

**Katedra i Klinika Endokrynologii**

**Diabetologii i Chorób  
Diabetology  
Metabolicznych and Metabolic**

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Lublin, dnia 29.11.2022

## **EVALUATION OF THE DOCTORAL THESIS OF PRZEMYSŁAW CZAJKOWSKI**

**„Associations between common FTO gene polymorphisms and diet, and their impact on obesity as well as its metabolic consequences”**

Skuteczne leczenie otyłości i jej powikłań wciąż stanowi wyzwanie dla współczesnej medycyny, bowiem określenie przyczyn nadmiernego gromadzenia tkanki tłuszczowej pozostaje nadal nierozwiązane. Masa ciała znajduje się pod ścisłą kontrolą złożonych mechanizmów neuroendokrynych, a otyłość jest stanem, w którym ilość energii dostarczonej istotnie przewyższa jej zużycie przez organizm, dając dodatni bilans energetyczny. Brak równowagi w przyjmowaniu i wydatkowaniu energii może wynikać ze zmian w obwodowych sygnałach (z tkanki tłuszczowej, trzustki czy jelit), a także z predyspozycji genetycznych i wpływu czynników środowiskowych, jak dieta czy aktywność fizyczna. W ostatniej dekadzie coraz więcej uwagi poświęca się interakcji wzorców żywieniowych i ich związkom z genetycznym ryzykiem otyłości. Dlatego badanie zależności pomiędzy jakością i ilością składników żywieniowych diety a wariantami genetycznymi mogą stać się podstawą do opracowania

spersonalizowanych zaleceń żywieniowych dostosowanych do genomu w profilaktyce otyłości.

W świetle tych wstępnych rozważań, należy podkreślić celowość i ważność tematyki przedstawionej do oceny pracy na stopień doktora nauk medycznych przez mgr. Przemysława Czajkowskiego prowadzonej pod kierunkiem Associate Professor Edyta Adamska-Patrano from Clinical Research Support Centre, Medical University of Białystok, Poland and Professor Coral Barbas from Department of Chemistry and Biochemistry, "Centre for Metabolomics and Bioanalysis" (CEMBIO), Faculty of Pharmacy at Universidad CEU San Pablo Madrid, Spain

Autor uwagę swoją skoncentrował na ocenie związków pomiędzy spożyciem energii i niezbędnych składników odżywczych, a wybranymi wariantami genetycznymi, w tym genu FTO, otyłością i metabolizmem glukozy.

Wydaje się to być bardzo trafny wybór, bowiem pomimo istotnego udziału znanych, modyfikowalnych czynników środowiskowych, jak dieta czy aktywność fizyczna, to rola czynników genetycznych pozostaje wciąż niejasna.

Dissertation was prepared in the form of a publication cycle in the field of medical science and health sciences in the medical sciences discipline. Articles included in the dissertation spójne tematycznie i opublikowane w ciągu ostatnich 2 lat:

1. "The Impact of FTO Genetic Variants on Obesity and Its Metabolic Consequences is Dependent on Daily Macronutrient Intake"

Przemysław Czajkowski, Edyta Adamska-Patrano, Witold Bauer, Joanna Fiedorczuk, Urszula Krasowska, Monika Moroz, Maria Górka, Adam Krętowski,

published in *Nutrients*, 2020; 12: 3255. doi:10.3390/nu12113255

Impact Factor: 5.719 MNiSW points: 140

2. "Dietary Fiber Intake May Influence the Impact of FTO Genetic Variants on Obesity Parameters and Lipid Profile—A Cohort Study of a Caucasian Population of Polish Origin"

Przemysław Czajkowski, Edyta Adamska-Patrano, Witold Bauer, Urszula Krasowska, Joanna Fiedorczuk, Monika Moroz, Maria Górka, Adam Krętowski,



published in *Antioxidants*, 2021; 10(11): 1793. doi:10.3390/antiox10111793

Impact Factor: 7.675 MNiSW points: 100

Łączny IF= 13,394 MNiSW points: 240

Doktorant jest pierwszym autorem w każdej z wymienionych prac i jasno określa swój udział procentowy w każdej z nich, co potwierdzają współautorzy.

Aby odpowiedzieć na wiele poruszanych zagadnień Doktorant postawił sobie dwa następujące cele:

1. Exploration of the potential effect of the dietary factors and FTO gene polymorphisms on the obesity-related parameters in the Polish population.
2. Evaluation of whether dietary factors could modify the association between some common genetic variants of the FTO gene and obesity and obesity-related parameters.

