Thyroid functioning, adipocytokines, bone turnover and vitamin D - review of literature

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ABSTRACT

The most common public health problems include, among others, overweight, obesity, and cardiovascular diseases. In addition, the number of people with thyroid disturbances is still growing. Thyroid abnormalities can lead to many metabolic dysfunctions, including secondary osteoporosis, alterations in body mass, lipid profile, and insulin resistance. Recently, the studies have been focused on the connections between thyroid gland function, obesity, metabolic syndrome and cardiovascular diseases, as well as bone turnover. Fatty tissue plays an important role in whole body homeostasis. Adipose tissue hormones, such as leptin, resistin and adiponectin are proteins having immunomodulatory lproperties, and their balance is needed to control immune response, as well as inflammation processes. The following article constitutes a review of literature concerning thyroid function with regard to adipocytokines and vitamin D, as well as the influence of this gland on the skeletal system. For this purpose, Medline Pub Med base and Google Scholar were used. All the citied studies in this review article underline how much should be done to achieve more efficient treatment of thyroid disorders, specifically, how to prevent its complications, for instance, osteoporosis, over-weight, obesity or cardiovascular diseases.

Key words: Thyroid gland, obesity, adipokines, vitamin D

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INTRODUCTION

Overweight, obesity and also thyroid diseases are serious public health problems [1]. The number of obese people is growing all over the world [2]. Thyroid function plays an important role in body mass changes [3,4]. The thyroid gland is involved in basic metabolic rate (BMR) regulation [1,5]. Lately, the number of studies concerning the role of the thyroid gland in the development of obesity has increased [5]. Additionally, vitamin D deficiency is another worldwide health problem [6]. The thyroid gland is responsible for production and secretion of two hormones into the blood stream, namely thyroxin T_4 (80%) and triiodothyronine T_3 (20%) [1]. They regulate many crucial processes, i.e. heat production and energy expenditure. They are important for regulating body's homeostasis [7]. Too low and too high secretions of these hormones lead to thyroid disturbances, namely hypothyroidism and hyperthyroidism [1]. The most common thyroid disturbances are, among others, autoimmune thyroid diseases (AITDs), which include Grave's disease and Hashimoto's disease [4,8,9]. They could affect about 2% of the population. The diseases in question occur 10-fold more frequently in women and cause many health complications [10]. Thyroid abnormalities lead to many metabolic dysfunctions, such as alterations in body mass, lipid profile and insulin resistance [7,11]. In summary, thyroid dysfunctions may have an impact on the musculoskeletal, nervous and circulatory systems [12].

Recently, the studies have been focused on the connections between thyroid gland function, obesity, metabolic syndrome and cardiovascular diseases [13]. Overt hypothyroidism increases the risk of cardiovascular morbidity and mortality [14]. Even low-normal thyroid function (defined in the article as higher TSH and/or lower fT_4 levels within the euthyroid reference range) may lead to increased risk of developing metabolic syndrome, obesity, insulin resistance, and cardiovascular diseases [14]. These connections are not clear enough, however, thyroid function along with body fat distribution, and the state of low grade inflammation processes could be linked [3].

The following article is a review of literature concerning thyroid function with regard to adipocytokines and vitamin D, as well as the influence of this gland on the skeletal system. For this purpose, Medline Pub Med base and Google Scholar were used. Keys words used for searching: thyroid gland, obesity, adipokines, vitamin D. Among all searched publications 37 fulfilled the criteria: publications of the last 5 years and described relations between functioning of thyroid gland and skeletal system, obesity as well as adipocytokines. All of 37 were included to final work.

