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METABOLIČKI FENOTIP GOJAZNE DECE I ADOLESCENATA S OČUVANOM SENZITIVNOŠĆU NA INSULIN

Sažetak: Porast prevalencije gojaznosti u populaciji dece i adolescenata dovodi do povećanja rizika za nastanak udruženih metaboličkih i drugih poremećaja zdravlja. Ipak, uočeno je da određen broj gojaznih ima normalan metabolički fenotip, i oni se nazivaju metabolički zdravim gojaznim. Prevalencija metabolički zdravih u populaciji gojaznih iznosi i do 44%. Metabolički zdravi gojazni imaju manji rizik za poremećaje u regulaciji glukoze, dislipidemiju, steatozu jetre i hipertenziju, a očuvana senzitivnost na insulin je najčešće korišćen kriterijum za identifikaciju ove podgrupe gojaznih. Istraživanje učinjeno u Institutu za zdravstvenu zaštitu majke i deteta Srbije „Dr Vukan Čupić“ ukazuje da i u populaciji gojazne dece i adolescenata u Srbiji postoji podgrupa sa malom učestalošću metaboličkih komplikacija gojaznosti. Rezultati takođe ukazuju i na značajnu povezanost povoljnog metaboličkog fenotipa sa očuvanom senzitivnošću na insulin. Nalazi istraživanja ukazuju da je potreban drugačiji pristup u lečenju gojaznosti kod metabolički zdravih gojaznih, zbog čega ih je neophodno zasebno posmatrati u daljim istraživanjima.

Ključne reči: gojaznost, deca, rezistencija na insulin

Uvod

Porast prevalencije gojaznosti u populaciji dece i adolescenata širom sveta predstavlja značajan javno-zdravstveni problem (1). Između 110 i 150 miliona dece i adolescenata u svetu je prekomerno uhranjeno ili gojazno, a trend povećanja pre-

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valencije gojaznosti kod mladih povezan je sa porastom morbiditeta i mortaliteta od metaboličkih, kardiovaskularnih i drugih bolesti (1–4).

Učestalost prekomerne uhranjenosti mladih u svetu je nejednako raspoređena, tako da je ukupna prevalencija predgojaznosti i gojaznosti u nekim zemljama Azije i Afrike značajno manja od 10%, dok je u određenim zemljama Evrope i Amerike veća od 20% (1, 5). U Srbiji, prema rezultatima Istraživanja zdravlja stanovništva Srbije u 2006. godini, 18% dece i adolescenata uzrasta 7–19 godina bilo je prekomerno uhranjeno, od čega je 11,6% dece bilo predgojazno, a 6,4% gojazno (6). Zajedno sa već visokom prevalencijom prekomerne uhranjenosti, uočava se i trend povećanja prevalencije gojaznosti kod dece i adolescenata širom sveta (4). Tokom poslednje dve decenije prevalencija gojaznosti u zemljama evropskog regiona trostruko je povećana, a trend godišnjeg porasta prevalencije predgojaznosti i gojaznosti u populaciji dece i adolescenata ima karakteristike epidemije od izuzetnog zdravstvenog, ekonomskog i demografskog značaja sa dalekosežnim posledicama za narednu generaciju odraslih (1).

Opisani trend porasta prevalencije gojaznosti, koja u savremenom svetu dostiže razmere, pandemije dovodi do povećanja rizika za nastanak udruženih endokrinoloških, metaboličkih, kardiovaskularnih i drugih poremećaja zdravlja. Udruženost abdominalne gojaznosti, dislipidemije, poremećaja tolerancije na glukozu i hipertenzije kao poznatih faktora rizika za kardiovaskularna oboljenja i T2DM, nekada poznata kao „sindrom insulinske rezistencije“, a danas kao „metabolički sindrom“, zajedno sa tipom 2 dijabetesa melitusa, predstavlja jednu od najznačajnijih komplikacija gojaznosti (7, 8). Skoro četvrtina populacije odraslih ima metabolički sindrom, a u populaciji dece i adolescenata njegova učestalost se povećava uporedo sa pandemijom gojaznosti koja je glavna fenotipska karakteristika sindroma i ima centralnu ulogu u njegovom razvoju (8–10). Nalazi istraživanja ukazuju da skoro 50% gojaznih mladih osoba ima jednu ili više komponenti metaboličkog sindroma, kao i da je prevalencija faktora rizika za kardiovaskularna oboljenja direktno proporcionalna stepenu prekomerne uhranjenosti, odnosno gojaznosti (11).

