

THE ASSOCIATION OF OBESITY AND LIVER ENZYME ACTIVITIES IN A STUDENT POPULATION AT INCREASED RISK FOR CARDIOVASCULAR DISEASE

VEZA IZMEĐU GOJAZNOSTI I AKTIVNOSTI JETRENIH ENZIMA
U STUDENTSKOJ POPULACIJI SA POVEĆANIM RIZIKOM
ZA NASTANAK KARDIOVASKULARNIH BOLESTI

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Summary

Background: It has been reported that obesity is associated with metabolic syndrome, insulin resistance, cardiovascular risk but also with nonalcoholic fatty liver disease (NAFLD). The prevalence of obesity in children and adolescents is increasing rapidly all over the world. The aim of this study was to analyze the value of liver enzymes: AST, ALT and γ GT in a group of obese students in order to establish their correlation to anthropometric parameters such as: BMI (body mass index), WC (waist circumference), HC (hip circumference), and WHR (waist-to-hip ratio) compared to non-obese students who comprised the control group (CG).

Methods: In this study, 238 students from the University of Novi Sad of both sexes (126 men and 112 women) with a mean age of 22.32 ± 1.85 years were included. According to the body mass index (BMI) lower and higher than 25 kg/m^2 and waist circumference (WC) lower and higher than 94 cm (80 cm for females) the whole group of 238 students was divided into 2 subgroups: the obese group at increased risk for CVD (Group 1) and the group at lower risk for CVD (Group 2). AST, ALT and γ GT activities were determined in fasting blood samples.

Results: Statistical processing data revealed significantly higher values of AST, ALT and γ GT in the group of students with $\text{BMI} > 25 \text{ kg/m}^2$, $\text{WC} > 94 \text{ cm}$ for males and $\text{WC} > 80 \text{ cm}$ for females, $\text{HC} > 108 \text{ cm}$ for males and $\text{HC} > 111 \text{ cm}$ for females, and $\text{WHR} > 0.90$ for males and $\text{WHR} > 0.80$ for females ($P < 0.001$). Significant association was established

Kratak sadržaj

Uvod: Poznato je da je gojaznost povezana sa metaboličkim sindromom, insulinskom rezistencijom i kardiovaskularnim rizikom, ali takođe i sa nealkoholnom hroničnom jetrenom bolešću. Prevalenca gojaznosti kod dece i adolescenata je u značajnom porastu svuda u svetu. Cilj ovog rada bio je da se odrede i analiziraju vrednosti jetrenih enzima: aspartat aminotransferaze (AST), alanin aminotransferaze (ALT) i γ -glutamil transferaze (γ GT) u jednoj grupi gojaznih studenata i da se utvrdi njihova korelacija sa antropometrijskim parametrima: indeksom telesne mase (ITM), obimom struka (OS), obimom kuka (OK) kao i odnosom struk–kuk (OSK).

Metode: Dve stotine trideset osam studenata Novosadskog univerziteta je uključeno u ovu studiju; od toga 126 muškaraca i 112 žena, prosečne starosti $22,32 \pm 1,85$ godina. Na osnovu vrednosti ITM manjeg ili većeg od 25 kg/m^2 i OS manjeg ili većeg od 94 cm (za muškarce) tj. 80 cm (za žene), cela grupa studenata podeljena je u dve podgrupe: Grupu 1 (gojazni) – sa povećanim rizikom za nastanak kardiovaskularnih bolesti i Grupu 2 – sa smanjenim rizikom za nastanak istih. Aktivnost enzima AST, ALT i γ GT određivana je u uzorcima krvi uzetih natašte.

Rezultati: Statističkom obradom podataka utvrđene su statistički značajno veće vrednosti enzima AST, ALT i γ GT u grupi studenata sa $\text{ITM} > 25 \text{ kg/m}^2$ i $\text{OS} > 94 \text{ cm}$ (za muškarce) tj. $\text{OS} > 80 \text{ cm}$ (za žene), $\text{OK} > 108 \text{ cm}$ (za muškarce) tj. $\text{OK} > 111 \text{ cm}$ (za žene) i $\text{OSK} > 0,90$ (za muškarce) tj. $\text{OSK} > 0,80$ (za žene). Utvrđena je takođe i značajna asoci-

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between anthropometric parameters and liver enzyme levels ($P < 0.0001$).

Conclusions: Obese students with higher BMI, WC, HC and WHR values have higher liver enzyme activities and a higher chance to develop NAFLD in the future.

