investigation* 1999, 79, 1489–1499.
35. Hofmann, S.R., Laass, M.W., Fehrs, A., et.al. IL10 Promoter Haplotypes May Contribute to Altered Cytokine Expression and Systemic Inflammation in Celiac Disease. *Clinical Immunology* 2018, 190, 15–21.

36. De Nitto, D., Monteleone, I., Franzè, E., et al. Involvement of Interleukin-15 and Interleukin-21, Two γ -Chain-Related Cytokines, in Celiac Disease. *World Journal of Gastroenterology* 2009, 15, 4609–4614.
37. Sapone, A., Lammers, K.M., Mazzarella, G., et.al, A. Differential Mucosal IL-17 Expression in Two Gliadin-Induced Disorders: Gluten Sensitivity and the Autoimmune Enteropathy Celiac Disease. *International Archives of Allergy and Immunology* 2009, 152, 75–80.
38. Nasserinejad, M., Shojaee, S., Ghobakhlou, M., et.al. The Effects of IL-8, IL- 6, and IL-1 on the Risk of Celiac Disease: A Bayesian Regression Analysis. *Gastroenterology and Hepatology from Bed to Bench* 2019, 12, S117–S122.
39. Ferretti, G., Bacchetti, T., Masciangelo, S., Saturni, L. Celiac Disease, Inflammation and Oxidative Damage: A Nutrigenetic Approach. *Nutrients* 2012, 4, 243–257.
40. Lerner, A., Shoenfeld, Y., Matthias, T. Adverse Effects of Gluten Ingestion and Advantages of Gluten Withdrawal in Nonceliac Autoimmune Disease. *Nutrition Reviews* 2017, 75, 1046–1058.
41. Rowicka, G., Czaja-Bulsa, G., Chelchowska, M., et.al. Oxidative and Antioxidative Status of Children with Celiac Disease Treated with a Gluten Free-Diet. *Oxidative Medicine and Cellular Longevity* 2018, 2018, 1324820.
42. Murray, I.A., Daniels, I., Coupland, K., et al. Increased Activity and Expression of INOS in Human Duodenal Enterocytes from Patients with Celiac Disease. *American Journal of Physiology Gastrointestinal and Liver Physiology* 2002, 283, G319-326.
43. Moretti, S., Mrakic-Sposta, S., Roncoroni, L., et al. Oxidative Stress as a Biomarker for Monitoring Treated Celiac Disease. *Clinical and Translational Gastroenterology* 2018, 9, 157.
44. Stojiljković, V., Todorović, A., Pejić, S., et.al. Antioxidant Status and Lipid Peroxidation in Small Intestinal Mucosa of Children with Celiac Disease. *Clinical Biochemistry* 2009, 42, 1431–1437.
45. Itzlinger, A., Branchi, F., Elli, L., Schumann, M. Gluten-Free Diet in Celiac Disease- Forever and for All? *Nutrients* 2018, 10, 1796.
46. Aljada, B., Zohni, A., El-Matary, W. The Gluten-Free Diet for Celiac Disease and Beyond. *Nutrients* 2021, 13, 3993.
47. Niland, B., Cash, B.D. Health Benefits and Adverse Effects of a Gluten-Free Diet in Non-Celiac Disease Patients. *Gastroenterology and hepatology (New York)* 2018, 14, 82–91.

48. Gupta, K.B., Dhiman, M., Mantha, A.K. Gliadin Induced Oxidative Stress and Altered Cellular Responses in Human Intestinal Cells: An in-Vitro Study to Understand the Cross-Talk between the Transcription Factor Nrf-2 and Multifunctional APE1 Enzyme. *Journal of Biochemical and Molecular Toxicology* 2022, 36, e23096.
49. Lim, S.D., Min, H., Youn, E., et al. Gliadin Intake Induces Oxidative-Stress Responses in *Caenorhabditis Elegans*. *Biochemical and Biophysical Research Communications* 2018, 503, 2139–2145.
50. Diaz-Castro, J., Muriel-Neyra, C., Martin-Masot, R., et.al. Oxidative Stress, DNA Stability and Evoked Inflammatory Signaling in Young Celiac Patients Consuming a Gluten-Free Diet. *European Journal of Nutrition* 2020, 59, 1577–1584.
51. Monguzzi, E., Marabini, L., Elli, L., et al. Gliadin Effect on the Oxidative Balance and DNA Damage: An in-Vitro, Ex-Vivo Study. *Digestive and Liver Disease* 2019, 51, 47–54.
52. Kumar, S., Lal, S., Bhatnagar, A. Regulatory T Cell Subsets in Peripheral Blood of Celiac Disease Patients and TLR2 Expression: Correlation with Oxidative Stress. *Acta Pathologica et Microbiologica Scandinavica* 2017, 125, 888–901.
53. Luciani, A., Vilella, V.R., Vasaturo, A., et al. Lysosomal Accumulation of Gliadin P31-43 Peptide Induces Oxidative Stress and Tissue Transglutaminase-Mediated PPARgamma Downregulation in Intestinal Epithelial Cells and Coeliac Mucosa. *Gut* 2010, 59, 311–319.
54. Henriques, H.K.F., Fonseca, L.M., de Andrade, K.S., Shivappa, N., Hébert, J.R., et.al. Gluten-Free Diet Reduces Diet Quality and Increases Inflammatory Potential in Non-Celiac Healthy Women. *Journal of the American Nutrition Association* 2022, 41, 771–779.
55. Szaflarska-Popławska, A., Siomek, A., Czerwionka-Szaflarska, M., et.al. Oxidatively Damaged DNA/Oxidative Stress in Children with Celiac Disease. *Cancer Epidemiology, Biomarkers & Prevention* 2010, 19, 1960–1965.
56. Gałęcki, P., Talarowska, M. Inflammatory Theory of Depression. *Psychiatria Polska* 2018, 52, 437–447.
57. Ortigoza-Escobar, J.D., Alfadhel, M., Molero-Luis, M., et al. Thiamine Deficiency in Childhood with Attention to Genetic Causes: Survival and Outcome Predictors. *Annals of Neurology* 2017, 82, 317–330.

58. Ortí, J.E. de la R., Cuerda-Ballester, M., et.al. Vitamin B1 Intake in Multiple Sclerosis Patients and Its Impact on Depression Presence: A Pilot Study. *Nutrients* 2020, 12, 2655.
59. Leonard, B.E., Myint, A. Changes in the Immune System in Depression and Dementia: Causal or Coincidental Effects? *Dialogues in Clinical Neuroscience* 2006, 8, 163–174.
60. Wang, M., Wei, J., Yang, X., et al. The Level of IL-6 Was Associated with Sleep Disturbances in Patients with Major Depressive Disorder. *Neuropsychiatric Disease and Treatment* 2019, 15, 1695–1700.
61. Ye, G., Yin, G.Z., Tang, Z., et al. Association between Increased Serum Interleukin-6 Levels and Sustained Attention Deficits in Patients with Major Depressive Disorder. *Psychological Medicine* 2018, 48, 2508–2514.
62. Ting, E.Y.-C., Yang, A.C., Tsai, S.-J. Role of Interleukin-6 in Depressive Disorder. *International Journal of Molecular Sciences* 2020, 21, 2194, doi:10.3390/ijms21062194.
63. Martin, C., Tansey, K.E., Schalkwyk, L.C., Powell, T.R. The Inflammatory Cytokines: Molecular Biomarkers for Major Depressive Disorder? *Biomarkers in Medicine* 2015, 9, 169–180.
64. Lee, S.C., Liu, W., Dickson, D.W., et al. Cytokine Production by Human Fetal Microglia and Astrocytes. Differential Induction by Lipopolysaccharide and IL-1 Beta. *The Journal of Immunology* 1993, 150, 2659–2667.
65. Myung, W., Lim, S., Woo, H.I., Park, J.H., et.al. Serum Cytokine Levels in Major Depressive Disorder and Its Role in Antidepressant Response. *Psychiatry Investigation* 2016, 13, 644–651.
66. Köhler, C.A., Freitas, T.H., Stubbs, B., et al. Peripheral Alterations in Cytokine and Chemokine Levels After Antidepressant Drug Treatment for Major Depressive Disorder: Systematic Review and Meta-Analysis. *Molecular Neurobiology* 2018, 55, 4195–4206.
67. Ehrlich, L.C., Hu, S., Sheng, W.S., et.al. Cytokine Regulation of Human Microglial Cell IL-8 Production. *The Journal of Immunology* 1998, 160, 1944–1948.
68. Nothdurfter, C., Milenkovic, V.M., Sarubin, N., et.al. The Cytokine IL-17A as a Marker of Treatment Resistance in Major Depressive Disorder? *European Journal of Neuroscience* 2021, 53, 172–182.
69. Liu, Y., Ho, R., Mak, A. Interleukin (IL)-6, Tumour Necrosis Factor Alpha (TNF- α) and Soluble Interleukin-2 Receptors (SIL-2R) Are Elevated in Patients with Major

- Depressive Disorder: A Meta-Analysis and Meta-Regression. *Journal of Affective Disorders* 2012, 139, 230–239.
70. Eller, T., Vasar, V., Shlik, J., Maron, E. Pro-Inflammatory Cytokines and Treatment Response to Escitalopram in Major Depressive Disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 2008, 32, 445–450, doi:10.1016/j.pnpbp.2007.09.015.
71. Dahl, J., Ormstad, H., Aass, H.C.D., et al. Recovery from Major Depressive Disorder Episode after Non-Pharmacological Treatment Is Associated with Normalized Cytokine Levels. *Acta Psychiatrica Scandinavica* 2016, 134, 40–47.
72. Khairova, R.A., Machado-Vieira, R., Du, J., Manji, H.K. A Potential Role for Pro-Inflammatory Cytokines in Regulating Synaptic Plasticity in Major Depressive Disorder. *International Journal of Neuropsychopharmacology* 2009, 12, 561–578.
73. Kim, Y.-K., Na, K.-S., Shin, K.-H., et.al. Cytokine Imbalance in the Pathophysiology of Major Depressive Disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 2007, 31, 1044–1053.
74. Laske, C., Zank, M., Klein, R., et.al. Autoantibody Reactivity in Serum of Patients with Major Depression, Schizophrenia and Healthy Controls. *Psychiatry Research* 2008, 158, 83–86.
75. Gold, S.M., Irwin, M.R. Depression and Immunity: Inflammation and Depressive Symptoms in Multiple Sclerosis. *Immunology and Allergy Clinics of North America* 2009, 29, 309–320.
76. Korczak, D.J., Pereira, S., Koulajian, K., et al. Type 1 Diabetes Mellitus and Major Depressive Disorder: Evidence for a Biological Link. *Diabetologia* 2011, 54, 2483–2493.
77. Bierhaus, A., Wolf, J., Andrassy, M., et al. A Mechanism Converting Psychosocial Stress into Mononuclear Cell Activation. *Proceedings of the National Academy of Sciences of the United States of America* 2003, 100, 1920–1925.
78. Miller, G.E., Chen, E., Sze, J., Marin, T., et.al. A Functional Genomic Fingerprint of Chronic Stress in Humans: Blunted Glucocorticoid and Increased NF-KB Signaling. *Biological Psychiatry* 2008, 64, 266–272.
79. Danese, A., Pariante, C.M., Caspi, A., et al. Childhood Maltreatment Predicts Adult Inflammation in a Life-Course Study. *Proceedings of the National Academy of Sciences of the United States of America* 2007, 104, 1319–1324.

80. Del Rio, D., Stewart, A.J., Pellegrini, N. A Review of Recent Studies on Malondialdehyde as Toxic Molecule and Biological Marker of Oxidative Stress. *Nutrition, Metabolism and Cardiovascular Diseases* 2005, 15, 316–328.
81. Rybka, J., Kędziora-Kornatowska, K., Banaś-Leżańska, P., et.al. Interplay between the Pro-Oxidant and Antioxidant Systems and Proinflammatory Cytokine Levels, in Relation to Iron Metabolism and the Erythron in Depression. *Free Radical Biology and Medicine* 2013, 63, 187–194.
82. Bajpai, A., Verma, A.K., Srivastava, M., Srivastava, R. Oxidative Stress and Major Depression. *Journal of Clinical and Diagnostic Research for doctors* 2014, 8, CC04–CC07.
83. Ozcan, M.E., Gulec, M., Ozerol, E., et al. Antioxidant Enzyme Activities and Oxidative Stress in Affective Disorders. *International Clinical Psychopharmacology* 2004, 19, 89–95.
84. Talarowska, M., Gałęcki, P., Maes, M., et.al. Malondialdehyde Plasma Concentration Correlates with Declarative and Working Memory in Patients with Recurrent Depressive Disorder. *Molecular Biology Reports* 2012, 39, 5359–5366.
85. Alvarez-Mon, M.A., Ortega, M.A., García-Montero, C., et al. Differential Malondialdehyde (MDA) Detection in Plasma Samples of Patients with Major Depressive Disorder (MDD): A Potential Biomarker. *Journal of International Medical Research* 2022, 50, 03000605221094995.
86. Kodydková, J., Vávrová, L., Zeman, M., et.al. Antioxidative Enzymes and Increased Oxidative Stress in Depressive Women. *Clinical Biochemistry* 2009, 42, 1368–1374.
87. Tsai, M.-C., Huang, T.-L. Increased Activities of Both Superoxide Dismutase and Catalase Were Indicators of Acute Depressive Episodes in Patients with Major Depressive Disorder. *Psychiatry Research* 2016, 235, 38–42.
88. Bakunina, N., Pariante, C.M., Zunszain, P.A. Immune Mechanisms Linked to Depression via Oxidative Stress and Neuroprogression. *Immunology* 2015, 144, 365–373.
89. Martín-de-Saavedra, M.D., Budni, J., Cunha, M.P. et al. Nrf2 Participates in Depressive Disorders through an Anti-Inflammatory Mechanism. *Psychoneuroendocrinology* 2013, 38, 2010–2022.
90. Hamed R., Elmalt H., Salama A., et al. Biomarkers of Oxidative Stress in Major Depressive Disorder | Open Access Macedonian Journal of Medical Sciences. 2020, 31, 501-506.

91. Rawdin, B.J., Mellon, S.H., Dhabhar, F.S., et al. Dysregulated Relationship of Inflammation and Oxidative Stress in Major Depression. *Brain, Behavior, and Immunity* 2013, 31, 143–152.
92. Sarandol, A., Sarandol, E., Eker, S.S. et.al. Major Depressive Disorder Is Accompanied with Oxidative Stress: Short-Term Antidepressant Treatment Does Not Alter Oxidative-Antioxidative Systems. *Human Psychopharmacology: Clinical and Experimental* 2007, 22, 67–73.
93. Michel, T.M., Frangou, S., Thiemeyer, D., et.al. Evidence for Oxidative Stress in the Frontal Cortex in Patients with Recurrent Depressive Disorder—a Postmortem Study. *Psychiatry Research* 2007, 151, 145–150.
94. Schieber, M., Chandel, N.S. ROS Function in Redox Signaling and Oxidative Stress. *Current Biology* 2014, 24, R453–R462.
95. Wang, X., Michaelis, E. Selective Neuronal Vulnerability to Oxidative Stress in the Brain. *Frontiers in Aging Neuroscience* 2010, 2

BIGOREXIA: THE PERILS OF CHASING AN IDEAL BODY

Michał Bolek, Justyna Klimczak, Dominika Musialska

Wroclaw Medical University

INTRODUCTION

Bigorexia, reverse anorexia, Adonis complex or muscle dysmorphia are all names for a type of body dysmorphic disorder that is characterized by an intense desire to increase one's body size.

It is a mental health disorder that primarily affects men who engage in bodybuilding or weightlifting.

It is characterized by an excessive preoccupation with muscularity and body size, and can lead to distorted body image and severe anxiety about perceived physical inadequacies.

This monograph will explore the causes, symptoms, diagnosis, and treatment of bigorexia, as well as its impact on physical and mental health.

PREVALENCE

The prevalence of bigorexia is difficult to estimate because it is a relatively new disorder, and there is still a lack of consensus among experts about its classification and diagnostic criteria. However, research suggests that the disorder affects mostly men, particularly those who engage in competitive bodybuilding or weightlifting [1].

According to a study conducted by Pope et al. (2005), 25% of male bodybuilders in the United States showed symptoms of muscle dysmorphia. Another study conducted by Olivardia et al. (2000) found that 22.5% of male gym-goers in Boston had muscle dysmorphia symptoms [2].

It is important to note that bigorexia is not limited to men and can affect individuals of any gender or age who engage in excessive muscle-building activities. Additionally, individuals with bigorexia may also experience other mental health issues such as depression, anxiety, and obsessive-compulsive disorder.

CAUSES

The causes of bigorexia are complex and multifaceted. Some researchers believe that genetic factors may play a role, as individuals with a family history of mental health disorders may be more susceptible to developing bigorexia. Others suggest that environmental factors, such as societal pressure to conform to a certain body type, may contribute to the development of bigorexia.

One study found that men who had experienced childhood teasing or bullying about their appearance were more likely to develop bigorexia later in life [3].

Another study suggested that bigorexia may be more prevalent among individuals who have experienced adverse life events, such as trauma or loss [4].

SYMPTOMS

Symptoms of bigorexia include spending excessive amounts of time in the gym or engaging in other forms of exercise, obsessively counting calories and macronutrients, and using anabolic steroids or other performance-enhancing drugs to achieve desired body shape. Individuals with bigorexia may also experience social isolation, depression, and anxiety, as they feel that they cannot achieve the desired muscular physique.

Research has identified a number of factors that are associated with bigorexia, including body dissatisfaction, low self-esteem, and anxiety about body image [5].

Individuals with bigorexia may also have distorted perceptions of their own body size, and may engage in compulsive behaviors such as constantly checking their appearance in mirrors or other reflective surfaces [6].

DIAGNOSIS

Some researchers believe that the disorder is one of the forms of dysmorphic disease [7], while others see bigorexia as a type of eating disorder [8, 9, 10].

Diagnosing bigorexia can be challenging, as there is currently no standardized diagnostic criteria for the disorder. However, mental health professionals may use criteria from other related disorders, such as body dysmorphic disorder (BDD) or obsessive-compulsive disorder (OCD), to identify bigorexia.

According to the American Psychiatric Association's Diagnostic and Statistical Manual

of Mental Disorders (DSM-5), BDD is characterized by preoccupation with one or more perceived defects or flaws in physical appearance that are not observable or appear only slight to others [11]. Individuals with BDD may engage in compulsive behaviors such as excessive grooming or skin picking, and may avoid social situations or other activities due to anxiety about their appearance.

In addition, some researchers have suggested that bigorexia may be related to OCD, which is characterized by intrusive, unwanted thoughts or obsessions that lead to repetitive behaviors or compulsions [12].

TREATMENT

Treatment for bigorexia typically involves a combination of psychotherapy, medication, and lifestyle changes. Cognitive-behavioral therapy (CBT) is a common form of psychotherapy used to treat bigorexia. It can help individuals understand and manage their distorted body image and anxiety, while medication can help alleviate symptoms of depression and anxiety. Lifestyle changes, such as reducing excessive exercise and steroid use, can help improve physical health and reduce the risk of injury.

Studies have also suggested that mindfulness-based interventions may be effective in treating bigorexia [13]. Mindfulness-based interventions involve teaching individuals to be more aware of their thoughts and feelings in the present moment, without judgment.

It is important to note that recovery from bigorexia can be a long and difficult process. Individuals with bigorexia may struggle with feelings of shame, guilt, and inadequacy, which can make seeking treatment challenging. However, with the help of a mental health provider who is experienced in treating this condition, individuals with bigorexia can learn to manage their symptoms and achieve a healthier relationship with their bodies.

PHYSICAL AND MENTAL HEALTH IMPLICATIONS

Ignoring bigorexia can lead to serious negative consequences on a person's physical and mental health. Increased risk of injury, depression, anxiety, and social isolation are just a few of the potential outcomes. Steroid use, which is common among individuals with bigorexia, can also lead to a number of serious health problems, including liver damage, kidney failure, and heart disease.

Research has shown that individuals with bigorexia are also at an increased risk of

developing eating disorders, such as anorexia nervosa or bulimia nervosa. This is because individuals with bigorexia may engage in restrictive eating behaviors or purging behaviors in order to achieve the desired muscular physique.

One of the health risks of trying to be as muscular as possible is the use of anabolic steroids [1, 14]. By using these substances, people with bigorexia are at a much higher risk of coronary heart disease, kidney and liver damage, including immune system damage [15]. Steroids are injected into large muscle groups (buttocks, thighs, shoulders), however, not intravenously. The risk of needle sharing among steroid users and the associated transmission of other diseases such as HIV and hepatitis may also be associated with the application of steroids [15]. Users usually take steroids in cycles of 6 to 12 weeks, followed by the same time period without taking steroids and then resuming the course of treatment. At the beginning of the cycle, small doses are taken with a gradual increase, but continuous use is not unusual. It is used to increase muscle volume and avoid withdrawal symptoms. The side effects of these substances are also associated with aggression, paranoia, anxiety or depression, a reduction in sexual libido, erectile dysfunction (especially at the end of the steroid cycle), or severe acne [1].

CONCLUSION

Bigorexia is a serious mental health disorder that primarily affects men who engage in bodybuilding or weightlifting. Symptoms include excessive preoccupation with muscularity and body size, as well as social isolation, depression, and anxiety. Treatment typically involves a combination of psychotherapy, medication, and lifestyle changes. It is important to seek professional help if you or someone you know is struggling with bigorexia. Recovery from bigorexia can be a long and difficult process, but with the help of a mental health provider who is experienced in treating this condition, individuals can learn to manage their symptoms and achieve a healthier life.

REFERENCES

1. Pope G C., Pope G H., Menard W., Fay C., Olivardia R.: Clinical features of muscle dysmorphia among males with body dysmorphic disorder. *Body Image*, 2005, 2(4), 395-400.
2. Olivardia R., Pope G H., Hudson I.: Muscle dysmorphia in male weightlifters: a case-control study. *The American Journal of Psychiatry*, 2000, 157(8), 1291-1296.

3. Gattario K., Linwall M., Frisé A.: Life after childhood bullying: Body image development and disordered eating in adulthood. *International Journal of Behavioral Development*, 2019, 44(3), 246-255.
4. Cerea S., Bottesi G.: Muscle Dysmorphia and its Associated Psychological Features in Three Groups of Recreational Athletes. *Scientific reports*, 2018, 8, 8877 (2018).
5. Compte, E. J., Sepúlveda, A. R., Torrente, F.: Approximations to an Integrated Model of Eating Disorders and Muscle Dysmorphia among University Male Students in Argentina. *Men and Masculinities*, 2020, 23(2), 288–305.
6. Olivardia R.: Mirror, Mirror on the Wall, Who's the Largest of Them All? The Features and Phenomenology of Muscle Dysmorphia. *Harvard Review of Psychiatry*, 2001, 9(5), 254-259.
7. Kanayama G., Pope H. G.: Gods, men, and muscle dysmorphia. *Harvard Review of Psychiatry*, 2011, 19(2), 95–98.
8. Mosley E. P.: Bigorexia: Bodybuilding and Muscle Dysmorphia. *European Eating Disorders Review*, 2009, 17(3):191-198.
9. Stuart B., Murray BSc.: Muscle dysmorphia and the DSM-V conundrum: Where does it belong? A review paper. *International Journal of Eating Disorders*, 2010, 43(6), 483-491.
10. Raevuori A., Keski-Rahkonen A., Hoek H., Sihvola E., Rissanen A.: Lifetime anorexia nervosa in young men in the community: Five cases and their co-twins. *International journal of eating disorders*, 2018, 41(5), 458-463.
11. Tod D., Edwards C., Cranswick I.: Muscle dysmorphia: Current insights. *Psychology Research and Behavior Management*, 2016, 9, 179-188.
12. Phillips K., Castle D.: Body dysmorphic disorder in men. *BMJ Clinical Research*, 2001, 3, 323(7320), 1015-1016.
13. Zheng Y., Zhang L., Shao P.: The Association of Muscle Dysmorphia, Social Physique Anxiety, and Body Checking Behavior in Male College Students With Weight Exercise. *Frontiers in psychology*, 2021. Pope G C., Gruber A., Choi P., Olivardia R.: Muscle Dysmorphia: An Underrecognized Form of Body Dysmorphic Disorder. *Psychosomatics*, 1997, 38(6), 548-557.
14. Tovt Š., Hricová A.: Introduction to bigorexia. *Kontakt*, 2021, 23(2) , 1-5.

COPING WITH STRESS IN THE 21ST CENTURY

Michalina Toborek¹, Katarzyna Sudelska¹, Tomasz Król², Grzegorz Tarsa²

1. Faculty of Medical Sciences, Medical University of Silesia in Katowice
2. Brothers Hospitallers of Guardian Angels Hospital in Katowice

INTRODUCTION

People living in the 21st century have witnessed rapid advancements in technology, communication, and globalization, shaping a world that is more interconnected and fast-paced than ever before. While these developments have brought about numerous benefits, they have also introduced new challenges and stressors that affect individuals across all walks of life. Coping with stress has become a critical concern in today's society, as the demands and pressures of modern life continue to escalate.

Stress, defined as the body's response to any demand or challenge, is an inevitable part of the human life. It can arise from multiple sources, such as work-related pressures, financial difficulties, relationship problems, academic demands, and health concerns, among others. The impact of stress on individuals' physical and mental well-being cannot be overstated. Prolonged or excessive stress can lead to a range of adverse effects, including increased risk of chronic illnesses, compromised functioning of the immune system, mental health disorders, impaired cognitive abilities, and decreased overall quality of life.

The coping mechanisms and strategies employed to manage stress have undergone significant changes in the 21st century. Traditional approaches to stress management, such as exercise, relaxation techniques, and social support, remain relevant and effective. However, the advent of digital technologies and the rise of the internet have introduced novel coping mechanisms, as well as new stressors, requiring individuals to adapt and develop innovative ways to navigate the challenges of the modern era.

This review paper aims to explore the various coping strategies individuals employ to navigate and manage stress in the 21st century. By synthesizing and examining existing research, this paper seeks to shed light on both traditional and contemporary coping mechanisms, their effectiveness, and their implications for well-being. Additionally, it will delve into the unique stressors faced in the current era and how they have influenced the

development of coping strategies.

The paper will provide an overview of the theoretical frameworks and models that underpin stress and coping research, including Lazarus and Folkman's transactional model, the general adaptation syndrome, and the cognitive-appraisal model. Understanding these frameworks will serve as a foundation for comprehending the various coping strategies discussed throughout the review.

The subsequent sections will explore a wide range of coping mechanisms, beginning with traditional approaches such as social support, physical exercise, and relaxation techniques. These strategies have proven effective over time and continue to play a crucial role in stress management. Furthermore, the paper will examine emerging coping strategies in the digital age, including the utilization of technology for stress reduction, online support communities, mindfulness apps, and virtual reality therapy, among others. This section will highlight the benefits and limitations of these new approaches and their integration into individuals' coping repertoire.

In addition to discussing coping mechanisms, this review paper will also address the unique stressors and challenges faced by individuals in the 21st century. Factors such as information overload, constant connectivity, social media pressure, and work-life imbalance have significantly impacted stress levels and necessitated the development of innovative coping strategies. Understanding these stressors is crucial for tailoring effective interventions and support systems that meet the specific needs of individuals in today's rapidly changing world.

Finally, this paper will address the implications of coping with stress in the 21st century at the societal level. It will explore how organizations, educational institutions, and healthcare systems can play a role in promoting effective stress management practices. Additionally, it will highlight the importance of fostering a culture that recognizes and supports individuals in coping with stress, both in the workplace and in personal lives.

In conclusion, the challenges posed by stress in the 21st century demand a comprehensive understanding of coping mechanisms that are suitable for navigating the complexities of modern life. By examining both traditional and contemporary approaches to stress management, this review paper aims to contribute to the existing literature and offer insights into effective coping strategies. It is hoped that this exploration will provide a valuable resource for researchers, practitioners, and individuals seeking to enhance their ability to cope with stress in the fast-paced and interconnected world of the 21st century.

PURPOSE OF THE WORK

The purpose of this paper is to provide a comprehensive examination of coping strategies employed by individuals to manage stress in the 21st century. With the advent of technological advancements, globalization, and the ever-increasing demands of modern life, coping with stress has become a critical concern for individuals. By synthesizing and analyzing existing research, this paper aims to achieve the following objectives:

1. Explore the theoretical frameworks and models that underpin stress and coping research: The review will provide an overview of prominent theoretical frameworks, such as Lazarus and Folkman's transactional model, the general adaptation syndrome, and the cognitive-appraisal model. Understanding these frameworks will lay the foundation for comprehending the various coping strategies discussed throughout the paper.
2. Examine traditional coping mechanisms: The paper will delve into traditional approaches to stress management, including social support, physical exercise, and relaxation techniques. These time-tested strategies continue to play a crucial role in individuals' ability to cope with stress. The examination will highlight the effectiveness of these mechanisms and their continued relevance in the 21st century.
3. Investigate emerging coping strategies in the digital age: The review will explore the novel coping mechanisms that have emerged in response to the challenges of the modern era. With the rise of digital technologies, individuals have access to new tools and resources for stress reduction. The paper will discuss the utilization of technology for stress management, online support communities, mindfulness apps, virtual reality therapy, and other innovative approaches. The benefits and limitations of these new strategies will be examined to provide a comprehensive understanding of their effectiveness.
4. Address the unique stressors and challenges of the 21st century: The review will shed light on the specific stressors faced by individuals in the current era. Factors such as information overload, constant connectivity, social media pressure, and work-life imbalance have significantly impacted stress levels. Understanding these stressors is crucial for developing coping strategies that address the unique challenges of the 21st century.

5. Discuss the implications of coping with stress at the societal level: The paper will explore the broader implications of coping with stress in the 21st century. It will examine how organizations, educational institutions, and healthcare systems can play a role in promoting effective stress management practices. Additionally, the review will emphasize the importance of fostering a culture that recognizes and supports individuals in coping with stress, both in the workplace and in personal lives.

By achieving these objectives, this review paper aims to contribute to the existing literature on coping with stress in the 21st century. The synthesis of traditional and contemporary coping strategies, along with an understanding of the unique stressors faced in the current era, will provide valuable insights for researchers, practitioners, and individuals seeking to enhance their ability to navigate and manage stress in the fast-paced and interconnected world of today.

MATERIALS AND METHODS

This review paper on coping with stress in the 21st century is based on a comprehensive analysis of existing literature and research studies. The methodology employed in this study involved systematic literature review and analysis to achieve the objectives outlined in the previous sections. The following materials and methods were utilized:

1. Literature Search: A thorough search was conducted in academic databases, including PubMed, PsycINFO, Scopus, and Google Scholar, to identify relevant studies, review articles, meta-analyses, and theoretical frameworks related to coping with stress in the 21st century. The search terms included combinations of keywords such as "stress," "coping mechanisms," "stress management," "technology," "digital coping strategies," "traditional coping strategies," and "21st century."
2. Inclusion and Exclusion Criteria: The initial search results were screened based on predefined inclusion and exclusion criteria. Studies were included if they were published in peer-reviewed journals, written in English, focused on coping strategies employed in the 21st century, and provided insights into traditional or emerging approaches to stress management. Studies that focused solely on specific populations (e.g., clinical populations) or those that did not align with the objectives of this review paper were excluded.

3. **Data Extraction and Analysis:** Relevant data from the selected articles were extracted, including the study design, participant characteristics, theoretical frameworks, coping mechanisms investigated, and key findings. The extracted data were organized and synthesized based on thematic analysis to identify common themes, patterns, and trends in coping strategies employed in the 21st century. The analysis involved a qualitative synthesis of the literature, highlighting similarities, differences, and emerging approaches.
4. **Theoretical Frameworks and Models:** Theoretical frameworks and models related to stress and coping were reviewed to provide a conceptual framework for understanding the various coping strategies discussed. The transactional model of stress and coping by Lazarus and Folkman, the general adaptation syndrome by Hans Selye, and the cognitive-appraisal model were examined to gain insights into the underlying mechanisms and processes involved in coping with stress.
5. **Synthesis and Interpretation:** The extracted data and findings were synthesized and interpreted to address the objectives of this review paper. Traditional coping mechanisms, such as social support, physical exercise, and relaxation techniques, were examined in the context of their effectiveness and relevance in the 21st century. Additionally, emerging coping strategies in the digital age, such as the utilization of technology, online support communities, mindfulness apps, and virtual reality therapy, were evaluated to provide insights into their benefits, limitations, and implications for stress management.
6. **Ethical Considerations:** As this review paper is based on the analysis of existing literature, ethical approval was not required. However, appropriate citation and acknowledgment of the original authors' work were ensured to maintain academic integrity and give due credit to the contributors in the field.

By employing these materials and methods, this review paper aims to provide a comprehensive synthesis and analysis of coping strategies employed in the 21st century.

RESULTS

The systematic review and analysis of the existing literature on coping with stress in the 21st century yielded valuable insights into the various coping strategies employed by

individuals. The results are presented below based on the objectives outlined in the Materials and Methods section.

1. Traditional Coping Mechanisms:

- **Social Support:** Social support emerged as a vital coping mechanism in the face of stress. Studies consistently demonstrated that individuals who have strong social networks and receive emotional, instrumental, and informational support experience better stress management outcomes [1].
- **Physical Exercise:** Regular physical exercise was found to be effective in reducing stress levels and promoting overall well-being. Engaging in activities such as aerobic exercises, yoga, and mindfulness-based practices showed positive effects on stress reduction and improved mental health [2].
- **Relaxation Techniques:** Various relaxation techniques, including deep breathing, progressive muscle relaxation, and meditation, were reported to be effective in alleviating stress symptoms and promoting relaxation responses [3].

2. Emerging Coping Strategies in the Digital Age:

- **Technology-Assisted Stress Reduction:** The utilization of technology for stress reduction has gained significant attention. Mobile applications, wearable devices, and biofeedback tools have been developed to monitor stress levels, provide stress management techniques, and facilitate self-care practices [4][5].
- **Online Support Communities:** Online platforms and social media networks have given rise to virtual support communities. These communities enable individuals to connect with others facing similar stressors, share experiences, seek advice, and receive emotional support, fostering a sense of belonging and reducing feelings of isolation [6][7].
- **Mindfulness Apps:** Smartphone applications focused on mindfulness meditation and stress reduction have gained popularity. These apps provide guided meditation sessions, breathing exercises, and stress management techniques, empowering individuals to incorporate mindfulness practices into their daily lives [4].
- **Virtual Reality Therapy:** Virtual reality (VR) therapy has emerged as a promising tool for stress reduction. VR environments provide immersive and controlled settings that simulate real-life scenarios, allowing individuals to engage in exposure therapy, relaxation exercises, and stress management simulations [8, 9].

3. Unique Stressors of the 21st Century:

- Information Overload: The rapid increase in information availability and technology has led to information overload, causing stress related to managing vast amounts of data, keeping up with news, and distinguishing reliable sources [10][11].
- Constant Connectivity: The pervasive nature of technology has resulted in constant connectivity, blurring the boundaries between work and personal life. This constant availability can lead to work-related stress, reduced work-life balance, and increased pressure to always be online and responsive [11].
- Social Media Pressure: The use of social media platforms has introduced a new set of stressors, including fear of missing out (FOMO), social comparison, cyberbullying, and the pressure to present an idealized online self-image [12].
- Work-Life Imbalance: The demands of modern work environments, long working hours, and the expectation of multitasking have contributed to work-life imbalance, causing chronic stress and negatively impacting overall well-being [13].