In the first article included in the doctoral dissertation, titled "The Impact of FTO Genetic Variants on Obesity and Its Metabolic Consequences is Dependent on Daily Macronutrient Intake" the association between FTO single nucleotide polymorphisms (SNPs), daily macronutrient intake, and obesity and its metabolic consequences was evaluated. The gene-diet interaction analysis was performed in a group of 819 subjects of Polish origin, enrolled in the 1000PLUS Cohort Study and genotyped for the FTO SNPs (rs3751812, rs8044769, rs8050136, and rs9939609). In the examined group of patients the Author demonstrated an interplay between FTO genetic variants and dietary carbohydrate, protein, and fat intake, and the impact of these interactions on body weight, body fat content and distribution, and other anthropometric measures, as well as on glucose homeostasis and lipid profile, in a Polish population of adults. The study revealed that carriers of the GG genotype of rs3751812 presented a protective effect against obesity expressed as a lower body weight, body mass index (BMI), total body fat content, and hip and waist circumference and presented lower obesity-related markers if more than 48% of daily energy intake was derived from carbohydrates and lower subcutaneous and visceral fat content when energy intake derived from dietary fat did not exceed 30%. Similar results were observed for rs8050136 CC genotype carriers. Authors observed a significant impact of diet-gene associations. Body weight and BMI were significantly higher in TT and CT genotype carriers if daily energy intake



derived from carbohydrates was less than 48%. Moreover, in TT genotype carriers, we observed higher blood glucose concentration while fasting and during the OGTT test if more than 18% of total energy intake was derived from proteins.

The Author concludes that findings provide new insights into the role of the interactions between diet and FTO SNPs in the risk of obesity and its metabolic consequences. The obtained results indicate that daily macronutrient intake may modulate the impact of FTO genetic SNPs on obesity and obesity-related metabolic consequences. Detecting FTO risk genotype carriers and modifying dietary intake according to the genetic profile may be a novel, efficient strategy to prevent obesity development.

In the paper “Dietary Fiber Intake May Influence the Impact of FTO Genetic Variants on Obesity Parameters and Lipid Profile

- A Cohort Study of a Caucasian Population of Polish Origin” the Doctoral student continues research on the potential effect of fat mass and obesity-associated (FTO) rs3751812, rs8050136, rs9939609, rs6499640, rs8044769, and rs7190492 genotypes and dietary fiber intake on the obesity-related parameters and lipid profile in the Polish population. The study procedures were performed in the same group of patients. Daily fiber intake was analyzed based on 3-day food-intake diaries, and daily physical activity was evaluated based on the International Physical Activity Questionnaire—Long Form.

In this study the Author reveals that dietary fiber intake may modify the association of the FTO SNPs, rs3751812, rs8050136, rs9939609, rs6499640, rs8044769, and rs7190492, especially among those subjects who consume high levels of dietary fiber. The study demonstrated that associations of the FTO SNPs with hip circumference, visceral adipose tissue distribution, total cholesterol and LDL levels, and corrected insulin response levels may be dependent on daily fiber intake. The Author found that daily fiber intake above 18 g per day by carriers of the GG genotype (rs3751812), CC genotype (rs8050136), and GG genotype (rs6499640) may positively affect anthropometric parameters, decreasing hip circumference. What is interesting the obtained results also showed an unexpected observation that higher fiber intake can have a negative impact on lipid profile dependent on the FTO genotype what requires further studies. The conducted analyses bring valuable information for science and may have practical clinical relevance in the field of nutrition and in the future could be the basis for personalized dietary recommendations.



Niewątpliwą zaletą zwiększającą wartość prowadzonych przez Doktoranta badań jest szeroki panel badawczy obejmujący standardowe metody eksperymentalne (ocena danych antropometrycznych i kwestionariusze żywieniowe), analizę laboratoryjną, a także nowoczesne metody analizy statystycznej.

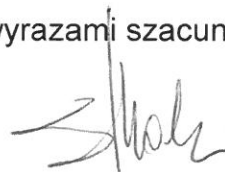
Zastanawiające jest wg jakich zaleceń wykonywano OGTT, bowiem krew pobierano w odstępach czasowych w 0, 30, 60 i 120 min po podaniu glukozy a nie 0 i 120 min ( wg EASD, ADA). Ponadto wydaje się, że lepszym markerem otyłości w kontekście ryzyka sercowo naczyniowego jest obwód brzucha a nie wskaźnik talia – biodra.

W wyniku przeprowadzonej analizy Doktorant formuuje liczne wnioski, które są w części powtórzeniem uzyskanych wyników. Jednocześnie słusznie ocenia, że konieczne są dalsze badania w celu weryfikacji tych wyników, w większych populacjach i różnych grup etnicznych.