Fatty tissue as an endocrine organ

Recently, the studies have proved that the role of fatty tissue should not be limited to fat storage only, but ought to be regarded as an active endocrine organ which is essential for maintenance of energy balance [3,7]. Fatty tissue secretes numerous hormones called adipocytokines or adipokines into the blood stream. They are responsible for many important functions, such as: thermogenesis, food intake control, reproductive and inflammatory processes [3]. Leptin polypeptide, for example, encoded as an obese (ob) gene is a hormone responsible for energy balance. Moreover, by the neuroendocrine mechanism, it has an influence on body weight, as well as plays a crucial role in metabolism of glucose and insulin [3,15]. Also, leptin has an impact on modulation of T cell function, and is involved in the pathogenesis of autoimmune diseases [4,15]. What is more, in the studies, leptin has proved to have a possibility to stimulate pituitary secretion of TSH [4]. Resistin takes part in inflammation processes and is considered a biomarker of cardiovascular diseases, as well as it may cause insulin resistance [7]. Additionally, proper production of adipocytokines is important for optimal immune response [8]. For example, interleukin-6 is overproduced in obesity and, recently, it has been proposed as a marker of inflammatory status [8,16]. Expression of this cytokine correlates positively with the degree of lymphocyte infiltration in Hashimoto's thyroiditis [8,16].

Moreover, central obesity is connected with endocrinological disturbances, among others, thyroid dysfunctions [10]. It can modify the thyroid hormone status by loop deregulation between adipose tissue and the hypothalamic-pituitary axis [4]. It is known that proper production of adipokines is needed to maintain proper immune response [16]. As mentioned above, leptin, resistin and adiponectin are proteins secreted by adipose tissue. They have immunomodulatory properties, and their balance is needed to control both immune response and inflammation [16].

Excess body mass, adipocytokines and thyroid functioning-study examples

Numerous studies have demonstrated an influence of overt thyroid dysfunction on body weight [17]. In general, hypothyroidism leads to body weight gain and hyperthyroidism to body weight loss. The connection between thyroid function and obesity has not been completely defined [17]. In the study by Milionis et al., the correlation between thyroid hormones and BMI was examined [17]. The study was conducted among 736 clinically healthy euthyroid individuals. Patients with some thyroid hormone abnormalities were excluded [17]. The research showed that alterations in normal thyroid functioning are connected with differences in BMI. The authors

underline that thyroid gland disorders along with environmental factors, namely diet and physical activity, can lead to obesity [17].

Abdu Allah et al. evaluated the relationship between leptin and resistin, as well as thyroid hormones, among patients with and without thyroid dysfunctions [3]. The study involved 28 patients with diagnosed hyperthyroidism and 26 patients with hypothyroidism. The control group consisted of 24 subjects with no thyroid dysfunctions [3]. For each of them BMI was calculated, and the concentrations of fT_3, fT_4, TSH, resistin and leptin were measured [3]. BMI was statistically higher in the group of hypothyroid patients. The groups were statistically different regarding serum leptin concentrations, which were highest in the hypothyroid group (34.9±2.8 ng/ml) versus the control group (11.2±2.7 ng/ml) and the hyperthyroid group (9.7±1.8 ng/ml) [3]. Serum resistin was statistically higher in the group of hyperthyroid patients (13.8±3.6 ng/ml) versus the hypothyroid (6.3±3.4 ng/ml) and control groups (6.9±1.9 ng/ml). Leptin significantly positively correlated with BMI in all study groups [3]. The studies indicated that thyroid hormones, by their influence on the body fat composition, may affect serum leptin [3].

Siemańska et al.[8] assessed the serum level of leptin, adiponectin, and also interleukin-6 among 98 postmenopausal women with Hashimoto's thyroiditis (confirmed by elevated thyroid peroxidase antibody-TPOAb, and an ultrasound exam) in comparison with 105 healthy postmenopausal women. BMI and WHR were calculated, and the concentrations of leptin, adiponectin, interleukin-6, TSH, FT_4, and TPOAb were measured. The concentration of interleukin-6 was significantly elevated among postmenopausal women with Hashimoto's thyroiditis (5.51 vs. 3.26 pg/ml). The concentrations of leptin and adiponectin were not statistically different between both study groups. Serum leptin concentrations correlated positively with BMI, WHR, TSH, and also with interleukin-6, yet negatively with adiponectin, as well as in Hashimoto's thyroiditis group, including all of the studied women. This study revealed that interleukin-6 is involved in Hashimoto's disease pathogenesis, but failed to confirm the connection between adiponectin and leptin in autoimmune thyroiditis [8].

