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Decrease in body mass index: Personal genotyping, individual diet, and exercise plan

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ABSTRACT

Introduction: Single nucleotide polymorphisms (SNPs) have lately been used for prediction of metabolic processes that may be related to obesity. The aim of our study was to examine the association of SNPs of several genes with obesity and physical activity in 18 healthy volunteers.

Methods: We used buccal swabs to collect and extract DNA from 18 volunteers. Pyrosequencing was used for molecular analysis of 13 polymorphisms in 10 genes (APOA2, MTHFR, MCM6, peroxisome proliferators-activated receptor gamma, FABP2, beta-2-adrenergic receptor (ADRB)2, ADRB3, A-actinin-3, angiotensin-converting enzyme, and FUT2). The volunteers' personal data included body mass index (BMI), dietary practice and information on daily fitness and workout routine. Association between the 13 observed gene polymorphisms and individual BMI status (normal or overweight) was analyzed. Results of the DNA analysis were used for the expert evaluation by nutritionists and physiologists to obtain optimal regulation of nutrition and exercise. The volunteers had a dietary and fitness program for 12 months which they tracked by filling in a suitable study form.

Results: 14 volunteers had a moderate genetic predisposition for abdominal adipose-tissue accumulation, while 4 of them had genotypes not associated with abdominal fat tissue accumulation. A statistically significant difference was found between the value of BMI before and after the implementation of personalized training and nutrition plan within the group of overweight volunteers (paired sample t=3.382; p = 0.006; exact p = 0.015). The single-locus F-test showed no association between the gene polymorphisms and BMI values. In addition, no correlation was detected between the gene polymorphisms and amount of BMI reduction prior and after the implementation of the personalized training and nutrition plan within the overweighed group of volunteers.

Conclusion: Optimal nutrition and training plan are crucial for the BMI reduction as observed in the overweighed volunteers after the 12-month personalized training and individualized nutrition plan. However, the analyzed polymorphisms were not significantly associated with the obesity in this study.

Key words: Single-nucleotide polymorphisms; nutrition; physical activity; body mass index

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INTRODUCTION

Significant technological advances of single-nucleotide polymorphisms (SNPs) have further strengthened research methodologies for genetic analyses used to predict metabolic process that might be associated with diet and physical activity (1). Obesity is a major epidemic problem of the public health worldwide, characterized as an excess of adipose tissue. The most commonly used measurement to determine weight status is body mass index (BMI) (2). The World Health Organization recommends the following BMI cut points to classify weight status in adults aged 20 or older: <18.5 kg/m^2 (underweight), 18.5-24.9 kg/m^2 (normal weight), 25.0-29.9 kg/m^2 (overweight), 30.0-39.9 kg/m^2 (obese), and ≥40 kg/m^2 (extremely obese) (3). Unhealthy diet and physical inactivity have been identified as primary determinants of increased obesity. Various studies have identified more than 500 candidate genes associated with body weight, motor, and functional abilities as well as their role in the development of obesity. Therefore, genetic factors might be important in determining an individual's susceptibility to obesity (4,5). A number of studies have reported a correlation between variations of a DNA sequence in specific genes and the phenotype of obesity (6,7). Genetic variants that influence an individual's response to diet are actually metabolic pathways of fatty acids and carbohydrates, as well as the fat cells formation and the production of energy and heat. Some genetic variants are related to physical activity in reducing the amount of adipose tissue after the endurance training.

The aim of our study was to examine the utility of the existing prediction SNP test possibly related to obesity and physical activity in 18 healthy volunteers.

METHODS

We conducted the research on a total of 18 healthy volunteers (50% male and 50% female), aged 20-50. The volunteers were assigned into a group with normal BMI (7 volunteers) and group with increased BMI (11 volunteers). Height and weight were measured with participants dressed in lightweight clothing and without shoes. BMI was calculated with the weight (in kg) divided by the square of height (in m). All the subjects gave their written informed consent for the use of their biological material and data while the ethical approval for this research was obtained from the Ethics Committee of the Institute for Genetic Engineering and Biotechnology, University of Sarajevo (Approval No. 296-1/14 dated May 13, 2015).

