

PPARGC1A GENE POLYMORPHISM AND ITS ASSOCIATION WITH OBESITY-RELATED METABOLIC TRAITS IN SERBIAN ADOLESCENT POPULATION

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Vidović V., N. Maksimović, S. Vidović, T. Damnjanović, I. Milovac, I. Novaković (2022). *PPARGC1A gene polymorphism and its association with obesity-related metabolic traits in Serbian adolescent population*. - Genetika, Vol 54, No.3, 1375 - 1384. *PPARGC1A* is involved in many metabolic processes including normal mitochondrial biogenesis, oxidation of glucose and lipids and transport of glucose into skeletal muscles. Previous researches linked this polymorphism with the higher risk of developing type 2 diabetes, metabolic syndrome and obesity. The aim of the study was to investigate the association of Gly482Ser with body mass index (BMI), fasting glucose levels and lipid profile in Serbian adolescents. The study included 147 boys and 150 girls, 15 years of age. Anthropometric and biochemical parameters were recorded. Cardiovascular and malignant diseases, type 2 diabetes, cerebral palsy and genetics syndrome were criteria for exclusion. Genotyping was performed by polymerase chain reaction-restriction fragment length polymorphism (RFLP) assay. The results showed that boys carriers of GG genotype had statistically higher mean values of TC compared to the boys who were carriers of GA+AA genotypes ($p=0.033$). However, statistical significance was not obtained for the other analyzed parameters. Furthermore, in the group of overweight and obese children, higher mean values of TC and LDL-C were observed in the carriers of GG genotype compared to carriers of GA+AA genotype for all the adolescents, as well as in the group of girls. No correlation was observed for values of BMI, fasting blood glucose and levels of triglycerides. To confirm these results, further research with larger sample size and non-genetics factor taking into consideration, would be of great interest.

Key words: Body mass index, glycaemia, lipid parameters, Gly482Ser polymorphism

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INTRODUCTION

Metabolic syndrome and *diabetes mellitus* type 2 as a major accompanying comorbidities of children and adolescent obesity are increasing worldwide, with approximately one-third of adolescents in the western countries being either overweight or obese (KANSRA *et al.*, 2021; BITEW *et al.*, 2020). In the recent time, many studies focused the aim of the research to the genetic basis of obesity and obesity-related metabolic traits. Among many gene candidates, peroxisome proliferator-activated receptor gamma coactivator 1-alpha (*PPARGC1A*) is one of the genes which role is very important in mitochondrial biogenesis, gluconeogenesis, insulin sensitivity, and β oxidation in the liver, as well as in the thermogenesis of brown adipose tissue (CARPENTIER *et al.*, 2018; ROWE and ARANY, 2014; XIA *et al.*, 2019).

The protein product of *PPARGC1A* (PGC-1 α) is involved in many metabolic processes, thus, it is not surprising that dysregulation of this protein is in a correlation with different metabolic conditions such as insulin resistance, type 2 diabetes and dyslipidemia (REGUERO *et al.*, 2021; BESSE-PATIN *et al.*, 2019). Within the *PPARGC1A* gene, the most frequently analyzed polymorphism is Gly482Ser (rs8192678), which causes the replacement of Glycine by Serine at the 482 codon. The presence of this polymorphism affects efficacy of the protein, where carriers of the Ser (A) variant have a reduced protein expression by 60% in comparison to the carriers of wild type genotype (MYLES *et al.*, 2011). In the adult populations, many studies have shown an association of this polymorphism with the increased risk of developing type 2 *diabetes mellitus*, excessed weight and metabolic syndrome, as one of the major accompanied comorbidities of obesity (CCULUUN-ERDENE *et al.*, 2020; DU *et al.*, 2019; XIA *et al.*, 2019). However, studies in children and adolescent population are not very common, thus this study was conducted to examine the correlation of rs8192678 polymorphism with levels of fasting blood glucose (FBG), lipid profile, and body mass index (BMI) in Serbian adolescent population.

MATERIALS AND METHODS

Experiment design

The 295 healthy children 15 years of age, of both genders were selected out of 6000 school children who were enrolled in the Yugoslav Study of the Precursors of Atherosclerosis in School Children (YUSAD). The YUSAD study lasted from 1989. until 2008. In 2003., during annual general medical examination in 11 pediatric centers throughout Serbia, data including age, gender, weight, height, fasting glucose level (FBG), and lipid status were collected. The biochemical parameters in terms of lipid status included values of triglycerides (TG), total cholesterol (TC), low- density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C). According to previously published charts from YUSAD study in terms of BMI values in children 15 years of age, participants were classified into three categories: normal body weight for boys (less or equal 23.5 kg/m²), overweight (>23.6 kg/m²) and obese (>27 kg/m²); for girls (less or equal 23.7 kg/m²), overweight (>23.8 kg/m²) and obese (>27.2 kg/m²) (NEDELJKOVIC *et al.*, 2006).

