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Original articles

ANALYSIS OF LEPTIN, ADIPONECTIN AND ADIPONECTIN GENE POLYMORPHISM AND LEPTIN RECEPTOR IN OBESE CHILDREN AND ADOLESCENTS

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Background: The aim of this study was to determine serum levels of leptin and adiponectin of obese children to identify the influence of leptin receptor gene polymorphisms on leptin resistance and leptin levels, as well as the association between the polymorphisms of adiponectin gene and adiponectin levels.

Materials and methods: A case-control study comparing a study group of 74 obese children (age 13.34±2.60 years) to a normal weight-age matched (age 13.39±2.64 years) control group of 69 children. In both groups, body mass index (BMI) and waist/hip circumference, systolic and diastolic blood pressure were measured. Also, the leptin and adiponectin levels, as well as glucose and lipid metabolism parameters, and highly sensitive C-reactive protein (hs-CRP) were measured. Insulin sensitivity was evaluated using fasting insulinemia and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR). All subjects were tested for genetic polymorphisms in LEPRQ223R (rs1137101), ADIPOQ G276T (rs1501299) and ADIPOT45G (rs2241766).

Results: The phenotypes of the obese children study group were significantly higher than in the control group in weight, BMI, waist/hip circumferences and systolic blood pressure (SBP) (P<0.001). We confirmed that in obese children the levels of leptin in the blood are increased and levels of adiponectin are decreased (P<0.001). The differences of the genotype distributions of leptin receptor (LEPRQ223R) and adiponectin (ADIPOG276T and ADIPOT45G) gene polymorphisms in the study group of obese children and a control group was not observed.

Conclusion: In this study, we demonstrated increased leptin level and significantly decreased level of adiponectin in the obese children group compared with the control group. The results of the analysis of glucose metabolism and lipidogram between the two groups showed that insulin, HOMA-IR, and triglycerides, as well as hsCRP were increased and significantly different in the group of obese children compared to the control group, as expected. However, by including a significantly larger number of tested and control samples of both sexes and age-specific groups, with a larger number of tested SNPs, the genes investigated in this study would probably give better insight into a multicomplex disease such as obesity.

Keywords: OBESITY, LEPTIN, ADIPONECTIN, GENE POLYMORPHISM

Introduction

Excessive accumulation of fatty tissue is the hallmark of obesity, a complicated multifactorial condition that is associated with a higher risk of developing a number of noncommunicable diseases. In the WHO European Region, overweight and obesity affect approximately 60% of adults and almost one in three children (29% of boys and 27% of girls). Early research from the Region's nations suggests that during the COVID-19 pandemic, the prevalence of overweight, obesity, and/or mean body mass index has increased in children and adolescents (1, 2). Etiology of obesity is complex, because it involves interaction between behaviour of the individual, its environment, and genetic factors (3).

Adipopkine leptin, which acts as a hormone was discovered in 1994. Leptin is secreted by adipose tissue and gastric mucosa and serves as the main "adipostat" in suppressing food intake and promotion of energy consumption. Leptin promotes satiety and has a central role in energy balance and weight management. The interaction of leptin with the hypothalamus, which modifies the central nervous system to control metabolic homeostasis, is a key signalling pathway of leptin. Additionally, the interaction between insulin and leptin affects the metabolism of glucose and lipids. Serum leptin increases in the fed state, drops in the fasting state, and is strongly connected with total body fat mass: greater adipose tissue means more leptin, which reflects the availability of long-term energy (4). Persons with mutations in leptin receptor are obese with paradoxically increased leptin levels in the blood, which can be explained by the leptin resistance.

The most significant adipokine released by adipose tissue is adiponectin. It plays a significant part in the metabolism and enhancing the performance of many organs (kidney, liver, vascular tissue). Adiponectin is the only one adipokine whose concentration in obesity is reduced (5). It is secreted exclusively by adipose tissue and placenta during pregnancy in large quantities compared to other hormones (6). Also, the level of adiponectin is associated with a distribution of adipose tissue and is significantly lower in those with more visceral than subcutaneous fat (7). Adiponectin influences insulin-sensitization through multiple mechanisms, by inhibiting hepatic gluconeogenesis and increasing glucose uptake in adipocytes and muscle cells (5). It appears that adiponectin could be potential target in several metabolic illnesses.