DNA was extracted from buccal swabs using Chelex® 100, Bio-Rad, according to the manufacturers protocol. Using public databases, we selected 13 most common polymorphisms (Table 1) which are related to obesity development, cardiovascular diseases, and metabolic disorders, as well as motor and functional

TABLE 1. List of polymorphisms of the genes related to diet and exercise

Gene	Polymorphism	Protein	NCBI
FABP2	c. 163A>G	p.Thr55Ala	rs1799883
PPARG	c.-2-28078C>G	p.Pro12Ala	rs1801282
APOA2	c.-323C>T	//////	rs5082
ADRB279	c. 79C>G	p.Gin27Glu	rs1042714
ADRB246	c. 46A>G	p.Gly16Arg	rs1042713
ADRB3	c. 190T>C	p.Trp64Arg	rs4994
ACTN3	c. 1858C>T	p.Arg620Ter	rs1815739
ACE	c. 584-109_584-108ins	/////	rs464994
MTHFR677	c. 665C>T	p.Ala222Val	rs1801133
MTHFR1298	c. 1409A>C	p.Glu470Ala	rs1801131
MCM6 (LCT-13910)	c. 1917+326C>T	/////	rs4988235
MCM6 (LCT-22018)	c. 1362+117G>A	/////	rs182549
FUT2	c. 461G>A	p.Trp154Ter	rs601338

PPARG: Peroxisome proliferators-activated receptor gamma; ADRB: Beta-adrenergic receptor; ACE: Angiotensin-converting enzyme; ACTN3: A-actinin-3

abilities of the locomotor system. DNA fragments in chromosome 1 (APOA2 and MTHFR), chromosome 2 (MCM6 LCT-13910 and MCM6 LCT-22018), chromosome 3 (peroxisome proliferators-activated receptor gamma [PPARG]), chromosome 4 (FABP2), chromosome 5 (beta-2-adrenergic receptor [ADRB]2 position 1 and position 2), chromosome 8 (ADRB3), chromosome 11 (A-actinin-3 [ACTN3]), chromosome 17 (angiotensin-converting enzyme [ACE]), and chromosome 19 (FUT2) were amplified using the polymerase chain reaction (PCR). A validated set of reagents (PyroMark PCR Kit, Qiagen) was used for PCR. Amplicon sequences were analyzed using pyrosequencing (PyroMark Q24, Qiagen) which was performed in GENOS Company. Amplified ACE fragments were separated using capillary electrophoresis by 3130 genetic analyzers (Applied Biosystems). The fragment size was determined based on the familiar molecular weight standard using GeneMapper® ID-X Software (Applied Biosystems).

Statistical analysis

The Kolmogorov–Smirnov test was applied to estimate the normality of the. To estimate the difference between BMI before and after the implementation of personalized training and nutrition plan, we used the paired samples *t*-test. Once the difference in BMI between overweight and normal groups was calculated, the independent samples *t*-test was performed. The observed sample size was small, therefore, we applied the exact permutation test ($n = 10000$). Biostatistical calculations were performed using the paleontological statistics software, version 3.14 (8). A single-locus case-control test (9) based on the exact *p*-value test was performed for the allele genotypic association between the 13 observed gene polymorphisms and individual BMI status (normal or overweight). When estimating the relationship between the gene polymorphisms and BMI value, a single-locus F-test was used. The same test was applied to estimate the relationship between the gene polymorphisms and the amount of BMI reduction after the implementation of personalized training and nutrition plan. Both the above-mentioned analyses were conducted using Powermarker v3.25 (10). The statistical significance of $p < 0.05$ was considered significant.