4. Implications for Society:

- Organizational Support: Organizations play a crucial role in supporting employees' stress management efforts. Implementing flexible work arrangements, promoting work-life balance, and providing resources and training on stress management can create a supportive work environment [14].
- Educational Interventions: Educational institutions can incorporate stress management programs and teach coping skills to students at various educational levels. Equipping individuals with effective coping strategies early on can foster resilience and well-being throughout their lives [15].
- Healthcare Interventions: Healthcare systems should recognize the impact of stress on overall health and well-being. Integrating stress management interventions into healthcare settings, promoting preventive care, and facilitating access to mental health services can aid individuals in coping with stress-related challenges [16].
- The results of this review paper highlight the importance of both traditional and emerging coping strategies in the 21st century. While traditional mechanisms like social support, physical exercise, and relaxation techniques remain effective, new coping strategies in the digital age offer innovative tools and resources. However, it is crucial to acknowledge the unique stressors faced in the modern era and the need for tailored coping interventions.

By addressing these stressors and providing support at the individual, organizational, and societal levels, effective stress management can be achieved, enhancing overall well-being in the 21st century.

DISCUSSION

The discussion section of this review paper aims to provide a comprehensive analysis and interpretation of the results obtained from the systematic review of literature. The following discussion incorporates the findings presented in the Results section and offers insights into the implications, limitations, and future directions for research and practice.

1. Traditional Coping Mechanisms

The results emphasize the continued relevance and effectiveness of traditional coping mechanisms, such as social support, physical exercise, and relaxation techniques, in managing stress in the 21st century. The consistent evidence supporting the positive impact of social support on stress management highlights the importance of fostering and maintaining strong social connections. Encouraging individuals to build and nurture social networks may prove instrumental in coping with stress and promoting overall well-being.

Similarly, the beneficial effects of physical exercise on stress reduction align with previous research. Regular exercise has been shown to reduce stress levels, enhance mood, and improve overall physical and mental health. Incorporating physical activity into daily routines, such as engaging in aerobic exercises, yoga, or mindfulness-based practices, can provide individuals with effective tools to cope with stress in the modern era.

Relaxation techniques, including deep breathing, progressive muscle relaxation, and meditation, have demonstrated their efficacy in managing stress. These practices induce a relaxation response, counteracting the physiological and psychological effects of stress. Encouraging individuals to incorporate these techniques into their daily lives, even for short durations, can help alleviate stress and promote a sense of calmness.

2. Emerging Coping Strategies in the Digital Age

The results highlight the emergence of new coping strategies in the digital age, leveraging technology to address stressors. Technology-assisted stress reduction tools, such as mobile applications and wearable devices, offer personalized approaches to stress management.

These technologies provide individuals with the means to monitor their stress levels, learn stress management techniques, and engage in self-care practices. However, the effectiveness and long-term impact of these tools warrant further investigation.

Online support communities have emerged as a valuable resource for individuals seeking social support and connection. These virtual platforms offer a space for sharing experiences, seeking advice, and receiving emotional support from like-minded individuals facing similar stressors. The accessibility and anonymity provided by online support communities can reduce feelings of isolation and provide a sense of belonging.

Mindfulness apps have gained popularity as a convenient and accessible means of incorporating mindfulness practices into daily life. These apps offer guided meditation sessions, breathing exercises, and stress management techniques. While research suggests that mindfulness-based interventions can be effective in stress reduction, the quality and efficacy of mindfulness apps may vary, underscoring the need for further evaluation and standardization.

Virtual reality therapy represents a promising avenue for stress management. By creating immersive and controlled environments, VR therapy allows individuals to engage in exposure therapy, relaxation exercises, and stress management simulations. While still in its early stages, VR therapy holds potential as an innovative approach to stress reduction, although its accessibility and cost-effectiveness need to be addressed.

3. Unique Stressors of the 21st Century

The discussion of unique stressors faced in the 21st century highlights the challenges posed by information overload, constant connectivity, social media pressure, and work-life imbalance. Information overload can lead to stress related to managing vast amounts of data, staying updated with news, and discerning reliable sources. Coping strategies that involve information management, critical thinking, and establishing boundaries with technology may prove effective in mitigating information overload.

Constant connectivity blurs the boundaries between work and personal life, contributing to work-related stress and reduced work-life balance. Strategies promoting time management, boundary setting, and self-care can help individuals establish healthier boundaries and enhance work-life integration.

Social media pressure introduces unique stressors, including fear of missing out (FOMO), social comparison, and the pressure to present an idealized self-image. Encouraging

digital literacy, promoting mindful social media usage, and fostering authentic connections can assist individuals in navigating the challenges of social media and reducing associated stress.

Work-life imbalance is a significant stressor in the modern era. Organizations can play a pivotal role in addressing this issue by implementing flexible work arrangements, promoting a supportive work culture, and providing resources for stress management. Additionally, individuals can benefit from prioritizing self-care, setting boundaries, and seeking support from their social networks to achieve a healthier work-life balance.

4. Implications for Society

The results have several implications for society, particularly in terms of organizational support, educational interventions, and healthcare initiatives. Organizations should recognize the impact of stress on employee well-being and productivity. Implementing supportive policies, providing stress management resources, and fostering a positive work environment can contribute to healthier and more engaged employees.

Educational institutions can play a crucial role in equipping individuals with effective coping strategies from an early age. Incorporating stress management programs and teaching coping skills can enhance resilience, emotional well-being, and academic performance. Educational interventions should focus on developing coping strategies specific to the challenges of the 21st century, such as information management, digital well-being, and work-life integration.

Healthcare systems need to acknowledge the impact of stress on overall health and well-being. Integrating stress management interventions into healthcare settings, promoting preventive care, and facilitating access to mental health services are essential in addressing the growing stress-related health concerns in the 21st century. Healthcare providers should adopt a holistic approach, considering both traditional and emerging coping strategies in their treatment plans.

5. Limitations and Future Directions

This review paper has several limitations that warrant acknowledgment. Firstly, the reliance on existing literature introduces the possibility of publication bias and may overlook unpublished or grey literature. Additionally, the quality and heterogeneity of the included studies may influence the generalizability of the findings. Future research should consider

conducting systematic reviews and meta-analyses to further consolidate the evidence base and evaluate the effectiveness of coping strategies in different populations.

Furthermore, given the rapid pace of technological advancements, emerging coping strategies require ongoing evaluation to assess their long-term effectiveness, user experience, and potential drawbacks. Continual monitoring of technology-assisted interventions, such as mindfulness apps and virtual reality therapy, will provide valuable insights into their sustainability, ethical considerations, and integration into mainstream healthcare practices.

Moreover, as the 21st century unfolds, new stressors may arise, requiring innovative coping strategies. Future research should be responsive to these evolving stressors and explore novel approaches to stress management in response to societal and technological changes.

In conclusion, this review paper highlights the importance of both traditional and emerging coping strategies in managing stress in the 21st century. It underscores the continued relevance of social support, physical exercise, and relaxation techniques while acknowledging the potential benefits of technology-assisted interventions, online support communities, mindfulness apps, and virtual reality therapy. Addressing the unique stressors of the modern era and fostering support at the individual, organizational, and societal levels can enhance stress management and promote overall well-being in the 21st century.

CONCLUSIONS

This review paper has provided a comprehensive analysis of coping with stress in the 21st century, examining both traditional and emerging coping mechanisms.

The results indicate the continued relevance and effectiveness of traditional coping strategies, such as social support, physical exercise, and relaxation techniques, in managing stress.

These strategies have demonstrated consistent positive outcomes in reducing stress levels, promoting well-being, and fostering resilience.

Furthermore, the review highlighted the emergence of innovative coping strategies in the digital age. Technology-assisted interventions, including mobile applications, online support communities, mindfulness apps, and virtual reality therapy, offer promising avenues for stress management. These tools leverage the accessibility and connectivity provided by technology to provide personalized and convenient solutions for individuals facing stressors in the modern era.

The discussion also shed light on the unique stressors of the 21st century, including information overload, constant connectivity, social media pressure, and work-life imbalance. These stressors present new challenges and call for tailored coping strategies that address the specific demands of the digital age. By recognizing and addressing these stressors, individuals, organizations, and society as a whole can better support stress management efforts and promote overall well-being.

The implications of this review paper extend to multiple domains. Organizations play a crucial role in supporting employees' stress management by implementing policies that promote work-life balance, creating a supportive work environment, and providing resources for stress reduction. Educational institutions can equip individuals with effective coping strategies from an early age, fostering resilience and well-being throughout their lives. Healthcare systems should integrate stress management interventions into healthcare settings, emphasizing preventive care, and facilitating access to mental health services.

However, it is important to acknowledge the limitations of this review. The reliance on existing literature introduces the possibility of publication bias, and the heterogeneity of the included studies may impact the generalizability of the findings. Additionally, the rapid pace of technological advancements necessitates ongoing evaluation of emerging coping strategies to assess their long-term effectiveness and potential drawbacks.

Future research should consider conducting systematic reviews and meta-analyses to consolidate the evidence base and evaluate the effectiveness of coping strategies in diverse populations. Continual monitoring of technology-assisted interventions and the exploration of novel coping approaches will contribute to our understanding of effective stress management in the evolving landscape of the 21st century.

In conclusion, coping with stress in the 21st century requires a multi-faceted approach that combines traditional coping mechanisms with emerging strategies facilitated by technology.

Social support, physical exercise, and relaxation techniques remain effective and relevant, while technology-assisted interventions, online support communities, mindfulness apps, and virtual reality therapy offer innovative tools for stress reduction.

By addressing the unique stressors of the modern era and fostering support at individual, organizational, and societal levels, effective stress management can be achieved, enhancing overall well-being in the 21st century and beyond.

REFERENCES

1. Buunk BP, Hoorens V. Social support and stress: the role of social comparison and social exchange processes. *British Journal of Clinical Psychology*. 1992, 31(4), 445-57.
2. Warburton D. E., Nicol C. W., Bredin S. S. Health benefits of physical activity: the evidence. *Canadian Medical Association Journal*, 2006, 174(6), 801-9.
3. Kabat-Zinn J. Full catastrophe living: Using the wisdom of your body and mind to face stress, pain, and illness. Delta, NY, 1990..
4. Huberty J, Green J, Glissmann C, Larkey L, Puzia M, et al. Efficacy of the Mindfulness Meditation Mobile App "Calm" to Reduce Stress Among College Students: Randomized Controlled Trial. *JMIR Mhealth Uhealth*. 2019, 25, 7(6), e14273.
5. Hunter JF, Olah MS, Williams AL, Parks AC, Pressman SD. Effect of Brief Biofeedback via a Smartphone App on Stress Recovery: Randomized Experimental Study. *JMIR Serious Games*. 2019, 26, 7(4), e15974.
6. Greenfield E. A. The role of online support communities: Benefits of expanded social networks to divorced, bereaved, and disability communities. *Journal of Community Psychology*, 2009, 37(7), 896-909.
7. Bolier L., Haverman M., Westerhof G. J., Riper H., Smit F., Bohlmeijer E. Positive psychology interventions: A meta-analysis of randomized controlled studies. *BMC Public Health*, 2013, 13(1), 1-20.
8. Zeng, N.; Pope, Z.; Lee, J.E.; Gao, Z. Virtual Reality Exercise for Anxiety and Depression: A Preliminary Review of Current Research in an Emerging Field. *Journal of Clinical Medicine*. 2018, 7, 42.
9. Donnelly MR, Reinberg R, Ito KL, Saldana D, Neureither M, et al. Virtual Reality for the Treatment of Anxiety Disorders: A Scoping Review. *The American Journal of Occupational Therapy*. 2021, 1, 75(6), 7506205040..
10. Burke M., Kraut R. E. The relationship between Facebook use and well-being depends on communication type and tie strength. *Journal of Computer-Mediated Communication*, 2014, 19(4), 265-281.
11. Lanaj K., Johnson R. E., Barnes C. M. Beginning the workday yet already depleted? Consequences of late-night smartphone use and sleep. *Organizational Behavior and Human Decision Processes*, 2014, 124(1), 11-23.
12. Abi-Jaoude E, Naylor KT, Pignatiello A. Smartphones, social media use and youth mental health. *Canadian Medical Association Journal*. 2020, 10, 192(6), E136-E141.

13. Al-Adawi S, Alameddine M, Al-Saadoon M, Al Balushi AA, Chan MF, et al. The magnitude and effect of work-life imbalance on cognition and affective range among the non-western population: A study from Muscat. Public Library of Science One. 2022, 3,17(2), e0263608.
14. Lomas T., Medina J. C., Ivztan I., Rupprecht S., Eiroa-Orosa F. J. The impact of mindfulness on well-being and performance in the workplace: An inclusive systematic review of the empirical literature. European Journal of Work and Organizational Psychology, 2017, 26(4), 492-513.
15. Waters L. A review of school-based positive psychology interventions. The Australian Educational and Developmental Psychologist, 2014, 31(2), 86-97.
16. Chida Y., Steptoe A. Positive psychological well-being and mortality: A quantitative review of prospective observational studies. Psychosomatic Medicine, 2008, 70(7), 741-756.

A MODERN VIEW ON WHETHER MARIJUANA SHOULD BE CONSIDERED A MEDICINE OR A NARCOTIC

Julia Błońska, Maciej Dyda, Tomasz Malinowski, Michał Orzechowski

Wrocław Medical University

ABBREVIATION LIST

- B. C. E- before the common era
- ECS- endocannabinoid system
- CB1/CB2- cannabinoid receptor 1/ cannabinoid receptor 2
- GPCRs- G protein-coupled receptors
- GABA- Gamma-Aminobutyric Acid
- CBD- Cannabidiol
- THC- Tetrahydrocannabinol
- USA- United States of America
- MS- multiple sclerosis
- EMA- European Medicines Agency
- LGS- Lennox-Gastaut Syndrome
- DS- Dravet Syndrome
- EEG- electroencephalogram
- AEDs- antiepileptic drugs
- IBD- Inflammatory Bowel Disease
- PTSD- post-traumatic stress disorder
- DEA- The United States Drug Enforcement Administration
- SUD- Substance Use Disorder

HISTORY OF MARIJUANA

Cannabis has been a well-known plant for many centuries for its various properties. As early as 650 B.C.E in Assyria its intoxicated features had been discovered and used [1]. Later on, cannabis was found as a medicine mainly analgesic, and nowadays especially in Eastern

countries the use of medical marijuana is considered something experimental, full of mystery, and even illegal. Therefore this paper aims to increase awareness of what marijuana is in terms of its use as a medicine and as a drug.

The human body has its endocannabinoid system (ECS) which produces endocannabinoids and consist of cannabinoid receptors, and enzymes which are also responsive to cannabinoids found in marijuana. CB1 and CB2 receptors are the most known for now. They are G protein-coupled receptors (GPCRs), primarily coupling to inhibitory G proteins. CB1 receptors are mainly found in certain GABAergic interneurons and on synaptic terminals where they are responsible for modulating synaptic transmission, but also appear in the skin, liver, adipose tissue, and probably many other places. CB2 receptors are present in immune cells and microglia where their activation has anti-inflammatory properties it is also believed that their occurrence in neurons is linked with some kind of pathological state [1].

Out of over 400 active substances contained in marijuana, the best known are from the group of cannabinoids: Cannabidiol (CBD) and Tetrahydrocannabinol (THC); they both have high affinity to CB1, CB2, and other GI-coupled receptors.

With only a few studies it is considered that THC is mainly responsible for psychoactive effects and CBD progressively influences THC-induced anxiety, psychosis, and cognitive deficits [1].

Therefore marijuana has been accompanying humanity for centuries, in today's world its active substances, dangers, and possibilities of use in medicine or industry are not well understood. It is probably related to the War on Drugs, which is the name of a global campaign led by the USA in the 1970s which established a zero-tolerance policy for any illegal substances including marihuana. It enabled many experiments, and studies and made it very difficult or even impossible to execute. Nowadays The War on drugs is still taking its toll which presents very high prices and enormous formal requirements to start the study on marihuana.

IMPACT OF CANNABINOIDS ON THE HUMAN BODY

To understand the cannabinoid impact on therapy use of various diseases first, it is important to establish what's the impact of cannabinoid-active substances on the human body. The primary psychoactive component of marijuana, delta-9-tetrahydrocannabinol (THC), interacts with the endocannabinoid system (ECS) in the Central nervous system. It is involved in the modulation of neurotransmission and synaptic plasticity which has a direct impact on cognitive processes [2].

During administration to the body, THC binds to cannabinoid receptors CB1 and CB2, located on presynaptic neurons. This action leads to alterations in the release of neurotransmitters such as dopamine, glutamate, and GABA. These changes in neurotransmission have an impact on neural oscillations. It has a significant influence on the theta and gamma frequency bands which are linked with cognitive processes including attention, memory, and emotional regulation. Disruption of neural oscillations may contribute to the observed changes in cognitive performance among marijuana users.

It is important to notice individual differences in response to the active agents, as well as the potential therapeutic applications of cannabinoids for specific neurological disorders [2].

Cannabinoids' active substance THC, interacts with CB1 and CB2 receptors in the endocrine system, influencing various endocrine organs. One objective of endogenous cannabinoids has been to regulate food intake and energy homeostasis. It has significant effects on activity regulation of the pituitary gland, adrenal cortex, thyroid gland, pancreas, and gonads. The interrelations between the substitute particles for the endocannabinoid system which have an impact on the endocrine system offer potential therapeutic targets for conditions like infertility, obesity, diabetes, and cardiovascular diseases [2].

CURRENT MEDICAL USAGE OF MARIHUANA IN MEDICINE

In this part, we will focus on the current uses of cannabinoids in medical fields. To segregate different diseases this chapter will segregate disorders into medical specializations. This way it will clarify current medical fields in which cannabinoids are used.

Neurology

In the field of neurology, cannabis products have gained interest due to their potential to influence neurological pathways in various ways.

For multiple sclerosis (MS) patients experiencing spasticity the cannabis-derived medicine nabiximols has been approved by several European countries, offering a new approach for managing the effects of spasticity in MS patients. A study published in the journal provides evidence of the positive impact of nabiximols (Sativex) treatment on brain connectivity in MS patients with spasticity [3]. The study found that patients treated with Sativex presented increased global brain connectivity, particularly in responders, and decreased connectivity of motor areas, as well as bidirectional connectivity changes of the left cerebellum with several cortical areas [3].

In many cases of MS, there is a subset of patients for whom spasticity symptoms are difficult to manage with conventional treatments or do not yield significant effects. This group has been classified under a new condition called "Spasticity-plus syndrome," characterized by the presence of spasticity alongside additional symptoms such as pain, fatigue, sleep disturbance, bladder or bowel dysfunction, and cognitive impairment. A real-world evidence study of nabiximols in multiple sclerosis patients with resistant spasticity analyzed data of 10,138 patients with MS spasticity and found that nabiximols treatment led to a 24.6% reduction in spasticity severity at week 4, and a 33.9% reduction of spasticity symptoms at the 18-month mark. Additionally, nabiximols were found to resolve various spasticity-associated symptoms at week 4, and after 18 months in treatment continue [4].

To support the use of cannabis in treating patients with multiple sclerosis, we can refer to the long-term observational study Evidence-based management of multiple sclerosis spasticity with nabiximols oromucosal spray in clinical practice: a 10-year recap, which monitored patients for 10 years, amassing statistical data from 150,000 patient-years. The conclusions of this research support the efficacy of administering nabiximols to treat spasticity syndromes in patients with multiple sclerosis [5].

Rare forms of epilepsy

In the context of rare forms of epilepsy, such as Lennox-Gastaut and Dravet syndromes, a CBD-based treatment is currently under review by the European Medicines Agency (EMA). The potential of the drug lies as an adjunctive treatment to reduce seizures. If approved, this medical product could provide a new approach to managing these challenging syndromes and improving the lives of patients.

Lennox-Gastaut Syndrome (LGS) and Dravet Syndrome (DS) are epileptic encephalopathies, predominantly seen in children. LGS is characterized by the onset of multiple seizure types, cognitive impairment, and a specific electroencephalogram (EEG) pattern[1]. DS, on the other hand, characterizes by frequent and prolonged seizures often triggered by fever or hot temperatures also presenting itself in the form of developmental delay [6].

The use of cannabinoids for the treatment of Lennox-Gastaut and Dravet syndromes shows a promising venue for therapeutic use in the field of epilepsy management. Those syndromes are severe forms of childhood-onset epilepsy. It is often characterized by multiple seizure types, cognitive impairment, and a generally poor prognosis. Some patients don't respond to treatment with the use of standard antiepileptic drugs (AEDs). Because of that some

healthcare systems fail to provide effective seizure control management for patients with these conditions. From this point, it is necessary to explore alternative treatments [6].

The study sample included 34 LGS patients and 10 DS patients aged between 2-18 years who initiated CBD treatment. CBD was administered orally at a starting dose of 5 mg/kg/day, and after a week, it was maintained at 10 mg/kg/day. Evaluation has been performed at 3 and 6 months based on caregiver reports and additional evaluations like electroencephalogram and blood tests [6].

In the LGS group, at the 3-month point, the overall reduction of seizure frequency has been noted at 52.9% (>50% reduction in 32.3% of the cases), which decreased to 29.4% at the 6-month evaluation (>50% reduction in 20.6% of the cases). In the DS group, the reduction of seizure frequency by more than 50% was 30% and 20% at the 3-month and 6-month evaluations, respectively. Adverse events were reported in 36.3% of the total patients, with gastrointestinal problems being mostly reported. No life-threatening adverse events were reported in the LGS and DS groups during the observation period. The study's findings suggest that CBD was safe, tolerable, and potentially effective in reducing seizure frequency in monitored groups. Despite these promising results, several important questions remain. The long-term efficacy and safety of CBD treatment in LGS and DS are not yet fully understood. It's also important to determine optimal dosing and administration strategies [6].

In conclusion, the use of cannabis, particularly CBD, offers a promising alternative for the treatment of LGS and DS[1]. It provides a novel approach to managing the severe cases of treatment-resistant epilepsies where conventional therapies often fail [1]. While further research is required to fully establish its role, the evidence to date suggests that CBD represents a valuable possibility for the therapeutic strategies of those conditions [1].

Oncology

Prostate cancer is one of the most prevalent forms of cancer in the male population. The potential use of cannabinoids in oncology is an emerging area of research that has shown promising results. This review presents a comprehensive discussion of the therapeutic potential of cannabinoids for the treatment of prostate cancer [7].

The therapeutic potential of cannabinoids is researched for potential treatment of prostate cancer. De Petrocellis et al. (2013) performed in vitro study which outlines that cannabinoids can trigger apoptosis in prostate cancer cells through CB1 and CB2 receptors, implying a potential mechanism for their anticancer effects [8]. Transitioning to another study by Olea-Herrero et al. (2009) which outlines that Δ^9 -tetrahydrocannabinol (THC) significantly

reduced tumor growth in a mouse xenograft model of prostate cancer. This research supports the in vivo antitumor activity of cannabinoids [9]. The study by Sarfaraz et al. (2005) spotted a significant decrease in the expression of androgen receptors - a key factor in the progression of prostate cancer [10]

These findings give strong insides for further investigation. It is important to note that these studies predominantly utilized in vitro models or animal studies. The translation of these findings to clinical practice necessitates further clinical trials in human subjects.

Pain Management

Cannabinoids have been increasingly recognized for their potential in managing chronic pain. Base on Bains et al. arguments for potential cannabinoid use in pain management have been outlined [11]. Studies provide statistical evidence to support this therapeutic potential. A survey of 984 chronic pain patients reported that two-thirds found cannabis administration with significant pain relief. Additionally, a reduction in opioid use by 64% was observed among chronic pain patients using medical marijuana. This provides potential as an alternative treatment [12].

It is essential to consider the patient-reported adverse effects and potential drug interactions. Furthermore, evidence regarding its effectiveness in acute pain and cancer pain is still limited. The growing interest in cannabinoid use for pain management potentially might be an alternative to the ongoing opioid crisis in the US. To ensure precise meaningful data to support the creation of clear and safe guidelines further research needs to be conducted.

Gastroenterology

Inflammatory Bowel disease presents a significant global health issue with growing incidence rates. Currently in use treatment protocols, mostly rely on immunosuppressive drugs and anti-inflammatory agents. Those types of treatments often have limited effectiveness and come with a range of potential side effects. Bringing cannabinoids as a potential therapeutic drug might give an advantage In some cases with limited treatment options. Inflammatory Bowel Disease (IBD) poses a significant challenge to the medical community. Patients have to endure its chronic nature, symptom severity, and lack of consistent, effective treatments. Recent research introduces the potential benefits of cannabinoid treatment for this condition.

Conducted observational studies, based on the overview of Naftali et al., outlined that a significant percentage of patients with IBD have reported an improvement in symptoms such as pain, appetite, and diarrhea after cannabis administration [13]. In the study, Crohn's disease

patients using licensed medical cannabis showed a significant reduction in the Harvey Bradshaw index (a measure of disease activity). A study of IBD patients licensed for medical cannabis use found a significant improvement in the same index over a median follow-up period of 44 months [14]. While these observational studies suggest a potential benefit of cannabis use in IBD, the data from randomized controlled trials remains inconclusive. A Cochrane review of three trials involving 93 participants found no definitive evidence regarding the efficacy and safety of cannabis and cannabis oil for active Crohn's disease [15]. The third trial showed a significant reduction in CDAI and improved quality of life scores with a CBD: THC ratio of 4:1, but no significant changes in other inflammatory markers [13].

In conclusion, some observational data and some clinical trials suggest potential benefits of cannabinoids in IBD treatment, still more randomized controlled trials are needed to further determine the effectiveness and safety of cannabinoid use in IBD.

Psychiatry

Some researchers noted cannabinoid potential for the prevalence of post-traumatic stress disorder (PTSD). A substantial part of research suggests a positive impact on the symptom-relieving impact of cannabinoids in PTSD [16]. Some monitored patients have done self-medication use of cannabis, largely driven by stress, tension, and anxiety. Studies indicate that cannabinoids may be particularly effective in managing hyperarousal symptoms and sleep disturbances associated with PTSD.

A retrospective study on Vietnam War veterans showed a correlation between the severity of PTSD symptoms and increased marijuana use [17]. A more recent study by Bonn-Miller et al. reported a higher use rate of cannabis and a greater frequency of use among medical users with high PTSD scores compared to those with low PTSD scores [18]. Improvements in sleep quality seemed to be a primary motivator for such use. Clinical trials by Fraser et al. have demonstrated the efficacy of cannabinoids in alleviating PTSD symptoms. Clinical data shows that 72% of PTSD patients report a significant reduction of nightmares after being administered a synthetic cannabinoid modulator, nabilone [19].

Overall, while more research is needed to fully understand the intricacies of this relationship, these findings suggest that cannabinoids hold promise as a potential therapeutic medicine in the treatment of PTSD.

In conclusion, cannabinoids have shown great promise in treating a range of medical conditions including chronic pain, chemotherapy side effects, inflammatory bowel diseases, Multiple Sclerosis, rare forms of epilepsy, and Post-traumatic stress disorder. Further research

is necessary to establish their safety and optimal usage guidelines. The broad spectrum in which cannabinoids are implemented suggests that it is prominent to support future research to explore therapeutic applications.

SAFETY OF CANNABINOIDS TREATMENT IN A POPULATION

The vital part of introducing new treatments and drug use is establishing potential safety concerns among the population. Among the population, genetic predispositions may vary. In concern of cannabinoid use, researchers have highlighted gene AKT1 which may have a direct impact on safety for potential cannabinoid treatment receivers.

Studies found that some polymorphism in gene AKT1 has differential responses among cannabinoid receivers. This chapter outlines potential risks that may occur in the affected population.

Among cannabinoid users medical professionals outlined increased occurrence risk of psychotic states. To determine the probability of such occurrences research has been conducted. One of the genetic factors influencing this relationship is the AKT1 gene, which plays a significant role in regulating synaptic plasticity, neuronal survival, and dopamine release.

A case study by Di Forti, et al. links cannabinoid intake with the AKT1 gene variant as the prominent factor for the development of psychotic states. The study identified specific AKT1 gene variants, such as the C/C genotype located at the rs2494732 locus, that increase probability of occurrence of psychotic symptoms upon cannabis use [20].

Analyzing a case-control study by Di Forti, et al. the interaction between the AKT1 rs2494732 single nucleotide polymorphism and cannabis use was tested. Increased risk of psychosis was investigated among 489 first-episode psychosis patients and 278 control subjects. The results indicated that the rs2494732 locus did not have a direct association with an increased risk of a psychotic disorder, lifetime cannabis use, or frequency of use. However, the researchers found a significant interaction between the rs2494732 locus and the effect of lifetime cannabis use on the risk of psychosis (likelihood ratio statistic for the interaction = 8.54; $p = .014$) [20].

Carriers of the C/C genotype with a history of cannabis use demonstrated a greater than twofold increased likelihood of a psychotic disorder (odds ratio = 2.18 [95% confidence interval: 1.12, 4.31]) when compared with users who were T/T carriers. The interaction between the rs2494732 genotype and frequency of use was significant at the 5% level (likelihood ratio = 13.39; $p = .010$). Among daily users, C/C carriers showed an increase by seven times in the

odds of psychosis compared with T/T carriers (odds ratio = 7.23 [95% confidence interval: 1.37, 38.12]) [20].

In summary, individuals carrying the C/C genotype at the rs2494732 locus in the AKT1 gene may have a higher risk of developing psychosis when using cannabis compared to those without this genotype. This highlights the importance of considering genetic factors when assessing the potential risks associated with cannabis use, especially concerning mental health outcomes like psychosis.

Health risks of medical use of cannabinoids

To fully appreciate the potential gains of medical treatment it is vital to establish possible negative outcomes to weigh the risks and gains of potential therapy for individual patients. This part outlines potential negative outcomes of cannabinoid therapy as well as the frequency of reporting adverse effects among patients.

Based on the report published by the European Monitoring Centre for Drugs and Drug Addiction following “Medical use of cannabis and cannabinoids: questions and answers for policymaking” Part 1; section: “ What health risks are associated with the medical use of cannabis and cannabinoids?”. Three main aspects can be outlined; short-term, long-term, and dependency risk of cannabinoid use [21].

The short-term risks

The short-term risks of medical cannabinoids and cannabis have been evaluated through randomized controlled clinical trials. The review conducted by the Health and Medicine Division, NASEM (1999) outlines the short-term adverse effects of cannabinoids were similar to those of other commonly used medicines. Research by Wang et al. (2008) did not find an increased risk of serious adverse effects in patients using cannabinoid drugs compared to placebo. Researchers outlined the problem of the limited ability to detect rare adverse events due to small sample sizes and lack of follow-up data from patients who left the trials [22, 23].

Research by Whiting et al. conducted a meta-analysis of short-term adverse events in 79 randomized trials evaluating the effectiveness of cannabinoids for the treatment of various conditions. It was established that the group receiving cannabinoids was more likely to report an adverse event (OR = 3.03) and slightly more likely to report a serious adverse event (OR = 1.41) compared to the group receiving a placebo. The most commonly reported adverse events were dizziness, dry mouth, disorientation, nausea, euphoria, confusion, and somnolence, with

serious adverse events being much rarer. Rarely reported were adverse events which included confusion, hallucinations, paranoia, and symptoms of psychosis [24].

The long-term risks

Long-term risks linked to the use of cannabinoids have been studied to a limited extent. The available evidence suggests that adverse events are generally reported between mild to moderate. The effects show similar outcomes to those observed in the short-term section [22]. In a study by Serpell et al., adverse events were linked to multiple sclerosis patients treated with nabiximols for spasticity, with a monitoring time of up to 3 years [25]. 84 % of patients (n=145) reported adverse events as mild to moderate, with the most common being dizziness, fatigue, and headache. It is important to outline the timeline of patients undergoing therapy stretched between one-year, two-year to three-year-long treatment. Sixteen percent of patients withdrew from the study due to these adverse events.

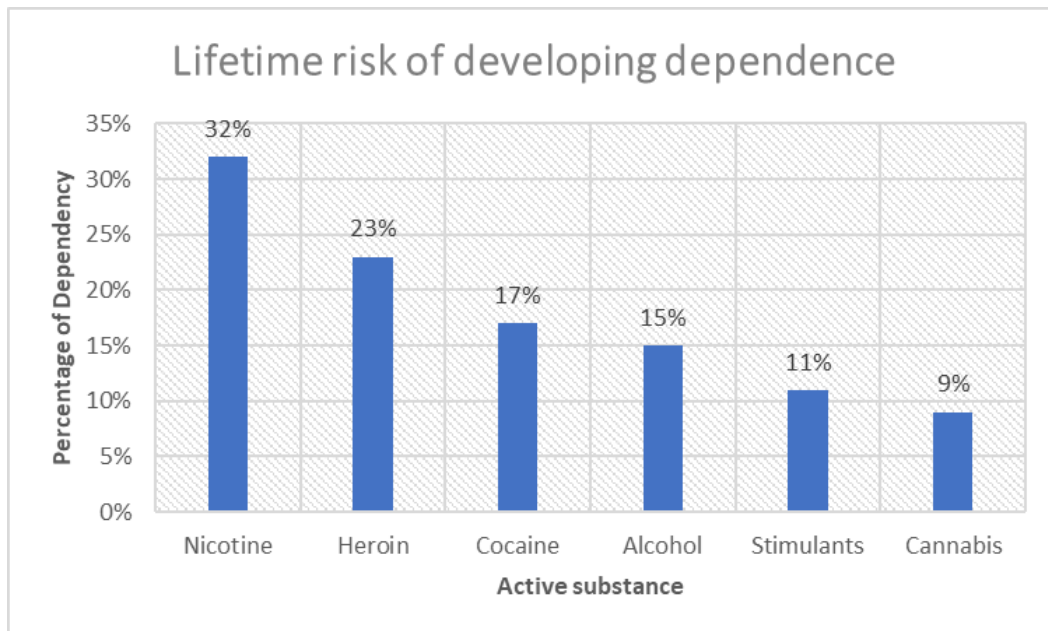
Two observational studies conducted on Israeli cancer patients and elderly patients reported similar results in both study groups. 31% of participants reported adverse events including 8% dizziness, 7,3% dry mouth, 3,6 % increased appetite, 3,3% sleepiness, and 2,8 % psychoactive effects. The prevalence and type of adverse events were similar in both groups of patients [26, 27].

Currently, there is a lack of research on the long-term use of CBD in children with intractable epilepsy, which should be considered a research priority due to concerns about potential effects on brain development [27].

Dependence on cannabinoids use

Cannabis dependence is a potential consequence of long-term cannabis use. Dependency may be shown as difficulties in controlling or stopping cannabinoid use despite negative impacts on health, well-being, or social functioning [28]. Most studies on cannabis dependence have focused on recreational users who typically start using during adolescence and consume potent cannabis products daily for extended periods.

In the early 1990s, the lifetime risk of developing cannabis dependence among recreational users in the United States was estimated at 9% [29]. This figure is lower than the corresponding risks for other substances: 32% for nicotine, 23% for heroin, 17% for cocaine, 15% for alcohol, and 11% for stimulants [30, 31]. These statistics suggest that although cannabis dependence is a potential concern, the likelihood of developing dependence is lower compared to other commonly used substances.



Graph data based on research [29].

IMPACT OF CANNABIS LEGALIZATION IN SOCIETY

Lowering opioid-related deaths

In the study by Livingston et al, which follows the cannabis legalization process in Colorado, recreational cannabis legalization impacted the number of opioid-related deaths in the region [32].

The results revealed a decrease in opioid-related deaths after the legalization of recreational cannabis in Colorado. When controlling trends in comparison states and Colorado's PDMP, there was a reduction of approximately 0.7 deaths per month compared to the baseline period. Comparing the numbers of opioid-related deaths before legalization with the numbers at the end of the follow-up study estimates a 6.5% reduction in opioid-related deaths [32].