Accumulating evidence strongly support genetic component in the development of obesity. Differences in the incidence of obesity among geographic and ethnic groups also provide insight into the genetic component (8). However, it is the challenge of identifying specific genetic causes of obesity because of the complex interactions involved in its regulation. The aim of this study was to determine serum levels of leptin and adiponectin in obese children and adolescents and to identify the influence of leptin receptor gene polymorphisms on leptin resistance and levels. In addition, we examined the association between the polymorphisms of adiponectin gene and adiponectin levels.

Materials and methods

This study was complied with the Declaration of Helsinki and its amendments and approved by the Ethical Committee of the University Hospital of Split, Croatia (No. 2181-198-03-04-13-0042). Parents of all participants signed informed consent. Both, the parents, and the participants were familiar with the study protocol.

The subjects were children and adolescents aged 10-17 years (n=74), who were treated at the University Hospital Split, Department of Paediatrics due to overweight and/or obesity and meet the following criteria: a BMI above the 85th percentile for age and sex, according to the WHO Reference 5 to 19 years (z-scores). The participants did not suffer from other chronic diseases (such as diabetes, hypothyroidism or obesity associated with syndromic state such as Down and Prader Willi syndrome).

The control group consists of children and adolescents aged 10-17 years (n=69), about the same distribution by gender as well as in the study group, who do not have any endocrine, cardiovascular, gastrointestinal, and renal chronic disease and have a BMI between the 5th and the 85th percentile for age and sex and are not blood related to the participants in the study group.

Before blood analyses, all subjects underwent physical examination by paediatric endocrinologist and detailed personal and family history were taken. The body height was measured on the Harpenden stadiometer, and as the final value was taken the arithmetic mean of the three measurements at intervals of five minutes. The body mass was measured on analogue scale with precision of 0.1 kg in light clothes and without shoes. BMI was calculated by the standard formula as the ratio of weight in kilograms and height in squared meters and expressed as the percentiles and corrected Z-score. Waist and hips were measured with inelastic meter ribbon just above the iliac crest and pubic symphysis in centimetres. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were the mean of three consecutive measurements in sitting position. A venous blood samples were taken from all subjects after overnight fasting (12 hours). Glucose, total cholesterol, triglycerides (Tg), high-density lipoprotein cholesterol (HDL) and low-density cholesterol (LDL) were determined in serum using routine enzymatic methods, using Architect 16200 instrument (Abbott, Chicago, Illinois, United States). High sensitivity CRP was measured in serum by immunoturbidimetry with related commercial kits of the same manufacturer. Fasting insulin was measured by electro-chemiluminescence immunoassay Elecsys Insulin MCE on Elecsys 2010, Roche, Germany; sensitivity 1.39 pmol/L.

Serum samples for leptin and adiponectin analysis was stored at -80°C until the analysis. Blood samples collected for the DNA and gene polymorphisms analyses was stored at -20°C. Concentrations of leptin and adiponectin were analysed by enzyme-linked immunosorbent assay (ELISA). Immunoassay kits Human Leptin ELISA Clinical Range (BioVendor-Lab Medicine, Brno, Czech Republic) with sensitivity of 0.2 ng/mL and Human Total Adiponectin ELISA kit (BlueGene Biotech, Shanghai, China) with sensitivity of 0.1 mg/mL were employed.