Kod osoba sa metaboličkim sindromom, u odnosu na ostatak populacije, incidencija infarkta miokarda ili moždanog udara je dva do tri puta, a tipa 2 dijabetesa melitusa čak pet puta veća (8), a istraživanja ukazuju na činjenicu da proces ateroskleroze počinje u dečijem uzrastu i da je u neposrednoj vezi sa prekomernom telesnom masom i metaboličkim sindromom u populaciji dece i adolescenata (12). U nekoliko istraživanja autopsijom je otkriveno postojanje masnih mrlja i fibroznih plakova u aorti i koronarnim arterijama gojaznih adolescenata (12, 13), što omogućava bolje razumevanje rezultata istraživanja koji su pokazali da nalaz komponenti metaboličkog sindroma u populaciji dece i adolescenata povećava incidenciju fatalnih i nefatalnih kardiovaskularnih događaja u kasnijim godinama (14).

Sa povećanjem prevalencije gojaznosti u populaciji dece i adolescenata u tim uzrasnim grupama dolazi i do povećanja učestalosti metaboličkih komplikacija gojaznosti, kao što su hipertenzija, dislipidemija i tip 2 dijabetesa melitusa. Ipak,

uočeno je da sva gojazna deca i odrasli nemaju metabolički sindrom i druge metaboličke komplikacije gojaznosti, odnosno da određen broj gojaznih ima normalan metabolički fenotip (15, 16). Ove gojazne osobe, koje se danas u literaturi opisuju kao „metabolički zdravi gojazni“, uprkos gojaznosti, imaju očuvanu senzitivnost na insulin, normalan krvni pritisak i homeostazu glukoze, a nemaju dislipidemiju, steatozu jetre, inflamatorne i imunološke poremećaje (16–19). Iako je većina podataka o metabolički zdravim gojaznim osobama poznata na osnovu istraživanja učinjenih kod odraslih gojaznih, ovaj metabolički fenotip je otkriven i u populaciji gojazne dece i adolescenata (20).

Karakteristike metabolički zdrave gojazne dece

Prevalencija metabolički zdravih gojaznih osoba u populaciji gojaznih različita je u različitim studijama, prvenstveno u zavisnosti od kriterijuma korišćenih za identifikovanje ovih gojaznih osoba. Iako koncept metabolički zdravih gojaznih postoji još od kraja prošlog veka, ne postoji opšteprihvaćena definicija, kao ni kriterijumi na osnovu kojih bi se utvrdilo da li je gojazna osoba „metabolički zdrava“ (21). Najčešće korišćen kriterijum u istraživanjima je očuvana senzitivnost na insulin, a u određenim istraživanjima metabolički zdravi gojazni su identifikovani i na osnovu toga što nisu imali nijednu, ili manje od određenog broja najučestalijih metaboličkih komplikacija gojaznosti kao što su hipertenzija, hipertrigliceridemija, nizak nivo HDL holesterola ili metabolički sindrom (22, 23). U zavisnosti od korišćenih kriterijuma, učestalost metabolički zdravih u populaciji gojaznih odraslih iznosi i do 44%, a utvrđena je i veća prevalencija u populaciji gojaznih belaca u odnosu na druge etničke grupe koje su sklonije rezistenciji na insulin i drugim metaboličkim komplikacijama gojaznosti (23, 24). Nalazi zasnovani na istraživanjima na većem broju gojazne dece i adolescenata za sada ne postoje. Istraživanjem kod 40 gojazne dece i adolescenata sa normalnom regulacijom glukoze utvrđena je prevalencija metabolički zdravih gojaznih od 35% s očuvanom senzitivnošću na insulin kao osnovnim kriterijumom (20).