The research refers to studies like Bachhuber et al. which suggests a potential protective effect of medical cannabis legalization on opioid-related deaths. The study recognizes its limitations, including the inability to randomize the legalization of recreational cannabis to different states, and emphasizes the need for continued research as more data become available [33].

Crash fatalities statistics

Preuss et al. analyzed the relationship between tetrahydrocannabinol (THC) concentration and the risk of car crashes. Researchers point to the significance of the legal cut-

off values for THC blood levels that vary across European countries for driving under the influence of cannabis. Studies have shown a higher risk for THC levels ≥ 5 ng/ml, with the risk increasing with higher THC concentration [34].

A study conducted in Australia by Drummer et al. concludes that drivers with blood THC concentrations of 5 ng/ml or higher were more likely to be responsible for fatal crashes and that the culpability odds increased with higher THC levels [35]. The study by conducted in France found that driving under the influence of cannabis increased the risk of fatal car crashes, even though the risk was lower than that for alcohol-influenced driving [36]. Another study corroborated the results of the French cohort study. Data shows that the risk of causing a fatal crash was multiplied by 1.65 for drivers under the influence of cannabis [37].

Based on mentioned data it is of great concern whether what levels might be established as safe for drivers. It is important to conduct more research in this field to establish a clear understanding of safe doses and limits for drivers.

Usage among the young people

According to the National Institute on Drug Abuse, usage of marihuana among young people between 19 and 30 years old has reached its historical record since 1988 in 2021, after a noticeable decrease in consumption during the covid-19 pandemic, and now in 2023 remains gradually increasing. On the other hand, statistics show that during the early onset of the pandemic and school closing the amount of marihuana usage among teenagers dramatically decreased and now it persists below pre-pandemic levels [38, 39]. National Center for Drug Abuse Statistics states that 45% of people in the USA claimed to use marihuana at some point in their life and 16.9% are currently using cannabis. We should also remember that this statistic might be inaccurate because in some states marihuana is still illegal and admitting usage may not correspond with accurate statistics.

The United States Drug Enforcement Administration (DEA) provides information on how cannabinoids influence the human body in terms of using them for self-satisfaction which includes: relaxation, disinhibition, increased appetite, increased sociability, affects memory and learning, difficulty in thinking and problem-solving, hallucinations, impaired judgment, reduced coordination, distorted perception.

Cannabis is believed to be the most commonly used substance of abuse after alcohol and tobacco [40]. Increasing use forces us to consider the risk of addiction. Proximately 9% of users will have problems with marihuana abuse. Some people are more likely to get dependent because of their genetic tendencies, age of first contact, consistency, environment, economics,

and many others, although the addiction potential rate is significantly lower than in for example alcohol [41].

The presented by Koob and Volkow 2016 common model of addiction consists of three stages describing disturbances in three major neurocircuits:

1. the binge/intoxication changes in the basal ganglia;
2. withdrawal/negative affect -changes in the extended amygdala;
3. preoccupation/anticipation changes in the prefrontal cortex.

As we know all drugs of abuse fortify dopamine release, in cannabis substance mainly responsible for DA release is considered THC, but in some studies, there is found no evidence that THC could be leading to increased DA release this might be caused by THC inducing quantitatively less DA release than other psychostimulants such as methylphenidate or amphetamine [42].

There are still uncertainties about how acute marijuana affects risk-taking in humans. In the experimental study, under laboratory conditions, results showed both reinforced and losing risky outcomes and are strongly correlated with dosage. Despite that, the statistics of taking risk behaviors revealed that marijuana users are more likely to have criminal records mainly: notably attempted homicide, drug trafficking, and delinquency [43].

DUIC which stents for Driving Under the Influence of Cannabis becomes a more and more concerning public problem. After alcohol marijuana is the second most detected substance in the general drivers' population as well as crash-involved population [44]. People under the influence may experience symptoms that enable them to drive for a long time of reaction, lack of automatic reactions, impaired judgment, and problem-solving skills, but for the majority of accidents, it is believed to be responsible for drowsiness. More research is needed, but looking through statistics in the USA from 2021, in terms of gender more males the age 21-25 drive after using drugs, and those who have THC in their blood are twice more likely to cause deadly crash than drivers who did not use any psychoactive substances [45].

Chronic use of marijuana can also damage cortical synaptic plasticity in the hippocampus and may cause permanent deficits in memory, mainly in the verbal domain, especially in younger populations. Another cannabis-associated dysfunction is impermanent in executive domains and functions such as IQ [42]. About 9% of common cannabis users develop SUD which stands for Substance Use Disorder. The characteristics of symptoms, time of occurrence, and severity are very similar to those of SUD after other substances withdrawal [42]. The clinical diagnosis is based on symptoms such as mood swings, presents of disrupted

thoughts, anxiety, sleep deprivation, and sexual disorders, and exacerbates the risk of psychoses including schizophrenia [46].

In terms of the overdosage of cannabis, there are very few statistics that show specific data on overdose cases and deaths. The Diagnostic and Statistical Manual of Mental Disorders described cannabis intoxication, the symptoms vary in specific age groups and are caused by the method of intake, type of consumption, and the pharmacokinetics of absorption- amount of THC per kilogram of body mass. The common symptoms include tachycardia, hypertension, visual changes, dizziness, confusion, nausea accompanied by abdominal pain, tachypnea, dry mucus membrane, red eye, and anxiety. Children more often present with physical disorders such as pain, vomiting, dry membranes, or dizziness while in adults we can observe more often confusion, dizziness, or hallucination. Laboratory tests revealed that with cannabis intoxication the lactate and leukocytosis levels are elevated proximately four times more often in children than adults [47].

There is almost no chance of dying after overdosing on marijuana, the fertility is linked with vehicle accidents after using cannabis or accidental intake by unsupervised children after taking intended for adult use preparations.

REFERENCES

1. Mikuriya T.H. Marijuana in medicine: past, present and future. *California Medicine*, 1969, 110, 34–40.
2. Borowska M., Czarnywojtek A., Sawicka-Gutaj N., et al. The effects of cannabinoids on the endocrine system. *Endokrynologia Polska*, 2018, 69, 705–719.
3. Gajofatto A., Cardobi N., Gobbin F., et al (2023) Resting-state functional connectivity in multiple sclerosis patients receiving nabiximols for spasticity. *BMC Neurology*, 2023, 23, 128.
4. Patti F., Chisari C.G., Fernández Ó. et al A real-world evidence study of nabiximols in multiple sclerosis patients with resistant spasticity: Analysis in relation to the newly described ‘spasticity-plus syndrome. *European Journal of Neurology*, 2022, 29, 2744–2753.
5. Chan A., Silván C.V. Evidence-based management of multiple sclerosis spasticity with nabiximols oromucosal spray in clinical practice: a 10-year recap. *Neurodegenerative Disease Management*, 2022, 12, 141–154.
6. Koo C.M., Kim S.H., Lee J.S., et al Cannabidiol for Treating Lennox-Gastaut Syndrome and Dravet Syndrome in Korea. *The Journal of Korean Medical Science*, 2020, 35, e427.

7. Fowler C.J., Gustafsson S.B., Chung S.C., et al Targeting the endocannabinoid system for the treatment of cancer--a practical view. *Current Topics in Medicinal Chemistry*, 2010, 10, 814–827.
8. De Petrocellis L, Ligresti A, Schiano Moriello A, et al. Non-THC cannabinoids inhibit prostate carcinoma growth in vitro and in vivo: pro-apoptotic effects and underlying mechanisms. *British Journal of Pharmacology*, 2013, 168, 79–102.
9. Olea-Herrero N, Vara D, Malagarie-Cazenave S, Díaz-Laviada I. Inhibition of human tumour prostate PC-3 cell growth by cannabinoids R(+)-Methanandamide and JWH-015: Involvement of CB2. *British Journal of Cancer*, 2009, 101, 940–950.
10. Sarfaraz S, Afaq F, Adhami VM, Mukhtar H. Cannabinoid Receptor as a Novel Target for the Treatment of Prostate Cancer. *Cancer Research*, 2005, 65, 1635–1641.
11. Bains S., Mukhdomi T. Medicinal Cannabis For Treatment Of Chronic Pain. In: StatPearls. StatPearls Publishing, Treasure Island (FL), 2023.
12. Piper BJ, Beals ML, Abess AT, et al. Chronic pain patients' perspectives of medical cannabis. *Pain*, 2017, 158, 1373–1379.
13. Naftali T. An overview of cannabis based treatment in Crohn's disease. *Expert Review of Gastroenterology & Hepatology*, 2020, 14, 253–257.
14. Naftali T., Bar-Lev Schleider L., Sklerovsky Benjaminov F. Medical cannabis for inflammatory bowel disease: real-life experience of mode of consumption and assessment of side-effects. *European Journal of Gastroenterology & Hepatology*, 2019, 31, 1376–1381.
15. Kafil T.S., Nguyen T.M., MacDonald J.K., Chande N. Cannabis for the treatment of Crohn's disease. *Cochrane Database Systematic Reviews*, 2018, 11, CD012853.
16. Mizrachi Zer-Aviv T., Segev A., Akirav I. Cannabinoids and post-traumatic stress disorder: clinical and preclinical evidence for treatment and prevention. *Behavioural Pharmacology*, 2016, 27, 561–569.
17. Bremner J.D., Southwick S.M., Darnell A., Charney D.S. Chronic PTSD in Vietnam combat veterans: course of illness and substance abuse. *The American Journal of Psychiatry*, 1996, 153, 369–375.
18. Bonn-Miller M.O., Boden M.T., Bucossi M.M., Babson K.A. Self-reported cannabis use characteristics, patterns and helpfulness among medical cannabis users. *The American Journal of Drug and Alcohol Abuse*, 2014, 40, 23–30.
19. Fraser G.A. The use of a synthetic cannabinoid in the management of treatment-resistant nightmares in posttraumatic stress disorder (PTSD). *CNS Neuroscience & Therapeutics*,

- 2009, 15, 84–88.
20. Di Forti M., Iyegbe C., Sallis H., et al. Confirmation that the AKT1 (rs2494732) Genotype Influences the Risk of Psychosis in Cannabis Users. *Biological Psychiatry*, 2012, 72, 811–816.
 21. European Monitoring Centre for Drugs and Drug Additions. Medical use of cannabis and cannabinoids: Questions and answers for policymaking. Publications Office of the European Union, Lisbon, 2018,
 22. Wang T., Collet J.P., Shapiro S., Ware M.A. Adverse effects of medical cannabinoids: a systematic review. *CMAJ*, 2008, 178, 1669–1678.
 23. Institute of Medicine (US) Marijuana and Medicine: Assessing the Science Base. National Academies Press (US), Washington (DC), 1999.
 24. Whiting P.F., Wolff R.F., Deshpande S., et al. Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. *JAMA*, 2015, 313, 2456–2473.
 25. Serpell M.G., Notcutt W., Collin C. Sativex long-term use: an open-label trial in patients with spasticity due to multiple sclerosis. *Journal of Neurology*, 2013, 260, 285–295.
 26. Bar-Lev Schleider L., Mechoulam R., Lederman V., et al Prospective analysis of safety and efficacy of medical cannabis in large unselected population of patients with cancer. *European Journal of Internal Medicine*, 2018, 49, 37–43.
 27. Abuhasira R., Schleider LB-L., Mechoulam R., Novack V. Epidemiological characteristics, safety and efficacy of medical cannabis in the elderly. *European Journal of Internal Medicine*, 2018, 49, 44–50.
 28. Hall W. What has research over the past two decades revealed about the adverse health effects of recreational cannabis use? *Addiction*, 2015, 110, 19–35.
 29. Anthony J.C. The epidemiology of cannabis dependence [In:] *Cannabis Dependence: Its Nature, Consequences, and Treatment*. Cambridge University Press, 2016, 58–105
 30. Hall W., Lynskey M.T., Degenhardt L. Heroin use in Australia: its impact on public health and public order. National Drug and Alcohol Research Centre, Kensington, N.S.W., 1999.
 31. Anthony J.C., Warner L.A., Kessler R.C. Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: Basic findings from the National Comorbidity Survey. *Experimental and Clinical Psychopharmacology* 1994, 2, 244–268.
 32. Livingston M.D., Barnett T.E., Delcher C., Wagenaar A.C. Recreational Cannabis Legalization and Opioid-Related Deaths in Colorado, 2000–2015. *American Journal of*

- Public Health, 2017, 107, 1827–1829.
33. Bachhuber M.A., Saloner B., Cunningham C.O., Barry C.L. Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. *JAMA Internal Medicine*, 2014, 174, 1668–1673.
 34. Preuss U.W., Huestis M.A., Schneider M., et al (2021) Cannabis Use and Car Crashes: A Review. *Frontiers in Psychiatry*, 12, 643315.
 35. Drummer O.H., Gerostamoulos J., Batziris H., et al. The involvement of drugs in drivers of motor vehicles killed in Australian road traffic crashes. *Accident Analysis & Prevention*, 2004, 36, 239–248.
 36. Laumon B., Gadegbeku B., Martin J-L., et al. Cannabis intoxication and fatal road crashes in France: population based case-control study. *BMJ*, 2005, 331, 1371.
 37. Martin J-L., Gadegbeku B., Wu D., et al. Cannabis, alcohol and fatal road accidents. *PLOS ONE*, 2017, 12, e0187320.
 38. Marijuana and hallucinogen use among young adults reached all time-high in 2021 [In:] National Institute on Drug Abuse, 2022. <https://nida.nih.gov/news-events/news-releases/2022/08/marijuana-and-hallucinogen-use-among-young-adults-reached-all-time-high-in-2021>. Accessed 27 May 2023
 39. Most reported substance use among adolescents held steady in 2022 [In:] National Institute on Drug Abuse, 2022 <https://nida.nih.gov/news-events/news-releases/2022/12/most-reported-substance-use-among-adolescents-held-steady-in-2022>. Accessed 27 May 2023
 40. Connor J.P., Stjepanović D., Le Foll B., et al. Cannabis use and cannabis use disorder. *Nature Reviews Disease Primers*, 2021, 7, 16.
 41. Comparison of acute lethal toxicity of commonly abused psychoactive substances. http://politicsofsin.50megs.com/risk/Toxicity.Comparison_Addiction.99,p686_2004.html. Accessed 30 May 2023.
 42. Zehra A., Burns J., Liu C.K., et al. Cannabis Addiction and the Brain: a Review. *Journal of Neuroimmune Pharmacology*, 2018, 13:438–452.
 43. Lane S.D., Cherek D.R., Tcheremissine O.V., et al. Acute marijuana effects on human risk taking. *Neuropsychopharmacology*, 2005, 30, 800–809.
 44. Costales B., Babalonis S.L., Brown J.D., Goodin A.J. Cannabis Effects on Driving Performance: Clinical Considerations. *Medical Cannabis and Cannabinoids*, 2023, 6, 8–14.

45. Substance Abuse Center for Behavioral Health Statistics and Quality. Results from the 2021 National Survey on Drug Use and Health: Detailed Tables, SAMHSA.
46. Hamilton I. Cannabis, psychosis and schizophrenia: unravelling a complex interaction. *Addiction*, 2017, 112, 1653–1657.
47. akakuwa K.M., Schears R.M. The emergency department care of the cannabis and synthetic cannabinoid patient: a narrative review. *The International Journal of Emergency Medicine*, 2021, 14, 10.

APPLICATION OF ARTIFICIAL INTELLIGENCE IN DIAGNOSING AND TREATING MENTAL DISORDERS

Maciej Pachana, Julia Marschollek, Hubert Sawczuk, Julia Letkiewicz, Piotr Kukula

Psychiatry Students' Scientific Association, Medical University of Silesian Piasts in Wrocław

INTRODUCTION

The advancement of AI technology has recently accelerated dramatically on a global scale, including the psychiatric sector. [1] Machine learning principles, which include the computer analyzing enormous volumes of text data and coming to its own conclusions based on that knowledge, are the foundation of AI technology. [2] AI is already being utilized effectively to diagnose and treat psychiatric patients from all over the world. [3], [4] Although applying AI technology has many advantages, could it be a threat to a real doctor? [4] In order to maximize the benefits of this technology in the future, several authors highlight potential problems related to the broad usage of AI, such as security concerns and the need for legal restrictions. [5] Due to the rapid rate of AI progress, the literature on the subject is continually changing. This work aims to highlight the current applications of AI in psychiatry, consider the potential future uses of this technology, and call attention to both the risks and ethical concerns that can have a significant impact on the global development of AI in the field of psychiatry in addition to the positive aspects of this technology.

CURRENT APPLICATIONS OF AI IN DIAGNOSING AND TREATING MENTAL DISORDERS

Over the past few years, the use of artificial intelligence (AI) in psychiatry has increased in response to the expanding demand for better access to mental health solutions [1]. To classify patients with psychiatric disorders, AI began incorporating neuroimaging studies of psychiatric patients with deep learning models. By extracting functional connectivity patterns from resting-state functional MRIs of schizophrenia patients and healthy controls, Kim et al. were able to

classify patients and controls with an accuracy of 85.5%. [3]

To help with clinical predictive modeling, Miotto et al. proposed Deep Patient, a deep learning architecture that constructs a universal patient representation from electronic health records (EHRs) to predict health status and improve clinical decision-making. It has been shown that Deep Patient can accurately predict psychiatric disorders such as attention deficit hyperactivity disorder and schizophrenia [6].

Other uses for artificial intelligence include digital gaming interventions and smartphone apps. Cognitive behavioral therapy, behavioral modification, social motivation, attention enhancement, and biofeedback may be among the services offered by digital gaming. Smartphone applications utilizing AI, such as mindLAMP (Learn, Assess, Manage, Prevent) and BiAffect, are additional uses of AI. MindLAMP is an application that utilizes smartphones and embedded sensors to comprehend people's experiences with mental illness and to predict their recovery by collecting surveys, cognitive tests, GPS coordinates, and exercise data. BiAffect employs machine learning algorithms and keyboard metadata such as typing dynamics, errors, and pauses in user messaging to predict manic and depressive episodes in bipolar disorder patients [7]. AI applications have already been used for assistance in making psychiatric diagnoses, monitoring symptoms, predicting acute disease exacerbations and recovery, and delivering psychoeducation [1].

Therapeutic devices that operate via SMS text messaging or other messaging devices are being investigated to treat psychiatric symptoms. Woebot is an automated conversational application accessible via Facebook Messenger or mobile apps that provides cognitive behavioral therapy (CBT) automation features. This instrument was designed to monitor symptoms and manage episodes of anxiety and depression using acquired skills such as recognizing and challenging cognitive distortions. Initial studies found that depression symptoms decreased more with the use of Woebot than with the use of electronic book resources, and another study found that Tess reduced depression and anxiety in users [1, 4]. Tess is another text-messaging-based program accessible via phone number that coaches individuals through times of emotional distress. This instrument allows the user to engage in therapeutic conversations like those with a therapist and provides emotional wellness coping strategies. Although integrative psychological AI is neither designed nor intended to replace the function of a trained therapist, the technology has the potential to augment the therapeutic process [1, 8].

Additionally, new forms of avatar therapy that enable therapeutic conversations with its users have been developed. Typically, these involve computer-generated images of features

displayed on computer screens or tablets that interact with a patient using intelligent algorithms. AVATAR therapy is an innovative treatment for disturbing auditory and verbal hallucinations. A digital simulation is created and used in a three-way conversation between the participant, the avatar, and the therapist. To date, therapy has been administered over the course of six sessions, with the initial phase concentrating on standing up to a hostile avatar and the second phase shifting the focus to individualized treatment objectives, such as beliefs about voices [9].

POTENTIAL USE OF AI IN THE FUTURE

AI's promise in clinical and translational research involves collaboration between methodologists, physicians and informaticians who can put these algorithms into practice [10]. The majority of AI, especially in medicine, is built on machine learning (ML). ML incorporates ideas from a variety of disciplines and provides novel approaches to psychiatric therapy by analyzing huge amounts of data to predict diagnosis, development of the disease in a patient and to choose a suitable treatment [2]. A variety of technological platforms, such as mobile apps, hardware, social services (e.g., chatbots), and clinical practice, can benefit from the application of machine learning (ML) [11]. The safe and successful use of AI technology to aid medical decision-making presents problems encompassing technological and human aspects, regulatory issues, and safety threats. To maximize the benefits of AI technology in the future, these problems must be identified and rigorously solved [5].

One of the reasons why numerous studies and clinical applications have been created, but only a few have effectively migrated from algorithms that perform well on standardized data sets to operational systems that have been shown to benefit clinical outcomes is the difficulty to identify specific problems that, given accessible data and techniques, AI can handle [10]. One of the research studies on commercial use of Emotion Artificial Intelligence [2] indicates that these algorithms should not be regarded as medical fact. Additionally, there are fears that commercial usage of emotion AI would promote stigma and prejudice, as well as having harmful implications for those with mental illnesses in everyday life. Although many technologies in widespread use remain poorly understood (for example, the actual mechanism of action of several psychiatric medicines), it is questionable how to effectively make statistical AI-based decision support systems acceptable to physicians [10]. Practitioners will have to adjust to their new responsibilities as information integrators, interpreters, and patient advocates. The medical education system will need to provide them with the necessary skills [12].

Discussing about potential use of AI in the future there are high expectations in the field of smartphone usage. Collecting the data from its sensors could lead clinicians to better understanding of the patients' conditions than they do now with 30-minute appointments every 3 to 6 months [7]. Data from personal digital devices is used to create apps with the help of clinical digital phenotyping [13]. For instance, there is a project called BiAffect [14], which shows that bipolar disorder symptoms appear to be correlated with certain variations in cell phone usage. The development of these models shows that it is possible to monitor and detect mood issues using passively obtained keyboard metadata. Future applications based on machine learning may present a few prospects regarding: data-centric approach, data augmentation approach, automated-learning approach, and data-integration approach. Additionally, the multi-modal integration of genetics, behavioral neuroscience, machine learning, and mobile health might clear the way for the creation of new technologies and procedures [11].

Some authors suggest that the real problem for AI-based mental disorder diagnosis is neither technological, nor is it entirely about data, but rather our comprehensive understanding of mental disorders in general [15]. The exact etiology of many psychiatric problems is still unknown and even classifying these disorders has been problematic despite the efforts of the researchers. The idea of the utilization of biomarkers in psychiatry offers much more than a basis for more accurate diagnoses. They might help with prognosticating an individual's disease and adjusting treatment [16]. Many of the machine learning-derived biomarker panels surpassed those chosen by experts or traditional statistical approaches [12]. Artificial intelligence and machine learning developments will probably serve as a significant foundation for converting new data into digital biomarkers that are clinically meaningful. However, like all indicators of health, influence will be based on clinical utility as well as statistical validity. [17] For example, while suicide prediction models yield accurate overall categorization models, they remain about 0% accurate at predicting the future. If used by itself, these models would produce noteworthy false-negative rates and high false-positive rates [18]. In short, current studies still face several difficulties with the application of biomarkers in psychiatry [16].

THE ADVANTAGES AND DISADVANTAGES OF USING AI IN PSYCHIATRY

The advantages of artificial intelligence are numerous, due to the growing demand for using these devices to manage psychiatric symptoms and supplement treatment procedures, their application in psychiatry seems to have a promising future. One benefit is the diminished stigma associated with disclosing mental illness symptoms with medical professionals and the

rise in self-disclosure comfort [1]. Chatbots are seen as less judgmental than humans, which encourages users to reveal more about themselves and provides for more conversational flexibility [19, 20]. Studies show that they express a high level of satisfaction with their interactions with chatbots, favorable opinions of chatbots, a preference for chatbots versus information control groups, and future interest in using it [19].

The other one is that AI-based solutions could help the overcrowded healthcare system, particularly now that there is a dearth of mental health doctors [1]. Due to the dearth of mental health specialists in rural areas in developing nations, AI can be utilized to provide services to patients in far-flung locations and enable access to specialty care [20].

Some authors claim that it can eliminate many of the tedious aspects of employment and ease repetitive chores. Employees may thus be able to concentrate on the more difficult and exciting aspects of many vocations [21].

AI systems are an excellent approach to help with some diagnostic challenges, for example, to identify between different types of dementia using structural MRI scans or distinguish between bipolar and unipolar depression based on aspects of brain imaging [22].

The accuracy of diagnosis based on changing psychiatric symptoms can be improved by using AI approaches that are effective at extracting patterns from longitudinal data. To create explanatory and mechanistic models of mental illness that range from self-report to molecular assessments, AI approaches can combine data from various sources, including the EHR, behavioral data from wearable sensors and digital phenotyping, social media, speech, neurophysiology, genetics, and imaging [23]. The same analyses can use both organized (quantitative) and unstructured (text, graphics, and sound) data [21].

AI systems can be configured to a patient's particular cultural characteristics, such as race or ethnicity or socioeconomic background. To better connect with a patient and enhance communication, a virtual therapist might, for example, alter its quirks (such as eye contact, speaking dialect, and other traits) to fit a particular ethnic group [20].

According to some writers, an intelligence framework can assist lower total healthcare costs by adjusting a triage-style approach to ensure that patients who need the most extensive treatment get it sooner [20, 24].

Without a doubt, this technology has a lot of drawbacks in addition to its benefits. AI bots may not have the complex emotional awareness and empathetic response that a human counterpart possesses. They are also limited in their ability to use personal patient details to help with the cognitive work needed by the patient [1, 19]. Due of the richness of human language, chatbots may easily misinterpret user responses. For instance, they have difficulty

understanding metaphors, ellipses, colloquialisms, hyperbole and lengthy or complicated messages; these issues can result in incorrect or irrelevant responses and will only worsen when more languages are added to chatbot development [19].

Additionally, studies suggest that because chatbot discussions feel repetitive, users commonly express unhappiness with them, which makes the chatbot seem less authentic [19].

Interaction between humans and AI- support tools may also result in automation bias [5]. It's a situation, when a user gives an automated tool more credibility than other sources of guidance. This can lead to the user acting without being explicitly prompted and the user acting incorrectly despite contradicting facts or past instruction. For example, inaccurate AI has decreased the precision of expert clinicians in the histopathologic classification of liver cancer and the identification of skin malignancies [5]. Making treatment decisions solely based on "big data" may lead to the elimination of experiences and values that cannot be reduced to discrete data points. Computer recommendations could have a fictitious authority that would supersede wise human judgment [25]. Deskilling of the medical staff due to a loss of individual abilities and a decline in skill development is a potential long-term effect of the overreliance on technology [5].

The other disadvantage is there are now no direct clinical applications accessible, and there is no national benchmark against which to measure technological improvement [7].

AI AND ETHICAL ISSUES

The more we use embodied AI in psychiatry, psychology, and psychotherapy, the more often we ask is it ethical and what are challenges in ethics due to using it? [4]. One of the most common ethical issues is data ownership because of unfair algorithm outcomes because their training data is biased [26]. The employment of assistive robots and intelligent virtual agents to monitor routines, movements, and other interactions raises concerns about confidentiality, information privacy, and secure data management. As the amount of data collected grows, privacy worries could become more acute [4]. Another issue with that is that scientists may develop AI using databases that lack sufficient information to make accurate judgments or predictions [27].

Furthermore, AI should be used in mental health as an extra resource, not as the exclusive instrument. Robots should not be used as a justification for cutting back on the high-quality care provided by qualified psychiatrists. It would not be positive if doctors lost a significant portion of their jobs and were excluded from the diagnosing system [4].

Moreover, there is a possibility that clinicians would not be able to cooperate with AI. For example, clinicians might not be confident in an AI-generated choice or know how to manage the level of detailed data [27]. Also, if a doctor disregards an algorithmic system's proposal that conflicts with their clinical judgment, they may face liability issues. Furthermore, a patient's freedom of making their own treatment decisions may be taken away in severe circumstances due to some AI forecasts, which may also weaken patients' credibility when speaking about their own experiences [28].

The next problem is that AI lacks the humility of a physician. It is a crucial trait of doctors that allows them to make therapeutic judgments based on patient history, the doctor's experience, and their capacity to comprehend the demands of the patient, in addition to scientific facts [28].

It is crucial to concentrate on the long-term consequences of using AI. First, patients may become excessively emotionally connected to robots, which might make them lonely, ruin their real-life relationships, and disconnect them from their everyday lives. Due to a robot's inability to provide care and humans incapacity to rely on them, one's values could be changed. It results from AI lacking human characteristics [4].

On the other hand, AI might be a comfortable solution for those who cannot physically seek medical care because of their residence's distance from medical facilities. Because of it, individuals like these can initially diagnose their psychological problems. As a result, it reduces social inequalities between urban dwellers and those who live elsewhere, which could be a significant issue nowadays. Another moral benefit of artificial intelligence in psychiatry is that some patients respond better to the non-human 'doctor'. They feel less embarrassed to discuss their personal issues because they are not being judged by a human [4].

In conclusion, there are many ethical issues with employing artificial intelligence in psychiatry, but it can also be useful in enabling some patients in receiving medical care. The majority of problems are caused by human characteristics that computers cannot replicate. The fact that AI is created and develops itself via algorithms and is dependent on personal data also poses a number of risks. Making rules for AI use and educating our clinicians on its proper application are necessary if we wish to use it in psychiatry to benefit our patients [4].

CONCLUSION

In this article, artificial intelligence (AI) applications in psychiatry are discussed along with prospective future uses for this technology. Only a small portion of the countless uses for

AI are mentioned, such as its role in radiology [3], the prediction of disease progression based on medical data [6], the monitoring of patient activity through smartphone applications [7], the support of therapy through chatbots [1, 4], and even AVATAR therapy for hallucinations [9].

In the future, the possible use of artificial intelligence (AI) in psychiatry may entail a growing reliance on information received via smartphones to comprehend the patient's sickness and develop new biomarkers for psychiatric disorders based on the databases gathered [7, 17]

The advantages of adopting AI include increased patient willingness to disclose their medical history [19, 20], providing healthcare to the underserved [20], easing the stress on the healthcare system [1], and lowering medical expenditures through superior patient classification, such as in triage systems [20, 24].

AI in psychiatry does have certain limitations, though. Inability to understand complicated linguistic patterns and a lack of emotional intelligence may deter patients from using this technology [19]. The automation and repetition of interactions can also have a negative effect on patient interactions, and the enormous AI databases might make healthcare workers less motivated to advance their own skill sets [5, 19]

Concerns about data security and privacy [4], the absence of human emotions [28], and the reliability of AI in the eyes of medical professionals are all brought up by ethical considerations [27]. Another ethical problem is patients developing emotional relationships to AI. [4]

Psychiatry is currently being significantly impacted by AI, which has many positive effects but also presents obstacles due to its limitations and ethical issues. To effectively use AI, it is imperative to prioritize patient safety, data privacy, and the promotion of cooperative research between AI and mental healthcare specialists.

REFERENCES

1. Pham K.T., Nabizadeh A., Selek S. Artificial Intelligence and Chatbots in Psychiatry, *Psychiatr Q*, 2022, 93(1), 249–253.
2. Monteith S., Glenn T., Geddes J. et al. Commercial Use of Emotion Artificial Intelligence (AI): Implications for Psychiatry, *Current Psychiatry Reports*, 2022, 24(3), 203–211.
3. Vieira S., Pinaya W. H. L., Mechelli A. Using deep learning to investigate the neuroimaging correlates of psychiatric and neurological disorders: Methods and applications, *Neuroscience & Biobehavioral Reviews*, 2017, 74, 58–75.

4. Fiske A., Henningsen P., Buyx A. Your Robot Therapist Will See You Now: Ethical Implications of Embodied Artificial Intelligence in Psychiatry, Psychology, and Psychotherapy, *Journal of Medical Internet Research*, 2019, 21(5), e13216.
5. Monteith S., Glenn T., Geddes J., et al. Expectations for Artificial Intelligence (AI) in Psychiatry, *Current Psychiatry Reports*, 2022, 24(11), 709–721.
6. Lin E., Lin C.H., Lane H.Y. Precision Psychiatry Applications with Pharmacogenomics: Artificial Intelligence and Machine Learning Approaches, *International Journal of Molecular Sciences*, 2020, 21(3), 696.
7. Allen S. Artificial Intelligence and the Future of Psychiatry, *IEEE Pulse*, 2020, 11(3), 2–6.
8. Fulmer R., Joerin A., Gentile B. et al. Using Psychological Artificial Intelligence (Tess) to Relieve Symptoms of Depression and Anxiety: Randomized Controlled Trial, *Journal of Medical Internet Research Mental Health*, 2018, 13, 5(4), e64.
9. Garety P., Edwards D.J., Ward T. et al. Optimising AVATAR therapy for people who hear distressing voices: study protocol for the AVATAR2 multi-centre randomised controlled trial, *Trials*, 2021, 22(1), 366.
10. Bernstam E.V., Shireman P.K., Meric-Bernstam F. et al., Artificial intelligence in clinical and translational science: Successes, challenges and opportunities *Clinical and Translational Science*, 2022, 15(2), 309–321.
11. Chen Z.S., Kulkarni P., Galatzer-Levy I.R. et al. Modern views of machine learning for precision psychiatry, *Patterns*, 2022, 3(11), 100602.
12. Yu K.H., Beam A.L., Kohane I.S. Artificial intelligence in healthcare, *Nature Biomedical Engineering*, v2018, 2(10), 719–731.
13. Huckvale K., Venkatesh S., Christensen H. Toward clinical digital phenotyping: a timely opportunity to consider purpose, quality, and safety, *Nature Partner Journals Digital Medicine*. 2019, 6(2), 88.
14. Zulueta J., Piscitello A., Rasic M. et al., Predicting Mood Disturbance Severity with Mobile Phone Keystroke Metadata: A BiAffect Digital Phenotyping Study, *Journal of Medical Internet Research*, 2018, 20(7), e241.
15. Yan W.J., Ruan Q. N., Jiang K. Challenges for Artificial Intelligence in Recognizing Mental Disorders, *Diagnostics (Basel)*, 2022, 13(1), 2.
16. Singh I., Rose N. Biomarkers in psychiatry, *Nature*, 2009, 460(7252), 202–207.

17. Torous J., Bucci S., Bell I.H. et al. The growing field of digital psychiatry: current evidence and the future of apps, social media, chatbots, and virtual reality, *World Psychiatry*, 2021, 20(3), 318-335.
18. Belsher B.E., Smolenksi D.J., Pruitt L.D. et al., Prediction Models for Suicide Attempts and Deaths: A Systematic Review and Simulation, *JAMA Psychiatry*, 2019, 76(6), 642–651.
19. Boucher E.M., Harake N.R., Ward H.E. et al., Artificially intelligent chatbots in digital mental health interventions: a review, *Expert Review of Medical Devices*, 2021, 18, 37–49.
20. Ray A., Bhardwaj A., Malik Y.K. et al. Artificial intelligence and Psychiatry: An overview, *Asian Journal of Psychiatry*, 2022, 70, 103021.
21. Bickman L., Improving Mental Health Services: A 50-Year Journey from Randomized Experiments to Artificial Intelligence and Precision Mental Health, *Administration and Policy in Mental Health and Mental Health Services Research*, 2020, 47(5), 795–843.
22. Lee E.E., Torous J., De Choudhury M. et al., Artificial Intelligence for Mental Health Care: Clinical Applications, Barriers, Facilitators, and Artificial Wisdom. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 2021, 6(9), 856–864.
23. Janssen R.J., Mourão-Miranda J., Schnack H.G. Making Individual Prognoses in Psychiatry Using Neuroimaging and Machine Learning, *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 2018, 3(9), 798–808.
24. Fonseka T.M., Bhat V., Kennedy S.H. The utility of artificial intelligence in suicide risk prediction and the management of suicidal behaviors, *Australian and New Zealand Journal of Psychiatry*, 2019, 53(10), 954–964.
25. Simon G.E., Yarborough B.J. Good news: Artificial intelligence in psychiatry is actually neither, *Psychiatric Services*, 2020, 71(3), 219–220.
26. Wiese W., Friston K.J. AI ethics in computational psychiatry: From the neuroscience of consciousness to the ethics of consciousness, *Behavioural Brain Research*, 2022, 420, 113704.
27. Graham S., Depp C., Lee E.E. et al. Artificial Intelligence for Mental Health and Mental Illnesses: An Overview,” *Current Psychiatry Reports*, 2019, 21(11), 116.
28. Mccradden M., Hui K., Buchman D.Z. Evidence, ethics and the promise of artificial intelligence in psychiatry, *The Journal of Medical Ethics*, 2022, 0, 1–7.