Keywords: obesity, liver enzymes, nonalcoholic fatty liver disease, cardiovascular risk

Introduction

Recently, obesity and related cardiovascular disease (CVD) have become a major physical, social and economic burden globally. The prevalence of obesity in children and adolescents is increasing rapidly both in high-income and middle and low-income countries. There are about 155 million overweight children and adolescents worldwide, of which about 30 to 45 million are obese (1, 2).

The association of obesity with chronic diseases in adults, in particular cardiovascular disease is well known (2). One of the most important cardiovascular diseases associated with obesity is hypertension. Risk estimates from population studies suggest that more than 75% of hypertension cases can be directly attributed to obesity (3).

Increasing weight also has a strong correlation with elevated triglycerides and low-density lipoprotein (LDL), total cholesterol levels as well as low levels of high-density lipoprotein (HDL). Some studies found that overweight was a significant risk factor for development of diabetes in women (4). The association of obesity with insulin resistance the metabolic syndrome and cardiovascular risk has also been reported, and is not only related to the degree of obesity but also to the body fat distribution. Individuals with a higher degree of central adiposity develop this syndrome more frequently than those with a peripheral body fat distribution (5–8).

Nonalcoholic fatty liver disease (NAFLD) is another consequence of obesity. NAFLD includes different types of liver pathologies and outcomes, from simple steatosis to nonalcoholic steatohepatitis (NASH) (9). NAFLD usually develops in children who are obese (10). While abnormalities in liver enzymes in pediatric NAFLD are moderate (11), a correlation between the degree of obesity and the severity of hepatic steatosis at ultrasonography has been reported (10, 12). Among adults, NAFLD markers such as alanine aminotransferase (ALT) might predict the metabolic syndrome independently. A study of Oliveira et al. (13) in children and adolescents found a strong association of elevated ALT values with the metabolic syndrome and obesity.

The aim of our study was to analyse the values of liver enzymes (AST, ALT and GT) in obese and non-obese students in order to establish their correlation

between anthropometric parameters and liver enzyme levels ($P < 0.0001$).

Zaključak: Na osnovu dobijenih rezultata može se zaključiti da gojazni studenti sa većim vrednostima ITM, OS, OK i OSK imaju i veće vrednosti jetrenih enzima i veću šansu da dobiju nealkoholnu hroničnu bolest jetre (steatozu) u budućnosti.

Ključne reči: gojaznost, jetreni enzimi, nealkoholna bolest jetre, kardiovaskularni rizik

to anthropometric parameters such as: body mass index – BMI, waist circumference – WC, hip circumference – HC, and waist-to-hip ratio – WHR, in relation to increased risk for NAFLD in the group of students at increased risk for CVD.

Materials and Methods

In a cross-sectional study conducted at the Student Health Protection Institute, University of Novi Sad, a total of 238 students aged 18 to 29 (22.32 ± 1.85) were examined (126 males and 112 females). They went through a regular medical checkup from April 2009 to April 2011. From the total number of students, 164 were obese or overweight ($BMI > 25 \text{ kg/m}^2$) and had a $WC > 94 \text{ cm}$ for men and $WC > 80 \text{ cm}$ for women, and they comprised the group with increased risk for CVD (Group 1). The remaining 74 students who had $BMI < 25 \text{ kg/m}^2$ and $WC < 94 \text{ cm}$ (80 cm for females) comprised the control group (Group 2). Each student filled in a questionnaire about their habits, including physical activity, smoking, alcohol intake, family history of CVD, etc. The blood samples for analysis were taken after a 12–14 hours overnight fast. In the blood samples taken from the subjects, the following parameters were analysed: glucose, lipo- and apoprotein levels, AST, ALT and γ GT activities. All laboratory tests were done immediately. All subjects gave their informed consent for participation in this study, approved by the local Ethics Committee.

Statistical analysis was performed by the MedCalc v.9.4.2.0 statistical package using the Student's t-test, Mann-Whitney U test, Chi-Square, and Fisher's exact test. Results were presented as mean \pm SD and median and interquartile range. Spearman's rank and Pearson's correlation test was used to define correlations of the individual parameters between and within the tested groups. All statistical tests were two-tailed. P values ≤ 0.05 were considered statistically significant. Logistic regression analysis was used to assess the association between the anthropometric parameters and the liver enzyme levels.

