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Influence of the FTO polymorphism rs17817449 on the risk of obesity, type 2 diabetes, and cardiovascular diseases in Upper Silesian population — a preliminary, cross-sectional study

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ABSTRACT

Introduction: Obesity is considered to be one of the most prevalent health problems which lead to diabetes and cardiovascular diseases thus increasing mortality rate and decreasing life expectancy, particularly in western countries. The variants within the FTO gene were identified to be associated with adiposity and diabetes in genome-wide association studies (GWAS).

Aim of the study: To investigate the association between FTO rs17817449 polymorphism and risk of obesity, type 2 diabetes, lipid disorders, and cardiovascular diseases: arterial hypertension and coronary artery disease (CAD).

Material and methods: Study group consisted of 295 patients (159 women and 136 men). Collected venous blood samples were stored at minus 70 C until the study group was completed. In the laboratory of the Department and Clinic of Internal Medicine, Diabetology and Nephrology, Medical University of Silesia in Zabrze the DNA material was isolated, proper concentration of the DNA (15 ng/μL) were prepared and quality and quantity were checked by spectrophotometry. Allelic discrimination was performed in Roche Lightcycler96 thermocycler with the use of fluorescent-labeled TaqMan Pre-designed SNP Genotyping Assay probes.

Results: BMI, body fat percentage, and waist circumference did not differ by rs17817449 genotype. There were no significant differences in genotypes distribution between patients with obesity and normal body weight. We found a significant association of GT, but not GG genotype with lower risk of arterial hypertension (OR, 0.55; 95% CI, 0.325–0.940; $p = 0.003$) and coronary artery disease (OR, 0.3; 95% CI, 0.145–0.620); $p = 0.001$). The frequencies of the FTO genotypes did not differ significantly between individuals with and without diabetes. Parameters of lipid profile (total cholesterol, HDL, LDL, TAG) and carbohydrate metabolism (fasting glucose, fasting insulin, HOMA-IR, QUICKI) did not differ by s17817449 genotype.

Conclusion: The association between the FTO polymorphism in rs17817449 and increased risk of obesity and type 2 diabetes mellitus in the Upper Silesian population was not confirmed in this study. The rs17817449 variant of FTO gene may be related to decreased risk of arterial hypertension and coronary artery disease. Further studies in a larger cohort are required to confirm the association between FTO polymorphism in rs17817449 or/and in other FTO gene polymorphisms and diabetes and cardiovascular diseases.

Key words: FTO (fat mass and obesity-associated protein), obesity, arterial hypertension, coronary artery disease (CAD), diabetes mellitus type 2

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Introduction

Obesity is one of the most prevalent civilization diseases, defined by a body mass index (BMI) (weight in kg/height in m2) ≥ 30 kg m^{-2} [1]. Obesity increases the risk of developing type 2 diabetes, arterial hypertension, and coronary artery disease [2]. Additionally, it has a negative impact on the quality of life leading to disability and increasing the risk of premature death. Among the most common causes of obesity, there are improper nutrition, physical inactivity, psycho-emotional disorders, socioeconomic conditions, and genetic predisposition [3]. Risk of obesity can be also estimated on the basis of body fat percentagee — BF% (> 25% for men, > 35% for women) and waist circumference (> 104 for men, > 88 cm for women [4]. In 2007, a genome-wide search for type 2 diabetes–susceptibility genes identified a common variant in the FTO gene which predisposes to diabetes through its effect on body mass index (BMI) [5]. A set of SNPs was identified in the first intron of the fat mass and obesity-associated (FTO) gene on chromosome 16q12.2, which is strongly associated with early-onset and severity of obesity in adults and children [6]. FTO is currently considered a predictor of polygenic obesity [7]. Since obesity contributes to the development of diabetes and cardiovascular diseases, genetic factors increasing susceptibility to obesity may also increase the risk of obesity-related disorders [8].

The present study aimed to explore the association between different variants of FTO polymorphism in rs17817449 and risk of obesity, diabetes mellitus type 2, lipid disorders, arterial hypertension, and coronary artery disease (CAD), in the population of Upper Silesia.

Material and methods

Recruitment

The study enrolled 295 patients who randomly attended the general outpatient clinic of the private health care institution in Dobieszowice (Poland). Inclusion criteria involved: age > 18, written informed consent, no serious illness such as cancer, end-stage renal disease (ESRD) and severe heart failure (New York Heart Association Class IV). Participants of the research were diversified in terms of place of residence, however, all the patients lived in Silesian voivodeship.