Genomic DNA was isolated by the method of "salting out" of a layer of leukocyte "buffy coat" remaining after centrifugation of blood samples. The amount of DNA extracted was determined by spectrophotometry. PCR-RFLP was used to identify SNPs gene LEPR (QR, QQ, RR) and ADIPOQ (TT, GT, GG). Certain polymorphisms were selected review of existing literature and GWAS's base polymorphisms of genes of interest. PCR-RFLP based assay was utilized to genotype SNPs of LERPQ223R and ADIPOG276T genes. PCR primers were LEPR SNP Q223R (rs1137101) F: 5'-ACC CTT TAA GCT GGG TGT CCC AAA TAG-3' and R: 5'-AGC TAG CAA ATA TTT TTG TAA GCA ATT-3'; ADIPOQ SNP G276T (rs1501299) F: 5'-GGC CTC TTT CAT CAC AGA CC-3' and R: 5'-AGA TGC AGC AAA GCC AAA GT-3'; ADIPOT45G F: 5'-GTG CTT GGT CCT GTG CTC A-3' and R: 5'-AAG TAG TGT CTG GAG GAT GT-3' (9-11).

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Table 1.
Anthropometric characteristics of the study group of obese children and a control group (N=143).

Parameters	Study group (N=74)	Control group (N=69)	P*
Gender ‡	34 males, 40 females	33 males, 36 females	0.81
Age (years) §	13.34±2.60	13.39±2.64	0.923
Weight (kg) §	82.61±18.1	54.82±14.49	<0.001
Height (cm) §	166.03±11.33	164.19±14.91	0.402
BMI (kg/m2) §	29.79±4.86	19.86±2.65	<0.001
BMI (percentiles) §	97±2.2	58.3±23.7	<0.001
BMI (z-score) §	2.01±0.4	0.23±0.72	<0.001
Waist circumference (cm) §	100.6±9.1	68±7.3	<0.001
Hip circumference (cm) §	111.1±11.1	83.3±10.6	<0.001
Waist-hip ratio§	0.89±0.06	0.81±0.05	<0.001
SBP (mmHg) §	121.2±12.3	106.5±9.3	<0.001
DBP (mmHg) §	69.3±9.6	70±11.3	0.721

‡ Results are shown as an absolute numerical value (N); § Results are presented as mean ± standard deviation. Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure

Statistical analysis

Statistical power calculation was performed to ensure the study has adequate sample size to detect the association of genetic variants and obesity and its related traits by using Quanto version 1.2.4 (http://biostats.usc.edu/Quanto.html). The statistical power was set to be 80% (two-sided) at 5% level of significance.

The data were analysed using Statistical Package for Social Sciences (SPSS) for Windows® Version 17.0 (SPSS Inc, Chicago, IL, USA). Allelic frequencies for each SNP were estimated by gene counting and the distribution of genotypes was tested for Hardy-Weinberg equilibrium using the Chi-square ($\chi 2$) test. The normality of distributions of continuous variables was tested with the Kolmogorov-Smirnov and Shapiro-Wilk tests. Data for continuous variables were presented as means ± standard deviations (SD) or median (interquartile range, IQR) and as frequency for categorical variables. Spearman's rank correlation was used to measure the strength and direction of association between two ranked variables. A P value of less than 0.05 was considered statistically significant.

Results

General anthropometric characteristics of all participants (N=143), along with glucose levels and lipid metabolic parameters are shown in Table 1 and Table 2. The observed parameters weight, BMI, waist/hip circumferences and systolic blood pressure (SBP) in the obese children study group were significantly higher than in the control group (P<0.001).

Table 2.
Results of the analysis of glucose metabolism and lipidograms in the study group of obese children and control group.

Parameters	Study group (N=74)	Control group (N=69)	P*
Fasting blood glucose (mmol/L)‡	4.62(±0.06)	5.12 (±0.05)	<0.001
Insulin (mU/L)‡	18.75±12.19	10.43±4.94	<0.001
HOMA-IR‡	3.97±2.9	2.29±1.14	<0.001
Total cholesterol (mmol/L)‡	4.01±0.75	4.08±0.77	0.614
LDL (mmol/L) ‡	2.29±0.58	2.25±0.65	0.679
HDL (mmol/L) ‡	1.12±0.24	1.45±0.32	<0.001
Triglycerides (mmol/L) ‡	1.07±0.49	0.79±0.01	<0.001
hsCRP (mg/L) ‡	2.94±2.79	0.72±1.03	<0.001

‡ Results are presented as mean ± standard deviation. Abbreviations: HOMA-IR, homeostatic model assessment for insulin resistance; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; hsCRP, high-sensitivity c-reactive protein

Table 3.
Serum levels of leptin and adiponectin in the study group of obese children and a control group.