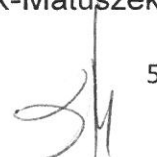
W podsumowaniu należy stwierdzić, że mgr Przemysław Czajkowski w swojej pracy doktorskiej podjął się analizy bardzo interesującego, ważnego społecznie i klinicznie problemu, jakim jest poszukiwanie wpływu czynników żywieniowych i polimorfizmów genu FTO na parametry związane z otyłością i jej powikłaniami w populacji polskiej. W pełni zrealizował postawione wstępnie cele. Zastosował w pracy nowoczesne metody badawcze, poprawnie przeanalizował uzyskane wyniki i sformułował adekwatne do celów wnioski.

Zatem stwierdzam, że przedstawiona do oceny rozprawa doktorska mgr Przemysława Czajkowskiego spełnia wszystkie wymogi ustawowe stawiane pracy doktorskiej określone w art.187 ustawy z dnia 20 lipca 2018 r. o stopniach naukowych i tytule naukowym oraz o stopniach i tytule w zakresie sztuki i wnoszę do Senatu Uniwersytetu Medycznego w Białymstoku o dopuszczenie mgr. Przemysława Czajkowskiego do dalszych etapów przewodu doktorskiego.

Z wyrazami szacunku



Prof. dr hab. n. med. Beata Matyjaszek-Matuszek

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**Beata Matyjaszek-Matuszek**

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Lublin, dn.29.11.2022

## **EVALUATION OF THE DOCTORAL THESIS OF PRZEMYSŁAW CZAJKOWSKI**

**"Associations between common FTO gene polymorphisms and diet, and their  
impact on obesity as well as its metabolic consequences"**

Effective treatment of obesity and its complications is still a challenge for modern medicine as the causes of excessive accumulation of adipose tissue have not been determined yet. Body weight is under strict control of complex neuroendocrine mechanisms and obesity is a condition in which the amount of energy supplied significantly exceeds its consumption by the body, which results in a positive energy balance. The imbalance in energy intake and expenditure may result from changes in peripheral signals from adipose tissue, pancreas or intestines as well as genetic predisposition and the impact of environmental factors such as diet or physical activity. The last decade has seen more and more attention being given to the interaction between dietary patterns and their relationship with the genetic risk of obesity. Therefore, the study of the relationship between the quality and quantity of dietary

components and genetic variants may become the basis for the development of individual nutritional recommendations adapted to the genome in obesity prevention.

In the light of these preliminary considerations, the desirability and importance of the subject matter presented for the evaluation of the dissertation for the degree of doctor of medical sciences Przemysław Czajkowski, MSc. under the guidance of Edyta Adamska-Patruno, Associate Professor from the Clinical Research Support Centre, Medical University of Białystok, Poland and Professor Coral Barbas from the Department of Chemistry and Biochemistry, "Centre for Metabolomics and Bioanalysis" (CEMBIO), Faculty of Pharmacy at Universidad CEU San Pablo Madrid, Spain should be underlined.

The author focused his attention on the assessment of the relationships between energy intake and essential nutrients and selected genetic variants, including the FTO gene, obesity and glucose metabolism.

It seems to be a very wise choice because despite the significant contribution of known, modifiable environmental factors, such as diet or physical activity, the role of genetic factors remains unclear.

The dissertation was prepared in the form of a publication cycle in the field of medical science and health sciences in the medical sciences discipline. The articles included in the dissertation which are thematically consistent and published in the last two years are:

1. "The Impact of FTO Genetic Variants on Obesity and Its Metabolic Consequences is Dependent on Daily Macronutrient Intake"

Przemysław Czajkowski, Edyta Adamska-Patruno, Witold Bauer, Joanna Fiedorczuk, Urszula Krasowska, Monika Moroz, Maria Górka, Adam Krętowski, published in *Nutrients*, 2020; 12: 3255. doi:10.3390/nu12113255

Impact factor: 5.719 MNiSW points: 140

2. "Dietary Fiber Intake May Influence the Impact of FTO Genetic Variants on Obesity Parameters and Lipid Profile—A Cohort Study of a Caucasian Population of Polish Origin"



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Total IF = 13.394 MNiSW points: 240

The PhD student is the first author in each of the given works and clearly defines his percentage share in each of them, which is confirmed by the co-authors.

In order to answer many of the issues raised, the PhD student set the following two goals:

1. Exploration of the potential effect of the dietary factors and FTO gene polymorphisms on the obesity-related parameters in the Polish population.
2. Evaluation of whether dietary factors could modify the association between some common genetic variants of the FTO gene and obesity and obesity-related parameters.