RESULTS

The volunteers' personal genotypes (Table 2) were subjected to the expert evaluation. Personalized training and nutrition plans were obtained for each volunteer.

According to the obtained genotypes, only 5 volunteers had a genetic predisposition for obesity development, while 13 were at moderate risk for the weight increase. The genotypes of 8 volunteers indicated a genetic predisposition for weight gain due to a diet rich in fats, while the genotypes of 10 volunteers showed moderate risk. Furthermore, 14 volunteers reported a moderate genetic predisposition for abdominal adipose-tissue accumulation, while it was not the case for the other 4 volunteers whose genotype was not associated with abdominal fat tissue accumulation. Regarding the training program, the personal genotypes of 8 volunteers showed a genetic predisposition for a more efficient physiological response to training based on strength exercises. According to the genotypes of 10 volunteers, a physiological response to training should be equally efficient regardless of whether the training is based on strength or endurance.

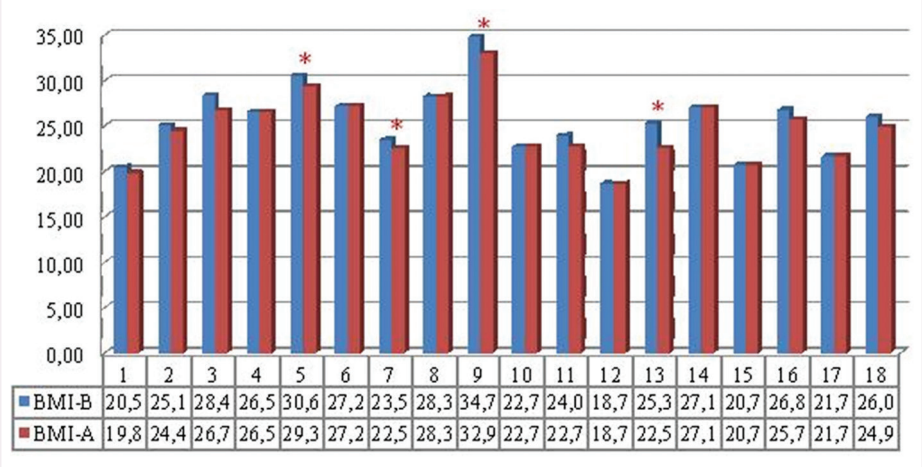
Before the 12-month diet and training program, 7 volunteers were in a BMI category with normal weight, 9 were in the overweight category, while the remaining 2 volunteers were in the obese BMI category. All 18 volunteers have followed the recommended exercise and diet plans. After 12 months, BMI values remained unchanged for 8 volunteers. Furthermore, 10 volunteers reduced the BMI value, and 4 of them even dropped to a lower BMI category (Figure 1).

The Kolmogorov–Smirnov test showed that all BMI values within observed groups were in a range of normal distribution ($p > 0.05$). A statistically significant difference was noticed between the values of BMI before and after the implementation of the personalized training and nutrition plan within the group of volunteers with overweight BMI values (paired samples $t = 3.382$; $p = 0.006$; exact $p = 0.015$). This result showed visible BMI reduction within the group of the overweighed volunteers following the implementation of the personalized training and nutrition plan. When having included only the volunteers within the normal BMI range,