Evaluation of DNA levels

Whole blood samples were collected for the examination. In preparation for storage, they were isolated using the column method. Collected venous blood samples were stored at minus 70 C until the study group was completed. The concentration of genetic material 15 ng/μL was obtained by mixing DNA with water according to the dilution protocol and checked with a denoviX spectrophotometer.

Preparation of samples

Preparation for PCR included: the preparation of the mixture by vortexing on a short spin probe, mixing with water, buffer, and mix (reaction mix to Roche device), revortexing, centrifugation. The solution was mixed with the DNA and transported to the PCR plate. PCR reaction was performed by Roche Lightcycler 96. Alleles were marked as G in VIC and T in FAM.

Anthropometric examination

Anthropomentric measurements of age, sex, height, weight, neck circumference, and waist circumference were performed on the patients. Based on the obtained data, the percentage of body fat was calculated using the BF% calculator.

Statistical analysis

Qualitative data are presented as numbers (n) and case percentage (%). Quantitative data were presented as mean (M) and standard deviation (SD). The Shapiro–Wilk test was used to assess the data distribution. Quantitative variables were compared using the one-way ANOVA or Kruskal–Wallis test with multiple comparisons. The significance between distributions of genotypes and alleles, gender, nicotinism, hypertension, coronary artery disease, and diabetes mellitus were tested using Pearson's χ2 test. P values < 0.05 were considered as significant. The statistical software STATISTICA 13 for Windows (TIBCO Software Inc., Palo Alto, CA, USA) was used to perform all analyses.

Results

A total of 295 patients were included in the study. Characteristic of patients is provided in Table 1. There were 159 (54%) men and 136 women (46%): 145 (49%) had arterial hypertension, 49 (17%) — coronary artery disease, 30 (10%) — diabetes mellitus. Sixty-nine (9%) of the patients were smokers.

Frequencies of genotypes in the group of patients with obesity and with the increased risk of abdominal obesity assessed on the base of various criteria (such as BMI, body fat percentage, and waist circumference) are provided in Tables 2–6. Comparison of lipid profile parameters (total cholesterol, HDL, LDL, TG) between genotypes is shown in Tables 7–8. FTO gene rs 17817449 did not possess any effect on lipid profile

Table 1. Characteristic of the patients

	TT		GT		GG		P-value
	n/mean	%/SD	n/mean	%/SD	n/mean	%/SD	
Gender							0.126
Women	40	25.16%	86	54.09%	33	20.75%	
Men	49	36.03%	62	45.59%	25	18.38%	
Age	54.28	16.84	52.26	16.86	52.6	17.36	0.587
Height (cm)	167.91	8.81	167.00	15.49	166.79	9.46	0.346
Weight (kg)	75.07	11.80	73.81	11.50	73.84	11.61	0.567
BMI	26.66	4.06	26.66	3.75	26.53	3.49	0.953
Percentage body fat (BF%)	31.35	8.63	32.62	7.61	32.38	7.44	0.448
Waist circumference	94.80	12.47	93.82	10.61	92.67	11.39	0.545
Fasting glucose	82.75	17.14	84.34	25.57	79.86	79.86	0.361
Fasting insulin	13.36	11.57	12.05	7.36	11.62	11.62	0.948
HOMA-IR	2.39	1.28	2.41	1.41	2.32	2.32	0.962
QUICKI	0.61	0.11	0.61	0.09	0.61	0.61	0.826
Diabetes mellitus							0.681
Yes	11	36.67%	13	43.33%	6	20.00%	
No	78	29.43%	135	50.94%	52	19.62%	
Total cholesterol	6.15	1.24	6.10	1.25	6.05	1.49	0.784
Triacylglycerols	1.46	1.07	1.44	1.18	1.23	0.57	0.438
HDL-C	1.26	0.40	1.31	0.35	1.32	1.32	0.418
LDL-C	4.25	1.06	4.20	1.11	4.17	4.17	0.832
Diastolic blood pressure	137.30	14.22	131.86	13.30	134.48	13.47	0.061, * < 0,01
Systolic blood pressure	81.52	9.37	79.16	8.68	80.52	8.31	0.104
Hypertension							0.069
Yes	51	35.17%	63	43.45%	31	21.38%	
No	38	25.33%	85	56.67%	27	18.00%	
CAD							< 0.01
Yes	23	46.94%	14	28.57%	12	24.49%	
No	66	26.83%	134	54.47%	46	18.70%	
Nicotinisma							0.848
Yes	22	31.88%	35	50.72%	12	17.39%	
No	67	29.65%	113	50.00%	46	20.35%	

*P-value GT *vs.* TT

parameters of patients. Similarly, we have not found any significant differences in the parameters of carbohydrate metabolism (fasting glucose, fasting insulin, HOMA-IR, QUICKI) between genotypes (Tab. 1).