Parameters	Study group (N=74)	Control group (N=69)	P*
Leptin (ng/mL) ‡	33.03±20.92	8.64±6.89	<0.001
Adiponectin (ng/mL) ‡	3.59±0.94	6.46±0.91	<0.001

‡ Results are presented as mean ± standard deviation.

Table 4.
Genotype distributions of leptin receptor (LEPRQ223R) and adiponectin gene polymorphisms (ADIPOG76T and ADIPOT45G) in group of obese children and a control group.

Polymorphism		Study group (N=74)	Control group (N=69)	P*
LEPRQ223R				0.947
	QQ	20 (52.6%)	18 (47.4%)	
	QR	41 (50.6%)	40 (49.4%)	
	RR	13 (54.2%)	11 (45.8%)	
ADIPOG276T				0.632
	GG	7 (63.6%)	4 (36.4%)	
	GT	45 (52.3%)	41 (47.7%)	
	TT	22 (47.8%)	24 (52.2%)	
ADIPOT45G				0.363
	GG	0 (0%)	1 (100%)	
	TG	13 (61.9%)	8 (38.1%)	
	TT	61 (50.4%)	60 (49.6%)	

‡ Results are shown as an absolute numerical value (N) and the percentage (%).

Table 5.
Correlation analysis between hsCRP and leptin and adiponectin serum levels.

Total sample (n=143)	LEPTIN (ng/mL)	ADIPONECTIN (ng/mL)	hsCRP (mg/L)
LEPTIN (ng/mL)	1.000	-0.568**	0.547**
		<0.001	<0.001
ADIPONECTIN (ng/mL)	-0.568**	1.000	-0.513**
	<0.001		<0.001
Study group (n=74)			
LEPTIN (ng/mL)	1.000	-0.035	0.346**
		0.767	<0.003
ADIPONECTIN (ng/mL)	-0.035	1.000	-0.093
	0.767		0.431

**Correlation is significant at 0.01 level (2-tailed). *Spearman's correlation coefficient.

Results of the analysis (Table 2) revealed that insulin, HOMA-IR, triglycerides along with hsCRP were increased and significantly different in the obese children group compared with the control group (P<0.001), while fasting blood glucose, and HDL were decreased in obese children compared with the control group (P<0.001). According to the modified IDF criteria for children and adolescents the overall prevalence of metabolic syndrome (MS) in our stu-

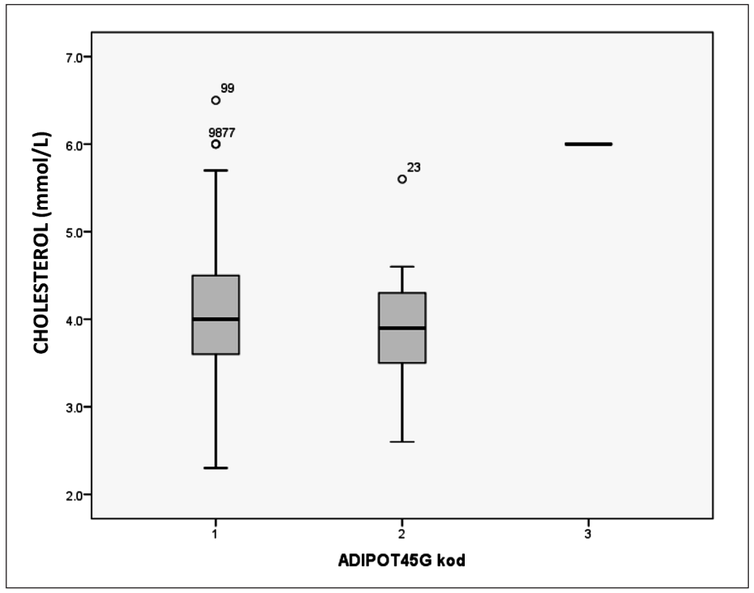

Figure 1a.
Association of ADIPOT45G with cholesterol levels in total sample/all tested subjects (n=143). (ADIPOT45G genotypes are coded: 1- TT, 2-TG, and 3-GG. Tested subjects whose cholesterol values deviate are shown numerically on the plot).