TABLE 2. Volunteers' personal genotypes

Parameters	Gene	PY-113/15	PY-114/15	PY-115/15	PY-116/15	PY-117/15	PY-118/15	PY-119/15	PY-120/15	PY-129/15
		Genotype	Genotype	Genotype	Genotype	Genotype	Genotype	Genotype	Genotype	Genotype
Nutrition	FABP2	GA	GG	GG	AA	GG	AA	GA	GA	GG
	PPARG	CC	CC	CC	CG	CC	CC	CC	CC	CG
	APOA2	TT	TT	TC	TC	TC	TC	TT	TC	TC
	ADRB2 79	GG	GG	GC	GC	GC	CC	GC	GC	CC
Nutrition and physical activity	ADRB2 46	GG	GG	GA	GA	GA	AA	GA	GA	GG
	ADRB3	TT	TT	TT	TT	TT	TT	TT	TT	TT
Physical activity	ACTN3	CC	GG	CC	CC	CT	CT	CC	CC	CT
	ACE	Ins/Ins	Ins/Del	Ins/Del	Del/Del	Ins/Del	Del/Del	Ins/Del	Ins/Ins	Del/Del
Folate metabolism	MTHFR 677	CC	CT	CC	CC	TT	CT	CT	CT	CT
	MTHFR 1298	AC	AC	AA	AA	AA	AA	AA	AA	AC
Lactose intolerance	MCM6 (LCT-13910)	CC	CT	CC	CC	CT	CT	CT	TT	CT
	MCM6 (LCT-22018)	GG	GA	GG	GG	GA	GA	GA	AA	GA
Secretor status	FUT2	GG	GG	GG	AA	GG	GG	GG	GA	GA
Parameters	Genes	PY-121/15	PY-122/15	PY-123/15	PY-124/15	PY-125/15	PY-126/15	PY-127/15	PY-128/15	PY-130/15
	FABP2	GA	GA	GA	GA	GA	AA	GG	GG	GG
Nutrition	PPARG	CC	CC	CC	CC	CC	CC	CC	CC	CC
	APOA2	TT	CC	TC	TC	CC	TT	TC	TC	TC
	ADRB2 79	GC	CC	GC	GG	GC	GG	CC	CC	CC
	ADRB2 46	GG	GA	GA	GG	GA	GG	GA	GA	GA
Nutrition and physical activity	ADRB3	TT	CT	TT	TT	TT	TT	TT	TT	TT
	ACTN3	CC	CC	CT	CT	CT	CT	CC	CC	CT
Folate metabolism	ACE	Del/Del	Ins/Ins	Ins/Del	Ins/Del	Ins/Del	Ins/Del	Ins/Del	Ins/Del	Ins/Del
	MTHFR 677	CC	CT	CC	TT	TT	CC	TT	CC	CT
Lactose intolerance	MTHFR 1298	AA	AC	AA	AA	AA	AC	AA	AC	AA
	MCM6 (LCT-13910)	CT	CT	CC	CC	CC	CT	CT	CT	CT
Secretor status	MCM6 (LCT-22018)	GA	GA	GA	GG	GG	GA	GA	GA	GA
	FUT2	GA	GA	GG	GA	GA	GA	GA	GG	AA

PPARG: Peroxisome proliferators-activated receptor gamma; ADRB: Beta-adrenergic receptor; ACE: Angiotensin-converting enzyme; ACTN3: A-actinin-3



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
BMI-B	20,5	25,1	28,4	26,5	30,6	27,2	23,5	28,3	34,7	22,7	24,0	18,7	25,3	27,1	20,7	26,8	21,7	26,0
BMI-A	19,8	24,4	26,7	26,5	29,3	27,2	22,5	28,3	32,9	22,7	22,7	18,7	22,5	27,1	20,7	25,7	21,7	24,9

FIGURE 1. Body mass index (BMI) values before and after the 12-month program (*individuals who dropped to a lower BMI category).

the result showed no difference between BMI values before and after the implementation of the personalized training and nutrition plan (paired samples $t = 2.006$; $p = 0.092$; exact $p = 0.25$). The difference between the volunteers with normal and increased BMI values was reported before (independent samples $t = 5.129$; $p = 0.000$; exact $p = 0.000$) as well as after (independent samples $t = 4.915$; $p = 0.000$; exact $p = 0.000$) the implementation of the personalized training and nutrition plan. Almost one-third of the total number of volunteers reduced BMI from overweighed to normal after applying the personalized diet and workout program (Table 3). There was no statistically significant allelic and genotype association between the 13 observed polymorphisms and individual BMI status (normal or overweight) (Table 4). No difference was found in the allele and genotype frequency of the observed gene polymorphisms between the male and female volunteers (Table 4). The single-locus F-test showed no association between the gene polymorphisms and BMI values. In addition, no correlation was detected between the gene polymorphisms and amount of BMI reduction prior and after the implementation of the personalized training and nutrition plan within the overweighed group of volunteers (Table 5).