In the first article included in the doctoral dissertation entitled “The Impact of FTO Genetic Variants on Obesity and Its Metabolic Consequences is Dependent on Daily Macronutrient Intake” the association between FTO single nucleotide polymorphisms (SNPs), daily macronutrient intake, and obesity and its metabolic consequences was evaluated. The gene-diet interaction analysis was performed in a group of 819 subjects of Polish origin, enrolled in the 1000PLUS Cohort Study and genotyped for the FTO SNPs (rs3751812, rs8044769, rs8050136, and rs9939609). In the study group, the Author demonstrated an interplay between FTO genetic variants and dietary carbohydrate, protein, and fat intake, and the impact of these interactions on body weight, body fat content and distribution, and other anthropometric measures, as well as on glucose homeostasis and lipid profile, in a Polish population of adults. The study showed that the carriers of the GG genotype of rs3751812 presented a protective effect against obesity expressed as a lower body weight, body mass index (BMI), total body fat content, and hip and waist circumference and presented lower obesity-related markers if more than 48% of daily energy intake was derived from carbohydrates and lower subcutaneous and visceral fat content when energy intake



derived from dietary fat did not exceed 30%. Similar results were observed for the rs8050136 CC genotype carriers. The Authors observed a significant impact of diet-gene associations. Body weight and BMI were significantly higher in TT and CT genotype carriers if daily energy intake derived from carbohydrates was less than 48%. Moreover, in the TT genotype carriers, the Authors observed higher blood glucose concentration while fasting and during the OGTT test if more than 18% of total energy intake was derived from proteins.

The Author concludes that findings provide new insights into the role of the interactions between diet and FTO SNPs in the risk of obesity and its metabolic consequences. The obtained results indicate that daily macronutrient intake may modulate the impact of FTO genetic SNPs on obesity and obesity-related metabolic consequences. Detecting FTO risk genotype carriers and modifying dietary intake according to the genetic profile may be a novel efficient strategy to prevent obesity development.

In the article “Dietary Fiber Intake May Influence the Impact of FTO Genetic Variants on Obesity Parameters and Lipid Profile - A Cohort Study of a Caucasian Population of Polish Origin” the PhD student continues research on the potential effect of fat mass and obesity-associated (FTO) rs3751812, rs8050136, rs9939609, rs6499640, rs8044769, and rs7190492 genotypes and dietary fiber intake on the obesity-related parameters and lipid profile in the Polish population. The study procedures were performed in the same group of patients. Daily fiber intake was analysed based on 3-day food-intake diaries, and daily physical activity was evaluated based on the International Physical Activity Questionnaire—Long Form.

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negative impact on lipid profile dependent on the FTO genotype, which requires further studies. The conducted analyses bring valuable information for science and may have practical clinical relevance in the field of nutrition and in the future could be the basis for individualised dietary recommendations.

An unquestionable advantage that increases the value of the study conducted by the PhD student is a wide research panel including standard experimental methods (assessment of anthropometric data and nutritional questionnaires), laboratory analysis, as well as modern methods of statistical analysis.

It is puzzling according to which recommendations the OGTT was performed because blood was collected at intervals of 0, 30, 60 and 120 minutes after glucose administration, and not 0 and 120 minutes (according to the EASD, ADA recommendations). In addition, it seems that a better marker of obesity in the context of cardiovascular risk is abdominal circumference than the waist-hip ratio, so why was this parameter chosen?

Following the analysis, the PhD student draws numerous conclusions, which are partly a repetition of the results obtained. Nonetheless, he rightly points out that further research is needed to verify these results, in larger populations and across ethnic groups.

In conclusion, it should be stated that in his doctoral thesis, Przemysław Czajkowski undertook to analyse a very interesting, socially and clinically important problem, which is the search for the influence of nutritional factors and FTO gene polymorphisms on parameters related to obesity and its complications in the Polish population. He fully achieved the initial goals. He applied modern research methods in his work, correctly analysed the results obtained and drew conclusions adequate to the objectives.

Therefore, I declare that the doctoral dissertation of Przemysław Czajkowski, M.Sc., submitted for evaluation meets all the statutory requirements for a doctoral dissertation set out in Article 187 of the Act of 20 July 2018 on Academic Degrees and Academic Title and Degrees and Title in Art, and I petition to the Senate of the Medical University of Białystok that Przemysław Czajkowski, MSc. be allowed to pursue further stages of the doctoral procedure.



Yours sincerely,

Prof. Beata Matyjaszek-Matuszek, MD, PhD

A handwritten signature in black ink, appearing to be 'B. Matyjaszek-Matuszek', written in a cursive style.