We observe that the GT heterozygotes were significantly more frequent in the groups of patients without arterial hypertension and coronary artery disease (Tab. 9 and 10). Furthermore, the proportion of the G allele carriers (GT + TT) was significantly higher in individuals without coronary artery disease (Tab. 9 and 10). Differences in the BMI between FTO rs17817449 genotypes were insignificant (Tab. 1). We have not found any significant association between obesity and diabetes mellitus occurrence with the FTO rs17817449 polymorphism (Tab. 2–6 and 11).

Discussion

The aim of the present study was to investigate the association between FTO gene in rs17817449 and the risk of obesity, arterial hypertension, diabetes mellitus,

Table 2. Comparison of genotype distributions in patients with and without obesity assessed with the use of BMI criteria

rs17817449						
Genotypes	**with obesity (BMI ≥ 30)**		**without obesity (BMI < 30)**		**P-value**	**OR (95% CI)**
	n	**%**	**n**	**%**		
TT	19	21.35%	70	78.65%		1.00 (Reference)
GT	22	14.86%	126	85.14%	0.203	0.643 (0.326–1.270)
GG	8	13.79%	50	86.21%	0.251	0.589 (0.239–1.453)
GT+GG	30	14.56%	176	85.44%	0.1529	0.628 (0.332–1.189)

Table 3. Genotype frequency of FTO SNP (rs17817449) gene polymorphism in patients with and without high risk of abdominal obesity (The waist circumference cut-off points for high risk of abdominal obesity: 88 cm for women and 102 cm for women)

rs17817449						
Genotypes	**with obesity (waist circumference > 88 cm for women, > 102 for men)**		**without obesity (waist circumference ≤ 88 cm for women, ≤ 102 for men)**		**P-value**	**OR (95% CI)**
	n	**%**	**n**	**%**		
TT	57	64.04%	32	35.96%		1,00 (reference)
GT	99	66.89%	49	33.11%	0.357	1.282 (0.756–2.175)
GG	38	65.52%	20	34.48%	0.932	0.971 (0.498–1.893)
GT + GG	99	48.06%	107	51.94%	0.503	1.186 (0.719–1.956)

Table 4. Genotype frequency of FTO SNP (rs17817449) gene polymorphism in non-obese and obese participants (The BF% cut-off points for obesity: 25% for men and 35% for women)

rs17817449						
Genotypes	**With obesity (percentage body fat (BF%) > 25% for men, > 35% for women)**		**Without obesity (percentage body fat (BF%) ≤ 25% for men, ≤ 35% for women)**		**P-value**	**OR (95% CI)**
	N	**%**	**N**	**%**		
TT	57	64,04%	32	35.96%		1.00 (reference)
GT	99	66.89%	49	33.11%	0.655	1.134 (0.653–1.970)
GG	38	65.52%	20	34.48%	0.856	1.067 (0.533–2.134)
GT + GG	137	66.50%	69	33.50%	0.682	1.115 (0.662–1.876)

Table 5. Genotype distribution of FTO SNP (rs17817449) gene polymorphism in women with and normal, elevated and high risk of abdominal obesity (estimated on waist circumference)

Women	**TT**		**GT**		**GG**		**P-value**
Waist circumference	**n**	**%**	**n**	**%**	**n**	**%**	
< 80 cm	5	26.32%	10	52.63%	4	21.05%	0.922
80–88 cm	10	23.26%	22	51.16%	11	25.58%	
> 88 cm	25	25.77%	54	55.67%	18	18.56%	

Table 6. Genotype distribution of FTO SNP (rs17817449) gene polymorphism in men with and normal, elevated and high risk of abdominal obesity (estimated on waist circumference)

Men	TT		GT		GG		P-value
Waist circumference	**n**	**%**	**n**	**%**	**n**	**%**	
< 94 cm	24	36.36%	28	42.42%	14	21.21%	0.908
94–102 cm	11	37.93%	14	48.28%	4	13.79%	
> 102 cm	14	34.15%	20	48.78%	7	17.07%	

Table 7. Parameters of lipid profile according to the FTO (rs 17817449) genotypes in women