LAZINESS, DAYDREAMING, RESTLESSNESS? TRY EXECUTIVE DYSFUNCTION, INATTENTIVENESS AND HYPERACTIVITY - ADHD IN ADULTS

Gabriela Świrkosz, Julia Wójcik, Katarzyna Logoń, Anna Łysik, Joanna Zapala

Wroclaw Medical University

ABBREVIATION LIST

- ADHD - Attention Deficit Hyperactivity Disorder
- NICE - National Institute for Health and Care Excellence
- CBT - Cognitive-Behavioral Therapy
- FDA - Food & Drug Administration
- DBT - Dialectical Behavioral Therapy
- CPAT - Computerized Progressive Attention Training
- MBSR - Mindfulness Based Stress Reduction
- tDCS - Transcranial Direct Current Stimulation
- GMT - Goal Management Training
- DSM-5 - Diagnostic and Statistical Manual, Fifth edition

INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is a common condition that typically manifests in childhood, and it is one of the most prevalent neuropsychiatric disorders. The dysfunction impacts approximately 5% of children and adolescents worldwide, with a prevalence of 2.5% among adults [1]. ADHD coexists with other psychiatric disorders in approximately 15% of adults who have been diagnosed. The main symptoms include inattention, hyperactivity or inability to rest, and impulsivity which can persist throughout a person's life, significantly impacting their development and increasing the likelihood of developing other psychiatric

conditions [2]. There is also a tendency towards sensation-seeking, impulsivity, and susceptibility to substance abuse. In practice, individuals with ADHD are constantly on the move and struggle to sustain focus on a single activity for extended periods. They often experience difficulty comprehending and adhering to lengthy commands, display impatience, frequently misplace items, and become easily distracted during monotonous tasks.

Decades of research have consistently shown that genes play a crucial role in the development of attention deficit hyperactivity disorder and its co-occurrence with other disorders. Genetic factors account for 74% of ADHD cases, with genes associated with dopaminergic transmission playing a significant role [3]. Additionally, ADHD is more likely to occur in cases where there are teratogenic effects on the fetus and when individuals have experienced family violence and abuse.

It was previously believed that this disorder resolves after childhood and only affects individuals during their younger years. There are now numerous studies that demonstrate the presence of this disorder in adulthood as well [4]. The studies on adults who had ADHD during childhood reveal that those with persistent ADHD (as opposed to those whose ADHD symptoms remit) tend to have lower educational achievements, diminished job performance, and heightened emotional difficulties. Newly developed ADHD in adults indicate an increased risk of traffic accidents, criminal behavior, unemployment, and substance misuse [1].

DIAGNOSIS

ADHD is susceptible to misdiagnosis due to the subjective nature of its symptoms, the resemblance it bears to various mental and behavioral disorders, and the diverse manifestation of its characteristics [5]. The guidelines of the American Psychiatric Association's Diagnostic and Statistical Manual, Fifth edition (DSM-5) are used to help diagnose ADHD [6]. Symptoms fall into two categories - inattention and hyperactivity/impulsivity. They should be present for at least 6 months and be inappropriate for developmental level. Inattention signs include i.a. easy distraction, losing things necessary for daily life and troubles in organization, holding attention or careful listening. Hyperactivity can manifest in excessive talking, interrupting others in conversation, trouble in waiting for their turn, feeling restless and fidgeting. In adults, only five symptoms in either list are needed whereas in children below the age of 17 years, six are required.

In addition, other conditions must be met. Several symptoms must have been present before age 12 years. Symptoms must occur in multiple settings. There should be apparent evidence that they create impairment in the social, school, or work functioning. The symptoms can not be better explained by another mental disease. According to the types of symptoms, three presentations of ADHD can occur: combined, predominantly inattentive and predominantly hyperactive.

Certain difficulties may be associated with diagnosing ADHD in adults. In particular, the DSM-5 criteria were created for children and adolescents therefore they can not always be applied to adults, as their symptoms might differ [7]. With increasing age, inattentiveness tends to persist and has significantly lesser reduction than the hyperactivity–impulsivity manifestations [8]. Inattentiveness can manifest as being unable to manage time effectively, paying less attention to the details, forgetfulness or being easily distracted [9]. Hyperactivity can be shown as not being able to sit through meetings, difficulty relaxing or frequent job changes [10,11]. What is more, current criteria require evidence of symptom onset before the age of 12, preferably other than the patient’s own recall, which may be impossible to provide for some individuals. Another difficulty include the occurrence of comorbidities such as social phobias, bipolar disorder, major depressive disorder, dysthymia and generalized anxiety disorder, in which symptoms may overlap ADHD symptoms [12].

Many adults with ADHD have developed coping strategies to minimize the influence of ADHD on their daily life [13]. These mechanisms include choosing a very organized spouse, working at a job below their potential, or rigorously structuring their daily tasks [10].

In a recent 2021 study, M.H. Sibley suggests a 7-step diagnostic procedure for diagnosing ADHD in adults [5]. Clinicians should start with a thorough interview with specific questions rather than unstructured patient’s storytelling or open-ended questions. Obtaining the information from informants who know the patient well may prevent both false negative and false positive diagnoses [14]. Next steps include assessing the impairment and timeline and ruling out the alternative diagnoses. For adults with ADHD, impairments may include frequent job changes, bad performance at work, poor academic grades, maladaptive parenting and relationships, and financial difficulties.

Additional tests that might be useful in differentiating ADHD from other conditions are laboratory tests such as complete blood count, metabolic profile, liver and thyroid function tests and B12 serum level. Electroencephalogram and computed tomography may be performed in

patients with recent head trauma or suspected seizure disorder [15]. Polysomnography may be performed to rule out obstructive sleep apnea [16].

For some patients, the primary care physician might establish the diagnosis and manage therapy unassisted. The physician may seek psychiatrist assistance, especially if he is uncertain of the diagnosis, if there are possible psychiatric comorbidities, or if there is a crisis in the patient's life requiring intervention [9].

DIFFERENCES BETWEEN MEN AND WOMEN

Results of majority studies show higher prevalence of ADHD in men than women [17, 18]. As a result of the fact that ADHD symptoms in women tend to be more subtle than in men and there are potential biases in the evaluation of both sexes, it is likely that a lot of women with ADHD may not receive a proper diagnosis [19].

There are also gender differences in the occurrence of ADHD subtypes. Women are more often diagnosed with the inattentive ADHD subtype. Combined subtype is more often diagnosed in men [18]. Girls with ADHD are rated by parents and teachers as less hyperactive than boys [19].

Males with ADHD more often experience externalizing problems - rule breaking, physical aggression, antisocial behavior. Antisocial personality disorder is more common in men with ADHD than in women with ADHD [20]. During observations of children during classroom activities, it was observed greater total aggression (verbal and physical aggression), hyperactivity in large motor skills (energy, standing up during lessons), interference to teachers in boys with ADHD compared to girls with ADHD [21]. Men more often seek help from family to compensate for ADHD symptoms, while women tend to isolate themselves. Men with ADHD have less difficulties in social situations than women. A Japanese study found greater marital problems and difficulties in professional life in women with ADHD [17].

ADHD in women is more commonly accompanied by internalizing problems. As the symptoms of ADHD are less stereotypical in women, the primary diagnosis may be depression, anxiety disorders or personality disorders, delaying a proper diagnosis. ADHD in women can be misdiagnosed as borderline disorder. This may result from the fact that women with ADHD self-harm more often than women without this disorder. Emotional instability, low frustration tolerance,

and irritability which can result in multiple disabilities in adulthood may be more common in women with ADHD [20].

They can expend a lot of work and effort to compensate for ADHD symptoms and function similarly to their peers. As they age and environmental demands increase, women with ADHD find it increasingly difficult to function on a daily basis at school, work and college. The fluctuations in hormone levels that occur during the menstrual cycle and menopause can contribute to the symptoms of ADHD and cause difficulties in treatment [22].

Results of a population-based study of over 1,7 million adults in Norway showed that people with ADHD 4-9 times more frequently have another mental disorder than the remaining population. Predispositions to various mental disorders are different between the genders. Women with ADHD have greater incidence of bipolar disorder, personality disorder, anxiety and depression than in men with ADHD, but schizophrenia and substance use disorder is more prevalent in men with ADHD [23].

Alcohol and drug abuse may be a more common problem in men with ADHD. Men and boys with ADHD present greater impulsivity than women with the same diagnosis [24].

Analysis of 25 neuropsychological studies indicates that people with ADHD perform worse on tests that examine attention capacity than control groups in The Stroop Colour and Word Test, Continuous Performance Test and Trail Making Test. In addition to the overall difference between the ADHD and control groups, there are differences between the genders of people with ADHD. These are particularly evident when analyzing the Stroop test. Men achieved worse results [25].

DIFFERENCES BETWEEN CHILDREN AND ADULTS

ADHD is considered to be affecting quite a high percentage of the general population, both adults and children. Several studies suggest a connection between the disorder and injuries, traffic collisions, substance abuse, suicide, health care expenditures, delinquency, unemployment, dissolution of marriages, hazardous sexual behaviour as well as premature mortality in general [26].

However, hyperactivity-impulsivity symptoms seem to fundamentally weaken with age in both males and females [27].

Due to the changes of responsibilities and social roles, adult patients struggling with ADHD

may exhibit symptoms differently than children. That seems to be visible especially considering hyperactivity and impulsivity [13,28]. Children with attention deficit experience difficulties with concentrating on tasks or games, they struggle with listening to others, following instructions and tend to lose their items, even the essential ones [29]. Those symptoms differ among adults and transmute into difficulties with ending one's sentence, poor time management, losing attention during reading or paperwork, forgetfulness and inability to focus [13,28].

According to Millstein's study the most commonly reported symptoms among adults with ADHD include troubles with completing sentences, focusing on tasks and frequent activity switching [30].

Hyperactive children tend to shift, run or climb amid situations where such behavior seems inappropriate, they have trouble with staying still or getting involved in free time activities and they demonstrate loquaciousness. Impulsive ones struggle with rushing into replying or impatiently waiting for their turn during either games or conversations [29].

Among adults, however, hyperactivity symptoms consist of anxiousness, demanding job choices and pursuing multiple careers [28].

Excessive adult impulsivity might be visible through ending sentences for interlocutors, interrupting others during conversations or disturbing others when they are occupied [28, 31].

A plethora of frustration leads to irritability and high levels of anger as well as frequent relationship changes [13].

Adult patients struggle to fulfill their potential, achieve both educational and professional goals. Some of them report interpersonal problems with establishing romantic and non-romantic relationships. Nevertheless, people experiencing those symptoms throughout the years adjust to them and develop compensatory strategies in order to minimize the visible dysfunction and overmask the disorder [13].

Such evolution of ADHD makes the diagnosis less obvious and harder to notice by medical practitioners. Compensatory strategies and behaviors might appear sporadically but their consequences may be serious. An example of such a strategy could be careful checking one's belongings and household appliances in order to avoid forgetting something and hence that person might be always late for work which results in poor performance evaluation. An extent to which a disorder is visible depends on one's intelligence, external demands as well as the ability to use compensatory strategies [32,33].

TREATMENT

ADHD, unlike most psychiatric disorders, can be managed effectively through pharmacotherapy, using stimulants as a first-line treatment. Several medications for ADHD have been approved by US Food & Drug Administration (FDA) - methylphenidate- and amphetamine-based stimulants, as well as non-stimulants, such as atomoxetine, viloxazine, clonidine and guanfacine [35].

According to National Institute for Health and Care Excellence (NICE) guidelines [36], medication should be offered to adults, whose ADHD symptoms impact at least one area of their life. For patients who haven't been treated before, a 6-week trial of lisdexamfetamine or methylphenidate at an adequate dose is advised as a first-line approach, as well as switching between these two if the other one doesn't provide satisfying outcomes. Atomoxetine, as a non-stimulant drug, is recommended for adults who can't tolerate or didn't benefit from either of the stimulants mentioned above. Immediate-release medications are ought to be used for initial dose adjusting and as an afternoon booster, while modified-release preparations, as more convenient ones, can be taken once daily in most cases. Successful dose optimization is achieved when a patient notices ADHD symptoms reduction and anticipated improvements in previously impacted life domains, without experiencing intolerable adverse effects of medication.

There exists a substantial body of evidence indicating significant medication advantage over placebo in adults with ADHD, both stimulants [36,37,38,39,40,41,42,43,44] and non-stimulants [45, 46, 47, 48, 49, 50, 51]. Guanfacine, as a non-stimulant medication, might be prescribed off-label as a potentially effective alternative treatment option for patients who didn't benefit from recommended stimulants or second-line pharmacotherapy [52], similarly as viloxazine [53]. A guanfacine supplementation, in addition to on-going stimulant treatment, showed promising outcomes especially in symptom reduction [54].

Adults with ADHD who were treated with stimulant or non-stimulant medication, reported noticeable improvement in executive function, overcoming everyday challenges and overall quality of life [36,40,41,43,46,45]. Individuals treated with stimulants showed reduced suicidal behaviour, compared to periods without medication [56]. Furthermore, studies show long-term efficacy of these medications [50,57].

As for individuals who don't want to take medicine or found it ineffective, NICE

recommends non-pharmacological treatment consisting of partial or full Cognitive-Behavioral Therapy (CBT). In order to lessen ADHD impact on a patient's life, all patients should be advised to make environmental modifications, which will vary based on individual needs and can include using headphones on commute or taking frequent movement breaks at work.

Symptom reduction, especially emotional ones, and increase in self-esteem, as well as in the quality of life, were reported as major effects of CBT in adults with ADHD [58,59,60,61]. Apart from CBT, Dialectical Behavioral Therapy (DBT) was found to long-term improve quality of life, executive function and ADHD symptoms in adults [62]. Transcranial Direct Current Stimulation (tDCS) alleviated cognitive function, especially in terms of planning and working memory [63]. Combination of DBT and tDCS resulted with significant therapeutic effect [64], same as using neurofeedback as a part of ADHD treatment [65]. Moreover, smartphone-assisted psychoeducation, provided to use as an app, helped improve attention [66], similarly as in a study on Goal Management Training (GMT) [67]. Recent research on particular exercises as a potentially beneficial tool in reducing ADHD symptoms in adults, showed rather negative correlation, except for improvement in temporal impulsivity [68]. Computerized Progressive Attention Training (CPAT), on the other hand, was found to improve ADHD symptoms, learning and reading, while Mindfulness Based Stress Reduction (MBSR) practice shortly improved self-reported quality of life [69].

CONCLUSIONS

ADHD is a common neuropsychiatric disorder characterized by inattention, hyperactivity and impulsivity. It can affect both children and adults, impacting important areas of life such as work, education, family, and emotional well-being. Depending on gender, other ADHD symptoms are more noticeable. Men show a lot of externalizing problems, which are more visible to others. Women try to compensate for the symptoms with their efforts and work, they have more internalizing problems. The DSM-5 guidelines are used to help diagnose ADHD. Several difficulties may be associated with diagnosing ADHD in adults. There are also some differences considering ADHD symptoms among children and adults because of the distinction between their social roles and responsibilities. Therefore, the diagnosis might be less obvious when the patient is an adult, since the symptoms are then more likely to concern love life, career choices, or work

performance. Moreover, adults develop compensatory strategies which make their problem less visible and the diagnostic process even more difficult. Methylphenidate- and amphetamine-based stimulants are an effective first-line treatment for ADHD. Non-stimulant medication, such as atomoxetine, can be beneficial in patients experiencing intolerable adverse effects of stimulants. Adults with ADHD using pharmacotherapy report significant symptom reduction and improved overall quality of life. CBT, as a non-pharmacological approach, is recommended especially for patients refusing drug treatment.

REFERENCES

1. Cayne A., Swanson JM., Coghill D., Rohde LA. Treatment strategies for ADHD: an evidence-based guide to select optimal treatment, *Molecular Psychiatry*, 2019, 24(3), 390-408.
2. Salvi V., Migliarese G., Venturi V. et. al. ADHD in adults: clinical subtypes and associated characteristics, *Rivista Di Psichiatria*, 2019, 54(2), 84-89.
3. Faraone SV., Larsson H. Genetics of attention deficit hyperactivity disorder, *Molecular Psychiatry*, 2018, 24(4), 562-575.
4. Zalsman G., Shilton T. Adult ADHD: A new disease? *International Journal of Psychiatry in Clinical Practice*, 2016, 20(2), 70–76.
5. Sibley MH. Empirically-informed guidelines for first-time adult ADHD diagnosis, *Journal of Clinical and Experimental Neuropsychology*, 2021, 43(4), 340-351.
6. American Psychiatric Association, DSM-5 Task Force. Diagnostic and statistical manual of mental disorders: DSM-5™ (5th ed.). American Psychiatric Publishing, 2013.
7. Rösler M., Casas M., Konofal E., Buitelaar J.: The World Journal of Biological Psychiatry: Attention deficit hyperactivity disorder in adults, 2010, 11(5), 684-698.
8. Spencer TJ., Biederman J., Mick E. Attention-Deficit/Hyperactivity Disorder: Diagnosis, Lifespan, Comorbidities, and Neurobiology, *Journal of Pediatric Psychology*, 2007, 32(6), 631-642.
9. Culpepper L., Mattingly G. Challenges in identifying and managing attention-deficit/hyperactivity disorder in adults in the primary care setting: a review of the literature, *The Primary Care Companion to the Journal of Clinical Psychiatry*, 2010, 12(6), PCC.10r00951.

10. Weiss MD., Weiss JR. A guide to the treatment of adults with ADHD, *The Journal of Clinical Psychiatry*, 2004, 65 Suppl 3:27-37.
11. Adamou M., Arif M., Asherson P. et al. Occupational issues of adults with ADHD, *BMC Psychiatry*, 2013, 17, 13, 59.
12. Kessler RC., Adler L., Barkley R. et al. The prevalence and correlates of adult ADHD in the United States: Results from the National Comorbidity Survey Replication, *American Journal of Psychiatry*, 2006, 163(4), 716-723.
13. Adler L., Cohen J. Diagnosis and evaluation of adults with attention-deficit/hyperactivity disorder. *Psychiatric Clinics of North America*, 2004, 27(2), 187-201.
14. Nelson JM., Lovett BJ. Assessing ADHD in college students: Integrating multiple evidence sources with symptom and performance validity data, *Psychological Assessment*, 2019, 31(6), 793-804.
15. Moss SB., Nair R., Vallarino A., Wang S. Attention deficit/hyperactivity disorder in adults, *Primary Care*, 2007, 34(3), 445-473.
16. Naseem S., Chaudhary B., Collop N. Attention deficit hyperactivity disorder in adults and obstructive sleep apnea. *Chest*, 2001, 119(1), 294-6.
17. Fraticelli S., Caratelli G., De Berardis D., et al. Gender differences in attention deficit hyperactivity disorder: an update of the current evidence, *Rivista di Psichiatria*, 2022, 57(4), 159-164.
18. Williamson D., Johnston C. Gender differences in adults with attention-deficit/hyperactivity disorder: A narrative review, *Clinical Psychology Review*, 2015, 40, 15-27.
19. Gershon J. A meta-analytic review of gender differences in ADHD, *Journal of Attention Disorders*, 2002, 5(3), 143-54.
20. Young S., Adamo N., Ásgeirsdóttir BB. et al. Females with ADHD: An expert consensus statement taking a lifespan approach providing guidance for the identification and treatment of attention-deficit/ hyperactivity disorder in girls and women, *BMC Psychiatry*, 2020, 20(1), 404.
21. Abikoff HB., Jensen PS., Arnold LL. et al. Observed classroom behavior of children with ADHD: relationship to gender and comorbidity, *Journal of Abnormal Child Psychology*, 2002, 30(4), 349-359.

22. Quinn PO. Treating adolescent girls and women with ADHD: gender-specific issues, *Journal of Clinical Psychology*, 2005, 61(5), 579-587.
23. Solberg BS., Halmøy A., Engeland A. et al. Gender differences in psychiatric comorbidity: a population-based study of 40 000 adults with attention deficit hyperactivity disorder, *Gender: Acta Psychiatrica Scandinavica*, 2018, 137(3), 176-186.
24. Rucklidge JJ. Gender differences in attention-deficit/hyperactivity disorder, *Psychiatric Clinics of North America*, 2010, 33(2), 357-373.
25. Bálint S., Czobor P., Komlósi S. Attention deficit hyperactivity disorder (ADHD): gender- and age-related differences in neurocognition, *Psychological Medicine*, 2009, 39(8), 1337-1345.
26. Zhang-James Y., Helminen E.C., Liu J. et al. Evidence for similar structural brain anomalies in youth and adult attention-deficit/hyperactivity disorder: a machine learning analysis, *Translational Psychiatry*, 2021, 11, 82.
27. Oerbeck B., Overgaard K., Pripp AH. Et al. Adult ADHD Symptoms and Satisfaction With Life: Does Age and Sex Matter? *Journal of Attention Disorders*, 2019, 23(1), 3-1.
28. Goodman DW. The consequences of attention- -deficit/hyperactivity disorder in adults, *Journal of Psychiatric Practice*, 2007, 13(5), 318-327.
29. Diagnostic and Statistical Manual of Mental Disorders. 4th ed, text rev. Washington, DC: American Psychiatric Association; 2000:85-93, 706.
30. Millstein RB., Wilens TE., Biederman J., Spencer TJ. Presenting ADHD symptoms and subtypes in clinically referred adults with ADHD, *Journal of Attention Disorders*, 1997, 2(3), 159-166.
31. Kessler RC, Adler L, Ames M, et al. The World Health Organization adult ADHD self-report scale (ASRS): a short screening scale for use in the general population, *Psychological Medicine*, 2005, 35(2), 245-256.
32. Safren SA, Otto MW, Sprich S, et al. Cognitive-behavioral therapy for ADHD in medication-treated adults with continued symptoms, *Behaviour Research and Therapy*, 2005, 43(7), 831-842.
33. Bramham J., Young S., Bickerdike A., et al. Evaluation of group cognitive behavioral therapy for adults with ADHD, 2009, *Journal of Attention Disorders*, 12(5), 434-41.

34. Medication guides. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=medguide.page>. Accessed 24 June 2023.
35. NICE guideline. Attention deficit hyperactivity disorder: diagnosis and management <https://www.nice.org.uk/guidance/ng87/resources/attention-deficit-hyperactivity-disorder-diagnosis-and-management-pdf-1837699732933>. Accessed 24 June 2023.
36. Adler LA., Dirks B., Deas P. et al. Self-Reported quality of life in adults with attention-deficit/hyperactivity disorder and executive function impairment treated with lisdexamfetamine dimesylate: a randomized, double-blind, multicenter, placebo-controlled, parallel-group study, *BMC Psychiatry*, 2013, 9, 13, 253.
37. Rösler M., Ginsberg Y., Arngrim T., et al. Correlation of symptomatic improvements with functional improvements and patient-reported outcomes in adults with attention-deficit/hyperactivity disorder treated with OROS methylphenidate, *The World Journal of Biological Psychiatry*, 2013, 14(4), 282-290.
38. Medori R., Ramos-Quiroga JA., Casas M. et al.: *Biological Psychiatry: A randomized, placebo-controlled trial of three fixed dosages of prolonged-release OROS methylphenidate in adults with attention-deficit/hyperactivity disorder*, 2008, 15, 63(10), 981-989.
39. Retz W., Rösler M., Ose C. et al. Multiscale assessment of treatment efficacy in adults with ADHD: a randomized placebo-controlled, multi-centre study with extended-release methylphenidate, *The World Journal of Biological Psychiatry*, 2012, 13(1), 48-59.
40. Casas M., Rösler M., Sandra Kooij JJ. et al. Efficacy and safety of prolonged-release OROS methylphenidate in adults with attention deficit/hyperactivity disorder: a 13-week, randomized, double-blind, placebo-controlled, fixed-dose study, *The World Journal of Biological Psychiatry*, 2013, 14(4), 268-81.
41. Huss M, Ginsberg Y, Tvedten T, et al. Methylphenidate hydrochloride modified-release in adults with attention deficit hyperactivity disorder: a randomized double-blind placebo-controlled trial. *Advances in Therapy*, 2014, 31(1), 44-65.
42. Adler LA., Dirks B., Deas PF. et al. Lisdexamfetamine dimesylate in adults with attention-deficit/ hyperactivity disorder who report clinically significant impairment in executive function: results from a randomized, double-blind, placebo-controlled study, *The World Journal of Biological Psychiatry*, 2013, 74(7), 694-702.

43. Buitelaar JK., Casas M., Philipsen A. et al. Dejonckheere J, van Oene JC, Schäuble B. Functional improvement and correlations with symptomatic improvement in adults with attention deficit hyperactivity disorder receiving long-acting methylphenidate, *Psychological Medicine*, 2012, 42(1), 195-204.
44. Cunill R., Castells X., Tobias A., Capellà D. Efficacy, safety and variability in pharmacotherapy for adults with attention deficit hyperactivity disorder: a meta-analysis and meta-regression in over 9000 patients, *Psychopharmacology (Berl)*, 2016, 233(2), 187-197.
45. Goto T., Hirata Y., Takita Y. et al. Efficacy and Safety of Atomoxetine Hydrochloride in Asian Adults With ADHD: A Multinational 10-Week Randomized Double-Blind Placebo-Controlled Asian Study, *Journal of Attention Disorders*, 2017, 21(2), 100–109.
46. Durell TM., Adler LA., Williams DW. et al. Atomoxetine treatment of attention-deficit/hyperactivity disorder in young adults with assessment of functional outcomes: a randomized, double-blind, placebo-controlled clinical trial, *Journal of Clinical Psychopharmacology*, 2013 Feb, 33(1), 45-54.
47. Adler LA., Liebowitz M., Kronenberger W. et al. Atomoxetine treatment in adults with attention-deficit/hyperactivity disorder and comorbid social anxiety disorder, *Depression and Anxiety*, 2009, 26(3), 212-221.
48. Adler LA., Spencer T., Brown TE. et al. Once-daily atomoxetine for adult attention-deficit/hyperactivity disorder: a 6-month, double-blind trial. *Journal of Clinical Psychopharmacology*, 2009, 29(1), 44-50.
49. Lee SI., Song DH., Shin DW. et al. Efficacy and safety of atomoxetine hydrochloride in Korean adults with attention-deficit hyperactivity disorder, *Asia-Pacific Psychiatry*, 2014 6(4), 386-396.
50. Wietecha L., Young J., Ruff D. et al. Atomoxetine once daily for 24 weeks in adults with attention-deficit/hyperactivity disorder (ADHD): impact of treatment on family functioning, *Clinical Neuropharmacology*, 2012, 35(3), 125-133.
51. Adler LA., Spencer TJ., Levine LR. et al. Functional outcomes in the treatment of adults with ADHD, *Journal of Attention Disorders*, 2008, 11(6), 720-727.
52. Yu S., Shen S., Tao M. Guanfacine for the Treatment of Attention-Deficit Hyperactivity Disorder: An Updated Systematic Review and Meta-Analysis, *Journal of Child and*

- Adolescent Psychopharmacology, 2023, 33(2), 40-50.
53. Robinson CL., Parker K., Kataria S. et al. Viloxazine for the Treatment of Attention Deficit Hyperactivity Disorder, Health Psychol Research, 2022, 23, 10(3).
54. Butterfield ME., Saal J., Young B., Young JL. Supplementary guanfacine hydrochloride as a treatment of attention deficit hyperactivity disorder in adults: A double blind, placebo-controlled study, Psychiatry Research, 2016, 28, 236, 136-141.
55. Brown TE, Landgraf JM. Improvements in executive function correlate with enhanced performance and functioning and health-related quality of life: evidence from 2 large, double-blind, randomized, placebo-controlled trials in ADHD. Postgraduate Medicine. 2010, 122(5), 42-51.
56. Chen Q., Sjölander A., Runeson B., et al. Drug treatment for attention-deficit/hyperactivity disorder and suicidal behaviour: register based study, BMJ, 2014, 18, 348, g3769.
57. Buitelaar JK., Trott GE., Hofecker M. et al. Long-term efficacy and safety outcomes with OROS-MPH in adults with ADHD, The International Journal of Neuropsychopharmacology, 2012, 15(1), 1-13.
58. Weiss M., Murray C., Wasdell M. et al. A randomized controlled trial of CBT therapy for adults with ADHD with and without medication, BMC Psychiatry, 2012, 5,12,30.
59. Liu CI., Hua MH., Lu ML., Goh KK. Effectiveness of cognitive behavioural-based interventions for adults with attention-deficit/hyperactivity disorder extends beyond core symptoms: A meta-analysis of randomized controlled trials, Psychology and Psychotherapy, 2023, 16
60. Young Z., Moghaddam N., Tickle A.: Journal of Attention Disorders: The Efficacy of Cognitive Behavioral Therapy for Adults With ADHD: A Systematic Review and Meta-Analysis of Randomized Controlled Trials, 2020 Apr, 24(6), 875-888.
61. Vidal-Estrada R., Bosch-Munso R., Nogueira-Morais M., Casas-Brugue M., Ramos-Quiroga JA.: Actas Españolas de Psiquiatría: Psychological treatment of attention deficit hyperactivity disorder in adults: a systematic review, 2012, 40(3), 147-154.
62. Halmøy A., Ring AE., Gjestad R. et al. Dialectical behavioral therapy-based group treatment versus treatment as usual for adults with attention-deficit hyperactivity disorder: a multicenter randomized controlled trial, BMC Psychiatry, 2022, 28, 22(1), 738.
63. Barham H., Büyükgök D., Aksu S. et al. Evidence for modulation of planning and working

- memory capacities by transcranial direct current stimulation in a sample of adults with attention deficit hyperactivity disorder, *Neuroscience Letters*, 2022, 1, 790, 136883.
64. Basiri N., Hadianfard H. Adult ADHD Treatment Based on Combination of Dialectical Behavior Therapy (DBT) and Transcranial Direct Current Stimulation (tDCS) as Measured by Subjective and Objective Scales. *Journal of Attention Disorders*, 2023, 27(1), 57-66.
65. Oliveira J., Pellow J., Tsele-Tebakang T., Solomon EM. Experiences of neurofeedback therapists in treating attention-deficit hyperactivity disorder, 2022, *Health SA*, 28, 27, 1874.
66. Selaskowski B., Steffens M., Schulze M. et al. Smartphone-assisted psychoeducation in adult attention-deficit/hyperactivity disorder: A randomized controlled trial, *Psychiatry Research*, 2022, 317, 114802.
67. Jensen DA., Lundervold AJ., Stubberud J. et al. Goal management training improves executive control in adults with ADHD: an open trial employing attention network theory to examine effects on attention, *BMC Psychology*, 2022 26, 10(1), 207.
68. Dinu LM., Singh SN., Baker NS. et al. The Effects of Different Exercise Approaches on Attention Deficit Hyperactivity Disorder in Adults: A Randomised Controlled Trial, *Behavioral Sciences (Basel, Switzerland)*, 2023 2, 13(2), 129.
69. Stern P., Kolodny T., Tsafirir S. et al. Near and Far Transfer Effects of Computerized Progressive Attention Training (CPAT) Versus Mindfulness Based Stress Reduction (MBSR) Practice Among Adults With ADHD, *Journal of Attention Disorders*, 2023, 27(7), 757-776.

DEEP BRAIN STIMULATION IN PSYCHIATRY

Zuzanna Lizoń, Paulina Typek

Psychiatry Students' Scientific Association, Medical University of Silesian Piasts in Wrocław

ABBREVIATION LIST

- DBS - Deep Brain Stimulation
- OCD - Obsessive-Compulsive Disorder
- TRD - Treatment Resistant Depression
- SCG - Subcallosal Cingulate Gyrus
- ALIC - Anterior Limb of Internal Capsule
- MFB - Medial Forebrain Bundle

INTRODUCTION

Deep Brain Stimulation (DBS) is a procedure where electrodes are surgically placed in specific areas of the brain. These electrodes are connected to a device, similar to a pacemaker, which is implanted under the skin, usually in the chest area. The device, called an implantable pulse generator, generates electrical impulses that can be adjusted by healthcare professionals. The stimulation parameters include the specific electrode contacts used, the intensity, frequency, and duration of the electrical pulses. Common targets for DBS in movement disorders are the subthalamic nucleus and the globus pallidus interna [1].

Deep brain stimulation has been used to treat movement disorders since the 1980s. Originally used to treat Parkinson's disease, DBS is now approved by the US Food and Drug Administration for the treatment of Parkinson's disease, essential tremor and dystonia [2].

As our understanding of neural networks and dysfunction in neuropsychiatric disorders advances, DBS is increasingly being considered in certain neuropsychiatric disorders.

The use of DBS in psychiatric disorders is still being researched and refined, but has shown promise in diseases such as Obsessive Compulsive Disorder [3], Depression [4], Tourette Syndrome [5], Alzheimer disease [6], addiction [7] and chronic pain [8].

OBSESSIVE-COMPULSIVE DISORDER

Obsessive-Compulsive Disorder (OCD) is a mental health condition characterized by recurrent and intrusive thoughts, known as obsessions, and repetitive behaviors or mental acts, known as compulsions. These obsessions and compulsions can significantly interfere with a person's daily life, causing distress and impairing their ability to function effectively [9]. The exact cause and neurobiology of OCD are not fully understood. However, there is increasing evidence suggesting a connection between OCD and dysfunction in a specific brain circuit known as the orbitofrontal-striatal-pallido-thalamic circuitry [10]. Abnormalities in the activity and synaptic connectivity of the orbitofrontal cortex, anterior cingulate cortex, and the striatal circuitry have suggested that DBS may be effective in treating refractory OCD [10]. According to research findings, approximately 53% of individuals who underwent deep brain stimulation targeting the ventral capsule/ventral striatum or nucleus accumbens experienced improvement in their obsessive-compulsive symptoms [11]. Similarly, around 41% of individuals who received DBS targeting the subthalamic nucleus showed improvement in obsessive-compulsive symptoms [11]. The range of responders across studies has been reported to be between 10% and 61% [12, 13].

ADDICTION

Drug addiction is a significant public health concern with high relapse rates despite standard treatments. Deep brain stimulation has emerged as a potential therapeutic option. The neurobiological foundation of drug reward is connected to the mesocorticolimbic dopamine system. Activation of neuronal activity in the ventral tegmental area by various drugs leads to elevated levels of dopamine in the nucleus accumbens shell. This increase in dopamine contributes to the pleasurable sensations or euphoria experienced during drug consumption [14]. Promising effects of deep brain stimulation in drug addiction have been observed in various studies. A notable finding is the beneficial effect of DBS nucleus accumbens in obsessive-compulsive disorder patients, leading to an improvement in their alcohol dependence [15]. Several reports and case series have also demonstrated positive outcomes on DBS in patients with Tourette syndrome, OCD, and anxiety disorders, including successful smoking cessation in three patients [16].