Exclusion criteria were generalized inflammation, genetic diseases, malignancies, *diabetes mellitus* type 1 or 2, and chronic immobility including cerebral palsy. The study protocol and design for this research was approved by Ethics Committee of University of Belgrade, Faculty of Medicine (approval number 29/X-9 from 12.10.2017.). Prior to the

experimental studies, for each participant enrolled in the study, informed consent form was signed by parents or legal guardians.

Biochemical analysis

Prior to the blood sample collection, each participants fasted for the minimum of 12 hours. Serum glucose, TC, HDL-C and TG levels were recorded according to previously described methodology (MAJKIC-SINGH *et al.*, 2006). Friedewald's equation was used to calculate the levels of LDL-C (FRIEDWALD *et al.*, 1972).

Genotyping

Molecular-genetic analysis were conducted at the University of Belgrade, Faculty of Medicine, Institute of Human genetics. Salting out method, according to MILLER *et al.* (1988), was used to isolate total genomic DNA from 5 ml of peripheral blood. Genotypes of Gly482Ser (rs8192678) were detected by restriction fragment length polymorphism (RFLP) analysis. Cycling settings included initial denaturation of 5 minutes at 94°C, as well as total of 34 cycles (denaturation of 30 seconds at 94°C, primer annealing at 54°C, polymerization and final extension at 72°C). Primers used in this research were (Fw: 5'-TTT GGA GGC AAG CAA GCAG-3', and Rev: 5'-TAT TAG GGT TTT GCC AAGG-3'). For 500 bp PCR products digestion, *Msp1* enzyme was used for 120 minutes at 37°C. After electrophoretic separation using 8.0% polyacrylamide gel electrophoresis, bands of 380bp and 120bp were present in case of G allele, while band of 500bp was present in case of allele A.

Statistical analysis

The results were analyzed by the SPSS statistical software, version 17. Mean and standard deviation were used to express the quantitative variables. In order to test the the association of selected genotypes with BMI, FBG and serum lipid levels, Kruskal Wallis test or Analysis of Variance (ANOVA) were used. Depending on the variable distribution, grouped genotypes were tested for the association with selected parameters by Mann-Whitney or Student's t-test.

RESULTS

The research included 295 children who at the moment of the study were 15 years old. Out of that number, 147 (49.5%) were boys and 150 (50.5%) were girls. In the group of boys, 26 (17.7%) were classified as overweight, while 20 (13.7%) were in the obese category. Of the total number of girls involved in the study, 26 (17.3%) were in overweight category, while 17 (11.3%) girls were classified as obese. Analysis of mean values of selected parameters according to gender are presented in table 1. The results have shown statistically higher mean values of TC ($p=0.02$) and LDL-C ($p=0.05$) in girls compared to boys. No statistical significance was found among other analyzed parameters. Allele and genotype frequencies are presented in table 2. Obtained genotypes were in Hardy-Weinberg equilibrium. Chi square did not reveal statistically significant difference in the genotype frequencies among genders ($p=0.8781$).

Table 1. Mean values of analyzed parameters according to gender for all adolescents

Parameters	Total	Boys	Girls	p Value
BMI (kg/m ²)	22.88±4.28	21.55±4.18	22.41±4.29	0.154
FBG (mmol/L)	4.67±0.64	4.78±0.61	4.61±0.67	0.490
TG (mmol/L)	0.93±0,50	1.00±0.64	0.98±0.47	0.634
TC (mmol/L)	4.34±0,86	4.17±0,75	4.50±0,94	0.002
HDL-C (mmol/L)	1.46±0,42	1.38±0,42	1.45±0,39	0.301
LDL-C (mmol/L)	2.43±0.83	2.33±0.74	2.54±0.91	0.057

BMI: body mass index; FBG: fasting blood glucose; TG: triglycerides; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol

Table 2. Frequencies of rs8192678 genotypes and alleles

rs8192678 genotypes frequency %	Boys	Girls	Total
GG	41.5	43.3	42.4
GA	49.0	48.7	48.8
AA	9.5	8.0	8.8
Alleles Frequencies			
G	64.4	65.8	65.1
A	35.6	34.2	34.9

Table 3. Mean values of analyzed parameters according to rs8192678 genotypes in overweight and obese adolescents