	Women						
	TT		GT		GG		P-value
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Total cholesterol	6.28	1.10	6.19	1.13	6.05	1.41	0.63
HDL	1.38	0.37	1.38	0.35	1.34	0.30	0.941
LDL	4.28	1.04	4.22	1.01	4.13	1.30	0.736
TG	1.26	0.46	1.35	0.86	1.29	0.59	0.962

Table 8. Parameters of lipid profile according to the FTO (rs 17817449) genotypes in men

Men

	TT		GT		GG		P-value
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Total cholesterol	6.04	1.34	5.96	1.39	6.06	1.62	0.942
HDL	1.16	0.40	1.20	0.33	1.28	0.36	0.328
LDL	4.22	1.08	4.17	1.25	4.22	1.31	0.920
TG	1.62	1.38	1.56	1.53	1.14	0.53	0.236

Table 9. Comparison of genotype distributions in patients with and without arterial hypertension

	rs17817449					
Genotypes	**With hypertension**		**Without hypertension**		**P-value**	**OR (95% CI)**
	N	**%**	**N**	**%**		
TT	51	57.30%	38	42.70%		1.00 (Reference)
GT	63	42.57%	85	57.43%	0.029	0.552 (0.325–0.940)
GG	31	53.45%	27	46.55%	0.646	0.856 (0.440–1.664)
GT + GG	94	45.63%	112	54.37%	0.067	0.625 (0.379–1.033)

Table 10. Comparison of genotype distributions in patients with and without coronary heart disease

	rs17817449					
Genotypes	**With coronary heart disease**		**Without coronary heart disease**		**P-value**	**OR (95% CI)**
	N	**%**	**N**	**%**		
TT	23	25.84%	66	74.16%		1.00 (Reference)
GT	14	9.46%	134	90.54%	0.001	0.3 (0.145–0.620)
GG	12	20.69%	46	79.31%	0.474	0.749 (0.339–1.654)
GT + GG	26	12.62%	180	87.38%	0.006	0.414 (0.221–0.777)

Table 11. Comparison of genotype distributions in patients with and without diabetes mellitus

	rs17817449					
Genotypes	**With diabetes mellitus**		**Without diabetes mellitus**		**P-value**	**OR (95% CI)**
	n	**%**	**n**	**%**		
TT	11	12.36%	78	87.64%		1.00 (Reference)
GT	13	8.78%	135	91.22%	0.379	0.682 (0.292–1.598)
GG	6	10.34%	52	89.66%	0.709	0.818 (0.285–2.349)
GT + GG	19	17.92%	187	90.78%	0.415	0.720 (0.328–1.585)

and coronary artery disease in Upper Silesian population. Obesity is considered to be one of the most prevalent health problems which affects 18% of adult women and 20% of adult men in Poland [9]. It is closely related to other civilization diseases including insulin resistance, type 2 diabetes mellitus, arterial hypertension, and coronary artery disease. Genome-wide association studies (GWAS) indicated that FTO gene might promote obesity development [10]. Indeed, In several investigations, genetic variants in FTO gene were demonstrated to be associated with increased BMI and markers of metabolic disorders [11]. In the present study, we did not observe any significant association between FTO rs17817449 and obesity (Tab. 2–6). Similarly, there were no significant differences in BMI value between genotypes (Tab. 1). Evidence regarding the relationship between FTO rs17817449 and increased adiposity is inconclusive and depends on the population enrolled in the research. The GG genotype and the G allele of FTO variant rs17817449 were found to be associated with increased BMI in Western European, North American, and Korean populations [6, 12–14]. On the contrary, such association was not confirmed in Chinese, Japanese, and African American populations [15–17]. To the best of our knowledge, this study is the first one that investigates the influence of FTO variant rs17817449 on adiposity in adult population of Upper Silesia.

Recent studies underline the role of genetic and environmental factors including increased body mass and incorrect nutritional habits as triggers for type 2 diabetes development. Among multiple genes whose variations appear to increase susceptibility to type 2 diabetes are also those associated with obesity which directly increases the risk of insulin resistance and diabetes. Since FTO gene was revealed to play some role in obesity development, several studies aimed to elucidate the influence of different SNPs in FTO on type 2 diabetes. Some research revealed association between FTO rs17817449 and parameters related to metabolic syndrome and type 2 diabetes such as BMI, fasting glucose, fasting insulin, and insulin resistance thus directly increasing the risk of type 2 diabetes development. Such observations were reported in populations of Egypt, the UK, France, Canada, and European Americans [18, 19]. In the Czech population the GG genotype of FTO variant rs17817449 was significantly more frequent in individuals with type 2 diabetes. Furthermore, the presence of GG genotype was associated with an increased risk of diabetic nephro- and neuropathy [20]. In this study, we have not found any significant associations between genotype distribution and type 2 diabetes mellitus (Tab. 11).