Further investigations have focused on DBS specifically for addiction. Clinical trials

exploring the DBS for cocaine and heroin addiction have shown positive results, such as decreased cravings and increased withdrawal time [17] and bilateral DBS in three patients with drug-resistant chronic alcoholism resulting in abstinence or a significant reduction in alcohol consumption [18,19].

Overall, clinical and preclinical evidence suggests that DBS can modulate brain networks and positively impact addictive behaviors. Nucleus accumbens is a particularly promising target for DBS in the treatment of drug addiction. However, longer-term controlled studies involving larger numbers of patients are needed to better understand the potential of DBS in the treatment of drug addiction [20] .

CHRONIC PAIN

Deep brain stimulation (DBS) has not only been successful in treating movement disorders but has also emerged as a therapeutic option for pain management. DBS targets for pain control include the internal capsule , the ventral posterolateral nucleus and ventral posteromedial nucleus of the sensory thalamus , the centro-median parafascicular region of the thalamus, the periaqueductal/paraventricular gray , the posterior hypothalamus , the motor cortex, the nucleus accumbens, and the anterior cingulate cortex [21]. There is a wide range of targets for deep brain stimulation (DBS) in pain treatment, including both white matter tracts [22] and gray matter regions [23]. The causes and types of chronic pain experienced by patients are also diverse. However, due to this variability and the lack of rigorous studies, the effectiveness of DBS for pain treatment remains inconsistent. The current literature primarily consists of retrospective case reports that lack important elements such as blinding, controls, and standardized pain measures.

Nevertheless, there is hope for more conclusive findings through recent and ongoing clinical trials [21].

DEPRESSION

According to estimates, approximately 30% of patients treated for depression remain resistant to conventional therapy methods. For these individuals neurosurgical approaches can provide an opportunity to control the disease, however DBS still serves as an experimental option [24].

Deep brain stimulation has shown an average response rate of 60% in chronically depressed patients who had not responded to previous treatments. However, the response rates can differ significantly among patients and studies [25].

Some adverse events specific to targeted regions may occur, however their relation to DBS therapy is unclear [26].

Researchers examine different targets in terms of their potential effectiveness in TRD. A connectomic analysis based on diffusion MRI data revealed that the current DBS targets can be grouped into four distinct categories depending on their connectivity within the cortico-striato-thalamo-cortical (CSTC) circuits. Two key regions, Brodmann area 10 and the amygdala, were functionally associated with all seven DBS targets investigated. Thus, these regions may have a significant and underexplored role in facilitating the positive effects of DBS for TRD patients [27].

In another study six DBS targets were evaluated: subcallosal cingulate gyrus (SCG), nucleus accumbens, ventral capsule/ventral striatum or anterior limb of internal capsule (ALIC), medial forebrain bundle (MFB), lateral habenula, and inferior thalamic peduncle. Stimulation of these locations had different effects on mood in patients, with SCG, ALIC and MFB showing more consistent antidepressant response rates [28]. The data on clinical outcomes of MFB DBS for treatment-resistant depression is generally limited due to small sample sizes, however findings from studies indicate a remarkably fast antidepressant effect, observable within a week after stimulation initiation [29]. In terms of responding to SCG DBS, the preoperative measurement of the volume of brain structures showed that preoperative volumes of subcallosal cingulate gyrus, thalamus and amygdala were significantly larger in responders to this kind of stimulation. No significant difference in hippocampal volume was observed, however cortical grey matter volume was smaller. These findings suggest that structural differences in the subcallosal cingulate gyrus and its connected areas may play an important role in determining response to SCG DBS [30]. Long-term efficacy is still examined. In a study on the group of eight patients, the individuals were followed for up to 28 months, with some followed for up to 4 years under SCG-DBS. The average response rate was 51%. However, due to the small size of the sample further studies confirming long-term improvement in patients are necessary [31]. The important role of individualized targeting with the potential use of tractography is also highlighted in research [32].

ALIC stimulation, in turn, was related to neither positive nor negative effect on patients' cognition [33], still there are individuals who benefit from this procedure [34].

TOURETTE SYNDROME

Tourette syndrome has its onset in childhood but symptoms, involving vocal and motor tics, typically improve with age. Nevertheless, patients may require pharmacological and behavioral treatment and in some cases the course of disease can be severe. For those presenting disabling tics that do not respond to traditional methods of treatment DBS emerged as a treatment option. Anatomical structures commonly targeted are the centromedian thalamus and the globus pallidus internus [35]. The 5 main pillars that should be counted when selecting patients to DBS are: high tic severity along with its impact on patients' life, failure of first-line therapies, 6 months stability of comorbid psychiatric disorders and 18-year age limit, with the latter still being discussed [36]. Ethical concerns appear when using deep brain stimulation as a treatment for pediatric patients, especially considering the fact that tics often decrease or even disappear during adolescence and young adulthood. However, recent guidelines suggest that age alone should not determine eligibility for DBS treatment, instead potential benefits and risks should be taken into account in each case [37]. Average response to treatment, defined as improvement in tic severity, is estimated at 40% [38]. DBS targeting the posteroventral globus pallidus interna has demonstrated long-term effectiveness and acceptable safety, with better results of treatment observed among younger individuals and those with longer treatment duration [39].

CONCLUSIONS

Deep brain stimulation is a surgical procedure where electrodes are implanted in specific brain regions and connected to a device that delivers electrical impulses [1]. It has shown promise in the treatment of psychiatric disorders such as Obsessive-Compulsive Disorder [11,12], addiction [17,18], chronic pain [22], depression and Tourette syndrome. In OCD, targeting brain circuits involved in the disorder has led to significant improvement in symptoms for a substantial number of patients [11,12]. DBS has also shown potential in reducing addictive behaviors and cravings in individuals with substance abuse disorders [17,18]. For chronic pain, DBS targets various brain regions involved in pain processing, although its effectiveness remains inconsistent and further research is needed [21]. In depression, DBS has demonstrated a response rate of around 60% in treatment-resistant patients, with different brain targets showing varying degrees of effectiveness [25, 27, 28]. In

Tourette syndrome, DBS targeting specific brain regions has been effective in reducing tic severity, particularly in cases that are unresponsive to traditional treatments [38, 39].

REFERENCES

1. Dougherty D. D.. Deep Brain Stimulation: Clinical Applications. *The Psychiatric clinics of North America*, 2018, 41(3), 385–394.
2. Krauss, J. K., Lipsman, N., Aziz, T., et al. Technology of deep brain stimulation: current status and future directions. *Nature reviews. Neurology*, 2021, 17(2), 75–87.
3. Nuttin, B., Cosyns, P., Demeulemeester, H., et al. Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder. *Lancet (London, England)*, 1999, 354(9189), 1526.
4. Aibar-Durán, J. Á., Rodríguez Rodríguez, R., de Diego Adeliño, F. J., et al. Long-Term Results of Deep Brain Stimulation for Treatment-Resistant Depression: Outcome Analysis and Correlation With Lead Position and Electrical Parameters. *Neurosurgery*, 2022, 90(1), 72–80.
5. Ackermans, L., Temel, Y., Visser-Vandewalle, V. Deep brain stimulation in Tourette's Syndrome. *Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics*, 2008, 5(2), 339–344.
6. Chang, C. H., Lane, H. Y., Lin, C. H. Brain Stimulation in Alzheimer's Disease. *Frontiers in psychiatry*, 2018, 9, 201.
7. Gonçalves-Ferreira, A., do Couto, F. S., Rainha Campos, A., et al. Deep Brain Stimulation for Refractory Cocaine Dependence. *Biological psychiatry*, 2016, 79(11), 87–89.
8. Alamri, A., Pereira, E. A. C.. Deep Brain Stimulation for Chronic Pain. *Neurosurgery clinics of North America*, 2022, 33(3), 311–321.
9. Rapinesi, C., Kotzalidis, G. D., Ferracuti, S. et al. A. Brain Stimulation in Obsessive-Compulsive Disorder (OCD): A Systematic Review. *Current neuropharmacology*, 2019, 17(8), 787–807.
10. Del Casale A., Kotzalidis G.D., Rapinesi C. et al. Functional neuroimaging in obsessive-compulsive disorder. *Neuropsychobiology*, 2011,64(2), 61–85.
11. Nuttin, B., Cosyns, P., Demeulemeester, H., et al. Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder. *Lancet (London, England)*, 1999, 354(9189), 1526.

12. Nuttin, B. J., Gabriëls, L. A., Cosyns, P. R., et al. Long-term electrical capsular stimulation in patients with obsessive-compulsive disorder. *Neurosurgery*, 2003, 52(6), 1263–1274.
13. Rapinesi, C., Kotzalidis, G. D., Ferracuti, S., et al. Brain Stimulation in Obsessive-Compulsive Disorder (OCD): A Systematic Review. *Current neuropharmacology*, 2019, 17(8), 787–807.
14. Koob, G. F., Le Moal, M. Addiction and the brain antireward system. *Annual review of psychology*, 2008, 59, 29–53
15. Kuhn, J., Lenartz, D., Huff, W., et al. Remission of alcohol dependency following deep brain stimulation of the nucleus accumbens: valuable therapeutic implications?. *Journal of neurology, neurosurgery, and psychiatry*, 2007, 78(10), 1152–1153.
16. Kuhn, J., Bauer, R., Pohl, S., et al. Observations on unaided smoking cessation after deep brain stimulation of the nucleus accumbens. *European addiction research*, 2009, 15(4), 196–201.
17. Gonçalves-Ferreira, A., do Couto, F. S., Rainha Campos, A., et al. Deep Brain Stimulation for Refractory Cocaine Dependence. *Biological psychiatry*, 2016, 79(11), 87–89.
18. Müller, U. J., Sturm, V., Voges, J., et al. Successful treatment of chronic resistant alcoholism by deep brain stimulation of nucleus accumbens: first experience with three cases. *Pharmacopsychiatry*, 2009, 42(6), 288–291.
19. Müller, U. J., Sturm, V., Voges, J., et al. Nucleus Accumbens Deep Brain Stimulation for Alcohol Addiction - Safety and Clinical Long-term Results of a Pilot Trial. *Pharmacopsychiatry*, 2016, 49(4), 170–173.
20. Ranjan, M., Ranjan, N., Deogaonkar, M., Rezai, A.. Deep Brain Stimulation for Refractory Depression, Obsessive-Compulsive Disorder and Addiction. *Neurology India*, 68(Supplement), 2020, 282–287.
21. Keifer, O. P., Jr, Riley, J. P., Boulis, N. M.. Deep brain stimulation for chronic pain: intracranial targets, clinical outcomes, and trial design considerations. *Neurosurgery clinics of North America*, 2014, 25(4), 671–692.
22. Fields, H. L., Adams, J. E.. Pain after cortical injury relieved by electrical stimulation of the internal capsule. *Brain : a journal of neurology*, 1974, 97(1), 169–178.
23. Young, R. F., Tronnier, V., Rinaldi, P. C. Chronic stimulation of the Kölliker-Fuse nucleus region for relief of intractable pain in humans. *Journal of neurosurgery*, 1992.

- 76(6), 979–985.
24. Filkowski MM, Sheth SA. Deep Brain Stimulation for Depression: An Emerging Indication. *Neurosurgery clinics of North America*, 2019, 30(2), 243–256.
 25. Figue M, Riva-Posse P, Choi KS, et al. Deep Brain Stimulation for Depression. *Neurotherapeutics. The journal of the American Society for Experimental NeuroTherapeutics*, 2022, 19(4), 1229–1245.
 26. Zhou C, Zhang H, Qin Y, et al. A systematic review and meta-analysis of deep brain stimulation in treatment-resistant depression. *Progress in neuro-psychopharmacology & biological psychiatry*, 2018, 2(82), 224–232.
 27. Zhu Z, Hubbard E, Guo X, et al. A connectomic analysis of deep brain stimulation for treatment-resistant depression. *Brain stimulation*, 2021, 14(5), 1226–1233.
 28. Dandekar MP, Fenoy AJ, Carvalho AF, et al. Deep brain stimulation for treatment-resistant depression: an integrative review of preclinical and clinical findings and translational implications. *Molecular psychiatry*, 2018, 23(5), 1094–1112.
 29. Sobstyl M, Stapińska-Synieć A.. Deep brain stimulation of the medial forebrain bundle for treatment-resistant depression - a narrative literature review. *Postępy Psychiatrii neurologii*, 2021, 30(3), 183–189.
 30. Sankar T, Chakravarty MM, Jawa N, et al. Neuroanatomical predictors of response to subcallosal cingulate deep brain stimulation for treatment-resistant depression. *Journal of psychiatry & neuroscience*. 2020, 45(1), 45–54
 31. Merkl A, Aust S, Schneider GH, et al. Deep brain stimulation of the subcallosal cingulate gyrus in patients with treatment-resistant depression: A double-blinded randomized controlled study and long-term follow-up in eight patients. *Journal of affective disorders*, 2018, 227, 521–529.
 32. Zhu Z, Han J, Zhu H, et al. Individualized targeting is warranted in subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression: A tractography analysis. *Human brain mapping*, 2023, 44(11), 4200–4210.
 33. Bergfeld IO, Mantione M, Hoogendoorn MLC, et al. Impact of deep brain stimulation of the ventral anterior limb of the internal capsule on cognition in depression. *Psychological Medicine*, 2017, 47(9), 1647–1658.
 34. Hitti FL, Cristancho MA, Yang AI, et al. Deep Brain Stimulation of the Ventral Capsule/Ventral Striatum for Treatment-Resistant Depression: A Decade of Clinical Follow-Up. *The Journal of clinical psychiatry*, 2021, 82(6), 21m13973.

35. Deeb W, Malaty I. Deep Brain Stimulation for Tourette Syndrome: Potential Role in the Pediatric Population. *Journal of child neurology*, 2020, 35(2), 155–165.
36. Martino D, Deeb W, Jimenez-Shahed J, et al. The 5 Pillars in Tourette Syndrome Deep Brain Stimulation Patient Selection: Present and Future. *Neurology*, 2021, 96(14), 664–676
37. Xu W, Zhang C, Deeb W, et al. Deep brain stimulation for Tourette's syndrome. *Translational neurodegeneration*, 2020, 13, 9, 4.
38. Casagrande SCB, Cury RG, Alho EJJ, Fonoff ET. Deep brain stimulation in Tourette's syndrome: evidence to date. *Neuropsychiatric disease and treatment*, 2019, 15, 1061–1075
39. Cui ZQ, Wang J, Mao ZQ, et al. Long-term efficacy, prognostic factors, and safety of deep brain stimulation in patients with refractory Tourette syndrome: A single center, single target, retrospective study. *Journal of Psychiatric Research*, 2022, 151, 523–530

POSTPARTUM PSYCHOSIS: RISK FACTORS, DIAGNOSIS AND TREATMENT

Wiktoria Lewicka, Michał Szyszka, Klaudia Włodarczyk, Paweł Drymluch, Marta Malicka, Julia Sobczak

Psychiatry Students' Scientific Association, Medical University of Silesian Piasts in Wrocław

ABBREVIATION LIST

- PP - postpartum psychosis
- DSM-5 - Diagnostic and Statistical Manual of Mental Disorders
- IPT - interpersonal therapy
- AED - antiepileptic drugs
- ECT - electroconvulsive therapy

INTRODUCTION

Postpartum psychosis (PP) is the most severe manifestation of postpartum mood disorders and as a psychiatric emergency has terrible effects on the mother, child, and other family members [1,2].

It is also a significant clinical and public health concern linked to considerable economic expenses, a higher risk of maternal suicide, and potential effects on child development [3].

In this review, we aim to summarize the current knowledge about the epidemiology, pathogenesis, clinical manifestations, diagnosis, and treatment of postpartum psychosis.

ETIOLOGICAL AND TRIGGERING FACTORS

The etiology of postpartum psychosis is likely to be complex as in other psychiatric disorders in general, but research points to genetic, immunologic, and hormonal factors [3]. Obstetric factors such as mode of delivery and complications of pregnancy or delivery also have been investigated with inconsistent results [4,5]. Only primiparity is a well-established risk factor for postpartum psychosis which might be explained by significant alterations in biological or psychosocial factors associated with the birth of a first baby [3,6].

Although psychological and social factors are important in the triggering of postpartum depression [7], no evidence has been found on the association between psychological factors or stressful life events and the development of postpartum psychotic illness [8,9]. Some studies suggest a lack of a partner may be related to postpartum psychosis, however, it is not clear whether it is a risk factor or a consequence of the disorder [3,10,11].

The quick onset of postpartum psychosis after delivery raises the possibility that hormonal changes are contributing to the disorder's pathophysiology. This theory is plausible considering that the peak period of the onset of postpartum psychosis coincides with the sudden withdrawal of progesterone and estrogen that occurs postpartum [12]. Progesterone and estrogen have been shown to have a facilitatory effect on dopaminergic systems, therefore, the abrupt drop in hormone levels after childbirth may result in dopaminergic hypersensitivity in some women vulnerable to the childbirth trigger [13,14]. Interestingly, according to a systematic review based on a small collection of case-reports and case-series an increased risk of postpartum psychosis in women with and without a history of psychiatric disorder may be associated with D2 receptor agonists (bromocriptine and cabergoline) [15].

Given the evidence that the risk of postpartum psychosis is increased with the first pregnancy and the fact that pregnancy is linked to significant and highly modulated changes in immunological functioning, it is possible that immunological system dysfunction or dysregulation may contribute to postpartum psychosis [16]. For example, regulatory T-cells and pro-inflammatory T-helper cell type 1 and 17 cytokine levels have been found to be changed in postpartum psychosis patients when compared to healthy parous controls [17]. Evidence also suggests that there is dysregulation of the immunoneuroendocrine set point in postpartum psychosis with over-activation of the monocytes and macrophages [18]. Additionally, lack of sleep may contribute to the onset of postpartum psychosis; however, the evidence is conflicting [3,19,20]. For instance, a small study discovered that 17 women who were diagnosed with postpartum psychosis tended to have longer labors and more nocturnal deliveries than the 17 controls [18]. According to another study, the sleep-wake cycle did not alter between 15 control participants and 23 women with a history of postpartum psychosis [21].

Finally, there is also compelling evidence linking genetic variables to the pathophysiology of postpartum psychosis. Up to 40–50% of women with a history of postpartum psychosis screened positive for a family history of mood disorders among first- and second-degree relatives, which is much higher than in the general population [19,20]. Another study found that 74% of women with bipolar disorder with a positive family history of postpartum psychosis in a first-degree relative had also gone through a severe mood episode

triggered by childbirth, as opposed to only 30% of bipolar disorder patients without such a family history [22,23].

EPIDEMIOLOGY AND LINKS TO OTHER PSYCHIATRIC DISORDERS

Developing postpartum psychosis is associated with an incidence rate of 89–2.6 per 1000 women and a prevalence of 5 per 1000 women [24]. Peak timing of onset is from days 1 to 14, with a duration of weeks to months, but women remain at risk of having severe mood and psychotic episodes for several months [25,26].

Women with a history of bipolar disorder are at a higher risk of developing postpartum psychosis. Similarly, after experiencing postpartum psychosis, mothers have a 50 to 80% chance of another psychiatric episode, which is usually within the bipolar spectrum. Evidence suggests that mania or a mixed-mood episode are characteristics of postpartum psychosis in many cases [27]. One study examined 479 pregnancies in 283 women with bipolar I disorder and found that 1.88% had an episode of postpartum psychosis during the first 6 months postpartum. Additionally, 7.93% of women had a manic episode and 6.47 % had a mixed episode. In total more than 16% of pregnancies were followed by a manic, mixed or psychotic episode, meaning that the risk of postpartum psychosis was 160-320-fold higher than the commonly quoted risk of 0.1-0.2% in the general population. None of the women with bipolar II disorder had a manic or psychotic episode in the postpartum period in this study [28]. Another research [3] indicates that most episodes of postpartum psychosis are manifestations of bipolar disorder, although approximately 40% of women experiencing postpartum psychosis have no history of severe psychiatric illness.

The DSM-5 does not recognize postpartum psychosis as a separate diagnosis, however, American Psychiatric Association [29] recommends the use of the peripartum onset specifier to characterize mood episodes of bipolar I, bipolar II, or major depressive disorder occurring during pregnancy or the postpartum period. A nationwide study from Taiwan found that women with postpartum psychosis were at increased risk of subsequent psychiatric disorders including schizophrenia, bipolar disorder, and major depressive disorder [30].

In a group of women with a history of serious mental illness, defined as psychotic or bipolar disorders, prior recent relapse was an independent predictor of relapse in the postpartum [31]. Suicide ideation and suicide attempts are frequent in this group of patients, especially among women with hypomanic or depressive symptoms in the postpartum period [32,33], however, suicide attempt is rare during the acute psychotic episode. One study reported only

two suicides in a sample of 4000 women with postpartum psychosis [34]. Evidence suggests that homicide thoughts are also common among women with postpartum psychosis, although infanticide is relatively rare, occurring in between 1 and 4.5% of cases [3]. Other research shows that the filicide rate was more than 5-fold higher in women with psychotic depression compared to those with psychosis alone [34]. Of women suffering from postpartum psychosis who decide to have more children, more than half are at risk of experiencing perinatal mood episodes again [3].

DIAGNOSING POSTPARTUM PSYCHOSIS

Due to its potential for serious harm to both the mother and the infant, early diagnosis and intervention when it comes to postpartum psychosis are crucial. Diagnosing postpartum psychosis involves a comprehensive evaluation of the woman's symptoms, medical history, and careful consideration of potential risk factors.

Postpartum psychosis typically develops within the first few days or weeks after childbirth, although it can occur up to several months after delivery [35,36]. The symptoms can manifest suddenly and progress rapidly, often leading to significant distress and impairment in the affected woman's daily functioning. Women may experience auditory or visual hallucinations and/or delusions, presented as false and irrational beliefs, usually relating to the baby's or the mother's abilities. Severe mood swings are often prevalent in this type of psychosis, with emotions fluctuating rapidly between manic and depressive states. Another common sign is insomnia or an altered sleep pattern, exacerbating the already challenging symptoms [35,36]. Women may have difficulty concentrating, making decisions, or they may be confused and disoriented. The affected mother may also exhibit agitated behavior, pacing, or restlessness. Suicidal and homicidal thoughts, strong feelings of guilt, or ideas about harming the baby might also be present [37,38].

It is important to collect information about the woman's medical history, including any previous psychiatric disorders or episodes. A physical examination may be conducted to rule out any underlying medical conditions that could be contributing to the symptoms, especially neurological ones. Blood tests including metabolic parameters and monitoring of thyroid function are also necessary. Risk factors associated with postpartum psychosis, such as a personal or family history of psychiatric disorders, previous episodes of postpartum psychosis, or a history of bipolar disorder, should also be assessed [36,37].

Differential diagnosis

The differential diagnosis of postpartum psychosis involves distinguishing it from other psychiatric conditions that can occur during the postpartum period. Several disorders share overlapping symptoms, making an accurate diagnosis crucial for appropriate treatment. Some conditions that may be considered in the differential diagnosis of postpartum psychosis include postpartum depression, bipolar disorder, schizophrenia, delusional disorder, and substance-induced psychosis [35]. Postpartum depression can present with symptoms of sadness, lack of interest, and changes in appetite and sleep, but typically lacks the severe psychotic features seen in postpartum psychosis. Bipolar disorder may exhibit similar manic or depressive symptoms, but the timing and rapid onset after childbirth can help differentiate it from postpartum psychosis. Schizophrenia and delusional disorder can also present with psychotic symptoms but are less likely to be triggered specifically by childbirth. Substance-induced psychosis should be considered in cases where substance abuse or withdrawal may contribute to the symptoms. A thorough evaluation of the woman's symptoms, history, and clinical presentation is crucial in making an accurate differential diagnosis and guiding appropriate treatment interventions [37,39,40].

CLINICAL MANIFESTATIONS OF POSTPARTUM PSYCHOSIS

Postpartum psychosis, also known as postpartum depression with psychotic features, is a serious mental disorder that can occur in women after childbirth. The onset is typically sudden and occurs within the first two weeks postpartum [41,42]. The clinical manifestations of postpartum psychosis include:

- **Mood changes:** A woman may experience rapid mood swings, which can include euphoria, unwarranted joy, irritability, anxiety, or depression. Extreme emotional fluctuations may occur.
- **Hallucinations:** A woman may experience auditory, visual, or sensory hallucinations. These can be auditory hallucinations where the woman hears voices that do not exist, or visual hallucinations where she sees images that are not real.
- **Intrusive thoughts:** A woman may have intrusive, uncontrollable thoughts that can be distressing, unpleasant, or even frightening. These thoughts may pertain to the child, caregiving, or the mother herself.

- Sleep disturbances: A woman may have difficulty falling asleep, maintaining sleep, or excessive sleeping. Insomnia or excessive sleepiness may occur as symptoms of postpartum psychosis.
- Disorganized thinking: A woman may have difficulty with concentration, logical thinking, and decision-making. Her thoughts may be disorganized, chaotic, or unrelated to each other.
- Disorganized behavior: A woman may exhibit disorganization in behavior, which can include aggression, unpredictability, inappropriate actions, or incomprehensible behavior.
- Self and child neglect: As a result of postpartum psychosis, a woman may neglect herself and her child's care. She may struggle with feeding, grooming, maintaining hygiene, or performing other daily caregiving tasks for the child [43].

A recent clinical cohort study tracked the phenotypic characteristics of 130 consecutive cases of PP and used latent class analysis to describe three separate symptom profiles: cases characterized by mania and/or agitation, with irritability much more common than elevated mood (34%) cases characterized by depression and/or anxiety (41%) cases showing an atypical or mixed profile (25%). Across all cases, 25% of patients were disorganized, 20% disoriented, 10% had disturbed consciousness, and 5% developed catatonia [44].

RISK OF SUICIDE/ INFANTICIDE

Postpartum psychosis is a severe mental health condition that can lead to possible risk of both the affected mothers and their infants [45]. This thesis aims to provide a comparative analysis of the risk factors, mechanisms, and preventive measures associated with suicide and infanticide in the context of postpartum psychosis. It is important to mention discussing postpartum psychosis and the analysis of statistics of suicide and infanticide associated with that.

On the base of Ian Brockington's thesis which highlights the frequency of suicide and infanticide in a literature of over 4000 cases, can be inferred that the overall suicide rate and infanticide rate is relatively rare in the year following childbirth [46,47]. Moreover, suicide risk can be highest during the early stages of postpartum psychosis, typically within the first month after childbirth. However, the risk can persist throughout the postpartum period and beyond, requiring ongoing monitoring and support [48]. Based on studies, 46 suicides per approximately 15 000 person-years or about 300/10 5 person-years have been reported [49,50,51].

In terms of an infanticide, the compilation of about 800 studies included 65 cases due to depression or psychosis within a year of birth. Moreover, 11 reports were associated with depressed patients without psychotic features and 48 with a feature of psychosis - just 1% of over 4000 reviewed. On the other hand, the latest American articles reported a higher figure of 4% [52]. This difference could be caused by a misunderstanding of a Scottish study in which 82 patients were followed for an average of 16 years [53]. The report revealed 29 people suffered from bipolar disorder and paranoid or schizophrenic affective psychosis. None of the infanticides were committed by a mother suffering from acute psychosis without depression.

TREATMENT

The evidence points to postpartum psychosis as an outward sign of bipolar disease that is timed to correspond with significant hormonal changes following delivery. The patient experiences frank psychosis, cognitive dysfunction, and severely disordered conduct, which mark a radical departure from how they were previously behaving. These agitations can have severe effects that put the safety and well-being of the affected woman and her children in danger, especially when combined with lapsed awareness of her sickness and symptoms [54,57,64].

Psychoeducation

Once the diagnosis has been made, the physician should educate the patient and her family about the condition, rule out organic reasons, begin medication and supportive care, and review the patient's function and safety status on a regular basis. Physicians will make a significant contribution by informing patients and their families about the symptoms, treatments, expected outcomes, and prevention efforts for PP recurrence. The psychoeducation process is critical. It will build the therapeutic connection; additionally, it will strengthen the patient's treatment decision-making process as well as her emotions of self-efficacy and mastery over sickness [57,64,66].

Before the patient leaves the hospital, a comprehensive discharge plan must be devised after stabilizing the patient and initiating acute medication for PP. For the first few weeks after release, referral to intensive outpatient therapy is recommended, coupled with closely spaced out-patient follow-up sessions. These techniques will ease the patient's return home and allow the doctor or nurse to closely evaluate treatment response, resolve drug intolerance issues, and detect clinical worsening early [57,58].

Treatment strategies work best when they are tailored to each patient and contain therapies that have proven to be effective in the past. Sleep deprivation is a primary cause of mania and PP. Physicians should encourage patients and their partners to enlist the assistance of other family members or friends, as well as doula services, to alleviate the burden on the sick mother and allow her to sleep and recover from illness. When symptoms recur, patients and their families should be reminded to contact their doctors as soon as possible [55,62,64].

Psychotherapy

Prior to hospital release, supportive psychotherapy may include parenting skills and early infant therapies to address maternal-baby attachment and newborn development. In-home services have the potential to improve both mother and newborn outcomes. Other psychotherapy alternatives for postpartum mood disorders include family-focused therapy, cognitive behavioral therapy, and interpersonal psychotherapy (IPT). IPT, in particular, was developed for women dealing with childbearing-related events and is designed to assist women who are struggling with losses, role shifts, or relationship problems. Once patients have achieved an organized level of thinking, these advanced forms of psychotherapy are indicated [63,67].

Pharmacotherapy

Acute medication is required to treat PP's psychotic and mood-related symptoms. Atypical antipsychotic medicines and mood stabilizers or antimanic agents, such as lithium or antiepileptic medications (AED), are among the therapeutic possibilities. Although monotherapy is preferred, some women require more than one medication to reach a satisfactory level of symptom control and sickness remission [59,60,61].

Electroconvulsive therapy (ECT)

The safety and efficacy of ECT in the treatment of pregnant women in all three trimesters is well established, as is its utilization in the case of postpartum psychosis. In one case series, women with PP and psychotic bipolar depression experienced >50% improvement in mania, depression, and psychosis with bilateral ECT.

Such individuals may benefit as well, with a bigger drop in suicidal thoughts and a lower likelihood of hospital readmission than before treatment. As a result, physicians are encouraged to assist their patients in considering the various medications available for PP management. In individuals admitted to the hospital with acute, florid psychosis, ECT looks to be an excellent

alternative that promotes rapid symptom relief. Patients who have failed multiple drug trials, patients who cannot wait for the delayed onset of action of these drugs, patients who have intolerable drug side effects, and patients who require immediate effective symptom relief due to gross impairments in self-care, cognition, and judgment that threaten their safety and well-being should consider ECT [56,68].

CONCLUSIONS

Postpartum psychosis is a serious mental disorder that can occur in women after giving birth, typically within the first two weeks. It is characterized by sudden mood changes, hallucinations, intrusive thoughts, sleep disturbances, disorganized thinking and behavior, and self and child neglect. The etiology of postpartum psychosis is complex, but research mostly points to biological factors, especially genetic, immunologic, or hormonal. Among obstetric factors, only primiparity is a well-established one.

Out of different psychiatric diagnoses, there is noticeable relation between bipolar disorder and postpartum psychosis - women with a history of bipolar disorder are at a higher risk of developing postpartum psychosis, and similarly, women who suffer from postpartum psychosis have a higher chance of another psychiatric episode, which is usually within the bipolar spectrum.

Diagnosing postpartum psychosis requires a careful evaluation of the woman's symptoms, medical history, and risk factors. The presence of rapid onset of severe symptoms, including hallucinations, delusions, extreme mood swings, and confusion is indicative of postpartum psychosis.

It is important to note that postpartum psychosis is a medical emergency that requires immediate attention. Early detection and intervention for postpartum psychosis, including timely and easy access to mental health services can help prevent suicide. If a healthcare professional suspects postpartum psychosis, they may recommend hospitalization to ensure the safety of the mother and the infant and to provide appropriate treatment and support. It is also important to mention adequate social support, including the involvement of family, friends, and healthcare professionals as a vital and fundamental help.

REFERENCES

1. Holford N., Channon S., Heron J., Jones I.: The impact of postpartum psychosis on partners. *BMC Pregnancy and Childbirth*, 2018, 18(1), 1-10.

2. Brockington I.: Suicide and filicide in postpartum psychosis. *Archives of Women's Mental Health*, 2017, 20(1), 63-69.
3. Perry A., Gordon-Smith K., Jones L., Jones I.: Phenomenology, Epidemiology and Aetiology of Postpartum Psychosis: A Review. *Brain Sciences*, 2021, 11(1), 1-14.
4. Nager A., Sundquist K., Ramírez-León V., Johansson L.M.: Obstetric complications and postpartum psychosis: A follow-up study of 1.1 million first-time mothers between 1975 and 2003 in Sweden. *Acta Psychiatrica Scandinavica*, 2008, 117(1), 12–19.
5. Meltzer-Brody S., Maegbaek M.L., Medland S.E., et al. Obstetrical, pregnancy and socio-economic predictors for new-onset severe postpartum psychiatric disorders in primiparous women. *Psychological Medicine*, 2017, 47(8), 1–15.
6. Munk-Olsen T., Jones I., Laursen T.M.: Birth order and postpartum psychiatric disorders. *Bipolar Disorder*, 2014, 16(3), 300–307.
7. Zhao X.H., Zhang Z.: Risk factors for postpartum depression: An evidence-based systematic review of systematic reviews and meta-analyses. *Asian Journal of Psychiatry* 2020, 53, 1-13.
8. Warselius P., Cnattingius S., Li J., et al. Maternal bereavement shortly before or during pregnancy and risk of postpartum psychotic illness: a population-based study from Denmark and Sweden. *Clinical Epidemiology*, 2019, 11, 285-298.
9. Perry A., Gordon-Smith K., Webb I., et al. Postpartum psychosis in bipolar disorder: No evidence of association with personality traits, cognitive style or affective temperaments. *BMC Psychiatry*, 2019, 19(395), 1-10.
10. Nager A., Johansson L.-M., Sundquist K.: Are sociodemographic factors and year of delivery associated with hospital admission for postpartum psychosis? A study of 500,000 first-time mothers. *Acta Psychiatrica Scandinavica*, 2005, 112(1), 47–53.
11. Upadhyaya S.K., Sharma A., Raval C.M.: Postpartum psychosis: Risk factors identification. *North American Journal of Medicine and Science*, 2014, 6(6), 274-277.
12. Maguire J., McCormack C., Mitchell A., Monk C.: Neurobiology of maternal mental illness. *Handbook of Clinical Neurology*, 2020, 171, 97–116.
13. Barth C., Villringer A., Sacher J.: Sex hormones affect neurotransmitters and shape the adult female brain during hormonal transition periods. *Frontiers of Neuroscience*, 2015, 9, 1–20.
14. Appleby L.: The aetiology of postpartum psychosis: Why are there no answers? *Journal of Reproductive and Infant Psychology*, 1990, 8(2), 109–118.