El-Shenawy determined the concentration of adiponectin, interleukin-6 and interleukin-15 in the group of patients with Hashimoto's thyroiditis suffering from hypothyroidism (28 subjects), euthyroidism (18 subjects) and subclinical hypothyroidism (24 subjects). Afterwards, they were compared with the control group (17 subjects). The study revealed that both interleukin-6 and interleukin-15 could be involved in the pathogenesis of Hashimoto's thyroiditis regardless of the thyroid functional status. However, there was no evidence that adiponectin could also play a role in Hashimoto's thyroiditis [16].

Marzullo et. al. enrolled 165 obese individuals in their study. The control group consisted of 118 age and sex-matched subjects with normal BMI. Thyroid disorders, including autoimmune thyroid diseases, constituted one of the exclusion criteria in this study [4]. Parameters of thyroid function, such as TSH, thyroglobulin, antithyroid antibodies and BMI, body composition, leptin concentrations were evaluated. Hypothyroidism and prevalence of antibodies were more frequently observed among obese patients. Leptin concentrations were statistically higher in this group (34.3±16 μg/liter) than in the control group with normal weight (9.5±8.9 μg/liter). Thyroid auto-antibodies were found in 23.6% of obese and in 12.7% of control participants. The authors came to the conclusion that obesity may increase the susceptibility to autoimmune thyroid disease [4]. The authors indicate that future studies are necessary in order to confirm the role of leptin in autoimmune thyroid diseases [4].

Koyuncu et al. determined the concentrations of resistin and insulin growth factor 1 (IGF-1) among patients with hyperthyroidism and hypothyroidism. The authors divided the subjects enrolled in the study into the following groups: 15 cases with hypothyroidism, 16 with subclinical hypothyroidism, 15 with hyperthyroidism, 15 with subclinical hyperthyroidism, and 17 healthy individuals constituting the control group. Resistin concentrations were significantly higher in the hypothyroid group than in the control group (12.6±6.0 vs. 8.4±2.9 ng/ml). According to the authors, increased resistin concentrations are connected with thyroid dysfunctions. Changes in the thyroid hormone concentrations may affect the synthesis and/or resistin secretion by adipose tissue. Additionally, they reported that the levels of IGF-1 decrease in hypothyroidism and correlate negatively with TSH [7].

The study by De Pergola and co-workers involved 311 subjects, 160 of whom were treated with levothyroxine upon the diagnosis of subclinical hypothyroidism (defined as TSH higher than 4.0 μU/ml), (Group 1). The next group consisted of 151 euthyroid individuals (TSH 0.7-3.0 μU/ml), but with autoimmune thyroiditis (Group 2) [10]. Obesity defined as BMI >30 kg/m^2 was found among 44.4% of subjects from group 1 and 22.3% from group 2. The results of the research show that overweight and obesity are connected with higher risk of autoimmune thyroiditis, which, according to the authors, could be related to generalized inflammation and increased adipokine production [10].

In other studies by Dipankar et al. 105 patients were examined and divided into three groups, namely healthy subjects (35 patients), a hypothyroid group (35 patients) and a hyperthyroid group (35 patients) [11]. Anthropometrical and

biochemical (lipid profile, TSH, T_3 and T_4) parameters were taken. In the group of hypothyroid patients, the parameters like LDL-C (low density cholesterol) and TG (triglyceride) were increased versus the healthy group. Moreover, the hypothyroid group showed a significant increase in BMI, WHR, BFR (Body Fat Percentage) [11]. The authors recommended TSH screening among patients with dyslipidemia [11].

The goal of Garcia et al. was to check how thyroid functioning is associated with insulin resistance and cardiovascular risk factors among 525 healthy adolescent high school students, who had been detected with risk factors characteristic of diabetes mellitus II (overweight, obesity, family history) [13]. Lipid profile, a thyroid function test, a glucose tolerance test and anthropometry were performed. As a result, there was no correlation between BMI and TSH. The correlations were found between fasting insulin, HOMA IR (Homeostatic Model Assessment) and thyroid hormones [13].