Results

Statistical processing data revealed significantly higher values of ALT ($P < 0.0001$), AST ($P < 0.0001$)

Table I Anthropometric parameters and liver enzyme values in the group of obese students at increased risk for CVD and nonobese students.

Parameters	Group 1	Group 2	P
N	164	74	–
M/F	105/59	21/53	–
BMI (kg/m ²) ^b	28.02 25.95–30.88	20.3 19.05–22.2	<0.0001
WC (cm) ^b	96.5 90.0–104.0	73.0 68.0–79.0	<0.0001
HC (cm) ²	115 110–120	98.0 94.75–103.0	<0.0001
WHR ^a	0.84±0.066	0.74±0.045	<0.0001
AST (U/L) ^b	25.6 20.55–32.73	23.1 21.0–25.0	0.0003
ALT (U/L) ^b	25.1 17.45–41.65	17.6 15.0–21.5	<0.0001
γGT (U/L) ^b	28.5 21.9–37.2	20.3 17.0–23.3	<0.0001

^a Arithmetic mean ± 1 standard deviation (SD)

^b Median and interquartile range

BMI – body mass index, WC – waist circumference, HC – hip circumference, WHR – waist-to-hip ratio

and GT ($P < 0.0001$) in the group of students with a BMI > 25 kg/m² (Group 1) compared to nonobese students (Table I). There was no difference in glucose values between the tested groups ($P > 0.05$). Higher waist circumference (WC) was found in 137 (83.5%) students in Group 1 and only 1 student (1.4%) in Group 2 ($P < 0.01$). The WC values were significantly higher in Group 1 (90–104 cm) compared to Group 2 (68–79 cm) ($P < 0.000$), as well as HC values ($P < 0.000$) and the waist-to-hip ratio ($P < 0.000$). The average BMI value in Group 1 was 28.85 ± 3.86 kg/m², and that was significantly higher compared to the BMI value in Group 2 (20.52 ± 2.07 kg/m²) ($P < 0.000$).

A family history of CVD was found in 135 students (82.3%) from the group at increased risk for CVD (Group 1), and also in 48 students (64.9%) from the control group (Group 2) ($P < 0.01$). A total of 134 students from Group 1 (81.7%) had a normal arterial blood pressure (BP; up to 120/80 mmHg), 10 students had a slightly higher BP (prehypertension; BP up to 130/90 mmHg) (6.1%) and 20 students had hypertension (140/90 mmHg) (12.2%). Compared to Group 2, there was no significant difference in BP frequency between the studied subgroups of students ($\chi^2 = 3.87$; $P > 0.05$).

Significantly higher values of AST and ALT ($P = 0.005$) but not γGT ($P = 0.138$) were found in the

Table II The calculated odds ratio between anthropometric parameters and liver enzyme levels.

Parameters	OR	95% CI	χ ²	P
BMI > 25 kg/m ² & ALT	1.09	1.05–1.13	45.04	<0.0001
BMI > 25 kg/m ² & AST	1.19	1.07–1.18	28.72	<0.0001
BMI > 25 kg/m ² & γGT	1.14	1.09–1.20	51.68	<0.0001
WC > 80 cm & ALT	1.02	0.99–1.05	2.05	0.152
WC > 80 cm & AST	1.01	0.96–1.07	0.275	0.600
WC > 80 cm & γGT	1.05	1.00–1.09	6.40	0.011
WC > 94 cm & ALT	1.04	1.01–1.06	12.38	0.0004
WC > 94 cm & AST	1.05	0.998–1.095	4.65	0.031
WC > 94 cm & γGT	1.08	1.03–1.14	15.99	0.0001
WHR > 0.90 & ALT	1.04	1.015–1.06	18.05	<0.0001
WHR > 0.90 & AST	1.09	1.04–1.15	18.00	<0.0001
WHR > 0.90 & γGT	1.03	1.00–1.06	5.01	0.025
WHR > 0.80 & ALT	1.04	1.02–1.08	8.46	0.0036
WHR > 0.80 & AST	1.11	1.04–1.20	10.31	0.0013
WHR > 0.80 & γGT	1.01	0.98–1.05	0.686	0.407
HC > 108 cm & ALT	1.06	1.00–1.11	9.86	0.0017
HC > 108 cm & AST	1.13	1.03–1.23	10.63	0.0011
HC > 108 cm & γGT	1.12	1.03–1.20	13.29	0.0003
HC > 111 cm & ALT	1.03	1.00–1.06	4.45	0.035
HC > 111 cm & AST	1.02	0.97–1.08	0.643	0.422
HC > 111 cm & γGT	1.04	1.00–1.08	5.48	0.019