15. Snellen M., Power J., Blankley G., Galbally M.: Pharmacological lactation suppression with D2 receptor agonists and risk of postpartum psychosis: A systematic review. *Australian and New Zealand Journal of Obstetrics and Gynecology*, 2016, 56(4), 336-340.
16. Mor G., Cardenas I.: The Immune System in Pregnancy: A Unique Complexity. *American Journal of Reproductive Immunology*, 2010, 63(6), 425–433.
17. Kumar M.M., Venkataswamy M.M., Sathyanarayanan G., et al. Immune system aberrations in postpartum psychosis: An immunophenotyping study from a tertiary care neuropsychiatric hospital in India. *Journal of Neuroimmunology*, 2017, 310, 8–13.
18. Bergink V., Burgerhout K.M., Weigelt K., et al. Immune system dysregulation in first-onset postpartum psychosis. *Biological Psychiatry*, 2013, 73(10), 1000-1007.
19. Sharma V., Smith A., Khan M.: The relationship between duration of labour, time of delivery, and puerperal psychosis. *Journal of Affective Disorders*, 2004, 83(2-3), 215-20.
20. Bilszta J.L., Meyer D., Buist A.E.: Bipolar affective disorder in the postnatal period: investigating the role of sleep. *Bipolar Disorder*, 2010, 12(5), 568-78.
21. Robertson E., Jones I., Haque S., et al. Risk of puerperal and non-puerperal recurrence of illness following bipolar affective puerperal (post-partum) psychosis. *The British Journal of Psychiatry*, 2005, 186(3), 258-259.
22. Benvenuti P., Cabras P.L., Servi P., et al. Puerperal psychoses: A clinical case study with follow-up. *Journal of Affective Disorders*, 1992, 26(1), 25-30.
23. Jones I., Craddock N.: Familiality of the puerperal trigger in bipolar disorder: Results of a family study. *American Journal of Psychiatry*, 2001, 158, 913–917.
24. VanderKruik R., Barreix M., Chou D., et al. Maternal Morbidity. The global prevalence of postpartum psychosis: a systematic review. *BMC Psychiatry*, 2017, 17, 1-9.
25. Heron J., McGuinness M., Blackmore E.R., et al. Early postpartum symptoms in puerperal psychosis. *An International Journal of Obstetrics and Gynecology*, 2008, 115(3), 348-353.
26. Kendell R., Chalmers J., Platz C.: Epidemiology of puerperal psychoses, *British Journal of Psychiatry*, 1987, 150, 662-673.
27. Friedman S.H., Prakash C., Nagle-Yang S.: Postpartum psychosis: protecting mother and infant. *Current Psychiatry*, 2019, 18(4), 12-21.
28. Viguera A., Tondo L., Koukopoulos A., et al. Episodes of mood disorders in 2,252

- pregnancies and postpartum periods. *American Journal of Psychiatry*, 2011, 168(11), 1179-1185.
29. Diagnostic and Statistical Manual of Mental Disorders (5th ed.), American Psychiatric Association, 2013.
30. Chen M., Pan T., Bai Y.M., et al. Postpartum depression and psychosis and subsequent severe mental illnesses in mothers and neurodevelopmental disorders in children: a nationwide study. *Journal of Clinical Psychiatry*, 2021, 82(4).
31. Taylor C.L., Stewart R.J., Howard L.M.: Relapse in the first three months postpartum in women with history of serious mental illness. *Schizophrenia Research*, 2019, 204, 46-54.
32. Pope C.J., Xie B., Sharma V., Campbell M.K.: A prospective study of thoughts of self-harm and suicidal ideation during the postpartum period in women with mood disorders, *Archives of Women's Mental Health*, 2013, 16(6), 483-488.
33. Babu G.N., Subbakrishna D.K., Chandra P.S.: Prevalence and correlates of suicidality among Indian women with post-partum psychosis in an inpatient setting, *The Australian and New Zeland Journal of Psychiatry*, 2008, 42(11), 976-980.
34. Brockington I.: Suicide and filicide in postpartum psychosis, *Archives of Women's Mental Health*, 2017, 20(1), 63-69.
35. Friedman S.H., Reed E., Ross N.E.: Postpartum Psychosis. *Current Psychiatry Reports*, 2023, 25(2), 65–72.
36. Tinkelman A., Hill E. A., Deligiannidis K. M.: Management of new onset psychosis in the postpartum period. *The Journal of Clinical Psychiatry*, 2017, 78(9), 1423-1424.
37. Bergink V., Rasgon N., Wisner K. L.: Postpartum Psychosis: Madness, Mania, and Melancholia in Motherhood. *American Journal of Psychiatry*, 2016, 173(12), 1179–1188.
38. Wesseloo R., Burgerhout KM., Koorengevel KM., Bergink V.: Postpartum psychosis in clinical practice: diagnostic considerations, treatment and prevention. *Tijdschrift Voor Psychiatrie*, 2015, 57(1), 25-33.
39. Perry A., Gordon-Smith K., Webb I., et al. Postpartum psychosis in bipolar disorder: No evidence of association with personality traits, cognitive style or affective temperaments. *BMC Psychiatry*, 2019, 19, 1-10.
40. Rai S., Pathak A., Sharma I.: Postpartum psychiatric disorders: Early diagnosis and management. *Indian Journal of Psychiatry*, 2015, 57(2), 216-221.

41. Kendell R.E., Chalmers J.C., Platz C.: Epidemiology of puerperal psychoses. *British Journal of Psychiatry*, 1987, 150, 662–73.
42. Klompenhouwer J, van Hulst A., Tulen J., et al. The clinical features of postpartum psychoses. *European Psychiatry*, 1995, 10(7), 355–367.
43. Osborne L.M.: Recognizing and Managing Postpartum Psychosis: A Clinical Guide for Obstetric Providers. *Obstetrics and Gynecology Clinics of North America*, 2018, 45(3), 455–468.
44. Kamperman A.M.: Phenotypical characteristics of postpartum psychosis: A clinical cohort study. *Bipolar Disorder*, 2017, 19(6), 450–457.
45. Kendell R.E., Chalmers J.C., Platz C.: Epidemiology of puerperal psychoses. *British Journal of Psychiatry*, 1987, 150, 662–673.
46. Brockington I. Suicide and filicide in postpartum psychosis. *Archives of Women's Mental Health*, 2017, 20(1), 63-69.
47. Appleby L., Mortensen P.B., Faragher E.B.: Suicide and other causes of mortality after post-partum psychiatric admission. *British Journal of Psychiatry*, 1998, 173, 209–211.
48. Bergink V., Lambregtse-van Den Berg M.P., Koorengevel K.M., et al. First-onset psychosis occurring in the postpartum period: a prospective cohort study. *Journal of Clinical Psychiatry*. 2011, 72, 1531–1537.
49. La Vecchia C., Luchini F., Levi F.: Worldwide trends in suicide mortality 1955-1989. *Acta Psychiatrica Scandinavica*, 1994, 90(1), 53–64.
50. Schöpf J. Postpartum-Psychosen: Beitrag zur Nosologie. Zürich: Thesis, 1992.
51. Klompenhouwer J.L. Puerperal psychosis. Rotterdam: Thesis; 1992.
52. Spinelli M.G.: Postpartum psychosis: detection of risk and management. *American Journal of Psychiatry*, 2009, 166, 405–408.
53. Davidson J., Robertson E.: A follow-up study of postpartum illness, 1946-1978. *Acta Psychiatrica Scandinavica*, 1985, 71(5), 451-457.
54. Wilkinson A., Anderson S., Wheeler S.B.: Screening for and Treating Postpartum Depression and Psychosis: A Cost-Effectiveness Analysis. *Maternal and Children Health Journal*, 2017, 21(4), 903-914.
55. Doucet S., Jones I., Letourneau N., Dennis C.L., Blackmore E.R.: Interventions for the prevention and treatment of postpartum psychosis: a systematic review. *Archives of Women's Mental Health*, 2011, 14(2), 89-98.
56. Focht A., Kellner C.H.: Electroconvulsive therapy (ECT) in the treatment of postpartum psychosis. *The Journal of ECT*, 2012, 28(1), 31-3.

57. Sharma V.: Treatment of postpartum psychosis: challenges and opportunities. *Current Drug Safety*, 2008, 3(1), 76-81.
58. Rodriguez-Cabezas L., Clark C.: Psychiatric Emergencies in Pregnancy and Postpartum. *Clinical Obstetrics and Gynecology*, 2018, 61(3), 615-627.
59. Bergink V., Burgerhout K.M., Koorengevel K.M., et al. Treatment of psychosis and mania in the postpartum period. *American Journal of Psychiatry*, 2015, 172(2), 115-123.
60. Nurnberg H.G.: An overview of somatic treatment of psychosis during pregnancy and postpartum. *General Hospital Psychiatry*, 1989, 11(5), 328-38.
61. Hill R., Law D., Yelland C., Sved Williams A.: Treatment of postpartum psychosis in a mother-baby unit: do both mother and baby benefit? *Australasian Psychiatry*, 2019, 27(2), 121-124.
62. Sharma V.: Pharmacotherapy of postpartum psychosis. *Expert Opinion on Pharmacotherapy*, 2003, 4(10), 1651-1658.
63. Wesseloo R., Burgerhout K.M., Koorengevel K.M., Bergink V.: Postpartum Psychose in de klinische praktijk: diagnostiek, behandeling en preventie [Postpartum psychosis in clinical practice: diagnostic considerations, treatment and prevention]. *Tijdschrift voor Psychiatrie*, 2015, 57(1), 25-33.
64. Sit D., Rothschild A.J., Wisner K.L.: A review of postpartum psychosis. *Journal of Women's Health*, 2006, 15(4), 352-68.
65. Teodorescu A., Dima L., Popa M.A., et al. Antipsychotics in Postpartum Psychosis. *American Journal of Therapeutics*, 2020, 28(3), 341-348.
66. Okano T., Nomura J., Kumar R.: An epidemiological and clinical investigation of postpartum psychiatric illness in Japanese mothers. *Journal of Affective Disorders*, 1998, 48(2-3), 233-240.
67. Robinson G.E., Stewart D.E.: Postpartum psychiatric disorders. *Canadian Medical Association Journal*, 1986, 134(1), 31-37.
68. Volpe F.M., Travares A.: Manic patients receiving ECT in a Brazilian sample. *Journal of Affective Disorders*, 2004, 79(1-3), 201-208.

REM SLEEP BEHAVIOR DISORDER - WHAT DO WE KNOW?

Zuzanna Lizoń, Hubert Sawczuk, Paulina Typek

Psychiatry Students' Scientific Association, Medical University of Silesian Piasts in Wrocław

ABBREVIATION LIST

- PD - Parkinson's disease
- RBD - REM sleep behavior disorder
- UPDRS - unified Parkinson's disease rating scale

INTRODUCTION

REM sleep, short for rapid eye movement sleep, is one of the stages of sleep that occurs cyclically throughout the night. It is characterized by rapid eye movements, increased brain activity, and vivid dreaming. During a typical sleep cycle, REM sleep usually occurs multiple times, with each cycle lasting about 90-120 minutes [1]. It is also characterized by almost complete paralysis of the skeletal muscles, except for the diaphragm and extraocular muscles [1].

The purpose and functions of REM sleep are still not fully understood. However, it is considered essential for various cognitive processes, emotional regulation and memory consolidation [2].

Rapid eye movement (REM) behavior disorder (RBD) is a parasomnia with loss of skeletal muscle atonia that can lead to dream enactment [3]. RBD is characterized by elaborate and often violent motor behaviors during otherwise normal REM sleep [4]. Behaviors can vary from basic physical actions, like speaking, yelling, and sudden movements of the limbs, to more intricate motions that appear intentional and aimed at achieving a specific goal, such as gesturing, striking, or kicking. Injuries occur when individuals with forceful movements of their limbs unintentionally collide with a wall, window, object or their bed partner while responding to an imaginary threat. Falling out of bed is also a common consequence [5]. RBD has a low prevalence in young adults, but is a more frequent parasomnia among the elderly, with an estimated prevalence up to 7.7% [6]. The recent interest in RBD by neurologists is because,

apart from being classified as a parasomnia, it is most commonly caused by alpha-synuclein neurodegeneration, characterized by abnormal accumulation of alpha-synuclein protein which aggregates in neurons [1] .

In the long run, the majority of individuals with rapid eye movement sleep behavior disorder tend to develop a neurodegenerative disorder. RBD has been linked to diseases such as Parkinson's, dementia with Lewy bodies and multiple system atrophy [4]. RBD can also be seen in the course of neurological diseases such as narcolepsy type 1, discrete pons lesions affecting REM generators such as stroke, multiple sclerosis demyelinating disease, brainstem tumors, neurogenetic disorders such as spinocerebellar ataxia type 3 as well as paraneoplastic neurological disorders and autoimmune diseases [7].

In individuals under the age of 50, the most common cause of rapid eye movement sleep behavior disorder is the use of antidepressant medications, specifically those that affect serotonin levels. This type of RBD is referred to as serotonergic RBD or 5-HT RBD, indicating its association with serotonin and the medications that influence its activity [8]. Mild RBD may often go undiagnosed, because patients may be unaware of their nocturnal behavior or neglect that dream-associated behavior reflects a medical condition that should be reported to their physician [9].

RBD AS A PROGNOSTIC FACTOR IN PARKINSON'S DISEASE

REM sleep behavior disorder receives scientists' attention for being a clear predictor for neurodegeneration, as it precedes development of full-blown symptoms of disorders such as Parkinson's disease, dementia with Lewy bodies and multiple system atrophy, with PD being the most common of them. According to the large study which involved multicentric, prospective follow-up data, the conversion rate from idiopathic RBD to clinical manifestation of parkinsonism and dementia was 6.3% per year. In 12-year follow-up the percentage of patients who converted rose to 73.5 [10]. Some individuals that remained disease free for more than 10 years after diagnosis of RBD were described. However, through measurement of patients' motor and cognitive function, the features of underlying neurodegeneration were observed [11]. Coexistent hyposmia was identified as a potential factor that increases short-term risk for developing synucleinopathy in general, but it doesn't enable to differentiate between conversion to PD and dementia with Lewy bodies [12]. Because comprehensive research on risk factors is still lacking, a currently conducted Italian study was designed to stratify the risk of transition to neurodegenerative pathologies [13].

Among individuals affected by Parkinson's disease we can distinguish three subgroups, depending on coexistence of RBD symptoms: confirmed RBD, non-RBD and those without definitive polysomnographic diagnosis, referred to as probable RBD. In a meta-analytic study published in 2021 the comparison between those groups was conducted. Both probable RBD patients and confirmed RBD individuals were associated with longer PD duration and higher dosage of levodopa, Hoehn-Yahr scale and UPDRS-motor score in comparison with those without diagnosis of RBD. The main differences involved older age, lower MMSE scores, higher stage in Hoehn-Yahr scale and higher incidence of insomnia in confirmed RBD group compared to probable RBD [14].

Patients with PD accompanied by RBD typically had poorer performance in neuropsychological assessment, which consists of evaluation of memory, language, attention and executive functions. Mild cognitive impairment can be diagnosed in patients affected by PD with or without parasomnia, however coexistence of RBD is related to higher frequency of MCI diagnosis [15]. Interestingly, in a study carried out in 2020 PD with probable RBD individuals exhibited poor performance generally in all neuropsychological functions, whereas in isolated PD only language abilities' decline was described. In terms of emotional outcome both PD groups reported greater levels of depression and anxiety when compared to healthy participants [16].

The concomitance of cognitive decline and sleep disturbances may be associated with the fact that these two states tend to affect each other. As a result of existing sleep problems neurocognitive difficulty may occur, with fatigue being a substantial but nonspecific causative factor. Abnormal architecture of sleep was suggested to be another potential variable directly affecting neurocognition. Neurodegenerative disorders may, in turn, affect structures of the brain related to circadian rhythm but also worsen sleep hygiene among patients [17]. In terms of RBD specifically, global cognitive deficits may come from abnormalities involving frontal networks and posterior cortical areas [18].

PD in RBD positive individuals is more likely to be manifested as a non-tremor subtype with dominant motor symptoms [19]. Dermal alpha-synuclein deposition may be a factor of some importance in terms of PD/RBD+ phenotype, as alpha-synuclein deposits were found with greater frequency in skin biopsies extracted from those suffering from RBD. Both in patients with isolated RBD, presenting no symptoms of parkinsonism at the moment of study, and in patients with coexisting PD and RBD the deposits were associated with involvement of peripheral nerves [20].

Overall, findings support the fact that RBD is related to poor prognosis, as the severity of both motor and non-motor symptoms is increased [21], along with greater risk of developing functional dependency [22].

ROLE OF BIOMARKERS

As people with isolated REM sleep behavior disorder can convert into alpha-synuclein aggregation illnesses, stratifying groups of risk in the prodromal condition may be crucial. We need biomarkers that are less intrusive than cerebrospinal fluid, as well as universally applicable screening tools for prodromal patients. Other biomarkers such as fecal microbiota, miRNA or inflammatory panels are yet to be reliable screening tools for patients at risk of disease conversion. The identification of people with iRBD who are at a high risk of short-term phenoconversion will probably be improved with the help of a combination of biomarkers. [23] There are currently no reliable biological indicators available. Numerous studies have been conducted on neurofilament light chain (NFL) and glial fibrillary acidic protein (GFAP) as indicators of cognitive impairment. [24] For phenotypic conversion prediction, baseline plasma NFL levels may be helpful. [25] When used together, NFL and GFAP performed well in differentiating PD-RBD patients from PD-nRBD. Serum NFL and GFAP were revealed as distinct risk factors for RBD when potential confounding variables such as age and disease duration were taken into account. To sum up, serum NFL and GFAP may be useful biomarkers for the RBD subtype of PD. [24] Biomarker function of tissue biopsy in REM sleep behavior disorder is also taken into consideration. Future research on patients with alpha-synucleinopathy, and particularly on those with iRBD, could benefit from tissue biopsy as it offers a minimally invasive in-vivo assay for the accumulation of alpha-synuclein. Studies are required to determine the association between the pattern and density of alpha-synuclein deposition in the skin and enteric nervous system (ENS) and the potential risk of phenoconversion in individuals with iRBD. [26] Surprisingly, in addition to cerebrospinal fluid, skin, and nasal mucosa, where alpha-synuclein aggregates build up in patients with iRBD, stool is now an important and convenient resource with the potential to be used for diagnostic purposes. These aggregates are excreted in the feces and can be detected using the surface-based fluorescence intensity distribution analysis (sFIDA) assay, which may aid in the diagnosis of prodromal synucleinopathies. The researchers have found overlap between patients and controls who were healthy, resulting in a specificity of 49.0% and a sensitivity of 76.4% for distinguishing iRBD patients from healthy controls, and a specificity of 52.1% and

a sensitivity of 80.6% for distinguishing iRBD and Parkinson's disease patients [27].

Despite the lack of a definitive standard, a growing number of studies have produced encouraging findings that suggest a variety of imaging modalities can support the evaluation of RBD progression and give predictions about the course of the disease. Neuroimaging could make it easier to identify neurodegenerative brain changes in RBD at an early stage. It would enable the identification of people who are at a higher risk of phenoconversion to a progressive neurological disorder. RBD patients have persistent network-level metabolic anomalies that are astonishingly similar to those seen in PD patients, indicating that these disorders have a shared pathophysiology [28].

Among the radiotracer imaging varieties (using a combination of PET and SPECT) presynaptic dopaminergic imaging seems to have an advantage over other forms of imaging (postsynaptic dopaminergic, metabolic and cerebral perfusion ones). The current findings suggest that imaging of presynaptic dopaminergic integrity is appropriate for monitoring disease development and identifying individuals at high risk of phenoconversion. Other forms of radiotracer imaging are lacking the evidence or longitudinal studies, so they are less recommended, and their usefulness is less well-established [28]. Magnetic resonance imaging (MRI) which allows us to avoid potentially hazardous ionizing radiation exposure [29] has yet to be proven beneficial in monitoring RBD progression. Diffusion tensor imaging (DTI) technique has been widely applied to explore microstructural abnormalities in Parkinson's disease and atypical parkinsonism, and it has demonstrated potential for early disease detection and differential diagnosis of parkinsonian disorders, but a limited number of studies have used DTI in RBD, and the results are mixed. [28] The usefulness of this imaging must be assessed further. Another neuroimaging technique, transcranial sonography, which has proven to be highly beneficial in the clinical differentiation of Parkinson's disease patients from the healthy population [30], unfortunately presents rather low sensitivity and specificity when used alone for the RBD. [28] Future research should take into account the possibility that combining various imaging modalities could improve prognosis accuracy. In addition, extra longitudinal research is required to support the current discoveries.

Another diagnostic approach, summarized by the meta-analysis [31], monitored sleep changes in idiopathic REM sleep behavior disorder. Compared with the control group, iRBD patients were presented with reduced total sleep time, sleep efficiency, apnea hypopnea index (this result could be attributed to RBD patients' loss of muscle atonia during REM sleep, which could protect against obstructive sleep apnea by limiting upper airway collapse) and increased sleep latency, slow wave sleep and periodic limb movement index. Sleep continuity and

architecture are disrupted in iRBD patients and may be associated with neuropathological alterations.

TREATMENT OF RBD

Clonazepam

Clonazepam, a benzodiazepine, is considered as a treatment option for RBD. It works by enhancing the activity of gamma-aminobutyric acid (GABA), a neurotransmitter that helps regulate neuronal excitability [32]. Although clonazepam is widely regarded as the first-line treatment for RBD, its effectiveness in treatment has not been conclusively proven in randomized controlled trials, which showed that low doses of clonazepam (0.5 mg/day) showed a similar degree of improvement in symptoms compared to placebo. Therefore, based on this study, the efficacy of clonazepam in the treatment of isolated RBD remains uncertain [33].

Melatonin

The other drug used in treatment is melatonin. Melatonin is a hormone secreted in accordance with the circadian rhythm by the pineal gland and is influenced by the dark environment, which begins to grow shortly after dark and peaks in the middle of the night. Studies have shown that melatonin reduced the percentage of REM sleep without atonia from 39.2% to 26.8%, the delay in falling asleep by 1.96 minutes and led to a significant improvement in overall clinical impression compared to baseline but no statistically significant change from placebo [34]. In other studies doses of 3-12 mg of melatonin at bedtimes were used successfully to reduce injuries, with few adverse effects [35]. These findings suggest that melatonin can be used in monotherapy or as add-on therapy in selected patients with RBD.

Dopaminergic agonist

There is currently a lack of randomized controlled studies specifically investigating the use of dopaminergic agonists for RBD in Parkinson's disease (PD). The available evidence primarily consists of uncontrolled studies, including those involving new dopaminergic agonists, which have yielded inconclusive results [36]. Therefore, further research is needed to determine the efficacy of dopaminergic agonists in treating RBD.

Sodium oxybate

Sodium oxybate, which is the sodium salt of γ -hydroxybutyrate (GHB), is primarily

used for the treatment of sudden muscle weakness and excessive daytime sleepiness in patients with narcolepsy. However, there have been reports suggesting that sodium oxybate may also be effective in improving symptoms of RBD in various conditions.

Studies have indicated clinical improvement in RBD symptoms in patients with isolated RBD [37] as well as RBD associated with Parkinson's disease [38] and narcolepsy type 1 [39]. These reports suggest that sodium oxybate has shown positive effects in managing RBD symptoms in these specific patient populations.

It's worth noting that further research is needed to establish the efficacy of sodium oxybate specifically for RBD treatment.

Antidepressants and serotonergic drugs

Some reports suggest potential improvements in RBD (rapid eye movement sleep behavior disorder) symptoms with various antidepressants and serotonergic drugs. These include tricyclic antidepressants like desipramine and imipramine, selective serotonin reuptake inhibitors like fluvoxamine and paroxetine, trazodone, agomelatine, and vortioxetine [40,41]. However, the efficacy of these medications in RBD treatment requires further investigation. Nelotanserin, an inverse agonist of the serotonin receptor subtype 5-HT_{2A} primarily used for insomnia, was tested in a short-term trial but did not show positive results in patients with RBD associated with dementia with Lewy bodies (DLB) or Parkinson's disease dementia (PDD). On the other hand, a recent short-term randomized crossover trial demonstrated a beneficial effect of 5-hydroxytryptophan (a serotonin precursor) in treating RBD symptoms in patients with Parkinson's disease and RBD [42] .

CONCLUSIONS

RBD has been linked to neurodegenerative disorders such as Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy [4]. It serves as a clear predictor for the development of these disorders [1].

Individuals with Parkinson's disease accompanied by RBD experience poorer performance in neuropsychological assessments and a higher frequency of mild cognitive impairment compared to those without RBD. RBD in Parkinson's disease is associated with greater severity of both motor and non-motor symptoms and an increased risk of developing functional dependency [15, 21, 22].

Biomarkers play an essential role in identifying individuals at high risk of developing neurodegenerative disorders. Several potential biomarkers, including neurofilament light chain (NFL), glial fibrillary acidic protein (GFAP), and alpha-synuclein deposits in peripheral tissues, are being investigated for their predictive value in RBD [24, 25, 26]. Neuroimaging modalities such as presynaptic dopaminergic imaging and magnetic resonance imaging (MRI) hold promise in monitoring RBD progression and identifying early neurodegenerative changes [28, 29]. The treatment of RBD includes clonazepam, melatonin, dopaminergic agonists, sodium oxybate, and certain antidepressants and serotonergic drugs. Clonazepam and melatonin are commonly used, although the evidence for their efficacy is not conclusive [33, 34]. Further research is needed to determine the effectiveness of these treatments and explore new therapeutic options for RBD. Overall, early detection and intervention for RBD may help in identifying individuals at risk and implementing appropriate management strategies. Further research is necessary to enhance our understanding of RBD and its role in neurodegeneration.

REFERENCES

1. Howell, M., Avidan, A. Y., Foldvary-Schaefer, N., et al. Management of REM sleep behavior disorder: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine*, 2023,19(4), 769–810.
2. Ackermann, S., Rasch, B. Differential effects of non-REM and REM sleep on memory consolidation?. *Current Neurology And Neuroscience Reports*, 2014, 14(2), 430.
3. McCarter, S. J., St Louis, E. K., Boeve, B. F. REM sleep behavior disorder and REM sleep without atonia as an early manifestation of degenerative neurological disease. *Current Neurology And Neuroscience Reports*, 2012, 12(2), 182–192.
4. Iranzo, A., Tolosa, E., Gelpi, E., et al. Neurodegenerative disease status and post-mortem pathology in idiopathic rapid-eye-movement sleep behaviour disorder: an observational cohort study. *The Lancet Neurology*, 2013,12(5), 443–453
5. Schenck, C. H., Lee, S. A., Bornemann, M. A., Mahowald, M. W. . Potentially lethal behaviors associated with rapid eye movement sleep behavior disorder: review of the literature and forensic implications. *Journal of Forensic Sciences*, 2009, 54(6), 1475–1484.
6. Boeve, B. F., Molano, J. R., Ferman, T. J., et al. Validation of the Mayo Sleep Questionnaire to screen for REM sleep behavior disorder in an aging and dementia cohort. *Sleep medicine*, 2011, 12(5), 445–453.

7. Howell MJ. Rapid eye movement sleep behavior disorder and other rapid eye movement parasomnias. *Continuum (Minneapolis, Minn)*, 2020, 26(4), 929–945.
8. Teman, P. T., Tippmann-Peikert, M., Silber, M. H., et al. Idiopathic rapid-eye-movement sleep disorder: associations with antidepressants, psychiatric diagnoses, and other factors, in relation to age of onset. *Sleep Medicine*, 2009, 10(1), 60–65.
9. Iranzo, A., Santamaria, J., Tolosa, E.. Idiopathic rapid eye movement sleep behaviour disorder: diagnosis, management, and the need for neuroprotective interventions. *The Lancet. Neurology*, 2016, 15(4), 405–419.
10. Postuma, R. B., Iranzo, A., Hu, M., et al. Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: a multicentre study. *Brain : a Journal Of Neurology*, 2019, 142(3), 744–759.
11. Yao, C., Fereshtehnejad, S. M., Dawson, B. K., et al. Longstanding disease-free survival in idiopathic REM sleep behavior disorder: Is neurodegeneration inevitable?. *Parkinsonism & Related Disorders*. 2018, 54, 99-102.
12. Iranzo A, Marrero-González P, Serradell M, et al. Significance of hyposmia in isolated REM sleep behavior disorder. *Journal of Neurology*. 2021, 268(3), 963-966
13. Puligheddu, M., Figorilli, M., Antelmi, E. Et al. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*. 2022, 43(12), 6919-6928.
14. Xie C, Zhu M, Hu Y. Risk stratification for REM sleep behavior disorder in patients with Parkinson's disease: A PRISMA-compliant meta-analysis and systematic review. *Clinical Neurology And Neurosurgery*. 2021, 202, 106484
15. Jozwiak, N., Postuma, R. B., Montplaisir, J., et al. REM Sleep Behavior Disorder and Cognitive Impairment in Parkinson's Disease. *Sleep*. 2017, 40(8).
16. Mahmood Z, Van Patten R, Nakhla MZ, et al. REM Sleep Behavior Disorder in Parkinson's Disease: Effects on Cognitive, Psychiatric, and Functional outcomes. *Journal of the International Neuropsychological Society : JINS*. 2020, 26(9), 894-905.
17. Shenker JJ, Singh G. Sleep and Dementia. *Missouri medicine*. 2017, 114(4), 311-315.
18. Maggi G, Trojano L, Barone P, Santangelo G. Sleep Disorders and Cognitive Dysfunctions in Parkinson's Disease: A Meta-Analytic Study. *Neuropsychology review*. 2021, 31(4), 643-682.
19. Kim Y, Kim YE, Park EO, et al. REM sleep behavior disorder portends poor prognosis in Parkinson's disease: A systematic review. *Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia*. 2018, 47, 6-13.

20. Doppler, K., Mammadova, S., Kuzkina, A., et al. Association between probable REM sleep behavior disorder and increased dermal alpha-synuclein deposition in Parkinson's disease. *Parkinsonism & related disorders*. 2022, 99, 58-61.
21. Hu, Y., Yu, S. Y., Zuo, L. J., Cao, C. J., et al. Parkinson disease with REM sleep behavior disorder: features, α -synuclein, and inflammation. *Neurology*. 2015, 84(9), 888-894.
22. Kim R, Yoo D, Im JH, Kim HJ, Jeon B. REM sleep behavior disorder predicts functional dependency in early Parkinson's disease. *Parkinsonism & related disorders*. 2019, 66, 138-142.
23. Grover, V. P. B., Tognarelli, J. M., Crossey, M. M. E., et al. Magnetic Resonance Imaging: Principles and Techniques: Lessons for Clinicians. *Journal of Clinical and Experimental Hepatology*, 2015, 5(3), 246
24. Heller, J., Brcina, N., Dogan, I., et al. Brain imaging findings in idiopathic REM sleep behavior disorder (RBD) - A systematic review on potential biomarkers for neurodegeneration. *Sleep Medicine Reviews*, 2017, 34, 23–33.
25. Högl, B., Arnulf, I., Bergmann, M., et al. Rapid eye movement sleep behaviour disorder: Past, present, and future. *Brit Mollenhauer*, 2022, 31(4), e13612.
26. Li, D. H., He, Y. C., Liu, J., Chen, S. Di. Diagnostic Accuracy of Transcranial Sonography of the Substantia Nigra in Parkinson's disease: A Systematic Review and Meta-analysis. *Scientific Reports*, 2016, 6, 20863.
27. Schaffrath, A., Schleyken, S., Seger, A., et al. Patients with isolated REM-sleep behavior disorder have elevated levels of alpha-synuclein aggregates in stool, *Nature partner journals Parkinson's disease*, 2023, 2, 9(1), 14.
28. Teng, X., Mao, S., Wu, H., et al.. The relationship between serum neurofilament light chain and glial fibrillary acidic protein with the REM sleep behavior disorder subtype of Parkinson's disease. *Journal of Neurochemistry*, 2023, 165(2), 165(2):268-276.
29. Zhang, X., Ma, L., Liang, D., et al. Neurofilament Light Protein Predicts Disease Progression in Idiopathic REM Sleep Behavior Disorder. *Journal of Parkinson's Disease*, 2023, 13, 485–499.
30. Zhang, Y., Ren, R., Yang, L., et al. Polysomnographically measured sleep changes in idiopathic REM sleep behavior disorder: A systematic review and meta-analysis. *Sleep Medicine Reviews*, 2020, 54, 101362.
31. Zitser, J., Gibbons, C., Miglis, M. G. The role of tissue biopsy as a biomarker in REM sleep behavior disorder. *Sleep Medicine Reviews*, 2020, 51:101283.

32. Schenck, C. H., Bundlie, S. R., Ettinger, M. G., Mahowald, M. W. Chronic behavioral disorders of human REM sleep: a new category of parasomnia. *Sleep*, 1986, 9(2), 293–308.
33. Shin, C., Park, H., Lee, W. W., et al. Clonazepam for probable REM sleep behavior disorder in Parkinson's disease: A randomized placebo-controlled trial. *Journal of the Neurological Sciences*, 2019, 401, 81–86.
34. Kunz, D., Mahlberg, R. A two-part, double-blind, placebo-controlled trial of exogenous melatonin in REM sleep behaviour disorder. *Journal of Sleep Research*, 2010,19(4), 591–596.
35. Kunz, D., Bes, F.. Melatonin as a therapy in REM sleep behavior disorder patients: an open-labeled pilot study on the possible influence of melatonin on REM-sleep regulation. *Movement disorders*, 1999,14(3), 507–511.
36. Dusek, P., Busková, J., Růžicka, E., et al. Effects of ropinirole prolonged-release on sleep disturbances and daytime sleepiness in Parkinson disease. *Clinical neuropharmacology*, 2010, 33(4), 186–190.
37. Shneerson J. M. Successful treatment of REM sleep behavior disorder with sodium oxybate. *Clinical neuropharmacology*, 2009, 32(3), 158–159.
38. Liebenthal, J., Valerio, J., Ruoff, C., Mahowald, M. A Case of Rapid Eye Movement Sleep Behavior Disorder in Parkinson Disease Treated With Sodium Oxybate. *JAMA neurology*, 2016, 73(1), 126–127.
39. Mayer, G. Efficacy of sodium oxybate on REM sleep behavior disorder in a patient with narcolepsy type 1. *Neurology* 2016, 87, 2594–259.
40. Takahashi, T., Mitsuya, H., Murata, T. et al. Opposite effects of SSRIs and tandospirone in the treatment of REM sleep behavior disorder. *Sleep Medicine*, 2008 ,9(3), 317–319.
41. Du, Y., Jiang, J., Ng, C. H., et al. Vortioxetine improves rapid eye movement sleep behavior disorder: A case report. *Medicine*, 2020, 99(26), e21003.
42. Meloni, M., Figorilli, M., Carta, M., et al. Preliminary finding of a randomized, double-blind, placebo-controlled, crossover study to evaluate the safety and efficacy of 5-hydroxytryptophan on REM sleep behavior disorder in Parkinson's disease. *Sleep & breathing = Schlaf & Atmung*, 2022, 26(3), 1023–1031.

PSYCHOTHERAPY AS A SUPPORTIVE METHOD IN PSYCHIATRIC DISORDERS AND SCHIZOPHRENIA

Paulina Zegarska, Eliza Mędrek

Medical Faculty, Collegium Medicum. Cardinal Stefan Wyszyński University in Warsaw

INTRODUCTION

Schizophrenia is a chronic endogenous disease classified as a psychotic disorder - a condition characterized by distorted pathological, perception, experience and evaluation of reality. To improve long-term prognosis, it is crucial to provide patients with psychotherapeutic support from the first episode of the disease [1].

Psychotherapy is defined as , "the conscious and intentional use of clinical methods and interpersonal interventions derived from the proven claims of psychological science to accompany people in modifying their behavior, cognitive properties, emotions and/or other personal characteristics to those that appear desirable to the participants in the process" [1].

The use of psychotherapy as a method to support the treatment of mental and somatic disorders requires the patient's cooperation and commitment, as well as the willingness and ability to establish a proper interpersonal relationship, which is the basis for creating a psychotherapeutic relationship [1].

Its beneficial effect on changing the patient's thoughts, beliefs and behavior has been proven. Psychotherapy helps the patient distinguish between issues over which he has control and those over which he has no control. There are different approaches used to treat schizophrenia, which depend on the interpretation of the psychopathological essence and unanimously aim to prevent relapse and improve the patient's quality of life [2].