In the study by Alevizaki and others, an ultrasound was used to check possible association between thyroid functioning and measurements of peripheral and central obesity [18]. Finally, 275 apparently healthy subjects took part in this research and were evaluated for indices of metabolic syndrome [18]. Parameters such as BMI, waist circumference, as well as abdominal subcutaneous and preperitoneal fat were estimated and correlated with the thyroid parameters [18]. Thickness of subcutaneous fat was associated with lower concentrations of fT_4 and, additionally, with higher TSH among slightly (BMI $\geq$25 kg.m^2) overweight and euthyroid subjects [18]. Subcutaneous fat correlated positively with WHR (Waist To Hip Ratio), and also with HOMA IR, total cholesterol levels, as well as triglyceride and LDL cholesterol [18].

It should be noted that patients with Hashimoto's thyroiditis, although euthyroid, could have higher anthropometrical parameters, namely BMI, WHR, body mass and fat mass versus healthy individuals. The replacement therapy with the use of L-thyroxine could help the anthropometrical parameters return to normal [5].

Anthropometrical parameters as predictors of fatty tissue functioning

One of the most famous anthropometrical parameters is BMI (Body Mass Index), which has been used for 200 years [2]. Nowadays, it is not considered an accurate predictor because it leads to misinformation about fatty tissue location [2,19]. Currently, a new index called BAI (Body Adiposity Index) has been introduced as an alternative to BMI. It is also based on a simple calculation formula presented by Bergman. This parameter was validated according to DEXA (Dual-energy X Ray Absorptiometry). An unusual feature of this parameter is that it may be obtained without weighing, as it is calculated on the basis of hip circumference and height (formula1). The parameter can be useful for clinical and epidemiological estimation of adiposity, either as an alternative or as a complement to BMI [2].

Formula 1. Body Adiposity Index (BAI)- formula.

$$\boldsymbol{BAI} = \frac{\text{waist cimcuference in cm}}{(\text{height in cm})1{,}5} - 18$$

Another proposition described by Amato and Giordano for evaluation of fatty tissue functioning is VAI (Visceral Adiposity Index), termed as a new indicator of adipose tissue dysfunction [19,20]. VAI is a gender-specific mathematical model based on the following data: BMI (Body Mass Index), WC (Waist Circumference), triglycerides, HDL cholesterol (formula 2).

Formula 2. Visceral Adiposity Index (VAI)- formulas.

$$\boldsymbol{Male}:$$

$$VAI = \left(\frac{\text{WC}}{39{,}68 + (1{,}88\text{xBMI})}\right) \times \left(\frac{TG}{1{,}03}\right) \times \left(\frac{1{,}31}{HDL}\right)$$

$$\boldsymbol{Female}:$$

$$VAI = \left(\frac{\text{WC}}{36{,}58 + (1{,}89\text{xBMI})}\right) \times \left(\frac{TG}{0{,}81}\right) \times \left(\frac{1{,}52}{HDL}\right)$$

It allows the assessment of fat tissue function and disturbances [19,20]. In general population, it can be used as a marker of cardiometabolic risk. In addition, it can be used among young patients diagnosed with endocrine diseases with developing or overt metabolic syndrome [19].

New anthropometrical parameters described above could give important information about fatty tissue functioning when a biochemical analysis of adipocytokines is not possible to be performed.

Bone turnover and thyroid functioning

In 1891 Von Recklinghausen described the relationship between thyroid functioning and bone metabolism [21]. The proper functioning of the skeleton depends upon many factors, including genetic factors, mechanical load, a well-balanced diet and hormonal homeostasis [22]. Imbalance in each of them could cause fractures or skeletal deformation. It is very important to properly diagnose the conditions which can have an influence on bone mineral density [22].