Pored očuvane senzitivnosti na insulin, koja je najčešće korišćen kriterijum za identifikaciju metabolički zdravih, kod ovih osoba je utvrđen veliki broj kliničkih i metaboličkih karakteristika po kojima se razlikuju od ostalih gojaznih. Poznato je da visceralna mast, a prvenstveno nakupljanje masti u jetri gojaznih predstavlja značajan faktor rizika za rezistenciju na insulin i druge metaboličke komplikacije gojaznosti (25). Metabolički zdrave gojazne osobe imaju drugačiju distribuciju prekomerne telesne mase, i prema rezultatima više istraživanja, i do 54% manje visceralnih depoa masti u odnosu na druge gojazne (26). Kod metabolički zdravih gojaznih utvrđene su niže vrednosti glikemije u 120. minutu nakon oralnog opterećenja glukozom i niži nivoi glikoziliranog hemoglobina A_{1c} (27). U više istraživanja kod metabolički

zdravih gojaznih utvrđeni su niži nivoi triglicerida, LDL holesterola, transaminaza i manje vrednosti krvnog pritiska, a više koncentracije HDL holesterola u odnosu na ostale gojazne (22, 27). Takođe, kod metabolički zdravih gojaznih nivoi interleukina 6 i C-reaktivnog proteina su niži u odnosu na druge gojazne osobe (22, 28).

Do danas nije poznato zašto se kod nekih gojaznih osoba razviju komplikacije gojaznosti, a drugi gojazni ostaju metabolički zdravi. Ipak, utvrđeni su određeni faktori koji doprinose verovatnoći da će gojazna osoba biti metabolički zdrava. Veća telesna masa na rođenju i rani nastanak gojaznosti u dečijem uzrastu, odnosno adolescenciji, povezani su sa većim stepenom senzitivnosti na insulin (29, 30). Veruje se da kod osoba koje imaju veću senzitivnost na insulin zbog prekomernog kalorijskog unosa dolazi do ranijeg nastanka gojaznosti, dok je kod osoba koje su rezistentne na insulin dobijanje u telesnoj masi usporeno zbog manje senzitivnosti na insulin i da je zbog toga ovim osobama, koje su kasnije u životu sklonije metaboličkim poremećajima, potreban duži vremenski period povećanog kalorijskog unosa da bi postale gojazne (31). Na osnovu ovoga može se zaključiti da kasniji nastanak gojaznosti nije uzročno povezan sa većom prevalencijom metaboličkih komplikacija gojaznosti, već rana posledica rezistencije na insulin, za koju se smatra da ima centralnu ulogu u nepovoljnom metaboličkom fenotipu gojaznih osoba.

Karakteristike metabolički zdrave gojazne dece i adolescenata u Srbiji

Do danas nisu dostupni podaci o podgrupi metabolički zdrave gojazne dece i adolescenata u Srbiji, zbog čega je u Institutu za zdravstvenu zaštitu majke i deteta Srbije „Dr Vukan Čupić“ u Beogradu tokom 2011–2012. godine učinjeno ispitivanje kojim je obuhvaćeno 248 gojazne dece i adolescenata (150 devojčica i 98 dečaka) uzrasta 5,9 – 18,9 godina. Osnovni kriterijum za uključivanje u studiju bila je vrednost indeksa telesne mase ≥ 95 . percentila za odgovarajući uzrast i pol, a ispitivanjem nisu obuhvaćena deca sa genetskim sindromima i drugim uzrocima sekundarne gojaznosti. Cilj istraživanja bila je procena učestalosti metaboličkih poremećaja kod gojazne dece koja imaju očuvanu senzitivnost na insulin u odnosu na decu sa rezistencijom na insulin. Prikupljeni podaci obuhvatali su demografske, antropometrijske i druge nalaze iz fizikalnog pregleda, a od laboratorijskih ispitivanja svima je učinjen test oralnog opterećenja glukozom i određeni nivoi glukoze, insulina, transaminaza, triglicerida, HDL, LDL i ukupnog holesterola.

Svim ispitanicima su određene vrednosti HOMA indeksa insulinske rezistencije (glikemija našte (mmol/l) x insulinemija našte (mIU/l) / 22,5), na osnovu kojih su podeljeni u kvartile. Prvi kvartil sastojao se od dece senzitivne na insulin, sa vrednostima HOMA IR indeksa $\leq 2,75$ (n = 62), a četvrti kvartil od dece koja su imala veoma izraženu rezistenciju na insulin (HOMA IR $\geq 6,16$). Izabrane dve grupe dece i adolescenata sa ekstremnim vrednostima HOMA IR indeksa poredene su parame-

tarskim i neparametarskim testovima razlike po pitanju metaboličkih komplikacija gojaznosti.