The choice and duration of therapy depends on a number of factors, such as the form of schizophrenia, the clinical course, the type and severity of symptoms, the history of the disease, previous treatment, and the patient's approach to therapy. The purpose of this paper is to present the theoretical and practical aspects of psychotherapy that are important in supporting patients with schizophrenia.

PSYCHODYNAMIC THERAPY

Psychodynamic therapy focuses on providing support, providing a corrective experience, resolving patients' emotional conflicts and avoiding situations that could cause regression [2]. A study by Gunderson [3] compared the impact of exploratory psychotherapy, focused on insight (into disease symptoms), with social skills training. All patients (164 patients) received standard doses of medication, and the therapy was conducted for a period of 2 years, including after leaving the hospital. In the group undergoing exploratory therapy, improvements were observed in ego functions, progress in coping with the symptoms of the disease, and a reduction in the tendency to deny the disease. In contrast, the group subjected to social skills training showed improved social functioning, an increase in the frequency of employment, and a decrease in anxiety and depression. Grinspoon [4] estimates the effectiveness of pharmacotherapy to psychotherapy as a 3:2 ratio, based on the results of a group of 20 patients treated with psychoanalytically oriented psychotherapy for three years at Boston State Hospital.

COGNITIVE-BEHAVIORAL THERAPY

In the cognitive-behavioral approach, mastering coping skills, solving ongoing problems, and compensating for deficits that result from neurocognitive deficits are considered most important. A study by Tarrier and colleagues [5-7] tested therapeutic protocols involving a set of specific cognitive and behavioral techniques, such as the Coping Strategy Enhancement (CSE) program. The study included patients with chronic illness for whom first-line treatment was ineffective, patients with a first episode of schizophrenia, as well as those with a dual diagnosis (schizophrenia and addiction). In 50% of patients, those using the CSE program showed an improvement in the reduction of hallucinations and delusions compared to the control group. A study by Drury and colleagues [8] conducted after a 9-month follow-up showed that only 5% of patients treated with cognitive-behavioral therapy experienced negative symptoms, compared to a 50% frequency in patients treated with pharmacological therapy alone. Granholm [9], on the other hand, reports improvements in social activation, coping with difficult situations and problem-solving after cognitive-behavioral therapy. However, the observed benefits also occurred in the group treated with pharmacological therapy alone. The study included elderly patients with chronic schizophrenia.

GROUP THERAPY

Group therapy is aimed at developing the ability to establish, maintain and strengthen relationships with people. Its field also includes family therapy and education, part of community therapy, which aims to restore the family's psychological balance in such a way that it provides support for the patient and individual family members. The 17-year study, conducted by a team of researchers from the Department of Adult Psychiatry in Krakow, Poland, compared the effectiveness of "community-based" treatment (psychosocial interventions and psycho-education of families) and "individual" treatment (outpatient treatment after leaving the hospital). Both groups of patients consisted of 40 patients each. Inclusion criteria for the study were: first psychiatric hospitalization, diagnosis of schizophrenia, and residence with family in Krakow. Patients were assessed in psychopathological (including relapse and rehospitalization) and social dimensions. A reduction in relapse rates (62% vs. 88%) and inpatient rehospitalizations (49% vs. 71%) was observed in patients treated in a community-based approach [10]. Orwid and colleagues, on the other hand, in a 5-year catamnestic study of adolescents with a diagnosis of schizophrenia using group therapy, observed no reduction in relapse rates compared to the control group. In contrast, a stronger need to establish and maintain interpersonal relationships was observed in control group patients undergoing group therapy [11].

SUMMARY

Psychotherapy as a psychological method has a beneficial effect on changing the patient's thoughts, beliefs and behavior. It is helpful in gaining control over intrusive thoughts, commanding voices and other sensory disturbances that often persist despite the use of pharmacotherapy. In addition, psychological therapy helps to accept states taking place outside the patient's control or consciousness and also to distinguish between matters over which the patient has control and those over which he has no control. An important aspect of psychotherapy is to interpret the symptoms prevalent during psychosis and look for their subliminal content and function.

REFERENCES

1. Cierpiałkowska L., Sęk H.: Psychologia kliniczna, Wyd: Edra Urban &Partner, 2020.

2. Murzyn A., Mielimaka M., Müldner-Nieckowski Ł.: Psychoterapia schizofrenii: cele, skuteczność, specyfika oddziaływań: indywidualna psychoterapia psychodynamiczna: przegląd literatury. *Psychiatria i psychoterapia*, 2010, 6(2), 33-43.
3. Gunderson G.: Effects of psychotherapy in schizophrenia: II. Comparative outcome of two forms of treatment. *Schizophrenia Bulletin*, 1984, 10(4), 564-598.
4. Grinspoon L., Ewalt J., Shader R.: Schizophrenia: Pharmacotherapy and psychotherapy in chronic schizophrenia. *The American Journal of Psychiatry*, 1968, 124, 1645-1652.
5. Tarrier N., Beckett R., Harwood S., et al. Trial of two cognitive-behavioural methods of treating drug-resistant residual psychotic symptoms in schizophrenic patients: I. Outcome. *British Journal of Psychiatry*, 1993, 163, 409-410.
6. Tarrier N.: Cognitive-behavioural therapy in first-episode and early schizophrenia. 18-month follow-up of a randomised controlled trial. *British Journal of Psychiatry*, 2004, 184, 231-239.
7. Haddock G., Barrowclough C., Tarrier N.: Cognitive-behavioural therapy and motivational intervention for schizophrenia and substance misuse. 18-month outcomes of a randomised controlled trial. *Psychiatry*, 2003, 183, 418-426.
8. Drury V., Birchwood M., Cochrane R., Cognitive therapy and recovery from acute psychosis: a controlled trial. Five-year follow-up. *Psychiatry*, 2000, 177, 8-14.
9. Granholm E. A randomised controlled trial of cognitive behavioral social skills training for Middle-aged and older outpatients with chronic schizophrenia. *Psychiatry*, 2005, 162, 520-529.
10. Kanas N.: Group Therapy for Schizophrenic Patients. Wyd. American Psychiatric Press, Kraków, 2004, 142- 144.
11. Ślosarczyk M., Ślosarczyk K., Furgał M.: A 45-year follow-up study of adolescent schizophrenia. Part IV: Clinical status and level of social adaptation 5 years after the first hospitalization in the context of illness course and long-term social functioning of patients., *Psychiatria*, 2020, 186, 1-16.

SEXUALITY AND GENDER ISSUES IN AUTISM SPECTRUM DISORDER

Klaudia Włodarczyk, Natalia Nowak, Weronika Biziorek, Haytham Al Hamaydeh, Diana Ranja Rabih

Psychiatry Students' Scientific Association, Medical University of Silesian Piasts in Wrocław

ABBREVIATION LIST

ASD - autism spectrum disorder

HC - healthy control

TTT - Tackling Teenage Training

INTRODUCTION

Autism spectrum disorder (ASD) is a phrase used to describe a group of early-onset social communication deficiencies and repetitive sensory-motor behaviors that have a strong genetic component as well as other causes [1].

ASD frequently manifests itself in the early stages of life through repetitive sensory-motor activities, which entail actions or motions requiring sensory input and motor responses. Communication problems are also a feature of the condition [2].

Autism is not just a genetic illness, though genetics definitely play a role in its development. Autism has progressed from a poorly known and uncommon childhood illness to a well-researched and common condition in the last 50 years [1].

Psychosocial therapies have been utilized to improve speech and social skills in autistic people, but more research is needed to determine the best approaches to treat them and support their long-term independence. Modern research also emphasizes family involvement in real-world interventions, acknowledging that families are the primary source of support [3].

SEXUALITY IN PEOPLE WITH AUTISM SPECTRUM DISORDER

People with autism spectrum disorders (ASDs) exhibit the whole spectrum of sexual behaviours, just as unaffected individuals. However, certain ASD persons may develop

numerically above-average or nonnormative sexual behaviours and interests because of the disease spectrum's basic symptoms, such as social skill deficiencies, sensory hypo- and hypersensitivity, and repetitive behaviours. Studies on the general population reveal that people without ASD have fewer hypersexual and paraphilic dreams and behaviours than those with ASD do. However, the observations for the male participants with ASD are mostly responsible for this discrepancy. This might be because women with ASD are typically more socially adept and exhibit fewer ASD symptoms. Both sexual education and therapy techniques should take into account the unique sexual behaviours displayed by ASD patients [4].

Prior studies revealed that, although being primarily thought of as heterosexual, there were greater rates (up to 15% to 35%) of gay or bisexual orientation in the ASD community than in the non-ASD group [5,6]. Less people with ASD reported being heterosexual than healthy controls (HCs) in the current study as well, but it must be noted that HCs were all heterosexual, making them unrepresentative of the broader population. 10% of respondents to the Global Online Sexuality Survey said they were homosexual [7]. Various presumptions have been made regarding the ASD population's wider spectrum of sexual orientation. Due to limited access to romantic or sexual interactions, as well as limited experience and sociosexual interchange with their peers, gender may not be as important in choosing a partner. This could result in a limited understanding of sexual orientation or preference when coupled with a lack of sexual education [8,9]. Furthermore, there is evidence that people with ASD may be more accepting of same-sex relationships¹⁵, and it is possible that people with ASD choose their sexual preferences independently of what is socially expected or demanded, possibly in part because they are less sensitive to gender roles or social norms [10].

A greater proportion of HCs than people with ASD reported being in a relationship with obvious gender disparities. Women with ASD were more likely to be in relationships than men. Although the findings of other research exploring gender differences in relationship status are ambiguous, there is some evidence that ASD women are more frequently in a romantic and sexual relationship, even if men prefer dyadic relationships more than women do [11,12]. This might be because the ASD women were able to use more sophisticated coping mechanisms, such as emulating their non-ASD counterparts' social abilities, which resulted in less impairment in social functioning [13]. Women with ASD expressed less desire to have sexual contact with a partner and more solitary than person-oriented sexual behaviour when it came to frequency of sexual behaviour. Males with ASD showed a similar tendency, which is consistent with prior studies [14,15].

The probability of engaging in nonnormative or statistically above-average sexual behaviours, however, may also be increased by rejecting social norms, commonly seen limited social skills, and sensory hyposensitivities or hypersensitivities [16]. We discovered that ASD patients were more likely to report hypersexual behaviour than HCs, supporting this hypothesis. However, these differences were mostly driven by the male ASD patients, and no differences between the female groups were seen. Uncertainty surrounds the potential causes of the increased rates of hypersexuality in ASD men, but it is reasonable to speculate that they may be linked to repetitive behaviours or affected by sensory abnormalities. Small sample numbers have limited studies on the prevalence of hypersexual behaviours in women, and estimates of prevalence in the general population range from 4% to 40% [17].

GENDER IDENTITY AND SEXUAL ORIENTATION IN AUTISM SPECTRUM DISORDER

Clinical perceptions suggest that gender dysphoria is overrepresented in people with autism spectrum disorder. The demographics of gender-identity difficulties in autism spectrum disorder are currently poorly understood. We made a hypothesis based on the few information available that gender dysphoria would be more common in people with autism spectrum disorder than in people who are normally developing [18,19].

Comparatively to their sex-matched peers, males and females with an ASD were less likely to identify as heterosexual but more likely to identify as gay, bisexual, and asexual. Males and girls with ASD were less likely to report being heterosexual and more likely to describe being asexual in the area of sexual encounters. No group differences are found in bisexual contact [19].

TRANSGENDER

A wide range of people, including those who identify as transgender, make up this population. When examining the relationship between gender identity and autism spectrum disorder (ASD), it is clear that transgender people on the spectrum experience particular difficulties and concerns. By addressing the difficulties they face and the value of inclusive assistance, this essay seeks to shed light on the experiences of transgender people within the ASD community [20].

The interaction of gender identity and autism spectrum disorder presents particular

difficulties for transgender people within the ASD community. Their understanding and expression of gender identity may be complicated by the social and communicative challenges associated with ASD, complicating their process of self-discovery. Additionally, gender dysphoria or gender affirmation processes may be impacted by the sensory sensitivities frequently seen in ASD patients. Inability to express one's gender identity or pursue gender-affirming activities might be caused by sensory aversions to particular clothes textures, sounds, or social circumstances. The combination of these elements emphasizes even more how crucial it is for the ASD community to provide complete knowledge and support for transgender people [21].

Within the ASD community, transgender people need specialized care and consideration. First and foremost, medical practitioners should offer inclusive and affirming care that takes into account their special sensory and social needs. The general health and contentment of transgender people within the ASD community can be raised during gender-affirming procedures by adjusting healthcare services to meet their demands. Second, it's crucial to establish welcoming surroundings that promote tolerance and acceptance. The intersectional difficulties faced by transgender people on the spectrum must be addressed through the use of inclusive support networks such support groups, counseling services, and peer mentoring programs. Throughout their journey, these materials make sure they feel understood, supported, and empowered. Finally, it's critical to educate and raise awareness within both the ASD community and society at large. fostering empathy [21, 22].

With difficulties arising from both their autism and their gender identity, transgender people within the community of those with autism spectrum disorders manage a complicated intersection of identities. Giving inclusive and affirming assistance requires recognizing and addressing these issues. We can build a more accepting culture that accepts and elevates the various experiences and identities of transgender people on the autistic spectrum by making sure that everyone has access to inclusive care, encouraging supportive environments, and promoting education and awareness [12,20].

SEXUAL DISORDERS IN THIS FIELD

People with autism spectrum disorder (ASD) frequently experience sexual difficulties. According to research, people on the autism spectrum may experience unusual sexual behaviors or issues at a higher incidence than people in the general community. However, because of communication problems and ASD's own overlapping symptoms, it can be difficult to identify

and diagnose these conditions. The population of people with ASD exhibits a wide variety of sexual habits. While some people express hypersexuality, which is characterized by excessive or improper sexual actions, others may exhibit hyposexuality, which is characterized by a lack of interest in sexual engagement [19].

Additionally, strange obsessions, repetitive actions, or fixations on sexuality may be seen. In order to provide appropriate assistance and specialized interventions for people with ASD, it is essential to comprehend and address the complexity of sexual issues in these people [18].

Sexual difficulties may arise in people with autism spectrum disorder (ASD) due to a variety of circumstances. First and foremost, there are major changes in sensory processing. People with ASD frequently have unusual sensory sensitivity or aversions, which might affect how they experience sexuality. An individual's sexual preferences, responses, or interests may be impacted by sensory problems with touch, texture, or other sensory inputs. Second, the development and comprehension of appropriate sexual practices and norms may be hampered by the social and communication difficulties associated with ASD. The way people with ASD interact with and understand sexual situations can be influenced by their lack of social skills, their inability to read non-verbal signs, and their difficulties managing interpersonal relationships [23].

It is critical to their wellbeing to offer assistance and interventions to people with sexual difficulties and autism spectrum disorder (ASD). This process is greatly aided by education and awareness, which provide the ASD community with information on sexual development and appropriate conduct. To teach people with ASD about personal space, setting boundaries, consent, and healthy relationships, age-appropriate resources and materials can be used. Another beneficial intervention is social skill instruction. ASD patients' social and communication skills can be improved by targeted therapy, which has a knock-on effect on how well they comprehend and regulate sexual behavior. These interventions aid people with ASD in understanding social signs more clearly, expressing their emotions in the right ways, and developing deep connections [23,24].

Autism spectrum sexual disorders are a complicated and nuanced subject. It's critical to acknowledge the particular difficulties people with ASD have in this area and to offer the necessary assistance and interventions. We can improve the wellbeing and quality of life for people on the autism spectrum with regard to their sexual development by raising awareness, implementing focused education, encouraging the development of social skills, and providing tailored assistance [25].

SEX EDUCATION

Mackin [26] qualitative study involved telephone interviews with parents of 15 adolescents with ASD to learn how they teach their kids about sex. The majority of parents, it was discovered, taught their children about healthy sexual behaviour; nevertheless, they all agreed that other sources, such as schools and health care facilities, should also teach children about healthy sexual behaviour. Sexual relationships, anatomy and physiology of sex reactions and behaviours, consequences of sex, birth control, and personal boundaries are among the sexuality-related subjects that, in the parents' opinion, should not be covered in sex education. Pornography, fetishisms, and sex trafficking are among the subjects that should not be covered. Additionally, a lot of parents expressed concern that sex education was not tailored to the unique needs of the ASD population and suggested that it be delivered visually, interactively, specifically for ASD, technologically based, and at the student's own pace.

In a one-year randomised controlled trial, authors investigated the effectiveness of the Tackling Teenage Training (TTT) programme, which provided psychoeducation (concerning puberty, sexuality, and intimate relationships) and communication skills practise to cognitively capable adolescents (12–18 years old) with ASD. In self-rated and parent-rated knowledge exams, the young participants' knowledge, particularly their sexual knowledge, grew during the programme. Parents also stated that their children were better able to understand interpersonal boundaries in both public and private settings [27].

SUMMARY

In this paper, we highlighted the intersection of gender identity and autism spectrum disorder (ASD), as well as sexual disorders within the ASD community. Transgender individuals with ASD face unique challenges in understanding and expressing their gender identity, often complicated by the social and communication difficulties associated with ASD. Sensory sensitivities can also impact their experience of gender dysphoria or gender affirmation processes. Inclusive and affirming care, supportive environments, and education are crucial in providing adequate support for transgender individuals within the ASD community. Additionally, sexual disorders can occur at higher rates in individuals with ASD, but diagnosing and addressing these issues can be complex due to communication difficulties. Sensory processing differences and challenges in social and communication skills contribute to sexual difficulties in individuals with ASD. Providing education, social skills training, and

individualized support and counseling are important interventions for addressing sexual difficulties in individuals with ASD. By understanding and addressing these complex issues, we can foster acceptance, support, and well-being for individuals with ASD and their diverse experiences [4,25].

REFERENCES

1. Lord C., Elsabbagh M., Baird G., Veenstra-Vanderweele J.: Autism spectrum disorder. *Lancet*, 2018, 392(10146), 508-520.
2. Kodak T., Bergmann S.: Autism Spectrum Disorder: Characteristics, Associated Behaviors, and Early Intervention. *Pediatric Clinics of North America*, 2020, 67(3), 525-535.
3. Hirota T., King B.H.: Autism Spectrum Disorder: A Review. *JAMA*, 2023, 329(2), 157-168.
4. Schöttle D., Briken P., Tüscher O., Turner D.: Sexuality in autism: hypersexual and paraphilic behavior in women and men with high-functioning autism spectrum disorder. *Dialogues in Clinical Neuroscience*, 2017, 19(4), 381-393.
5. Dewinter J., Vermeiren R., Vanwesenbeeck I., van Nieuwenhuizen C.: Autism and normative sexual development: a narrative review. *Journal of Clinical Nursing*, 2013, 22(23-24), 3467–3483.
6. Hellemans H., Colson K., Verbraeken C., Vermeiren R., Deboutte D.: Sexual behavior in high-functioning male adolescents and young adults with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, 2007, 37(2), 260–269.
7. Shaeer O., Sheer K.: The Global Online Sexuality Survey: the United States of America in 2011: homosexuality among English-speaking men. *Human Andrology*, 2015, 5(3), 45–48.
8. Lai M., Lombardo MV., Pasco G.: A behavioral comparison of male and female adults with high functioning autism spectrum conditions. *PLoS One*, 2011, 6(6):e20835.
9. Mandy W., Chilvers R., Chowdhury U. et al. Sex differences in autism spectrum disorder: evidence from a large sample of children and adolescents. *Journal of Autism and Developmental Disorders*, 2012, 42(7), 1304–1313.
10. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; . 1994
11. Ousley OY., Mesibov GB. Sexual attitudes and knowledge of high-functioning

- adolescents and adults with autism. *Journal of Autism and Developmental Disorders*, 1991, 21(4), 471–481.
12. Strunz S., Schermuck C., Ballerstein S., et al. Romantic relationships and relationship satisfaction among adults with Asperger syndrome and high-functioning autism. *Journal of Clinical Psychology*, 2017, 73(1), 113–125.
13. Van Wijngaarden-Cremers PJM., van Eeten E., Groen WB., et al. Gender and age differences in the core triad of impairments in autism spectrum disorders: a systematic review and meta-analysis. *Journal of Autism and Developmental Disorders*, 2014, 44(3), 627–635.
14. Byers ES., Nichols S.: Sexual satisfaction of high-functioning adults with autism spectrum disorder. *Sexuality and Disability*, 2014, 32(3), 365–382.
15. Cottenceau H., Roux S., Blanc R., et al. Quality of life of adolescents with autism spectrum disorders: comparison to adolescents with diabetes. *European Child and Adolescent Psychiatry*. 2012, 21(5), 289–296.
16. Brown-Lavoie SM., Vieceili MA., Weiss JA. Sexual knowledge and victimization in adults with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, 2014, 44(9), 2185–2196.
17. Klein V., Rettenberger M., Briken P.: Self-reported indicators of hypersexuality and its correlates in a female online sample. *The Journal of Sexual Medicine*, 2014, 11(8), 1974–1981.
18. George R., Stokes M.A.: Gender identity and sexual orientation in autism spectrum disorder. *Autism*, 2017, 1-13.
19. George R., Stokes M.A.: Sexual Orientation in Autism Spectrum Disorder. *Autism Research*, 2017, 11(1), 133–141.
20. Warrier V., Greenberg D.M., Weir E., et al. Elevated rates of autism, other neurodevelopmental and psychiatric diagnoses, and autistic traits in transgender and gender-diverse individuals. *Nature Communications*, 2020, 11(1), 3959.
21. van der Miesen A.I.R., Cohen-Kettenis P.T., de Vries A.L.C.: Is There a Link Between Gender Dysphoria and Autism Spectrum Disorder? *Journal of the American Academy of Child and Adolescent Psychiatry*, 2018, 57(11), 884-885.
22. Strang J.F., McClellan L.S., Li S., et al. The autism spectrum among transgender youth: default mode functional connectivity. *Cerebral Cortex*, 2023, 33(11), 6633-6647.
23. Lai M.C., Lombardo M.V., Auyeung B., et al. Sex/gender differences and autism:

setting the scene for future research. *Journal of the American Academy of Child and Adolescent Psychiatry*, 2015, 54(1), 11-24.

24. Kellaher D.C.; Sexual behavior and autism spectrum disorders: an update and discussion. *Current Psychiatry Reports*, 2015, 17(4), 562.
25. Van Der Miesen A.I., Hurley H., De Vries A.L.: Gender dysphoria and autism spectrum disorder: A narrative review. *International Review of Psychiatry*, 2016, 28(1), 70-80.
26. Mackin M.L., Loew N., Gonzalez A.: Parent perceptions of sexual education & needs for their children with autism. *Journal of Pediatrics Nursery*, 2016, 31, 608-618.
27. Visser K., Greaves-Lord K., Tick N.T.: A randomized controlled trial to & examine the effects of the tackling teenage psychosexual training program for adolescents with autism spectrum disorder. *Journal of Child Psychology and Psychiatry*, 2017, 58, 840-850.

THE NATURE OF ADDICTION TO COMMON DRUGS

**Julia Wójcik, Karol Zagórski, Tomasz Dudzik, Ewa Szczęsna,
Izabella Sośniak**

Wroclaw Medical University

ABBREVIATION LIST

- OUD - Opioids Use Disorder
- BPD - Borderline Personality Disorder
- SUD - Substance use disorder

INTRODUCTION

Addiction is a primary, chronic disease involving brain reward, motivation, memory and related circuitry; it can lead to relapse, progressive development, and the potential for fatality if not treated [1].

Substance addiction (or drug addiction) is defined as a neuropsychiatric disorder characterized by a recurring desire to continue taking the drug despite harmful consequences.

Non-substance addiction (or behavioral addiction) covers for instance pathological gambling, food addiction, internet addiction, and mobile phone addiction [2]. Numerous substances can promote addiction. According to the 2020 Substance Abuse and Mental Health Services Administration (SAMHSA) and National Survey on Drug Abuse and Mental Health (NSDUH) the most common are: alcohol, nicotine, marijuana, opioids, inhalants, cocaine, heroin, stimulants (range from prescription drugs, such as Adderall or Ritalin, to illicit substances like meth), benzodiazepines and barbiturates [3].

Addiction to these substances is a very serious global problem. Data from the World Health Organisation says that about 270 million people (or about 5.5% of global population aged 15-64) had used psychoactive drugs in the previous year and about 35 million people are estimated to be affected by drug use disorders (harmful pattern of drug use or drug dependence). It is estimated that about 0.5 million death annually are attributable to drug use with about 350 000 male and 150 000 female deaths [4].

In this article, we discuss some of the most common drug addictions.

Z-DRUGS

Once considered a safe alternative to benzodiazepines, the Z-drugs - zaleplon, zolpidem and zopiclone - have been linked in recent years to cases of abuse, dependence and the occurrence of withdrawal syndrome [5].

Despite the fact that Z-drugs have favorable pharmacokinetics compared to benzodiazepines, which has been associated with high hopes for their safety [6], cases of rebound insomnia [7, 8], and symptoms of withdrawal syndrome after discontinuation of these drugs have been reported, especially among patients with alcohol dependence and a history of psychoactive substance abuse [5].

It is worth defining and distinguishing between the symptoms of withdrawal syndrome, rebound insomnia and recurrence of insomnia after systematic drug intake. Rebound insomnia is a significant exacerbation of sleep problems relative to the state before taking the drug, occurring after withdrawal; it occurs early, the symptoms are transient. Recurrence of insomnia, on the other hand, is observed slowly and gradually over 2-3 weeks after discontinuation of the drug. In withdrawal syndrome, there is an association of physical withdrawal symptoms with psychological symptoms of addiction [9]. Withdrawal syndrome symptoms occur especially after abrupt termination of long-term Z-drug use and may be expressed as insomnia, euphoric state, irritability, anxiety, tremor, speech problems, abdominal pain, hypertension, tonic-clonic seizures, among others [10–12].

Certain routes of administration of the drug, including injection or use of high doses, may increase the risk of Z-drug abuse. Zolpidem should be used with caution in patients with a history of substance abuse. Zolpidem addiction should be considered when a patient is considered to have an increase in dose intake, a change in psychological status, or manipulative behaviour such as using lies to obtain an increased supply of the drug [9].

Within the Z-drugs, some differences can be noted when considering abuse, development of dependence and abstinence syndrome. Compared to zaleplon, abuse appears to be less frequent with zopiclone and zolpidem; of the two however, zopiclone appears to be less frequently associated with abuse and the development of an abstinence syndrome. Zolpidem, on the other hand, appears to be the drug most likely to cause dependence among Z-drugs; reports of zolpidem overdose are also the most common. Among the Z-drugs,

zolpidem is most often taken intravenously; in very high doses; along with concomitant intake of other substances [5].

BENZODIAZEPINES

The mechanism of action involves influencing the GABA-ergic system. Medications bind to the GABA-A receptor, sensitizing it to the effects of gamma-aminobutyric acid (GABA), which is considered the most important inhibitory amino acid in the central nervous system [13].

Benzodiazepines are classified based on their half-life. Those with a short duration of action include brotizolam, lorazepam, and tiazolam. Among the drugs with a medium duration of action, alprazolam, bromazepam, clonazepam, lorazepam, lormetazepam, nitrazepam, oxazepam, and temazepam are distinguished. Benzodiazepines with proven long-lasting effects include chlordiazepoxide, diazepam, flurazepam, ketazolam, clobazam, clorazepate, metachlorophenylpiperazine, and oxazolam [14]. It is worth mentioning that midazolam, triazolam, flunitrazepam, and diazepam have been studied in animal models, demonstrating dose-dependent effects [15–18], indicating a greater tendency to cause addiction.

Additionally, their impact on cognitive abilities has been demonstrated without inhibitory effects on the respiratory center, distinguishing them from opioids [19].

Referring to a study conducted in the USA in 2015/2016 with 86,186 participants, it was observed that as many as 12.6% of the subjects reported using drugs from this group in the past year, with 10.4% obtaining them through a legal prescription and 2.2% taking them without consultation. Furthermore, the study showed that the use of benzodiazepines among adult patients in the United States is increasing compared to previous years' research [20]. Conversely, a similar study conducted in Brazil (n=5037) in 2020 showed that only 3.6% of the participants used benzodiazepines. It was also determined that only 7.8% of individuals with a psychiatric diagnosis were treated with this group of drugs [21].

Addiction to benzodiazepines is most commonly observed in individuals receiving treatment for sleep disorders as well as various types of anxiety disorders [22]. Their use in these cases stems from the therapeutic effects of muscle relaxation, anxiolysis, and sedation. However, studies on diazepam have shown a higher potential for dependence in individuals with social disorders or during an ongoing anxiety disorder. The causes of addiction are often attributed to self-dosing, dose escalation by the physician, or experimental tendencies [23, 24].

Symptoms of benzodiazepine addiction include increased aggression, and their use has also been associated with a tendency towards criminal behavior. It has been demonstrated that they lead to aggressive behaviors more frequently when combined with alcohol [25, 26]. They also contribute to dementia and other cognitive problems [27]. Benzodiazepine abuse is also associated with increased mortality [28]. There is also a positive correlation between the frequency of falls and the use of this group of drugs [29].

Treating addiction is challenging. To prevent seizures and acute withdrawal symptoms, benzodiazepine withdrawal should be carried out over a period of 4-6 weeks, sometimes even 8 weeks (in the case of diazepam >30 mg daily). It is advised to reduce the dose by 50% each week [30]. It has also been established that withdrawal can be more difficult when the patient also has other conditions such as estrogen deficiency with vasomotor symptoms or anxiety disorders [22].

OPIOIDS

Opioids can occur in the form of natural opiates as well as semi-synthetic or synthetic drugs with similar effects [31]. Natural opiates include morphine, codeine, pseudomorphine and oripavine. Semi-synthetic opioids include oxycodone, hydromorphone, oxymorphone and heroin. Synthetic opioids include tramadol, fentanyl, buprenorphine, methadone, tapentadol, meperidine, and propoxyphene. They may act as agonists, partial agonists or antagonists through receptors: μ (mu), δ (delta), and κ (kappa). Opioid agonists bind to specific G protein-coupled receptors and modulate intracellular calcium ion influx. They close calcium channels at presynaptic nerve terminals, inhibiting the release of neurotransmitters (such as glutamate), and also inhibit postsynaptic neurons by opening potassium channels [32].

Opioids are the most potent available analgesics in clinical practice and are commonly used in pain treatment, especially in patients with cancer and chronic pain [33]. Opioid Use Disorder (OUD) is a long-lasting and recurrent brain condition where individuals struggle to control their opioid use. It leads to cognitive impairments, mood disturbances, altered pain perception, and changes in autonomic function. While OUD is a treatable condition with periods of recovery and relapse, it can result in severe health consequences and even death if left untreated [34, 35].

Common side effects of opioids include problems with the digestive system (constipation, nausea, and vomiting), and central nervous system leading to symptoms like

dizziness, confusion, sedation, feelings of euphoria or dysphoria, and restlessness. Opioids may cause urinary retention, dry mouth, slow heart rate, weight gain, excessive sweating, flushing, itching, hives, and a decrease in the cough reflex. Overdose of opioids can result in several effects such as slowed breathing (respiratory depression), increased pain sensitivity (hyperalgesia), and hormonal disorders including reduced sexual drive, hypogonadism, and osteoporosis. The risk of respiratory depression is higher when opioids are used in conjunction with sedatives like benzodiazepines or alcohol. Additionally, individuals with underlying pulmonary conditions such as severe chronic obstructive pulmonary disease or central and obstructive sleep apnea are also at an increased risk of experiencing respiratory depression when using opioids. [36].

Many people initially start using opioids seeking euphoria or relief from pain. However, with continued use, tolerance develops quickly as the opioid receptors become less responsive, leading to a need for higher doses to achieve the same effects [37].

This tolerance can be observed as reduced pain relief even at a stable dose, shorter duration of pain relief, less sedative effects, or less euphoria [38].

Uncontrolled intake and intense cravings are key symptoms of opioid addiction, along with the development of tolerance and experiencing withdrawal symptoms upon cessation [37].

Opioid withdrawal symptoms can start within 4 hours of the last dose, reach their peak in 48 to 72 hours, and typically improve within a week. Withdrawal symptoms consist of various manifestations, including feelings of restlessness, frequent sneezing, yawning, lacrimation, rhinorrhea, goosebumps (piloerection), profuse sweating, difficulty sleeping, tremors, muscle aches (particularly in the back and legs), nausea, vomiting, diarrhea, abdominal pain, fever, high blood pressure, rapid heart rate, and increased breathing rate [38].

The studies show that women commonly experience higher acute and chronic pain levels than men. When comparing women and men with chronic pain, it becomes evident that women receive the majority of prescription opioids. Unfortunately, the use of these prescribed medications has become the primary route leading to misuse and addiction among women [39].

Borderline Personality Disorder (BPD) has been linked to opioid abuse in several studies. A 2014 10-year follow-up study of 263 BPD patients revealed a higher likelihood of prolonged prescription opioid use compared to other personality disorders [40].

Additionally, a 2020 US study with 68 individuals in a SUD (Substance use disorder) treatment facility found that individuals with BPD pathology experienced more negative outcomes related to opioid use [41].

There are medications that have been proven to be effective in treating OUD: methadone (a full opioid agonist), buprenorphine (a partial agonist), and naltrexone (an opioid antagonist) [42]. Methadone is administered by the oral route, which produces a much weaker euphoric effect and effectively inhibits withdrawal states and has the strongest evidence for effectiveness. Buprenorphine taken orally attenuates craving for the drug and is also used sublingually with Naloxone. Naloxone and Naltrexone are both opioid antagonists. Long-acting injectable naltrexone works by blocking opioid receptors, reducing cravings, and lowering the risk of opioid overdose. Lofexidine is also used to inhibit withdrawal syndrome or together with naltrexone to induce rapid detoxification. [37, 42, 43]

CONCLUSIONS

Addiction, whether substance or behavioral, is a significant global concern due to its chronic nature, involving brain circuitry related to reward, motivation, and memory. It can lead to relapse, progressive deterioration, and even potential fatality if left untreated. The prevalence of substance addiction contributes to a substantial number of individuals affected by drug use disorders and a considerable number of deaths worldwide.

Z-drugs were initially considered safer alternatives to benzodiazepines but have been associated with cases of abuse, dependence, and withdrawal syndrome. Patients may develop rebound insomnia, withdrawal symptoms, and recurrence of insomnia after discontinuation, particularly those with alcohol dependence or substance abuse history.

Opioid addiction is a long-lasting and intricate illness characterized by periods of relapse and remission. If left untreated, opioid use disorder (OUD) is linked to considerable disease and death rates. Furthermore, OUD is accompanied by numerous adverse effects. As part of the treatment approach, Buprenorphine, Methadone and Naloxone are commonly employed.

Benzodiazepines, particularly in individuals with sleep disorders and various anxiety conditions, possess addictive potential and can contribute to aggression, increased risk of criminal behaviors, as well as cognitive impairment, dementia, heightened mortality, and fall frequency. Withdrawal from benzodiazepines can be challenging, necessitating a gradual dose reduction over several weeks. Caution should be exercised when prescribing benzodiazepines to older adults and those with cognitive impairments, with physicians considering alternative approaches for managing anxiety and insomnia.