Parameters	Genotype	BMI>85 th pc	p Value	Boys	p Value	Girls	p Value
BMI (kg/m ²)	GG	28.24±4.30	0.303	27.94±4.26	0.724	28.20±4.43	0.317
	GA+AA	26.94±2.40		26.89±2.56		26.74±2.31	
FBG (mmol/L)	GG	4.70±0.55	0.440	4.77±0.43	0.473	4.69±0.62	0.932
	GA+AA	4.80±0.54		4.89±0.49		4.67±0.56	
TG (mmol/L)	GG	1.04±0.35	0.830	1.16±0.51	0.743	1.05±0.38	0.537
	GA+AA	1.13±0.75		1.08±0.72		1.16±0.78	
TC (mmol/L)	GG	4.72±0.97	0.019	4.37±0.85	0.529	4.90±0.99	0.045
	GA+AA	4.28±0.83		4.22±0.71		4.28±0.98	
HDL-C (mmol/L)	GG	1.32±0.36	0.450	1.23±0.34	0.924	1.36±0.37	0.876
	GA+AA	1.27±0.29		1.24±0.32		1.37±0.34	
LDL-C (mmol/L)	GG	2.96±0.95	0.019	2.66±0.99	0.621	3.06±0.93	0.007
	GA+AA	2.45±0.89		2.51±0.92		2.28±0.86	

Since only 26 adolescents harboured a minor genotype (AA), GG/GA+AA genotypes were grouped for further analysis. However, we analyzed an association of GG/GA+AA genotypes with selected parameters in the group of overweight and obese adolescents. Obtained results are shown in table 3. Overweight and obese children who were carriers of wild type genotype had statistically higher mean values of LDL-C and TC compared to the carriers of GA+AA genotype. The same results were obtained in the group of overweight and obese girls. Multiple linear regression analysis confirmed both of these results. Obtained values are (for TC $\beta=-0.242$, $p=0.039$; LDL-C $\beta=-0.283$, $p=0.021$; TC $\beta=-0.352$, $p=0.033$; LDL-C $\beta=-0.451$, $p=0.007$; respectively). BMI and glycaemia were used as covariates.

DISCUSSION

Metabolic processes including mitochondrial biogenesis, oxidation of glucose and lipids, transport of glucose into skeletal muscles, and many other are regulated by PGC-1 α protein (LV *et al.*, 2017). It has been shown that PGC-1 α has high expression in brain, heart, kidneys, white and brown adipose tissue (BESSE-PATIN *et al.*, 2019; POVEL *et al.*, 2010). Patients with *diabetes mellitus* type 2 have significantly lower expression of this gene in skeletal muscles compared to the patients with no blood glucose disorder (TAGHVAEI *et al.*, 2021). Bearing in mind that association studies of this polymorphism with various metabolic parameters and diseases in children are still rare, this study was conducted to investigate whether the rs819267 polymorphism is associated with values of fasting blood glucose, lipid profile and BMI in 15 years old children.

The results of our study do not implicate the association of rs8192678 polymorphism with BMI values. BRITO *et al.* (2009) conducted a study in Danish and Estonian population in 1255 healthy children and 855 adolescents between 5 and 18 years of age, where results did not show correlation between BMI and this polymorphism in both study group. Similar results were obtained by QUEIROZ *et al.* (2015) in Brazilian children 7-14 years of age. No association with BMI values was observed. On the other side, a research in Portugal which included 730 children of 7-12 years of age, an association of allele A has been linked to increased BMI values in children, however the result was on the verge of statistical significance (ALBUQUERQUE *et al.*, 2014).

Regarding research of lipid profile, overweight and obese girls who were carriers of wild type genotype had higher mean values of TC compared to the girls carriers of GA+AA genotypes. Also, in the group of overweight and obese children, LDL-C values were higher in the carriers of GG genotype compared to the carriers of GA+AA genotypes. Statistical significance was not reached for the other analyzed lipid parameters. In the same analyzed group, results have shown that girls who were carriers of wild type genotype had statistically higher values of LDL-C compared to the carriers of GA+AA genotypes. Differences in the mean values of triglycerides and HDL-C in correlation to rs8192678 genotype was not detected. Korean study conducted in the population of children and adolescents, did not find correlation between levels of TC, TG, and HDL-C and rs8192678, which is in line with our results (ALBUQUERQUE *et al.*, 2014). Also, study by BRITO *et al.* (2009) conducted in the Caucasian population, did not report a statistical significance in terms of mean values of lipid parameters in correlation with Gly482Ser genotype.