The major role is attributed to calciotropic hormones, which include PTH, 1,25 $(OH)_2$,

calcitonin. Other important hormones responsible for the development and maintenance of bone mass are: insulin, growth hormone, glucocorticoids, sex steroids, which regulate bone metabolism [23]. Thyroid hormones belong to them as well [12,22, 24]. Their function is to regulate bone metabolism and achieve peak bone mass [22]. The expression of thyroid hormone receptors (TR) in bones shows that thyroid function could have an important impact on bone homeostasis [22]. Thyroid hormones have pleiotropic effects on many tissues [23]. Thyroid hormones, steroids and Vitamin D belong to molecules by activating nuclear receptors, and have multipotential effects on bone metabolism [23]. T_3 is responsible for proper chondrogenic processes, and also for mineralization processes. Additionally, T_3 increases such processes as proliferation, differentia-tion, and apoptosis of osteoblasts [22,23]. T_3 functions in a synergistic way with parathyroid hormone (PTH) and vitamin D (VD) [23]. It has also been featured that T_3 has an influence on the expression of the receptor activator of nuclear factor-κβ ligand (RANKL) in osteoblasts [23]. All possible actions of T_3 on bone functioning have not been recognized in every respect [23]. Thyroid stimulating hormone receptors (TSHR) are present in osteoclasts and osteoblasts. According to the research data, TSH, by its action, can lead to bone remodeling and, finally, to osteoporosis [22]. Moreover, the effect of thyroid hormone therapy on bone mineral density has not been substantially defined [21]. Overt hyperthyroidism is strictly connected with bone fractures because of acceleration in bone turnover [12,21,22,25,26]. Also, people with hyperthyroidism have elevated interleukin-6 concentrations which stimulate the production of osteoclasts [22]. Hyperthyroidism is connected with such conditions as: hypercalcemia, negative calcium balance and hypercalciuria [22]. Hyperthyroidism leads to increased urinary and fecal calcium extraction [23]. Furthermore, hyper-thyroidism is one of the most frequent cause of secondary osteoporosis, and it is considered a major risk factor [25,27]. Many medical reports describe reduction in bone mineral density (BMD) among females [27].

The influence of hypothyroidism on bone metabolism is still under discussion [22]. One of the potential mechanism involves increased risk of fall among elderly people with hypothyroidism [12]. Hypothyroidism generally leads to hypometabolism, as well as to delayed bone formation processes [22,24]. Due to lower bone turnover, hypothyroidism can lead to the reduction in osteoblasts formation, as well as to the prolongation of the mineralization processes [23]. The mechanism related to the influence of hypothyroidism and hyperthyroidism on bone fractures is still unclear [12,22].

Bone turnover and thyroid functioning-study examples

Osteoporosis may cause bone fractures and have a serious impact on life quality, disability or mortality [22]. Secondary osteoporosis may result from numerous endocrinological conditions, for example, thyroid disturbances [22]. It is worth noting that secondary osteoporosis is diagnosed among younger age groups [22].

The impact of TSH abnormalities and metabolic bone disorders are still controversial and require future studies [21]. One of the authors decided to check the relationship between osteopenia, osteoporosis with primary hypothyroidism in women [21]. The study popu-lation consisted of 150 women over 50 years of age, and 50 of them were diagnosed with primary hypothyroidism. Another group of 50 subjects was diagnosed with primary hypothyroidism, undergoing levothyroxine treatment for at least two years. The last group consisted of 50 healthy subjects [21]. Thyroid parameters were measured and dual X ray absorptiometry was used to measure the T score of the lumbar vertebra (L2-L4) and femoral neck [21]. T score of the lumbar spine was significantly lower in the group of women treated with levothyroxine for two years [21].

The aim of the study by Ercolano and co-workers was to determine bone mineral density (BMD) in pre-and postmenopausal euthyroid women, as well as in those with previous hyperthyroidism caused by Graves' disease [27]. 57 women participated in this study, 30 of whom were premenopausal and 27 were postmenopausal. They stayed euthyroid for 6 months. The control group included 52 subjects, namely 36 premenopausal and 16 postmenopausal females. In the research, the following parameters were measured: T_4, TSH, TRAb and BMD [27]. Postmenopausal euthyroid women with Graves' disease history had lower whole body BMD in comparison with the control groups. Additionally, BMD of the lumbar spine expressed as Z-score in the group of postmenopausal patients correlated negatively with TRAb and positively with the duration of the disease, and also positively with the duration of euthyroidism [27]. According to the authors, a negative correlation of TRAb with the lumbar spine BMD in the postmenopausal group among women with Graves' disease history may suggest that this antibody could play a role in bone metabolism [27]. Future studies are required for better understanding of the influence of thyroid hormones and antibodies, like TRAb, on osteoblasts and osteoclasts.