Grupa gojazne dece i adolescenata senzitivnih na insulin (IS grupa) i rezistentnih na insulin (IR grupa) bile su usklađene po pitanju uzrasta, pola i stepena gojaznosti. Sa statističkom značajnošću je uočeno da je veći broj ispitanika u IS grupi bio u prepubertetskom stadijumu polnog razvoja (29,0%) u odnosu na decu i adolescente u IR grupi (9,7%). Deca u IS grupi bila su u manjem riziku za povećanu glikemiju našte, čija je učestalost iznosila 1,6% u odnosu na 21,0% u IR grupi ($p < 0,01$), kao i za poremećaj tolerancije na glukozu (4,8% u odnosu na 22,6%, $p < 0,01$). Po pitanju drugih ispitivanih metaboličkih komplikacija gojaznosti, kod ispitanika u IS grupi su sa statističkom značajnošću utvrđeni i manji nivoi transaminaza, triglicerida, LDL i ukupnog holesterola, a veće koncentracije HDL holesterola (tabela 1).

Tabela 1. Kliničke i metaboličke karakteristike gojazne dece i adolescenata senzitivnih i rezistentnih na insulin

	IS grupa	IR grupa	p
ITM (SSD) ¹	3,1 ± 1,2	3,3 ± 1,1	NZ ²
Prepubertetski stadijum (n)	18 (29,0%)	6 (9,7%)	0,01
Sistolni krvni pritisak (percentili)	72,3 ± 28,6	82,3 ± 24,5	0,04
Povećana glikemija našte (n)	1 (1,6%)	13 (21,0%)	< 0,01
Poremećaj tolerancije na glukozu (n)	3 (4,8%)	14 (22,6%)	< 0,01
Trigliceridi (mmol/l)	1,10 ± 0,71	1,60 ± 0,68	< 0,01
Ukupni holesterol (mmol/l)	4,05 ± 1,18	4,49 ± 0,97	0,03
HDL holesterol (mmol/l)	1,12 ± 0,27	0,91 ± 0,28	< 0,01
LDL holesterol (mmol/l)	2,58 ± 0,73	3,02 ± 0,86	0,02
AST (IJ/l)	23,00 ± 13,18	29,39 ± 26,08	0,04
ALT (IJ/l)	25,70 ± 22,26	44,31 ± 48,30	< 0,01

¹ Indeks telesne mase izražen skorom standardnih devijacija

² $p > 0,05$

Zaključak

Učinjeno istraživanje ukazuje da i u populaciji gojazne dece i adolescenata u Srbiji postoji podgrupa koja se odlikuje malom učestalošću metaboličkih komplikacija gojaznosti. Rezultati takođe ukazuju i na značajnu povezanost povoljnog metaboličkog fenotipa sa očuvanom senzitivnošću na insulin. Iz ovih nalaza ne treba zaključiti da ovim gojaznim osobama nije potrebna redukcija telesne mase, jer iako su u manjem riziku za metaboličke komplikacije gojaznosti, metabolički zdravi gojazni imaju kraći

očekivani životni vek od osoba sa normalnom težinom (32). Prirodno je zapitati se o kliničkom značaju identifikacije metabolički zdravih gojaznih, kada, uprkos manjoj učestalosti tipa 2 dijabetesa melitusa i drugih metaboličkih poremećaja, mortalitet ovih osoba odgovara mortalitetu u celokupnoj populaciji gojaznih, i samim time je neophodno lečenje, odnosno redukcija telesne mase kao i kod ostalih gojaznih. Kod metabolički zdravih gojaznih uočeni su drugačiji rezultati u lečenju, uključujući i značajno bolji terapijski učinak fizičke aktivnosti u odnosu na ostale gojazne osobe. Takođe, u istraživanju uticaja hipokalorijske dijeta na metabolički profil metabolički zdravih gojaznih posle šest meseci došlo je do smanjenja senzitivnosti na insulin, za razliku od ostalih gojaznih kod kojih je došlo do smanjenja rezistencije na insulin (33).

