DOI: 10.21554/hrr.042410

FTO Gene Polymorphism and Physical Activity in Relation to Body Mass Index

Original scientific paper

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Received: 2023/08/01

Accepted: 2024/10/01

Abstract

The aim of this study was to determine the frequencies of alleles and genotypes of the single nucleotide polymorphism of the FTO gene (rs17817449) and the intensity of physical activity in relation to the BMI of subjects in the student population. Genotyping was performed using the PCR-RFLP method. 94 subjects stated that they were not physically active, 57 subjects were moderately physically active and 52 were intensely physically active. In the total sample, the risk allele G of the investigated polymorphism rs17817449 of the FTO gene had a lower frequency (41.8%) compared to the normal allele T (58.13%). Although a higher frequency of the risk allele G was found in the group of overweight subjects compared to the group with BMI < 25, the difference was not statistically significant (p > 0.05).

Keywords: *BMI, FTO gene, physical activity;*

Obesity is becoming a serious public health problem that affects not only adults, but also children and adolescents, therefore the analysis of the frequency of this condition is very important. The causes of obesity are multifactorial, including genetic, emotional, behavioral and environmental factors and lifestyle including eating habits and physical activity, family history, endocrinological characteristics and others. On the other hand, the resulting comorbidities of excessive obesity are numerous and include hypertension, hypercholesterolemia, diabetes mellitus type II, myocardial infarction, infertility, osteoarthritis, anxiety, depression and others. The identification of risk factors for the development of obesity is of great importance for its prevention. Properly created lifestyle habits play important role in the prevention of occurrence of obesity. The aim of this study was to determine the frequencies of alleles and genotypes of the single nucleotide polymorphism of the *FTO* gene (rs17817449) and the intensity of

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physical activity in relation to the body mass index (BMI) of the subjects.

Anthropometric body mass index is the most commonly used tool for associating the risk of developing health problems with overweight at the population level. Calculation of BMI is based on the ratio of body weight expressed in kilograms and the square of a person's height expressed in meters. The recommended BMI values are the same for both sexes, ranging from 18.5 to 24.9 kg/m2. According to the classification of the World Health Organization for the adult European population, BMI values from 25.0 to 29.9 kg/m^2 indicate overweight, while people whose BMI is between 30.0 and 34.9 kg/m^2 belong to the first degree obesity group. Furthermore, obesity of the II degree means people whose BMI is from 35.0 to 39.9 kg/m^2, and the last category in which BMI values > 40.0 kg/m^2 mean obesity of the III degree, i.e. morbid obesity (James et al., 2001).

The *FTO* gene is the first identified gene associated with obesity according to genome-wide association studies. The association was confirmed in the European populations (Loos & Bouchard, 2008), although the relation of *FTO* gene polymorphism on obesity is not fully understood. Recent studies show that it is not only associated with obesity, but also with metabolic syndrome and the occurrence of cancer. One of the main roles of *FTO* gene is the regulation of food intake and energy expenditure in humans and animals. The *FTO* gene is expressed in all tissues, but it is mostly represented in the brain, in the region of the hypothalamus, which plays a key role in the regulation of food intake (Frayling et al., 2007). Some studies show that the levels of the *FTO* gene iRNA transcript are either unchanged in adipose tissue or elevated in peripheral blood cells in people who carry the *FTO* risk alleles for obesity compared to people who do not have the risk alleles. It is likely that the obese phenotype in individuals who do not carry risk alleles of the *FTO* gene is not a consequence of the loss of its function per se, but the obese phenotype is the cause of a change in the expression of the *FTO* gene or the expression of other genes that affect the expression of *FTO* (Mizuno et al., 2018).

The association of the *FTO* gene with obesity is undoubtedly proven in humans by the presence of the single nucleotide polymorphisms (SNPs) located within the regions of intron 1 and intron 2 of the *FTO* gene (Zhao et al., 2014). The SNP of rs17817449 *FTO* gene contains two variant alleles: the normal, wild-type, allele T and the mutated allele G. Carriers of the mutated GG genotype have a 1.7 × increased risk of developing obesity, while individuals with the GT genotype have a 1.3 × increased risk of developing obesity compared to individuals with the TT genotype (SNPedia, 2023).