In other studies, Jyotsna and coworkers examined the group of 80 patients diagnosed with Graves' disease and measured such parameters as: BMD, 25 (OH) vitamin D, calcium, phosphorous, alkaline phosphatase, PTH. Additionally, 54 of them underwent one-year follow-up, and 27 of

them underwent two-year follow-up [25]. The control group consisted of 80 euthyroid healthy controls [25]. In both groups of study participants, as well as of patients with Graves' disease and healthy controls, the concentration of vitamin D was insufficient, i.e. 12.6±6.2 ng/ml in the group of patients and 10.9±7.0 ng/ml in the control group respectively [25]. The observations showed that patients with hypothyroidism due to Graves' disease had significantly lower BMD at the hip, spine and forearm in comparison with the healthy and euthyroid control group [25]. Moreover, the research showed that the treatment process of hyperthyroidism could improve BMD at all sites. After adjustment of BMD according to age and BMI, damage in BMD, caused by excess thyroid hormones, was visible even 2 years after becoming euthyroid [25].

Belsing et al. found that both bone mass and density were reduced in the group of premenopausal women diagnosed with Graves' disease. During antithyroid drug therapy, they noticed marker improvement [26]. Furthermore, this study indicated possible influence of TRAb on bones [26].

In the prospective population-based study conducted in Norway, which involved approximately 25 205 individuals without self-reported thyroid dysfunction and without hip forearm fractures, the authors estimated the relation between baseline TSH and the risk of hip or forearm fractures. The relationship between TSH and fracture risk was not statistically significant. However, data indicated positive weak association with hip fracture risk among women with low and high TSH [12].

Vitamin D and thyroid gland

Vitamin D deficiency, observed at present, is not only associated with rickets [28]. Vitamin D deficiency accompanied by many chronic health disturbances, such as: cancer, cardiovascular diseases, diabetes mellitus I and II, hypertension, autoimmune diseases [6,28-30]. Vitamin D as an immune modulator is linked with systemic lupus erythematosus, diabetes mellitus type 1, rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis [30,31]. What is more, it is an immune modulator involved in the regulation of many immune processes [9]. The mechanism regarding the influence of vitamin D on autoimmunity is not clear, but it is probably connected with immune-modulatory and antiinflammatory properties of this vitamin [9,29]. 1,25 dihydroxyvitamine D regulates gene expression and cellular processes, including apoptosis, proliferation and differentiation [29,32]. Some genetic studies have showed associations between genetic polymorphism of, for example, VDR (Vitamin D Receptor), DBP (Binding Protein) and CYP1 α (1α Hydroxylase) with thyroid autoimmunity [9]. Some polymorphisms could have an impact on biological activity of vitamin D [9]. Moreover, vitamin D inhibits the production of cell cytokines like T helper 1: interleukin-2, interferon-γ, interleukin-5, tumor necrosis factor-α (TNF-α) [29]. Vitamin D is mostly produced by skin synthesis after sun exposure. The weather conditions in Central Europe and the solar angle allow suitable vitamin D synthesis only from April to early September [28]. Vitamin D intake in adequate doses is very important for appropriate bone mineralization and skeletal system functioning [28]. Vitamin D supplementation is preserved rigorously among children during their first months of life. In other age groups, vitamin D is either not supplemented or only occasionally [28]. Leader in the field of vitamin D defined vitamin D deficiency concentrations as < 20 ng/ml [<50 nmol/l]. Suboptimal vitamin D status is said to amount to 20-30 ng/ml [70-75nmol/l]. Target concentrations for the best vitamin effects amount to 30-50 ng/ml [75-125 nmol/l] [28].