Ovi nalazi ukazuju na potrebu za daljim istraživanjima u kojima bi metabolički zdravi gojazni bili posebno posmatrani u cilju određivanja najboljih postupaka u lečenju ove grupe gojaznih. Takođe, istraživanja u cilju određivanja činioca koji štite metabolički zdrave gojazne od metaboličkih komplikacija gojaznosti neophodna su radi boljeg uvida u patogenetske procese u osnovi nastanka metaboličkog sindroma i drugih komplikacija gojaznosti.

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METABOLIC PHENOTYPE IN OBESE CHILDREN AND ADOLESCENTS WITH PRESERVED INSULIN SENSITIVITY

Summary: Rising prevalence of childhood obesity is accompanied by the increased risk of associated metabolic complications and other comorbidities. Nevertheless, a distinct subgroup of the obese appear to have a normal metabolic phenotype, and these individuals are referred to as the metabolically healthy obese. Prevalence of metabolically healthy individuals within the population of the obese is estimated up to 44%. Metabolically healthy obese are at lesser risk for impaired glucose regulation, dyslipidemia, non-alcoholic fatty liver disease and hypertension, and the preserved insulin sensitivity is the most frequently used criterion in identification of these individuals. Results of the research conducted in Institute for Mother and Child Health Care of Serbia “Dr Vukan Čupić” indicate that a subgroup with low prevalence of metabolic complications of obesity is also present within population of obese children and adolescents in Serbia. A significant association of preserved insulin sensitivity with favorable metabolic phenotype is also supported by the results. Known data suggest the need for a different approach in the treatment of obesity in the subpopulation of the metabolically healthy obese. Due to differences in terms of complications and treatment, these individuals should also be regarded as a separate entity in further research.

Keywords: obesity, children, insulin resistance

Introduction

Worldwide increase in the prevalence of obesity in children and adolescents is one of the most significant public health problems (1). It is estimated that between

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110 million and 150 million children and adolescents are overweight or obese, and the rising prevalence of childhood obesity is associated with the increased morbidity and mortality due to metabolic, cardiovascular and other non-communicable diseases (1-4).

The prevalence of the childhood obesity varies widely in different regions, being lower than 10% in certain parts of Asia and Africa, while in a number of European and American countries the prevalence of obesity in youth is significantly higher than 20% (1, 5). According to the results of the "Study of population health in Serbia" performed in 2006, 18% of children and adolescents aged 7-19 years were overweight, with one third of these being obese (6). Along with the established high prevalence of overweight, a rise in the prevalence of childhood obesity is observed in many countries (4). During the past two decades there has been a triple increase in the prevalence of obesity in Europe, and the yearly increase in prevalence of overweight and obesity in children and adolescents resembles an epidemic of significant impact in the areas of healthcare and economics, with long term consequences in future generations of adults (1).

Rise in the prevalence of obesity, more often described as a worldwide pandemic is followed by an increased occurrence of endocrine, metabolic, cardiovascular and other co-morbidities. The association of abdominal adiposity, dyslipidemia, impaired glucose tolerance and hypertension as well known risk factors for cardiovascular diseases, once known as "insulin resistance syndrome", now as "metabolic syndrome", along with type 2 diabetes represents one of the most significant complication of obesity (7, 8). Nearly quarter of the entire adult population has metabolic syndrome, and its prevalence in the population of children and adolescents is increasing along with the pandemic of childhood obesity, which plays a dominant role in the pathogenesis of this syndrome (8-10). Results of recent research indicate that nearly 50% of the obese youth has one or more components of the metabolic syndrome, and that the prevalence of cardiovascular risk factors is in direct proportion with the degree of overweight or obesity (11).

The incidence of myocardial infarction or stroke is two to three times higher in individuals with the metabolic syndrome, and their risk for type 2 diabetes is as much as five times higher compared to the rest of the population (8). Recent research suggests that atherosclerosis begins in childhood and that it's directly associated with overweight and metabolic syndrome in the population of children and adolescents (12). Several autopsy studies confirmed findings of fatty streaks and fibrous plaques in aorta and coronary arteries of obese adolescents (12, 13), which provides a better insight into the research results showing that the presence of metabolic syndrome components in the population of children and adolescents increases the incidence of both fatal and non-fatal cardiovascular events in the adulthood (14).