According to the WHO recommendations, regular physical activities such as walking, cycling or dancing, can have significant health benefits. They can reduce the risk of cardiovascular disease, diabetes and osteoporosis, help control body weight and improve mental well-being. Adults need at least 150 minutes of moderate physical activity per week to maintain health, which can be replaced by 75 minutes of vigorous physical activity per week. The aim of this study was to determine the frequencies of alleles and genotypes of the single nucleotide polymorphism of the *FTO* gene (rs17817449) and the intensity of physical activity according to the BMI of the subjects in the student population of northeastern Bosnia and Herzegovina.

Materials and Methods

Subjects

The research included 203 subjects of both sexes from the student population of northeastern Bosnia and Herzegovina. Participation in the study was on a voluntary basis, which the subjects confirmed by signing the form for consent. The study was approved by the Ethics Committee for Scientific Research of the University of Tuzla.

Methods

Collecting of biological samples for genotyping, anthropological measurements and interviewing participants were carried out in the premises of the University of Tuzla. For DNA isolation, two swabs of the buccal mucosa were sampled using sterile collection tools, rubbing the inner surface of both cheeks for 20 seconds. Genotyping was

achieved by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) using a set of primers5'-AGGACCTCCTATTTGGGACA-3' and reverse primer 5'-AGCTTCCATGGCTAGCATTA-3'. The PCR reaction mixture in its final volume contained 25 µl: 2.5 µl 10X PCR buffer, 0.2 µlTaq polymerase 5 units/µl, 2 µl 25 mM MgCl2 and 2 µl 2.5 mMdNTP mixture (Taq DNA Polymerase 1000 units kit, Qiagen, Germany) and 2 µl of each primer (10 mM), 13,3 µl sterile water and 1 µl of DNA sample. Thermal cycling conditions for amplification were as follows: 95 °C for 3 min, followed by 35 cycles of 95 °C for 45 s, 61 °C for 45 s, 72 °C for 1 min, and a final extension at 72 °C for 7 min. The expected maximum size of the PCR product was 828 bp, which was verified by agarose gel electrophoresis with a follow-up DNA marker (50 bp DNA Ladder; New England Biolabs, UK).

The *FTO* gene amplification product (10 µl) was digested with the restriction enzyme AlwNI (New England Biolabs, UK), using 0.2 µl of this enzyme and 5 µl of rCutSmart buffer (New Englands Biolabs, UK), according to (Abdelmajed et al., 2017). The restriction products were separated on a 2% agarose gel, where fragments of 498 and 330 bp were observed in the homozygous wild type TT genotype, fragments of 828, 498 and 330 bp in the heterozygous - GT genotype, and in the homozygous mutated genotype - GG only a fragment of size 828 bp.

A medical scale was used to determine the body mass index. BMI values were calculated by determining the ratio of body weight expressed in kilograms and the square of a person's height expressed in meters.

In order to determine the level of physical activity, subjects were asked to fill out a survey containing questions about the usual frequency of physical activity (PA). Based on their responses and according to Bauman, the respondents were classified into three categories: (1) physically inactive (PI) – respondents who do not engage in physical activity; (2) moderately physically active (MPA) – subjects whose usual frequency of performing physical activity is less than 2 hours/week; (3) intensely physically active (IPA) – respondents who perform intense physical activity more than 2 h/week (Bauman et al., 2017).

The chi-square test of independence was used to analyze the distribution of the basic characteristics of the examined sample between groups of subjects according to BMI, formed according to genotypes, and then according to allele frequencies. All values of $p < 0.05$ were considered statistically significant.

Results

The study included a total of 203 subjects who were divided into two categories according to BMI, 42 subjects with BMI > 25 overweight and 161 subjects with BMI < 25, recommended body weight. Of the 42 subjects who were classified as overweight, i.e. BMI > 25 kg/m2, 6 had a value of 30 < BMI < 34.9, 3 subjects had a BMI > 35. In both groups, as well as in the total sample, the lowest relative frequency was determined for the genotype of the mutated homozygote GG, in the total sample 16.75%, in the group of subjects with excessive body weight 19.04%, and in the group of subjects with the recommended BMI 16,15%. Table 1 shows the frequencies of genotypes and alleles of the *FTO* gene polymorphism rs17817449 according to body mass index in two groups in relation to BMI.