Obesity may lead to metabolic disorders such as insulin resistance and diabetes, as well as an increase risk of cardiovascular diseases including hypertension and coronary artery disease. All the genetic factors which contribute to obesity development might also affect the risk of cardiovascular disorders. For that reason, the association between polymorphisms of FTO gene and the risk of arterial hypertension, atherosclerosis, coronary artery disease, and heart failure was explored in various populations. Falbova et al revealed that in group of Slovak midlife women blood pressure values did not differ significantly by rs17817449 FTO genotype both in normotensive and hypertensive individuals [21]. Results from our study showed a significant association of GT, but not GG genotype with a lower risk of arterial hypertension (Tab. 9, OR, 0.55; 95% CI, 0.325–0.940; p = 0.003) There is imited evidence from literature data about the impact of other SNPs in FTO gene on blood pressure, but the results are often inconclusive [22, 23]. Due to the strong association between obesity and cardiovascular diseases, several research investigated the link between polymorphisms in FTO gene and the risk of cardiovascular diseases. Obtained results are inconsistent and — to the best of our knowledge — there is no study that elucidated the role of FTO gene variant rs17817449. A study conducted on the Finish population by Äijälä et al investigated the influence of other SNP within FTO gene -rs9939609- on the risk of cardiovascular events. The AA genotype of another FTO gene polymorphism rs9939609 appears to be related to increased risk of coronary heart disease in the Finish population [24]. Metanalysis conducted by Chibo Liu et al confirmed a positive relationship between AA genotype of FTO rs9939609 and higher cardiovascular

disease risk, which was independent of BMI and other cardiovascular risk factors. In our work, we observed a significant association of GT, but not GG genotype in rs17817449 with a lower risk of coronary artery disease (Tab. 10, OR, 0.3; 95% CI, 1.38–3.92; p = 0.001). This finding as well as observations from another studies which investigated SNPs other than rs17817449 suggest that it is necessary to explore the association between different FTO polymorphisms and the risk of cardiovascular diseases in a larger cohort.

Obesity can have many metabolic consequences such as "metabolically obese normal weight" (MONW) or normal weight obesity (NWO). In our study, we did not analyze the relationship between the above-mentioned diseases and the assessed polymorphism.

So far, no clear definitions and criteria for the diagnosis of MONW have been established. Nine methods have been found in the available literature recognition used by various research groups. The lack of uniform criteria makes diagnostics difficult, and the most accurate methods and criteria (visceral fat area assessed in computed tomography > 100 cm2, adipose tissue content in DXA densitometry > 30%) were not assessed in the present study [25, 26]. Conducted research on genetic background does not prove a significant effect of genetic mutations on the frequency of MONW occurrence [27]. Hosseini-Esfahani et al proved that the occurrence of rs17817449 is associated with an increased BMI and WC, however, it can be modified by changing dietary patterns [28]. In our study we found no association between increased WC and the investigated polymorphism.

In the study conducted by Abdulhussein A. [29] the FTO rs17817449 significantly affected the markers of glycemic control and dyslipidemia. The effect of rs17817449 on cholesterol, triglycerides, VLDL, LDL, HDL, and fasting plasma insulin was investigated in obese patients with type 2 diabetes and a control group. It was observed that the FTO gene rs17817449 possesses significant effects on glycemic markers and serum lipid profile and can be used as a predictor for the development of diabetes among the obese Iraqi population via its effects on serum lipids, insulin and glucose levels. However, in the present study, we did not observe any relationship between FTO gene rs17817449, lipid parameters, and carbohydrate metabolism disorders.

Conclusions

1. The obtained results suggest that SNP in rs17817449 of FTO gene might be associated with the lower risk of arterial hypertension and coronary artery disease. Results from our study showed a significant association of GT, but not GG genotype with lower risk both of arterial hypertension (OR, 0.55; 95% CI, 0.325–0.940; p = 0.003) and coronary artery disease (OR, 0.3; 95% CI, 1.38–3.92; p = 0.001).
2. We have not found any significant association between investigated SNP and risk of obesity and type 2 diabetes mellitus. Further studies with a larger sample size are required to assess the relationship between the SNP in rs17817449 of FTO gene and the risk of obesity, metabolic disorders, and cardiovascular diseases.

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