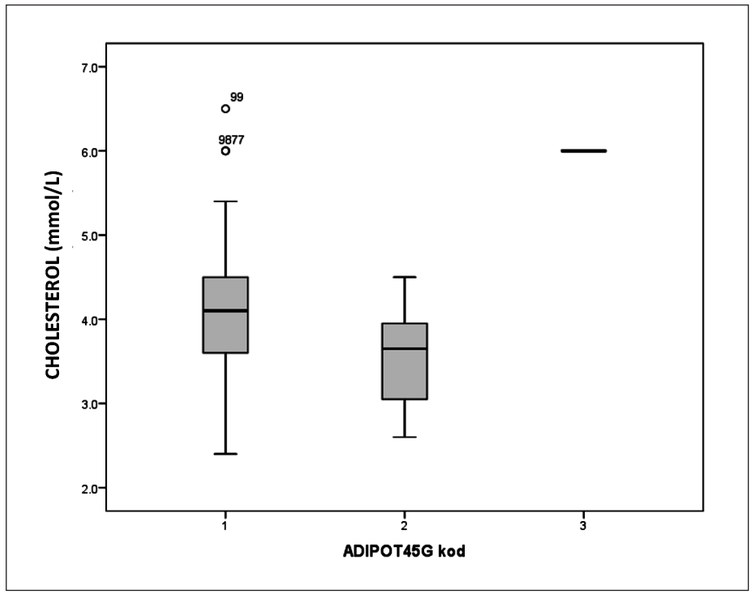

Figure 1b.
Association of ADIPOT45G with cholesterol levels in control sample (n=69). (ADIPOT45G genotypes are coded: 1- TT, 2-TG and 3-GG. Tested subjects whose cholesterol values deviate are shown numerically on the plot).

dy group was 19.6%. Most children and adolescents in our study had one or two components of MS.

The serum levels of leptin (Table 3) were significantly increased, while adiponectin levels were significantly decreased in the study group of obese children compared with the control group (P<0.001).

The genotype distribution of LEPRQ223R, ADIPOT45G, but not ADIPOG76T, were in Hardy-Weinberg equilibrium in total sample, obese children study group as well as in control group. The differences of the genotype distributions of leptin receptor (LEPRQ223R) and adiponectin gene polymorphisms (ADIPOG76T and ADIPOT45G) in the study group of obese children and a control group were not observed (Table 4).

There is a statistically significant positive correlation between the levels of leptin and hsCRP (r=0.547, P<0.001) and a negative correlation between leptin and adiponectin levels (r=-0.568, P<0.001) in the entire sample. Statistically significant correlation was observed between leptin and hsCRP in the study group (r=0.346, P<0.003) (shown in Table 5).

Discussion

In this study, we demonstrated increased leptin level and significantly decreased level of adiponectin in the obese children group compared with the control group. Anthropometric characteristics were significantly different in the obese group compared with the control group. The phenotypes of the obese children study group were significantly higher than in the control group in weight, BMI, waist/hip circumferences and systolic blood pressure (P<0.001). Interestingly, systolic blood pressure was significantly increased in the study group, while diastolic blood pressure was not different (Table 1). The data obtained in this study differ from the results of other studies. Friedmann et al. in a meta-analysis, which included 63 studies with 49.220 children, showed that children with obesity are at a significantly increased risk for cardiovascular disease, and they have higher SBP and DBP. This difference can

be attributed to the significantly smaller number of children in this study (12).