Along with the epidemic of childhood obesity, an increase in the metabolic complications like hypertension, dyslipidemia and type 2 diabetes is observed in

the population of children and adolescents. Nevertheless, it has been observed that not all obese children, as well as the obese adults, develop metabolic syndrome and other metabolic complications of the obesity, in other words a certain number of the obese have a normal metabolic phenotype (15, 16). This subgroup of the obese, now described in literature as the “metabolically healthy obese”, despite being obese have preserved insulin sensitivity, normal blood pressure and glucose regulation, and they are less prone to dyslipidemia, nonalcoholic fatty liver disease, inflammatory and immunological disturbances (16-19). Although most of the known data on metabolically healthy obese phenomenon is derived from the research conducted in the adult population, this favorable metabolic phenotype has also been confirmed in the population of the obese children and adolescents (20).

Characteristics of metabolically healthy obese children

Prevalence of metabolically healthy obese individuals in the obese population varies in the results of different studies, mainly because of differences in used criteria for defining this subgroup. Even though the concept of the metabolically healthy is long known, no consensus on the definition or the criteria used for identification of these individuals has yet been established (21). While the most frequently used criterion is preserved insulin sensitivity, some studies defined metabolically healthy obese by the presence of none, or less than a specified number of most frequent metabolic complications of obesity, like hypertension, high triglycerides, low HDL cholesterol levels or metabolic syndrome (22, 23). Depending on which criteria was used, the prevalence of metabolically healthy within the population of the obese adults is established up to 44%, and a higher prevalence of metabolically healthy obese has also been discovered in Caucasians in comparison to other ethnic subpopulations which are more prone to insulin resistance and other metabolic complications of the obesity (23, 24). To date, there are no available data based on research in substantial groups of obese children and adolescents. Results of the study performed in a group of 40 obese children and adolescents with normal glucose regulation established a prevalence of the metabolically healthy obese of 35%, defined by preserved insulin sensitivity (20).

Besides preserved insulin sensitivity as the most frequently used criterion in identifying metabolically healthy obese, a number of clinical and metabolic characteristics distinguishes this subgroup from the rest of the obese. Visceral adiposity, especially accumulation of fat in the liver of the obese is a significant risk factor for insulin resistance and other metabolic complications of obesity (25). Different distribution of overweight has been observed in metabolically healthy individuals and research shows that these individuals can even have 54% less visceral adipose stores compared to the rest of the obese (26). Metabolically healthy obese also have lower values of

120-minute glucose levels during oral glucose tolerance test and lower HbA_{1c} levels (27). Several studies discovered lower levels of triglycerides, LDL cholesterol and transaminases, lower blood pressure and higher HDL cholesterol in the metabolically healthy obese compared to other obese subjects (22, 27). Also, in metabolically healthy obese individuals, C-reactive protein and interleukin 6 concentrations were lower compared to the rest of the obese (22, 28).

It has yet to be determined why some of the obese develop co-morbidities of obesity while some remain metabolically healthy. However, several factors associated with higher probability of a person being obese but metabolically healthy have been identified. Larger birth weight and earlier onset of obesity in childhood are strongly associated with the preserved insulin sensitivity (29, 30). It is presumed that in insulin sensitive individuals excess caloric intake results in earlier onset of obesity, while this weight gain is buffered by the insulin resistance in those with impaired insulin sensitivity. This explains why insulin resistant individuals, who are more prone to the metabolic complications of obesity later in life, become obese after a longer period of increased caloric intake (31). This explanation would also imply that the later onset of obesity is not responsible for the higher prevalence of the metabolic complications of obesity, but an early consequence of insulin resistance which is thought to play a central role in the unfavorable metabolic phenotype of the obese.

Characteristics of metabolically healthy obese children and adolescents in Serbia

To date there were no available data regarding the subgroup of metabolically healthy obese children and adolescents in Serbia, which is why a study was conducted in the Mother and Child Health Care Institute of Serbia "Dr Vukan Čupić" in Belgrade. Study was performed during 2011-2012. in a group of 248 obese children and adolescents (150 girls and 98 boys) aged 5.9 – 18.9 years. Main inclusion criterion was body mass index value \geq 95. percentile for the appropriate age and gender, and children with genetic syndromes and other causes of secondary obesity were excluded from the study. Study goal was to analyze the differences in the occurrence of metabolic disturbances in obese children with preserved insulin sensitivity compared to those with insulin resistance. Acquired data included demographics, anthropometric and other clinical exam data, while laboratory analyses included the oral glucose tolerance test with glucose and insulin levels, serum transaminases, triglycerides, HDL, LDL and total cholesterol levels.