On the other side, many studies reported an association of rs8172678 polymorphism with the increased risk of developing *diabetes mellitus* type 2, but our study results did not indicate a statistically significant difference in FBG levels according to Gly482Ser genotype in neither examined groups. The results of available studies conducted in population of children and adolescents also do not present an association of rs8192678 polymorphism with glycemic values (BRITO *et al.*, 2009; HA *et al.*, 2015; QUEIROZ *et al.*, 2015). However, results of the studies conducted in adult populations are contradictory. One of the studies which analyzed the association of 353 polymorphisms with glycemic values, including this polymorphism, reported the association of allele A with lower FBG levels, but only in subjects with normal BMI (POVEL *et al.*, 2010). In the Meta-analysis, which included 20 studies with 16182 subjects, XIA *et al.* (2019) showed an association of allele A, especially in the carriers of AA genotype, with the higher risk of developing type 2 diabetes in the population of Caucasian and Indian origin. Besides these findings, many studies reported no association of Gly482Ser polymorphism and mean values of glycaemia (CHEEMA *et al.*, 2015; CSEP *et al.*, 2017; FANELLI *et al.*, 2005; NELSON *et al.*, 2007; RAI *et al.*, 2007; RIDDERSTRALE *et al.*, 2006).

Although, there are available data that could explain the differences in mean values of metabolic parameters among genders, such as increase in production and secretion of sex steroid hormones, growth hormone, gonadotropins and growth factors in total, as well as difference in sexual maturity (MAKSIMOVIĆ *et al.*, 2021; VIDOVIĆ *et al.*, 2021), there are very little available studies that could explain this phenomenon. Recent research conducted in the liver and brain of mice has shown that sex hormone signaling has impact on PGC-1 α expression. The sex hormone receptors can interact directly with PGC-1 α , thus increasing its expression. Lower levels of markers of hypothalamic inflammation in brain of female mice, are shown to have anti-inflammatory effects of PGC-1 α protein (MORSELLI *et al.*, 2014). Also, the estrogen of a female mice affects the increased expression of PGC-1 α protein in hepatocytes, thus having a beneficial effects on detoxification from radical oxygen particles as well as protection from nonalcoholic steatohepatitis. Given the importance of this protein on the protective effects of estrogen in the liver, female mice have been shown to be more susceptible to oxidative stress-induced obesity if the activity of this protein is reduced (VANDENBEEK *et al.*, 2018).

The study limitation is reflecting on lack of data about children's nutritional habits, level of physical activity and usage of prescribed drugs, which could affect the levels of blood glucose, lipid parameters and adiposity.

CONCLUSION

Higher mean values of TC were noticed in boys who were carriers of wild type genotype compared to the boys with GA+AA genotypes. Also, in the group of overweight and obese girls, carriers of GG genotype had higher values of TC and LDL-C compared to the girls with GA+AA genotypes. Bearing in mind the activity and role of PGC-1 α protein in various metabolic processes, it would be important to conduct further studies in pediatric population with a larger sample of participants.

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**POVEZANOST *PPARGC1A* GENSKOG POLIMORFIZMA SA METABOLIČKIM
KARAKTERISTIKAMA ASOCIRANIM SA GOJAZNOŠĆU U SRPSKIH
ADOLESCENATA**

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Izvod

PPARGC1A je značajan za brojne metaboličke procese uključujući normalnu mitohondrijalnu biogenezu, oksidaciju glukoze i lipida, te transport glukoze u skeletne mišiće. Prethodne studije su pokazale povezanost ovog polimorfizma sa povećanim rizikom od razvoja *diabetes mellitus*a tipa 2, metaboličkog sindroma i gojaznosti. Cilj studije je bio ispitati povezanost Gly482Ser polimorfizma sa indeksom telesne mase, vrednostima glukoze natašte i lipidnim statusom u populaciji adolescenata u Srbiji. Studija je obuhvatila 147 dečaka i 150 devojčica, uzrasta 15 godina. Biohemijski i antropometrijski podaci su prikupljeni. Kardiovaskularna i maligna oboljenja, diabetes tipa 2, cerebralna paraliza i genetički sindromi su bili kriterijumi za isključivanje iz studije. Genotipizacija je vršena RFLP metodom. Rezultati su pokazali da su dečaci nosioci GG genotipa imali statistički značajno više vrednosti TC u poređenju sa dečacima nosiocima GA+AA genotipova ($p=0,033$). Međutim, statistički značajna razlika nije dobijena za ostale analizirane parametre. Dalje, u grupi preuhranjenih i gojaznih devojčica, više srednje vrednosti TC i LDL-C su uočene kod nosioca GG genotipa u odnosu na nosioce GA+AA genotipova za sve ispitivane adolescente, kao i u grupi devojčica. Korelacija ovog polimorfizma sa vrednostima indeksa telesne mase, triglicerida i glukoze nije uočena. Da bi se potvrdili dobijeni rezultati potrebno je sprovesti istraživanje sa većim brojem uzoraka, te uzeti u obzir i negenetičke faktore.

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