Results of the analysis of glucose metabolism and lipidograms of the obese children and a control group revealed that insulin, HOMA-IR, triglycerides along with hsCRP were increased and significantly different in the obese children study group compared with the control group. We did not expect that fasting blood glucose would be lower in obese children compared to the control group. HDL was decreased in the obese children study group as already observed (Table 2) (13).

The serum levels of leptin were significantly increased, while adiponectin were significantly decreased in the obese children group compared with the control group (shown in Table 3). These findings coincide with research of Gherlan et al. in which the level of leptin in the plasma was significantly higher in the obese group compared to the control group, while the level of adiponectin was significantly lower in obese children compared to children of normal body weight (4). Also, Frithioff-Bøjsøe et al. showed that leptin, adiponectin, and their ratio could be used as markers of insulin resistance and cardiometabolic risk in childhood obesity (14). Higher leptin levels in the obese group might be caused by leptin receptor resistance in the obese group, leading to cell deficiencies of leptin and abnormal satiety regulation (15).

Several studies analysed basal concentrations of leptin and adiponectin in obese children and adolescents. Most of them compared levels of leptin and adiponectin in obese children and adolescents before and after the intervention (modification of lifestyle through diet and exercise) (16-18).

In Italian cohort, Cambuí et al., after a one-year intervention, recorded an increase in adiponectin levels in children whose BMI dropped, while leptin levels were independent of the change in BMI (8). While, in the study of Blüher et al. in Germany, also after of one-year duration of the modification of lifestyle, levels of leptin in obese children fall after the reduction of body weight, and adiponectin levels did not show significant changes (19). After 4-6 weeks of hospital treatment of obesity in children, Siegrist et al. noticed a decrease in leptin levels and increase in levels of adiponectin (20). A possible cause of the inconsistency of the results is the different number of subjects and study locations, due to the different impact of psychosocial factors in the hospital and at home, and the duration of the procedure.

The genotype distribution of LEPRQ223R, ADIPOT45G, but not ADIPOG76T, was in Hardy-Weinberg equilibrium in total sample, in obese children study group as well as in control group. The differences of the genotype distributions of leptin receptor (LEPRQ223R) and adiponectin (ADIPOG76T and ADIPOT45G) gene polymorphisms in the study group of obese children and a control group was not observed (Table 4). These findings are concordant with the results from Japanese cohort, in which Endo et al. investigated whether LEPRQ223R polymorphism for leptin receptor gene is associated with obesity in school-age children and showed that there is no connection between this polymorphism and obesity (21). Similarly, in the study of Pyrzak et al. there was no evidence for association of LEPR Q223R gene polymorphism in obese children BMI, lipid metabolism and leptin levels and insulin resistance (22). Interestingly, analysed levels of leptin from the umbilical cord of dizygotic and monozygotic twins showed statistically significant association of LEPR Q223R SNP with weight and later development of metabolic disease (23).

Just like the frequency of polymorphisms in the LEPR gene, the frequencies of genotypes in adiponectin gene (TT, GT and GG), were not statistically significant among studied groups. Results of a systematic review show that polymorphisms in ADIPOQ gene increase the risk of obesity and that polymorphism in the LEPR gene has no influence on the development of obesity. However, the included studies on LEPR gene polymorphisms had inadequate samples resulting in inadequate statistical processing. Thus, the present negative results are still underpowered and further clarification may be obtained from studies with a larger number of subjects (24, 25).

By reviewing available literature and comparing results, we observed that the levels of leptin and adiponectin and variations of their genes are most studied in the adult population and its geographic and gender subpopulations, as well as healthy children (16-18, 26-29).

Correlation analysis between hsCRP and leptin and adiponectin serum levels (shown in Table 5) revealed statistically significant positive correlation between the levels of leptin and hsCRP and a negative correlation between leptin and adiponectin in the entire sample. The statistically significant positive correlation was observed between the levels of leptin and hsCRP in obese children study group. The obtained results are in accordance with the literature on the endocrine function of adipose tissue in obese children, with elevated values of both pro-inflammatory cytokines and hsCRP, which was observed in studies of children who were monitored for a longer period (30). Statistical significance for total cholesterol levels was observed in both investigated groups. Subjects with genotype 1 (TT) has a higher level of cholesterol (Figure 1a and Figure 1b). However, for more credible results, it would be necessary to include a much larger number of subjects than in this study.