BMI – body mass index, WC – waist circumference, HC – hip circumference, WHR – waist-to-hip ratio, OR – odds ratio, 95%CI – 95% confidence interval, χ² – Chi-square, P – significance of difference

males of Group 1 compared to females in the same group. A significant and positive correlation was found between BMI and AST in Group 1 ($\rho = 0.305$; $P < 0.01$), BMI and ALT ($\rho = 0.295$; $P < 0.01$), as well as between WC and AST ($\rho = 0.360$; $P < 0.01$) and WC and ALT ($\rho = 0.414$; $P < 0.01$). A significant and moderate correlation was found between WHR and ALT ($\rho = 0.345$; $P < 0.001$), WHR and AST ($\rho = 0.230$; $P = 0.004$) and WHR and γGT ($\rho = 0.210$; $P = 0.008$).

A positive and significant correlation was found between ALT and BMI in both male ($\rho = 0.441$; $P = 0.000$) and female subgroups ($\rho = 0.236$; $P = 0.011$), as well as between γGT and BMI (males/ $\rho = 0.335$; $P = 0.000$ and females/ $\rho = 0.281$; $P = 0.002$), while AST correlated positively with BMI only in the male subgroup ($\rho = 0.440$; $\rho = 0.000$). Liver enzymes correlated positively with WHR > 0.90 in the male subgroup (ALT/ $\rho = 0.275$; $P = 0.005$, AST/ $\rho = 0.235$;

$P=0.017$, $\gamma\text{GT}/\rho=0.219$; $P=0.025$) as well as in the female subgroup of Group 1 ($\text{ALT}/\rho=0.311$; $P=0.021$, $\text{AST}/\rho=0.280$; $P=0.038$) except for γGT .

Using logistic regression analysis, a weak but significant association between liver enzymes and the tested anthropometric parameter values higher than their cutoff values was found (Table II). $\text{BMI}>25$ kg/m^2 was weakly but significantly associated with ALT (OR: 1.09, 95% CI 1.05–1.13, $P<0.000$), AST (OR: 1.19, 95% CI 1.07–1.18, $P<0.000$) and γGT (OR: 1.14, 95% CI 1.09–1.20, $P<0.000$); $\text{WC}>80$ cm (for females) was associated only with γGT (OR: 1.05, 95% CI 1.0–1.09, $P=0.011$); while $\text{WC}>94$ cm (for males) was associated with ALT (OR: 1.04, 95% CI 1.01–1.06, $P=0.0004$), AST (OR: 1.05, 95% CI 0.998–1.095, $P=0.031$) and γGT (OR: 1.08, 95% CI 1.03–1.14, $P=0.0001$). $\text{WHR}>0.90$ (for males) was significantly associated with ALT (OR: 1.04, 95% CI 1.015–1.06, $P<0.000$), AST (OR: 1.09, 95% CI 1.4–1.15, $P<0.000$) and γGT (OR: 1.03, 95% CI 1.0–1.06, $P=0.025$); while $\text{WHR}>0.80$ (for females) was significantly associated with ALT (OR: 1.04, 95% CI 1.02–1.08, $P<0.0036$) and AST (OR: 1.11, 95% CI 1.04–1.2, $P=0.0013$). $\text{HC}>108$ cm (for males) was associated with ALT (OR: 1.06, 95% CI 1.0–1.11, $P=0.0017$), AST (OR: 1.13, 95% CI 1.03–1.23, $P=0.0011$) and γGT (OR: 1.12, 95% CI 1.03–1.20, $P=0.0003$), and $\text{HC}>111$ cm (for females) was significantly associated with ALT (OR: 1.03, 95% CI 1.0–1.06, $P=0.035$) and γGT (OR: 1.04, 95% CI 1.0–1.08, $P=0.019$).