Homeostatic model assessment of insulin resistance (HOMA IR) index values were calculated for all subjects (fasting glucose (mmol/l) x fasting insulin (mIJ/l) / 22.5), and all subjects were divided into quartiles sorted by rising values of HOMA IR. First quartile consisted of insulin sensitive children, all of which had HOMA IR

values ≤ 2.75 ($n = 62$), while the fourth quartile consisted of children with marked insulin resistance ($\text{HOMA IR} \geq 6,16$). These two groups representing the extremes of insulin sensitivity were compared by means of parametric and non-parametric statistical tests in regards to the metabolic complications of obesity.

The group of obese insulin sensitive (IS group) and insulin resistant (IR group) children and adolescents were similar in terms of age, gender and the degree of obesity. Statistically significant difference was observed regarding pubertal development, with larger proportion of the IS subjects in prepubertal stage (29.0%) compared to the children and adolescents from the IR group (9.7%). Children in the IS group had lower prevalence of impaired fasting glucose (1.6%) compared to IR subjects (21.0%) ($p < 0.01$), and lower prevalence of impaired glucose tolerance (4.8% compared to 22.6%, $p < 0.01$). Regarding other investigated metabolic complications of obesity, children in the IS group had significantly lower levels of transaminases, triglycerides, LDL and total cholesterol and higher HDL cholesterol levels (Table 1).

Table 1: Clinical and metabolic characteristics of insulin sensitive and insulin resistant obese children and adolescents

	IS group	IR group	p
BMI (SDS) ¹	3.1 ± 1.2	3.3 ± 1.1	NS ²
Prepubertal stage (n)	18 (29.0%)	6 (9.7%)	0.01
Systolic blood pressure (percentile)	72.3 ± 28.6	82.3 ± 24.5	0.04
Impaired fasting glucose (n)	1 (1.6%)	13 (21.0%)	< 0.01
Impaired glucose tolerance (n)	3 (4.8%)	14 (22.6%)	< 0.01
Triglycerides (mmol/l)	1.10 ± 0.71	1.60 ± 0.68	< 0.01
Total cholesterol (mmol/l)	4.05 ± 1.18	4.49 ± 0.97	0.03
HDL cholesterol (mmol/l)	1.12 ± 0.27	0.91 ± 0.28	< 0.01
LDL cholesterol (mmol/l)	2.58 ± 0.73	3.02 ± 0.86	0.02
AST (IJ/l)	23.00 ± 13.18	29.39 ± 26.08	0.04
ALT (IJ/l)	25.70 ± 22.26	44.31 ± 48.30	< 0.01

¹ Body mass index expressed by standard deviation score

² $p > 0.05$

Conclusion

Results of the performed study suggest that a subgroup characterized by low occurrence of metabolic complications of the obesity exists within a population of obese children and adolescents in Serbia. A significant association of favorable metabolic phenotype with preserved insulin sensitivity was also established. These results do not suggest that there is no need for weight reduction in these obese individuals,

because even though they are less prone to metabolic complications of obesity, metabolically healthy obese have a shortened life expectancy compared to normal weight individuals (32). Clinical significance of identifying metabolically healthy obese could be questioned, having in mind that despite lower prevalence of type 2 diabetes and other metabolic co-morbidities, mortality of these individuals is similar to mortality in the rest of obese population, which alone establishes the need to reduce the excess weight, as in all other obese. In metabolically healthy obese, different results in treatment modalities was observed, including the superior therapeutic effect of the physical activity compared to other obese individuals. Also, in the study researching the influence of hypocaloric diet on the metabolic profile of the metabolically healthy obese, a decrease in insulin sensitivity was observed after six months, unlike in other obese subjects which developed an increase in insulin sensitivity (33).

These findings emphasize the need for further research, in which the metabolically healthy obese subjects should be regarded as a distinct entity in order to evaluate the best treatment strategies for this group of the obese. Also, further research directed towards defining the protective factors keeping these individuals metabolically unaffected by obesity are necessary in order to gain more insight into pathogenetic processes surrounding the development of metabolic syndrome and other complications of obesity.

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