REFERENCES

1. Smith D.E.: Editor's note: The process addictions and the New ASAM definition of addiction. *Journal of Psychoactive Drugs*, 2012, 44, 1–4.
2. Zou Z., Wang H., Uquillas O., Wang X.: Definition of substance and non-substance addiction. *Advances in Experimental Medicine and Biology*, 2017, 1010, 21–41.
3. Top 10 Most Common Addictions In The US - Addiction Center. <https://www.addictioncenter.com/addiction/10-most-common-addictions/>. Accessed 11 Jul 2023.
4. Drugs (psychoactive). https://www.who.int/health-topics/drugs-psychoactive#tab=tab_1 Accessed 11 Jul 2023.
5. Schifano F., Chiappini S., Corkery J.M., Guirguis A.: An Insight into Z-Drug Abuse and Dependence: An Examination of Reports to the European Medicines Agency Database of Suspected Adverse Drug Reactions. *International Journal of Neuropsychopharmacology*, 2019, Oxford University Press. 22, 270–277.
6. Gunja N.: The Clinical and Forensic Toxicology of Z-drugs. 2013, 9(2), 155–162.
7. Lader M.: Rebound insomnia and newer hypnotics. *Psychopharmacology*, 1992, 108, 248–255.
8. Ebert B., Wafford K.A., Deacon S.: Treating insomnia: Current and investigational pharmacological approaches. *Pharmacology and Therapeutics*, 2006, 112, 612–629.
9. Victorri-Vigneau C., Dailly E., Veyrac G., Jolliet P.: Evidence of zolpidem abuse and dependence: results of the French Centre for Evaluation and Information on Pharmacodependence (CEIP) network survey. *British Journal of Clinical Pharmacology*, 2007, 64, 198–209.
10. Flynn A, Cox D. Dependence on zopiclone. *Addiction*, 2006, 101, 898–900.
11. Aranko K., Henriksson M., Hublin C., Seppalainen A.M.: Misuse of zopiclone and convulsions during withdrawal. *Pharmacopsychiatry*, 1991, 24, 138–140.
12. Wong C.P., Chiu P.K.C., Chu L.W.: Zopiclone withdrawal: An unusual cause of delirium in the elderly. *Age and Ageing*, 2005, 34, 526–527.
13. Kostowski W., Herman Z.S.: *Farmakologia. Podstawy farmakoterapii. Podręcznik dla studentów medycyny i lekarzy. Tom 1 i 2.* 3rd ed. 2010, Wyd. Lekarskie PZWL, Warszawa.
14. Bilikiewicz A., Pużyński S., Wciórka J. R.J.: *Psychiatria. T. 3.* Urban & Parner, Wrocław, 2003.
15. Bai X., France C.P., Gerak L.R.: The discriminative stimulus effects of midazolam are

- resistant to modulation by morphine, amphetamine, dizocilpine and γ -butyrolactone in rhesus monkeys. *Psychopharmacology (Berl)*, 2011, 217, 495–504.
16. Fischer B.D., Rowlett J.K.: Anticonflict and Reinforcing Effects of Triazolam Pregnanolone Combinations in Rhesus Monkeys. *The Journal Of Pharmacology And Experimental Therapeutics*, 2011, 337, 805–811.
 17. Gomez T.H., Roache J.D., Meisch R.A.: Relative reinforcing effects of different benzodiazepine doses for rhesus monkeys. *Drug and Alcohol Dependence*, 2002, 68, 275–283.
 18. Gerak L.R., Woolverton W.L., Nader M.A. et al.: Behavioral effects of flunitrazepam: reinforcing and discriminative stimulus effects in rhesus monkeys and prevention of withdrawal signs in pentobarbital-dependent rats. *Drug and Alcohol Dependence*, 2001, 63, 39–49.
 19. Mak K.H., Wang Y.T., Cheong T.H., Poh S.C.: The effect of oral midazolam and diazepam on respiration in normal subjects. *The European Respiratory Journal*, 1993, 6, 42–47.
 20. Maust D.T., Lin L.A., Blow F.C.: Benzodiazepine Use and Misuse Among Adults in the United States. *Psychiatric Services*, 2019, 1, 70(2), 97-106.
 21. Campanha A.M., Ravagnani B., Milhoranca I.A., et al.: Benzodiazepine use in Sao Paulo, *Clinics*, 2020, 75, e1610.
 22. Khong E., Sim M.G., Hulse G.: Benzodiazepine dependence. *Australian Family Physician*, 2004, 33, 923–926.
 23. Kelly T.H., Delzer T.A., Martin C.A. et al.: Performance and subjective effects of diazepam and d-amphetamine in high and low sensation seekers. *Behavioural Pharmacology*, 2009, 20, 505–517.
 24. Helmus T.C., Tancer M., Johanson C.E.: Reinforcing effects of diazepam under anxiogenic conditions in individuals with social anxiety. *Experimental and Clinical Psychopharmacology*, 2005, 13, 348–356.
 25. Miczek K.A., Weerts E.M., DeBold J.F.: Alcohol, benzodiazepine-GABA(A) receptor complex and aggression: Ethological analysis of individual differences in rodents and primates. *Journal of Studies on Alcohol*, 1993, 54, 170–179.
 26. Jones K.A., Nielsen S., Bruno R. et al. Benzodiazepines their role in aggression and why GPs should prescribe with caution. *Australian Family Physician*, 2011, 40, 862–865.

27. Melinda J., Barker, Kenneth M. et al. Cognitive Effects of Long-Term Benzodiazepine Use A Meta-Analysis. *CNS Drugs*, 2004, 18, 37–48.
28. Zador D., Sunjic S.: Deaths in methadone maintenance treatment in New South Wales, Australia 1990-1995. *Addiction*, 2000, 95, 77–84.
29. Richardson K., Bennett K., Kenny R.A.: Polypharmacy including falls risk-increasing medications and subsequent falls in community-dwelling middle-aged and older adults. *Age and Ageing*, 2015, 44, 90–96.
30. Soyka M.: Treatment of Benzodiazepine Dependence. *New England Journal of Medicine*, 2017, 376, 1147–1157.
31. Pasternak E., Paśnik K., Plewka N.: Uzależnienie od opioidów-etiotogeneza, rozpoznawanie i leczenie oraz ważna rola pielęgniarstwa. *Pielęgniarstwo i Zdrowie Publiczne*, 2015, 5, 209–214.
32. Zaporowska-Stachowiak I., Oduah M.T.A., Celichowska M., et al.: Opioids in clinical practice. *Palliative Medicine Practice*, 2019, 13, 229–236.
33. Mercadante S., Porzio G., Gebbia V.: New opioids. *Journal of Clinical Oncology*, 2014, American Society of Clinical Oncology. 32, 1671–1676.
34. Holter K.M., Pierce B.E., Gould R.W.: Metabotropic glutamate receptor function and regulation of sleep-wake cycles. *International Review of Neurobiology*, 2023, 168, 93–175.
35. Jessica L. Taylor M., Jeffrey H. et al. : Opioid Use Disorder. *Annals of Internal Medicine*, 2022, 175, ITC1–16.
36. Nafziger A.N., Barkin R.L.: Opioid Therapy in Acute and Chronic Pain. *Journal of Clinical Pharmacology*, 2018, 58, 1111–1122.
37. Wang S.C., Chen Y.C., Lee C.H., Cheng C.M.: Opioid addiction, genetic susceptibility, and medical treatments: A review. *International Journal of Molecular Sciences*, 2019, 2, 20(17), 4294.
38. O'Malley G.F., O'Malley R.: Opioid Toxicity and Withdrawal - Special Subjects - MSD Manual Professional Edition. <https://www.msdmanuals.com/professional/special-subjects/illicit-drugs-and-intoxicants/opioid-toxicity-and-withdrawal> Accessed 12 Jul 2023.
39. Goetz T.G., Becker J.B. and Mazure C.M.: Women, opioid use and addiction. *FASEB Journal*, 2021, 35, 1–12.
40. Frankenburg F.R., Fitzmaurice G.M., Zamarini M.C.: The Use of Prescription Opioid

Medication by Patients with Borderline Personality Disorder and Axis II Comparison Subjects: A 10-year Follow-up Study NIH Public Access. *J Clin Psychiatry*, 2014, 75, 357–361.

41. Scamaldo K.M., Tull M.T., Gratz K.L.: Motives for opioid use explain the relation between borderline personality disorder pathology and opioid use problems. *Psychiatry Research*, 2021, Elsevier B.V. 296, 113609.
42. Bell J., Strang J.: Medication Treatment of Opioid Use Disorder. *Biological Psychiatry*, 2020, Elsevier Inc. 87, 82–88.
43. Przewłocki R.: Mechanizmy uzależnienia od analgetyków opioidowych. *Medycyna Paliatywna w Praktyce*, 2017, 11, 55–60.

CONTROVERSIES OVER PANDAS

Dominika Ziółkowska , Renata Fedyk, Kamila Florek, Jakub Grzonka, Wojciech Węgrzyn, Michał Szyszka, Paulina Tomecka

Student Scientific Circle at the Department of Psychiatry, Faculty of Medicine, Medical University of Piastów Śląskich in Wrocław

ABBREVIATION LIST

- PANDAS- Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections.
- OCD- Obsessive-Compulsive disorder
- PANS- Pediatric Acute Onset Neuropsychiatric Syndrome
- CBT-Cognitive-behavioral therapy
- RCT- randomized controlled trial
- GAS infection- group A streptococcal infection
- NSAIDs-nonsteroidal anti-inflammatory drugs
- COVID-19-coronavirus disease 2019
- SSRI- selective serotonin reuptake inhibitor

INTRODUCTION

PANDAS, which stands for Pediatric Autoimmune Disorder Associated with Streptococcal Infections, refers to a condition characterized by a sudden and significant onset of OCD, tics, or restricted eating following an infection caused by group A Streptococcus (GAS) [1]. GAS are the most common cause of bacterial throat infections in school-aged children [2] and recent studies have shown that these bacteria are also involved in the development of Tourette's syndrome or autism [3]. Reactions to streptococcal infections are rare after the age of 12, but scientists acknowledge that PANDAS can occur, albeit rarely, among teenagers [4].

The concept of this disease emerged from the hypothesis that its pathogenesis may be similar to that of Sydenham's chorea [5]. For the first time in 1998, Swedo et al. from the

National Institute of Mental Health in Maryland reported on 50 children with OCD and/or tic disorders that were associated with infections caused by GABHS and worsened from episode to episode [6,7]. Additionally, they exhibited various other symptoms, including changes in personality, separation anxiety, emotional instability, deterioration in handwriting, and physical manifestations such as insomnia, frequent urination, and bedwetting [8].

The majority of knowledge about PANDAS has been acquired through the study of patients who already have a known tic disorder or longstanding OCD in research settings and referral centers [9]. It is believed that the symptoms of OCD and tics in PANDAS result from disruptions in the corticothalamocortical circuits, which are thought to be caused by autoimmune or inflammatory disturbances [10].

Guidelines for diagnosing PANDAS were updated in 2017 to include the following criteria:

1. Presence of OCD and/or tics, mainly multiple ones, complex or not observable in other disorders.
2. Specific period of childhood and age (symptoms of PANDAS are more common between the age of 3 years old and period of puberty).
3. Acute onset and episodic changes in behavior.
4. Association with infection of Streptococci group A .
5. *Coexisting neurological impairments* [11].
6. Due to the variability of symptoms and their evolution, the diagnosis of PANDAS remains controversial [12]. A revision of the syndrome's criteria has defined a broader diagnostic entity known as PANS (Pediatric Acute-Onset Neuropsychiatric Syndrome), which still emphasizes the abrupt onset of OCD but removes tics as a key criterion while adding food intake restriction as a new criterion. Unlike PANDAS, the PANS syndrome does not require a prior streptococcal infection [13].

The aim of this study is to review the available literature and summarize the controversies related to autoimmune neuropsychiatric disorders in children associated with streptococcal infections (PANDAS) and Pediatric Acute Onset Neuropsychiatric Syndrome (PANS).

PREVALENCE

PANDAS/PANS estimated prevalence in the U.S. is 1 in 200 children, which is in contrast with another source stating that this disease occurs in 1:10 000 children [14,15].

Another article revealed that 1-2% of children with OCD meet the criteria of PANDAS in that group, whereas 81% of 700 family self-report data was caused by *Streptococcus* spp. and the rest was reported due to other pathogens. According to another report, 25% of kids diagnosed with OCD and tics may be assigned as PANDAS children. Majority of infected children were 4 to 9 years old (69%), and their primary symptoms were mainly associated with both- OCD and tics (49%) [14,15].

The true incidence of PANDAS/PANS is not known as this disease might be underdiagnosed, misdiagnosed or undiagnosed. There are estimations that 500 000 cases are undiagnosed per year [15,16].

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of PANDAS syndrome includes OCD, tics and Sydenham's chorea.

Obsessive Compulsive Disorder

PANDAS syndrome and obsessive-compulsive disorder both can occur in teenage years and manifest themselves in the form of neuropsychiatric symptoms . A diagnostic problem in distinguishing PANDAS syndrome from OCD might be a possible autoimmune subtype of OCD in pediatric patients without a diagnosis of acute onset pediatric neuropsychiatric syndrome. In OCD, the increase in psychological stress leads to the proliferation of immature monocytes that enter the brain and cause the release of pro-inflammatory cytokines [17]. These cytokines promote the neuroinflammatory response, thereby affecting brain function and the metabolism of various neurotransmitters. In PANDAS syndrome, the phenomenon of molecular mimicry, i.e., the production of autoantibodies after a streptococcal infection which targets the cells of the basal ganglia, is thought to be responsible for the symptoms [18].

Tics

Tics, particularly Tourette syndrome, are likely caused by disruptions in the corticostriatal thalamocortical circuit, resulting in the motor and limbic systems being disinhibited [19,20,21]. It is important to note that there is no evidence linking autoimmune neuropsychiatric disorders in children to the development of Tourette syndrome. Clinically, what sets PANDAS syndrome apart from Tourette syndrome is the presence of frequent, severe, and diverse motor and vocal tics in PANDAS syndrome, in contrast to the isolated, intermittent simple motor or vocal tics typically observed in Tourette syndrome. Additionally, Tourette

syndrome often has a milder course and more gradual onset [9,22].

Sydenham's chorea

In the pathogenesis of Sydenham's chorea, an important factor is the phenomenon of molecular mimicry. This occurs when antibodies produced against a specific part of beta-hemolytic streptococcus cross-react with other substances, such as lysoganglioside on the surface of nerve cells and the intracellular protein tubulin [23-25]. The basal ganglia may also be affected, similar to PANDAS syndrome. Sydenham's chorea clinically presents as a movement disorder characterized by chorea, emotional lability, and hypotonia. Both PANDAS syndrome and Sydenham's chorea have symptoms such as separation anxiety, hyperactivity, and random movements. However, one distinguishing feature is that Sydenham's chorea typically involves rapid, irregular, and non-stereotyped jerks that persist during wakefulness but improve during sleep [26-28].

When attempting to differentiate children with PANDAS syndrome from patients with similar neuropsychiatric syndromes based on clinical symptoms, several characteristics of PANDAS syndrome emerge. These include a rapid onset of symptoms, intermittent remissions of neuropsychiatric symptoms, a clinical course characterized by significant improvement, and remission of neuropsychiatric symptoms during antibiotic therapy [29].

TREATMENT

Standard medications as well as cognitive behavioral therapy proved to be beneficial for children with PANDAS symptoms. Antibiotics are recommended when there are positive results of rapid strep test or strep throat culture [30].

There was a study, which confirmed response to appropriate antibiotic therapy among PANDAS symptomatic children. They were treated for 10 days with penicillin, amoxicillin or amoxicillin/clavulanate potassium and cephalosporin. The mean time for the resolution of symptoms was 14 days which is thought to be a typical time for antibiotic response in PANDAS/PANS [31]. Beta-lactams are probably effective in PANDAS treatment and the same was noted for erythromycin, azithromycin and clindamycin [15]. Prophylaxis of PANDAS with antibiotics was recommended referring to its success in recurrences of rheumatic fever and the similarities between their pathomechanism [3]. However, the studies about prophylaxis of PANDAS with antibiotics differ and earlier data claimed

penicillin ineffectiveness, in contrast to the latest double-blind randomized trial assessing penicillin and azithromycin as effective in decreasing streptococcus infections and neuropsychiatric exacerbations [32]. Further trials about preventive use of antibiotics for an extended period in children with recurrent GAS infections, immunotherapy and frequent neuropsychiatric exacerbations are ongoing [30].

CBT is a treatment for pediatric obsessive-compulsive disorder as well as a presentation of PANDAS/PANS. There was a study conducted in which after 3-week intensive CBT 6 out of 7 participants were classified as treatment responders and in 3-month follow-up 3 of those 6 remained responders. There was no significant reduction in anxiety and depression symptoms [33].

The priority of treatment is to reduce suffering and eliminate symptoms causing the greatest disruption. The next rule is frequent evaluation of the effectiveness of the treatment, and the occurrence of any side effects should be closely monitored [34].

Among treatment methods there are also psychotropic drugs including SSRI. The basic principle of using SSRIs in children with PANDAS is to start therapy with a very low dose of the drug and slowly increase it until maximum improvement in the patient's condition is achieved. It is necessary to vigilantly observe the patient's reaction to treatment because there are reports that this group is exceptionally susceptible to side effects. If the symptoms of the disease worsen, the SSRI dose should be reduced immediately. However, SSRIs and other medications should not be abruptly discontinued, as this can also cause difficulties [4].

Analysis of the treatments given to a cohort of Swedish patients with suspected PANS and PANDAS (24 participants fulfilled criteria and 29 not) shows that the most common treatments given were antibiotics (88%), nonsteroidal anti-inflammatory drugs (67%), CBT (53%), and SSRI(42%). Antibiotics and intravenous immunoglobulin (IVIG) were rated as the most successful [35].

However, some research shows that immunomodulatory treatments such as non-steroidal antiinflammatory drugs, intravenous immune globulin (IVIG), corticosteroids, therapeutic plasma exchange (TPE), and rituximab, have unproven efficacy (see controversies below) [36].

COVID-19 AND PANDAS

Research shows that the COVID-19 pandemic has had a significant impact on OCD symptoms in both adults and children. Children with OCD have experienced worsened

depressive and anxiety symptoms. Interestingly, children who already have depressive symptoms or anxiety disorders are more susceptible to severe symptoms resulting from COVID-19 infection. It is also worth noting that COVID-19 infection in children has not only worsened existing symptoms but also led to the emergence of new neuropsychiatric disorders [1,37].

The relationship between COVID-19 infection and its impact on PANDAS/PANS is not yet fully understood. While there have been anecdotal reports of some children experiencing new or intensified PANDAS/PANS symptoms after COVID-19 infection, further research is needed to determine the extent and mechanisms of this association. There is a possible mechanism which explains this. COVID-19 patients have been observed to have greater levels of pro-inflammatory cytokines, such as IL-6, IL-2, IL-17 and TNF, which may cause neuropsychiatric symptoms. They can cause neuroinflammatory reactions or affect blood-brain integrity. This leads to migration of peripheral immune cells into CNS and activation of microglia and disruption of neurotransmission. The example of this disruption is change in basal ganglia GABAergic transmission. Also hypodopaminergic state of the basal ganglia can be caused by interferon alpha, which is believed to be a trigger for psychiatric disorders. This is very significant for PANS/PANDAS, considering that basal functioning is already disrupted [10].

A study was conducted, in which caregivers of children with PANS/PANDAS were asked to assess their perspective on COVID-19 vaccinations and the overall impact of the pandemic on children with this condition. A majority of caregivers in the study reported high levels of relationship dissatisfaction, burnout, and mild symptoms of stress and depression. This finding is comparable to pre-pandemic levels reported by caregivers of children with PANS/PANDAS [1,38].

It suggests that caregivers of children with PANS/PANDAS experienced a high level of burnout both before and during the pandemic, and therefore, this should continue to be an area of research and appropriate intervention. High levels of caregiver burden and stress are associated with worse outcomes for children with neurologic and medical disorders, highlighting the importance of addressing these dynamics. It is worth noting that the study found that children with PANDAS/PANS experienced worsened or new symptoms at the time of COVID-19 infection, but none of the symptoms proved to be fatal. Future research should thoroughly investigate the relationship between COVID-19 infection and the exacerbation of neuropsychiatric symptoms, as this line of inquiry can provide valuable information about the etiology of PANS/PANDAS and post-infectious neuropsychiatric sequelae [1].

CONTROVERSIES

Although working criteria for the diagnosis of PANDAS were proposed, it remains controversial if it is sufficiently different from obsessive-compulsive disorder, tic disorder and other neuropsychiatric disorders [39]. Furthermore, an association between PANDAS and GAS infection has been assessed in multiple studies with varying conclusions.

In one study of 109 prepubertal children with tics, OCD, or both, a group of 48 children who met the criteria for PANDAS differed significantly in several variables, which included the dramatic onset of symptoms, a clinical course marked by definite remissions, and remission of neuropsychiatric symptoms during antibiotic therapy [40]. In another observational study, 12 children with PANDAS were identified over a three-year period. All had positive throat cultures at the time of onset of neuropsychiatric symptoms and improvement of neuropsychiatric symptoms with antibiotic therapy. Moreover, in children who developed recurrent symptoms, each recurrence was associated with a new episode of culture-proven GAS tonsillopharyngitis and amelioration of symptoms with antibiotic therapy [41].

The two prospective multicenter studies' objective was to identify prospectively whether a streptococcal infection preceded the exacerbation of OCD or tic symptoms. Children meeting PANDAS criteria and matched controls with idiopathic or familial chronic OCD or a tic disorder received serial monthly and illness-based throat cultures and quarterly and illness-based antibody titers for 2 years. These studies found similar rates of infections and tic or OCD exacerbations in both groups [42,43]. One prospective longitudinal study also did not confirm that worsening of OCD or tic disorder symptoms was associated with antecedent newly diagnosed GAS infections[44]. In turn, another cohort study found higher rates of OCD in a group with a positive streptococcal test compared with control, however, it is not known whether the effect was attributed to PANDAS [45].

Molecular mimicry, or the development of autoantibodies after GAS infections that target cells of the basal ganglia, is the suggested pathophysiology of PANDAS, which is similar to Sydenham chorea and acute rheumatic fever. Numerous research has shown that individuals with PANDAS had higher levels of antineuronal antibodies than patients with OCD/tic disorders without evidence of GAS infection and patients with GAS infection without OCD/tic disorder [46-47]. However, other research has not been able to separate PANDAS or Tourette syndrome patients from control patients based on autoantibody patterns. Methodological variations may be responsible for the contradictory results. For instance, the amounts of antineuronal antibodies in the control sera utilized in various investigations may vary [48,49].

Treatment with psychiatric medications and behavioral interventions are supported by rigorous randomized controlled trials, however, this is not the case with immunomodulatory treatment approaches [36]. For example, in a longitudinal double-blind placebo-controlled trial of 29 children with PANDAS, plasma exchange, IVIG or sham IVIG proved better than placebo in reducing OCD and tics symptoms at 1-month follow-up, but the study had a risk of bias as randomization procedure was inadequately described [3]. In a systematic review Sigra et al. reported that 11 out of 12 treatment studies with published outcome data had moderate to high risk bias including selection bias, performance bias, detection bias, attrition, reporting bias, and other. Only one study, which had a low overall risk of bias was RCT comparing IVIG with placebo. No difference between IVIG and placebo groups in OCD severity scores or proportion of responders was shown [50]. There were reports that oral glucocorticoids and NSAIDs shortened the duration of flares in children diagnosed with PANS or PANDAS, however, data come from observational study not RCT [51,52].

CONCLUSIONS

PANDAS is a serious disorder, which contributes to many problems on different levels. Higher awareness among doctors according to PANDAS is needed to assess its proper prevalence and implement appropriate therapy in those patients. PANDAS have similar symptoms to OCD, Tourette's syndrome and Sydenham's chorea, thus, careful differential diagnosis is crucial.

Currently, many diseases are known, whose onset is associated with an immune response against surface proteins of streptococci. Knowing the pathophysiological mechanism and understanding the disease from the cellular basis enables us to institute appropriate treatment, however, the autoimmune etiology hypothesis of PANDAS is still unproven, as well as the use of NSAIDs, IVIG, corticosteroids, therapeutic plasma exchange (TPE), and rituximab. Studies do not even provide definite answers whether PANDAS is a documentable entity or there is a clear association between GAS and PANDAS development. Data from well-controlled prospective studies are necessary.

REFERENCES

1. O'Dor S.L., Zagaroli J., Belisle R. et al.: The COVID-19 pandemic and children with PANS/PANDAS: an evaluation of symptom severity, telehealth, and vaccination hesitancy. *Child Psychiatry & Human Development*, 2022, 5, 1-9.

2. Biała M., Wzrost liczby inwazyjnych zakażeń paciorkowcem z grupy A wśród dzieci w Europie https://infekcje.mp.pl/przeglad_badan/317431,wzrost-liczby-inwazyjnych-zakazen-paciorkowcem-z-grupy-a-wsrod-dzieci-w-europie. Accessed 11 Jul 2023.
3. Moretti G., Pasquini M., Mandarelli G., et al. What every psychiatrist should know about PANDAS: a review. *Clinical Practice and Epidemiology in Mental Health*, 2008, 4, 1-9.
4. <https://www.nimh.nih.gov/health/publications/pandas> Accessed 11 Jul 2023.
5. Swedo S. E.: Sydenham's chorea: a model for childhood autoimmune neuropsychiatric disorders. *Jama*, 1994, 272(22), 1788-1791.
6. Swedo S. E., Leonard H. L., Garvey M. et. al.: Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. *American Journal of Psychiatry*, 1998, 155(2), 264-271.
7. Windfuhr J. P.: Tonsillectomy remains a questionable option for pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). *GMS Current Topics in Otorhinolaryngology, Head and Neck Surgery*, 2016, 15, Doc07.
8. Rea I., Guido C. A., Spalice A. Clinical features in patients with PANDAS/PANS and therapeutic approaches: a retrospective study. *Frontiers in Neurology*, 2021, 28, 1726.
9. Pichichero M.: PANDAS: Pediatric autoimmune neuropsychiatric disorder associated with group A streptococci https://www-1uptodate-1com-12h8mosl80d0f.han.bg.umw.edu.pl/contents/pandas-pediatric-autoimmune-neuropsychiatric-disorder-associated-with-group-a-streptococci?search=pandas&source=search_result&selectedTitle=1~10&usage_type=default&display_rank=1. Accessed 11 Jul 2023.
10. Pallanti S., Di Ponzio M. PANDAS/PANS in the COVID-19 Age: Autoimmunity and Epstein–Barr Virus Reactivation as Trigger Agents? *Children*, 2023, 10(4), 648.
11. Baj J., Sitarz E., Forma A. et al. Alterations in the nervous system and gut microbiota after β -hemolytic streptococcus group A infection—characteristics and diagnostic criteria of PANDAS recognition. *International Journal of Molecular Sciences*, 2020, 21(4), 1476.
12. Guido C. A., Loffredo L., Zicari A. M. et. al. The impact of the COVID-19 epidemic during the lockdown on children with the Pediatric Acute-Onset Neuropsychiatric Syndrome (PANDAS/PANS): the importance of environmental factors on clinical conditions. *Frontiers in Neurology*, 2021, 11, 702356.
13. <https://www.pandasppn.org/polish/>. Accessed 11 Jul 2023.

14. Kronenberg S., Shouldice M. Frequency and impact of PANDAS/PANS diagnosis <https://cpsp.cps.ca/uploads/studies/Frequency-and-impact-of-PANDAS-PANS-diagnosis-protocol-rev.pdf>. Accessed 11 Jul 2023.
15. <https://pandasnetwork.org/get-involved/statistics/>. Accessed 11 Jul 2023.
16. Olsson R. Does My Child Have PANS/PANDAS? <https://www.bannerhealth.com/healthcareblog/teach-me/does-my-child-have-pandas>. Accessed 11 Jul 2023.
17. Wohleb ES, McKim DB, Sheridan JF, Godbout JP. Monocyte trafficking to the brain with stress and inflammation: a novel axis of immune-to-brain communication that influences mood and behavior. *Frontiers in Neuroscience*, 2015, 21, 8, 447.
18. Dunn AJ. Effects of cytokines and infections on brain neurochemistry. *Clinical Neuroscience Research*, 2006, 6, 52.
19. Thenganatt MA, Jankovic J. Recent Advances in Understanding and Managing Tourette Syndrome. *F1000Research*, 2016, 9, 5, F1000.
20. Worbe Y, Marakchi-Kacem L, Lecomte S, et al. Altered structural connectivity of cortico-striato-pallido-thalamic networks in Gilles de la Tourette syndrome. *Brain* 2015; 138(Pt 2), 472-482.
21. Singer HS, Augustine F. Controversies Surrounding the Pathophysiology of Tics. *Journal of child neurology*, 2019, 34, 851.
22. Swedo SE, Leonard HL, Rapoport JL. The pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) subgroup: separating fact from fiction. *Pediatrics*, 2004, 113, 907.
23. Husby G, van de Rijn I, Zabriskie JB. Antibodies reacting with cytoplasm of subthalamic and caudate nuclei neurons in chorea and acute rheumatic fever. *Journal of Experimental Medicine*, 1976, 144, 1094.
24. Kotby AA, El Badawy N, El Sokkary S. Antineuronal antibodies in rheumatic chorea. *Clinical and Diagnostic Laboratory Immunology*, 1998, 5, 836.
25. Kirvan CA, Cox CJ, Swedo SE, Cunningham MW. Tubulin is a neuronal target of autoantibodies in Sydenham's chorea. *The Journal of Immunology*. 2007, 178, 7412.
26. Bottas A, Richter MA. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). *Pediatric Infectious Disease Journal*, 2002, 21, 67.
27. Murphy TK, Goodman WK, Ayoub EM, Voeller KK. On defining Sydenham's chorea: where do we draw the line? *Biological Psychiatry*, 2000, 47, 851.
28. Swedo SE, Leonard HL, Schapiro MB. Sydenham's chorea: Physical and psychological symptoms of St Vitus dance. *Pediatrics*, 1993, 91, 706.

29. Murphy TK, Storch EA, Lewin AB. Clinical factors associated with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. *The Journal of Pediatrics*, 2012, 160(2), 314-319.
30. <https://www.pandasppn.org/antibiotics/>. Accessed 11 Jul 2023.
31. Murphy M. L., Pichichero M. E. Prospective identification and treatment of children with pediatric autoimmune neuropsychiatric disorder associated with group A streptococcal infection (PANDAS). *Archives of Pediatrics & Adolescent Medicine*, 2002, 156(4), 356-361.
32. Snider, L. A., Lougee, L., Slattery, M., et al. Antibiotic prophylaxis with azithromycin or penicillin for childhood-onset neuropsychiatric disorders. *Biological Psychiatry*, 2005, 57(7), 788-792.
33. Storch, E. A., Murphy, T. K., Geffken, G. R., et al. Cognitive-behavioral therapy for PANDAS-related obsessive-compulsive disorder: findings from a preliminary waitlist controlled open trial. *Journal of the American Academy of Child & Adolescent Psychiatry*, 2006, 45(10), 1171-1178.
34. Texas Pediatric Acute-Onset Neuropsychiatric Syndrom Advisory Council <https://www.hhs.texas.gov/sites/default/files/documents/laws-regulations/reports-presentations/2021/pansac-report-sept-2021.pdf>. Accessed 11 Jul 2023.
35. Hesselmark, E., Bejerot S. Patient satisfaction and treatments offered to Swedish patients with suspected pediatric acute-onset neuropsychiatric syndrome and pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. *Journal of child and adolescent psychopharmacology*, 2019, 29(8), 634-641.
36. Gilbert D. L., Mink J. W., Singer, H. S. A pediatric neurology perspective on pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection and pediatric acute-onset neuropsychiatric syndrome, *The Journal of Pediatrics*, 2018, 199, 243-251.
37. Al-Sarraj S., Troakes C., Hanley B. et. al. Invited Review: The spectrum of neuropathology in COVID-19. *Neuropathology and applied neurobiology*, 2021, 47(1), 3-16.
38. O'Dor S. L., Homayoun S., Downer O. M. et. al. A Survey of Demographics, Symptom Course, Family History, and Barriers to Treatment in Children with Pediatric Acute-Onset Neuropsychiatric Disorders and Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infections, *Journal of Child and Adolescent Psychopharmacology*, 2022, 32(9), 476-487.

39. Prato A, Gulisano M, Scerbo M, et al. Diagnostic Approach to Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections (PANDAS): A Narrative Review of Literature Data. *Frontiers in Pediatrics*, 2021, 27, 9, 746639.
40. Murphy TK, Storch EA, Lewin AB et al. Clinical factors associated with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. *The Journal of Pediatrics*, 2012, 160(2), 314-319.
41. Murphy ML, Pichichero ME. Prospective identification and treatment of children with pediatric autoimmune neuropsychiatric disorder associated with group A streptococcal infection (PANDAS). *Archives of Pediatrics and Adolescent Medicine*, 2002, 156(4), 356-361.
42. Kurlan R, Johnson D, Kaplan EL. Tourette Syndrome Study G. Streptococcal infection and exacerbations of childhood tics and obsessive-compulsive symptoms: a prospective blinded cohort study. *Pediatrics*, 2008, 121, 1188-1197 .
43. Leckman JF, King RA, Gilbert DL. et al. Streptococcal upper respiratory tract infections and exacerbations of tic and obsessive-compulsive symptoms: a prospective longitudinal study. *Journal of the American Academy of Child & Adolescent Psychiatry*, 2011, 50(2), 108-118.
44. Lin H, Williams KA, Katsoyich L, et al. Streptococcal upper respiratory tract infections and psychosocial stress predict future tic and obsessive-compulsive symptom severity in children and adolescents with Tourette syndrome and obsessive-compulsive disorder. *Biological Psychiatry*. 2010, 67(7), 684-691.
45. Orlovska S, Vestergaard CH, Bech BH, et al. Association of Streptococcal Throat Infection With Mental Disorders: Testing Key Aspects of the PANDAS Hypothesis in a Nationwide Study. *JAMA Psychiatry*. 2017, 1, 74(7), 740-746.
46. Xu J., Liu R. J., Fahey S. et. al. Antibodies from children with PANDAS bind specifically to striatal cholinergic interneurons and alter their activity. *American Journal of Psychiatry*, 2021, 178(1), 48-64.
47. Church A. J., Dale R. C., Lees A. J. et al. Tourette's syndrome: a cross sectional study to examine the PANDAS hypothesis. *Journal of Neurology, Neurosurgery & Psychiatry*, 2003, 74(5), 602-607.
48. Brilot F., Merheb V., Ding A. et al. Antibody binding to neuronal surface in Sydenham chorea, but not in PANDAS or Tourette syndrome. *Neurology*, 2011, 76(17), 1508-1513.
49. Dale R. C., Church A. J., Candler P. M. et.al. Serum autoantibodies do not differentiate

- PANDAS and Tourette syndrome from controls. *Neurology*, 2006, 66(10), 1612-1612.
50. Sigra S., Hesselmark E., Bejerot S. Treatment of PANDAS and PANS: a systematic review. *Neuroscience & Biobehavioral Reviews*, 2018, 86, 51-65.
 51. Brown K, Farmer C, Farhadian B. et. al. Pediatric Acute-Onset Neuropsychiatric Syndrome Response to Oral Corticosteroid Bursts: An Observational Study of Patients in an Academic Community-Based PANS Clinic. *Journal of Child and Adolescent Psychopharmacology*, 2017, 27(7), 629-639.
 52. Brown K, Farmer C, Freeman GM Jr, et. al. Effect of Early and Prophylactic Nonsteroidal Anti-Inflammatory Drugs on Flare Duration in Pediatric Acute-Onset Neuropsychiatric Syndrome: An Observational Study of Patients Followed by an Academic Community-Based Pediatric Acute-Onset Neuropsychiatric Syndrome Clinic. *Journal of Child and Adolescent Psychopharmacology*, 2017, 27(7), 619-628.

ISBN- 978-83-67454-29-2