Discussion

Based on the obtained results it can be concluded that students with higher BMI, WC, HC and WHR also had higher levels of the liver enzymes ALT, AST and γGT . The liver enzymes correlated positively with the tested anthropometric parameters in Group 1 and in the subgroups of males and females of Group 1. This study has documented that the values of $\text{BMI}>25$ kg/m^2 are significantly associated with all three tested liver enzymes, as well as a $\text{WC}>94$ cm (for males), while a $\text{WC}>80$ cm (for females) is associated only with γGT . Significant association was obtained also between $\text{WHR}>0.90$ and all three tested enzymes, while $\text{WHR}>0.80$ was associated with ALT and AST. HC was associated with ALT, AST and γGT in the male subjects, while $\text{HC}>111$ cm was associated with ALT and γGT in the female subjects. According to these results it can be concluded that female students with a $\text{BMI}>25$ kg/m^2 , $\text{WC}>80$ cm, $\text{WHR}>0.80$ and $\text{HC}>111$ cm have a higher chance of developing NAFLD in the future, as well as male students with a $\text{WC}>94$ cm, $\text{WHR}>0.90$, $\text{HC}>108$ cm and $\text{BMI}>25$ kg/m^2 , compared to students whose anthropometric parameters are below these cutoff values.

Overweight and obese children and adolescents are more likely to have elevated ALT and AST levels than normal-weight students. WC is a simple and effective indicator which can be used to screen central adiposity (14) as well as the cardiovascular risk profile (15–18). Oliveira et al. (13) demonstrated that for each 5 cm increase in WC and every 1-point increase in the BMI z-score, there was a 1.3-fold greater chance of having increased ALT levels.

Different studies have shown that a number of metabolic syndrome components, obesity and insulin resistance are strong predictors of increased ALT activity in NAFLD in children and adolescents (19, 20). Central obesity, raised triglycerides, reduced HDL-cholesterol, and elevated fasting glucose are the metabolic syndrome components that contribute to increased AST and ALT activities. Visceral adiposity, and in particular upper abdominal visceral adiposity is correlated with cardiometabolic risk factors in humans (21). Several hypotheses regarding the role of visceral fat in metabolic disease were suggested, including the secretion of proinflammatory molecules capable of inducing insulin resistance in other organs and a high rate of lipolysis in the visceral fat depot that increases the delivery of free fatty acids to the liver to induce hepatic insulin resistance (21). A major contributor to fatty liver is enhanced *de novo* synthesis of fatty acids (lipogenesis) which leads to hepatic steatosis. Kelishadi et al. (9) suggested that, in future interventional studies, in addition to liver enzymes, high-sensitive CRP, γGT , uric acid, vitamin D, adiponectin, ghrelin level, insulin level, insulin resistance and the oral glucose tolerance test could be the integral part of the evaluation of patients with NAFLD to further clarify the relationships among different biologic factors and the metabolic syndrome.

Some studies have shown that obesity and insulin resistance have also been associated with other risk factors such as elevated blood pressure (22, 23). The Coronary Artery Risk Development in Young Adults (CARDIA) study of 4576 young adults reported a weight-independent association between fasting insulin concentration and hypertension (24). Obesity, insulin resistance and increased circulating insulin concentration over time, at some point, lead to loss of blood glucose control, resulting in dietary glucose intolerance. It is known that obese individuals may develop different degrees of insulin resistance, and not all individuals develop glucose intolerance. The factors that make some individuals more likely to progress to type 2 diabetes mellitus are not well understood at the present time. It is not currently known what level of weight loss is necessary for adolescents to achieve improved glucose handling.

Obesity is known to be an independent risk factor for coronary artery disease, ventricular dysfunction, congestive heart failure and cardiac arrhythmias in adults (25). Increased left ventricular mass, systolic

and diastolic hypertension have been found in obese adults. The early impact of prehypertension and hypertension parameters in adolescents and young adults was examined in the Strong Heart Study (26). Compared to normotensive individuals, both prehypertensive and hypertensive individuals were more likely to be obese. Seventy-nine percent of the hypertensive and 69% of the prehypertensive individuals had central adiposity as determined by waist circumference. Baker et al. (27) investigated the association between BMI in childhood (7–13 years) and coronary heart disease in adulthood (25 years and older) in a huge cohort of men and women in whom childhood BMI data were available. The risk of either a nonfatal or fatal cardiovascular event was positively associated with BMI at 7–13 years old for boys and 10–13 years old for girls. Children with higher BMI were at increased risk for coronary heart disease in adulthood and the associations were linear for each age.

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- There is increasing evidence indicating that obesity in children and adolescents is associated with short- and long-term cardiovascular risks. The long-term health issues are serious and carry a heavy burden both clinically and financially. Therefore, the prevention of obesity in children and adolescents is one of the major tasks for early management of obesity which can abate or reverse almost all of the cardiovascular consequences of obesity.

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Conflict of interest statement

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