Table 1.
Total and relative frequencies of genotypes and alleles of the rs17817449 FTO gene polyorphism in relation to body mass index

	BMI (N%)		Total	χ2	p
Genotype	**BMI ≥ 25**	**BMI < 25**			
TT	13 (30.96%)	54 (33.54%)	67 (33.00%)	0.235	0.889
GT	21 (50.00%)	81 (50.31%)	102 (50.25%)		
GG	8 (19.04%)	26 (16.15%)	34 (16.75%)		
Total	42	161	203		
Genotype	**BMI ≥ 25**	**BMI < 25**	**Total**	**χ2**	**p**
TT	13 (30.96%)	54 (33.54%)	67 (33.00%)	0.101	0.751
GT+GG	29 (69.04%)	107 (66.46%)	136 (67.00)	**OR (95% CI)**	**p**
Total	42	161	203	1.126 (0.542-2.340)	0.750
Allele	**BMI ≥ 25**	**BMI < 25**	**Total**	**χ2**	**p**
Allele T	47 (55.95%)	189 (58.67%)	236 (58.13%)	0.206	0.650
Allele G	37 (44.05%)	133 (41.30%)	170 (41.87%)	**OR (95% CI)**	**p**
Total	84	322	406	1.119 (0.689-1.816)	0.650

Out of a total of 203 respondents, 94 stated that they did not practice physical activity (PI), 57 respondents were moderately physically active (MPA), exercising less than 2 hours/week, and 52 subjects were classified as intensely physically active (IPA) as they performed physical activity more than 2 h/week. Table 2 shows the frequencies of genotypes and alleles in relation to the above-mentioned categories.

Table 2.
Total frequencies of genotypes and alleles of the rs17817449 FTO polymorphism in relation to the intensity of physical activity

Genotype	Physical activity (N%)				χ2	p
	PI	**MPA**	**IPA**	**Total**		
TT	32 (34.04%)	17 (29.8%)	18 (34.62%)	67 (33.00%)	1.655	0,799
GT	45 (47.87%)	29 (50.9%)	28 (53.85%)	102 (50.25%)		
GG	17 (18.09%)	11 (19.3%)	6 (11.53%)	34 (16.75%)		
Total	94	57	52	203		
Genotype	**PI**		**MPA+IPA**	**Total**	**χ2**	**p**
TT	32 (34.04%)		35 (32.1%)	67	0.085	0.770
GT+GG	62 (65.96%)		74 (67.9%)	136	**OR (95% CI)**	**p**
Total	94		109	203	0.916 (0.510-1.647)	0.770
Alleles	**PI**		**MPA+IPA**	**Total**	**χ2**	**p**
Allele T	109 (57.98%)		127 (58.26%)	236	0.003	0.955
Allele G	79 (42.02%)		91 (41.74%)	170	**OR(95% CI)**	**p**
Total	188		218	406	1.011 (0.681-1.502)	0.955

Out of a total of 161 subjects with a recommended body weight (BMI < 25kg/m^2), 81 declared not physically active, 43 were moderately active, while 37 were classified as highly active. Table 3 shows the distribution of genotypes and alleles of subjects with a determined BMI < 25 kg/m2 in relation to the intensity of physical activity.

Table 3.
Total and relative frequencies of genotypes of the rs17817449 FTO polymorphism according to the intensity of physical activity in subjects with BMI < 25 kg/m2

	BMI < 25				χ2	p
Genotype	**PI**	**MPA**	**IPA**	**Total**		
TT	27 (33.33%)	14 (32.56%)	13 (35.14%)	54	4.318	0.365
GT	38 (46.91%)	21 (48.84%)	22 (59.46%)	81		
GG	16 (19.76%)	8 (18.6%)	2 (5.4%)	26		
Total	81	43	37	161		
Genotype	**PI**		**MPA+IPA**	**Total**	**χ2**	**p**
TT	27 (33.33%)		27 (33.75%)	54	0.003	0.955
GT+GG	54 (66.67%)		53 (66.25)	107	**OR (95% CI)**	**p**
Total	81		80	161	1.019 (0.530-1.960)	0.955
Alleles	**PI**		**MPA+IPA**	**Total**	**χ2**	**p**
Allele T	92 (56.8)		97 (60.63%)	189	0.488	0.485
Allele G	70 (43.2%)		63 (39.37%)	133	**OR (95% CI)**	**p**
Total	162		160	322	1.171 (0.751-1.826)	0.485

Of the 42 respondents who were found to be overweight (BMI ≥ 25), 13 of them were not physically active, 14 were moderately active, while 15 were classified as highly active. Table 4. shows the frequency distributions of genotypes and alleles in relation to the intensity of physical activity in subjects with BMI ≥ 25.