Vitamin D and thyroid gland-study examples

Lately, many studies have been conducted to evaluate the connection between vitamin D deficiencies and chronic diseases, including autoimmune diseases [33,34]. 94 adult individuals from Saudi Arabia were enrolled to the cross-sectional study. 42 of them were included with subclinical thyroid (elevated TSH and normal fT_4) dysfunctions and 52 were individuals without thyroid dysfunctions, and with no history of thyroid medications were enrolled in the study [35]. Patients with thyroid disturbances had statistically higher circulating triglycerides (1.9±0.46 vs. 1.2.±0.26 mmol/l) and body mass index (32.3±6.8 vs. 27.8±3.9 kg/m^2). Surprisingly, the concentration mean of 25 OH vitamin D in the group of patients with subclinical hypothyroid dysfunctions was higher in these studies (37.3±1.9 vs. 18.3±1.5 nmol/l) [35]. Additionally, lower fT_3 concentrations were associated with higher vitamin D concentrations [35].

In another study by Kivity et al. the concentrations of vitamin D were measured among 50 patients with autoimmune thyroid diseases (AITD), namely Graves' disease and Hashimoto's thyroiditis, among 42 patients with no AITD, and in the control group which included 98 healthy subjects [34]. In this research, prevalence of vitamin D deficiency (defined by the authors as <10 ng/ml) was significantly higher in the group of patients with AITD. What is more, vitamin D deficiency was correlated with the presence of thyroid antibodies [34]. Other studies also confirmed that hypovitaminosis of vitamin D is associated with severity and degree of hypothyroidism [6]

In the research by Sayki Arslan and co-workers, healthy volunteers participated. They were divided into groups according to vitamin D concentrations [29]. Anti TPO was present more frequently in the group of patients with severe

(defined in this research as: <10ng/ml) and moderate (defined in this research as: 10-19.9 ng/ml) vitamin deficiency versus the group with normal vitamin D concentration (defined in this research as: ≥20 ng/ml). A positive correlation was shown between vitamin D and TSH concentrations. Negative correlation was observed between anti-TPO and anti-TG and the vitamin D concentrations. The conclusion derived from this study is that the risk for presence of thyroid antibodies among healthy individuals increases as the concentration of vitamin D decreases [29]. The aim of the research conducted by Alhuzaim et al. was to evaluate the effect of vitamin correction in patients with the new onset of Graves' disease. Therefore, the authors concluded that vitamin D supplemented at a dose of 50, 000 IU per month could improve the clinical and biochemical results. According to the authors, vitamin D deficiency could exacerbate the development of Graves' disease [30]. More clinical studies need to be performed in order to confirm the effect of vitamin D on progression and treatment of Graves' disease.

Bazkurt et al. demonstrated in their study that the concentrations of vitamin D were significantly decreased in the group of patients with Hashimoto's thyroiditis. Furthermore, vitamin D deficiency correlate with the duration of the disease, thyroid volume and antibody levels. According to the authors, this result may suggest a potential role of this vitamin in the development of Hashimoto's thyroiditis and/or in the progression of this disease to hypothyroidism [32]. The researchers from South Korea also find the association between vitamin D and anti-TPO among patients diagnosed with AITDs [36].

Some studies did not confirm that the early stage of thyroid autoimmunity is associated with low vitamin D concentrations [31]. Also, Saler and coworkers failed to find correlations between the level of thyroid auto antibodies and vitamin D among women in Turkey [37].

CONCLUSIONS

All the citied studies underline how much should be done to achieve more efficient treatment of thyroid disorders, specifically, how to prevent its complications (osteoporosis, overweight, obesity or cardiovascular diseases). Also, the role of vitamin D in thyroid disorders should be defined more thoroughly. The following review article presents a few studies which examined the connections between vitamin D and thyroid functioning, the results of which are conflicting. What is more, each research focuses on various vitamin D cut off concentrations, which could be the reason for different results. Additionally, ethnic and geographical differences may modify the research results. The effect of vitamin D on thyroid functioning and the role of supplementation should be elucidated more precisely. Proper diagnosis of thyroid gland disturbances could be immensely effective in prevention of osteoporosis, cardiovascular problems, as well as obesity.

Conflicts of interest

The authors declare no conflicts of interest.

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