DISCUSSION

Obesity is increasing worldwide, and recent advances in the genomics technology enable the prediction of risks for obesity. Sedentary lifestyle and increased calories intake are prominent issues that often cause the obesity development and are associated with many metabolic disorders.

Recommendations for the diet and training plan were made according to the genotyping of 18 volunteers from the population of Bosnia and Herzegovina. Different studies show the association between obesity development and diet (3-7). According to the studies, FABP2, PPARG, APOA2, ADBR2, and ADRB3 polymorphisms are related to nutrition and ADRB2, ADRB3, ACE, and ACTN3 polymorphisms are related to exercise.

The intestinal fatty acid binding protein encoded by FABP2 is involved in lipid metabolism. Polymorphism c.163A>G (p.Thr55Ala) (NCBI: rs1799883) is related with the increased binding affinity for the long-chain fatty acid, which can cause an increase in BMI and the triglycerides level in the blood (11). A genotype AA of the FABP2 gene is associated with a moderate risk of increased weight gain. Both polymorphisms were detected in all the volunteers, regardless of the BMI category.

The PPARG is a transcription factor that plays a key role in the adipocyte gene expression and differentiation of adipocytes. Obesity and nutritional factors are crucial in the expression of PPARG in human adipocytes. A lower BMI is associated with polymorphisms c.-2-28078C>G (p.Pro12Ala) (NCBI: rs1801282) of this gene (12,13). However, CC homozygosity was reported in all the participants

except for two participants that presented no changes in BMI values throughout the study.

An apolipoprotein gene polymorphism c.-323C>T (NCBI: rs5082) is associated with the accumulation of abdominal fat and obesity development as a consequence of consuming food rich in saturated fats (14,15). The volunteers with TC genotype were recommended to reduce the intake of saturated fatty acids. The ADRB2 gene is expressed in adipocytes and regulates lipid metabolism. Both polymorphic variants of this gene c.79C>G (p.Gin27Glu) (NCBI: rs1042714) and c.46A>G (p.Gly16Arg) (NCBI: rs1042713) may lead to a decrease of lipid metabolism and accumulation of fat tissue (16).

The ADRB3 gene is predominantly expressed in the adipose tissue and regulates lipid metabolism and thermogenesis. A polymorphism c.190T>C (p.Trp64Arg) (NCBI: rs4994) of the ADRB3 gene may lead to impaired lipid metabolism which is related to overweight and enlarged waist circumference. Moreover, it has been reported that intensive workout decreases BMI in individuals with this genotype (17,18). The association between c.190T>C (p.Trp64Arg) polymorphisms and increased BMI is still controversial (19). In addition, ACE is important in blood pressure control. ACE gene insertion is related to a decreased ACE protein activity, therefore, better physical endurance. Deletion in this gene, is however, related to an increased ACE protein activity and the possibility to perform physical

TABLE 3. BMI values before (BMI-B) and after (BMI-A) the implementation of personalized training and nutrition plan; BMI reduction (BMI-diff)

Sample ID	BMI	Sex	BMI-P	BMI-A	BMI-diff
114	O	M	25.1	24.49	0.61
115	O	F	28.4	26.78	1.62
116	O	F	26.56	26.56	0
117	O	M	30.6	29.37	1.23
118	O	M	27.2	27.2	0
120	O	M	28.3	28.3	0
121	O	F	34.78	32.99	1.79
125	O	F	25.31	22.57	2.74
126	O	M	27.1	27.1	0
128	O	F	26.8	25.71	1.09
130	O	M	26	24.93	1.07
113	N	F	20.5	19.84	0.66
119	N	F	23.5	22.52	0.98
122	N	M	22.7	22.7	0
123	N	F	24	22.72	1.28
124	N	M	18.7	18.7	0
127	N	F	20.7	20.7	0
129	N	F	21.7	21.7	0