Table 4.
Total frequencies of genotypes of the rs17817449 FTO polymorphism according to the intensity of physical activity in the group of respondents BMI ≥ 25

Genotype	**BMI≥ 25**				χ^2	**p**
	PI	**MPA**	**IPA**	**Total**		
TT	5 (38.46%)	3 (21.43%)	5 (33.33%)	13 (30.95%)	2.535	0.638
GT	7 (53.85%)	8 (57.14%)	6 (40.0%)	21 (50.0%)		
GG	1 (7.69%)	3 (21.43%)	4 (26.7%)	8 (19.05%)		
Total	13	14	15	42		
Genotype	**PI**		**MPA+IPA**	**Total**	**χ2***	**p***
TT	5 (38.46%)		8(27.6%)	13	0.497	0.481
GT+GG	8 (61.54%)		21(72.4%)	29	**OR (95% CI)***	**p***
Total	13		29	42	0.610 (0.153-2.429)	0.482
Alleles	**BMI≥ 25**				**χ2**	**p**
	PI		**MPA+IPA**	**Total**		
Allele T	17 (65.4%)		30 (51.73%)	47	**1.359**	0.244
Allelel G	9 (34.6%)		28 (48.27%)	37	**OR (95% CI)***	**p***
Total	26		58	84	0.567 (0.218-1.479)	0.246

Discussion

Out of a total of 203 subjects who participated in the study, 42 were overweight, while 161 had the recommended body weight. These results were expected as the study was conducted in the student population, where the age of subjects ranged from 21 to 25 years. 94 of subjects stated they were not physically activitive (PI), 57 subjects were moderately physically active (MPA) and 52 were intensely physically active (IPA).

In the total sample of this study, the risk allele G of the *FTO* polymorphism rs17817449 had a lower frequency (41.8%) compared to the normal allele T (58.13%). Accordingly, the frequency of recessive GG genotype was lower compared to the TT and GT genotypes. Although a higher frequency of the risk allele G was found in the group of overweight subjects compared to the group with BMI < 25, the difference was not statistically significant. The results of this study suggest that the G allele may not be a risk factor for the development of obesity, but as other studies show, its frequency is higher in the group of subjects with excessive body weight.

According to various studies, the rs17817449 *FTO* polymorphism shows a significant association with body mass index in the populatios of Europe and North America (Dina et al., 2007; Frayling, 2007; Price et al., 2008; Hubacek et al., 2008; Hunt et al., 2008), Korea (Cha et al., 2008) and North India (Prakash et al., 2011), but no association was found for Hispanic and African American (Wing at al., 2009) and Chinese Han populations (Li et al., 2008). In these studies an association of the rs17817449 *FTO* polymorphism with the elevated blood glucose, insulin resistance, percentage of fat tissue and blood pressure was found.

The results of this study suggest that the moderate and intense levels of physical activity may not mitigate the harmful effect of the allele G or prevent the development of excessive body mass. A higher frequency of the G allele was found in the group of subjects with a higher BMI, who engaged in certain physical activity. Out of a total of 42 subjects with a BMI ≥ 25, 29 of them performed moderate or intense physical activity, 72.4% of which were carriers of the risk allele G, genotypes GT + GG. The frequency of the same category of genotypes, GT + GG in physically active subjects and who had the recommended body mass was lower, 66.25%. Physical activity in subjects with excessive body mass was not connected to the G allele genetic risk. It might be of interest in further studies to analyze muscle mass, also other factors, such as diet in this group of subjects. This study fails to imply that physical activity could overcome the genetic predisposition for obesity. However, the uneven distribution of subjects must be taken into consideration as a limiting factor of this study.

Conclusion

According to the best of our knowledge, this is the first study of the rs17817449 *FTO* gene polymorphism relation with body mass index in the student population of northeastern Bosnia and Herzegovina. A higher frequency of the risk allele G is found in the group of subjects with excessive body mass compared to the group with recommended values. However, the difference is not statistically significant. Further studies with an even distribution of BMI categories in connection with physical activity and diet would contribute to the understanding of the association of genetic factors, lifestyle and BMI and could provide an effective prevention of the development of obesity.

Conflict of Interests

The authors declare that they have no conflict of interests.

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