Conclusion

We confirmed that in obese children the levels of leptin in the blood are increased and levels of adiponectin are decreased. Contrary to expectations, the results suggest that genetic variability in leptin receptor does not affect the resistance of the leptin receptor and consequently is not associated with higher concentrations of leptin levels in obese children and adolescents. The distribution of the frequency of polymorphisms in genes for adiponectin in the examined groups of obese children as well as in the control group showed no connection between individual polymorphisms with levels of adiponectin in the blood. The reasons for these results, different from the assumed, could be insufficiently num-

ber of subjects involved in the study and control group, and the higher complexity of the pathogenesis in obesity. However, by including a significantly larger number of tested and control samples of both sexes and age-specific groups, with a larger number of tested SNPs, the genes investigated in this study would probably give better insight into a multicomplex disease such as obesity.

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Sažetak

ANALIZA LEPTINA, ADIPONECTINA I POLIMORFIZMA GENA ZA ADIPONECTIN I RECEPTORA ZA LEPTIN U PRETILE DJECE I ADOLESCENATA

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Cilj rada: Cilj ovog istraživanja bio je odrediti razine leptina i adiponektina u serumu pretile djece i utvrditi utjecaj polimorfizama gena receptora za leptin na razine leptina, kao i povezanost između polimorfizama gena za adiponektin i razine adiponektina.

Materijali i metode: U ovoj studiji je analizirana i uspoređena skupina pretile djece (N=74, dob 13,34±2,60 godina) s kontrolnom skupinom od 69 djece normalne težine (dob 13,39±2,64 godine). U obje skupine mjeren je indeks tjelesne mase (BMI) te opseg struka i bokova, sistolički i dijastolički krvni tlak. Također, mjerene su razine leptina i adiponektina, kao i parametri metabolizma glukoze i lipida, te visoko osjetljivi C-reaktivni protein (hs-CRP). Inzulinska osjetljivost procijenjena je pomoću inzulinemije natašte i homeostatskog modela procjene inzulinske rezistencije (HOMA-IR). Svim ispitanicima analiziran je genetički polimorfizam u LEPRQ223R (rs1137101), ADIPOQ G276T (rs1501299) i ADIPOT45G (rs2241766).

Rezultati: Parametri u skupini pretile djece bili su značajno viši nego u kontrolnoj skupini u težini, BMI-u, opsegu struka/bokova te sistoličkom krvnom tlaku (SBP) (P<0,001). Potvrdili smo da su u pretile djece razine leptina u krvi povišene, a razine adiponektina snižene (P<0,001). Nisu uočene razlike u raspodjeli genotipova polimorfizama gena za leptinski receptor (LEPRQ223R) i adiponektin (ADIPOG276T i ADIPOT45G) u ispitivanim skupinama pretile djece i u kontrolnoj skupini.

Zaključak: U ovoj smo studiji pokazali povećanu razinu leptina i značajno smanjenu razinu adiponektina u skupini pretile djece u usporedbi s kontrolnom skupinom. Rezultati analize metabolizma glukoze i lipidograma između dviju skupina pokazali su da su inzulin, HOMA-IR i trigliceridi, kao i hsCRP bili povećani i značajno različiti u skupini pretile djece u usporedbi s kontrolnom skupinom, kao što se očekivalo. Međutim, uključivanjem znatno većeg broja ispitivanih i kontrolnih uzoraka obaju spolova i dobno specifičnih skupina, s većim brojem testiranih SNP-ova, geni istraživani u ovoj studiji najvjerojatnije bi dali bolji uvid u multikompleksnu bolest kao što je debljina.

Ključne riječi: DEBLJINA, LEPTIN, ADIPONECTIN, POLIMORFIZAM GENA

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