BMI: Body mass index

TABLE 4. Single-locus case–control test results of the allelic and genotype association between the 13 observed gene polymorphisms, individual BMI status, and gender

Marker	BMI status (normal or overweight)		Gender distribution	
	Allele exact *p*	Genotype exact *p*	Allele exact *p*	Genotype exact *p*
FABP2	1.000	0.101	0.739	1.000
PPARG	1.000	1.000	0.473	0.461
APOA2	1.000	1.000	1.000	1.000
ADRB279	0.753	0.372	1.000	0.188
ADRB246	0.721	1.000	0.729	0.789
ADRB3	0.370	0.367	0.453	0.434
ACTN3	1.000	1.000	0.411	0.351
ACE	0.493	0.649	0.508	0.657
MTHFR677	0.493	0.691	0.191	0.107
MTHFR1298	0.686	0.617	1.000	1.000
LCT-13910	0.482	0.788	0.162	0.185
LCT-22018	0.735	0.789	0.168	0.262
FUT2	0.705	0.788	0.724	1.000

BMI: Body mass index; PPARG: Peroxisome proliferators-activated receptor gamma; ADRB: Beta-adrenergic receptor; ACE: Angiotensin-converting enzyme; ACTN3: A-actinin-3

TABLE 5. Single-locus F-test results of the gene polymorphisms and BMI values association

Marker	BMI		BMI-difference*	
	F-statistics	*p*	F-statistic	*p*
FABP2	0.2394	0.7900	0.0015	0.9986
PPARG	0.2420	0.6295	1.1623	0.3090
APOA2	0.2091	0.8137	3.2132	0.0946
ADRB279	3.5841	0.0534	1.0029	0.4086
ADRB246	0.1480	0.8637	0.6025	0.5705
ADRB3	0.5056	0.4873	NaN	NaN
ACTN3	0.1193	0.7343	0.0739	0.79193
ACE	0.8668	0.4403	1.0376	0.39751
MTHFR677	0.8585	0.4436	2.6599	0.13013
MTHFR1298	1.2724	0.2760	0.6140	0.45341
LCT-13910	0.8285	0.4557	1.0951	0.37985
LCT-22018	0.6089	0.5569	0.7250	0.51363
FUT2	0.1316	0.8777	0.2477	0.78637

*Group of individuals with an increased BMI. BMI: Body mass index; PPARG: Peroxisome proliferators-activated receptor gamma; ADRB: Beta-adrenergic receptor; ACE: Angiotensin-converting enzyme; ACTN3: A-actinin-3

activities that require strength and speed (20-22). ACTN3 protein is located in fast-contractile muscle fibers that enable explosive force production in a short period of time which is ideal for sprint sports (23). Regarding the training program of personal genotypes, of 8 volunteers showed a genetic predisposition for an effective physiological response to the strength training. According to the genotypes of 10 volunteers, a physiological response to the training should be equally effective regardless of the strength- or endurance-based training.

CONCLUSION

We conclude that optimal nutrition and training plan are crucial for the BMI reduction as observed in the overweighed volunteers after the 12-month personalized training and individualized nutrition plan. However, the analyzed polymorphisms were not significantly associated with the obesity in this study. An extended research including genotyping of a larger number of participants with the observation of additional anthropometric and physiological parameters would provide more reliable data. In general, an individual approach to the obesity problems is highly recommended, and a genetic analysis of associated polymorphisms can provide valuable information for personalized training and diet programs.

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CONFLICT OF INTERESTS

Authors declare no conflict of interests.

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