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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, know 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 (HOMA IR ≥ 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.

References

1. Banićević M, Zdravković D. Sprečimo gojaznost: sačuvajmo zdravlje dece i adolescenata Beograd: Udruženje pedijatara Srbije; 2008.
2. Olshansky SJ, Passaro DJ, Hershow RC, Layden J, Carnes BA, Brody J, et al. A potential decline in life expectancy in the United States in the 21st century. N Engl J Med. 2005;352:1138-45.
3. Haslam DW, James WP. Obesity. Lancet. 2005;366:1197-209.
4. Wang Y, Lobstein T. Worldwide trends in childhood overweight and obesity. Int J Pediatr Obes. 2006;1:11-25.
5. Lobstein T, Baur L, Uauy R. Obesity in children and young people: a crisis in public health. Obes Rev. 2004;5 Suppl 1:4-104.
6. MZRS. Istraživanje zdravlja stanovnika Republike Srbije. Ministarstvo zdravlja Republike Srbije; 2007.
7. Molnar D. The prevalence of the metabolic syndrome and type 2 diabetes mellitus in children and adolescents. Int J Obes Relat Metab Disord. 2004;28 Suppl 3:S70-4.
8. Alberti KG, Zimmet P, Shaw J. The metabolic syndrome - a new worldwide definition. Lancet. 2005;366:1059-62.
9. Weiss R, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, Yeckel CW, et al. Obesity and the metabolic syndrome in children and adolescents. N Engl J Med. 2004;350:2362-74.
10. Cook S, Weitzman M, Auinger P, Nguyen M, Dietz WH. Prevalence of a metabolic syndrome phenotype in adolescents: findings from the third National He-

alth and Nutrition Examination Survey, 1988-1994. Arch Pediatr Adolesc Med. 2003;157:821-7.

11. Freedman DS, Khan LK, Dietz WH, Srinivasan SR, Berenson GS. Relationship of childhood obesity to coronary heart disease risk factors in adulthood: the Bogalusa Heart Study. Pediatrics. 2001;108:712-8.
12. Berenson GS, Srinivasan SR, Bao W, Newman WP, 3rd, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. N Engl J Med. 1998;338:1650-6.
13. Wissler RW, Strong JP. Risk factors and progression of atherosclerosis in youth. PDAY Research Group. Pathological Determinants of Atherosclerosis in Youth. Am J Pathol. 1998;153:1023-33.
14. Baker JL, Olsen LW, Sorensen TI. Childhood body-mass index and the risk of coronary heart disease in adulthood. N Engl J Med. 2007;357:2329-37.
15. Ferrannini E, Natali A, Bell P, Cavallo-Perin P, Lalic N, Mingrone G. Insulin resistance and hypersecretion in obesity. European Group for the Study of Insulin Resistance (EGIR). J Clin Invest. 1997;100:1166-73.
16. Bluher M. The distinction of metabolically 'healthy' from 'unhealthy' obese individuals. Curr Opin Lipidol. 2010;21:38-43.
17. Karelis AD. Metabolically healthy but obese individuals. Lancet. 2008 Oct 11;372:1281-3.
18. Karelis AD, St-Pierre DH, Conus F, Rabasa-Lhoret R, Poehlman ET. Metabolic and body composition factors in subgroups of obesity: what do we know? J Clin Endocrinol Metab. 2004;89:2569-75.
19. Sims EA. Are there persons who are obese, but metabolically healthy? Metabolism. 2001;50:1499-504.
20. Weiss R, Taksali SE, Dufour S, Yeckel CW, Papademetris X, Cline G, et al. The "obese insulin-sensitive" adolescent: importance of adiponectin and lipid partitioning. J Clin Endocrinol Metab. 2005;90:3731-7.
21. Sims EA. Mechanisms of hypertension in the syndromes of obesity. Int J Obes. 1981;5 suppl 1:9-18.
22. Karelis AD, Faraj M, Bastard JP, St-Pierre DH, Brochu M, Prud'homme D, et al. The metabolically healthy but obese individual presents a favorable inflammation profile. J Clin Endocrinol Metab. 2005;90:4145-50.
23. Wildman RP, Muntner P, Reynolds K, McGinn AP, Rajpathak S, Wylie-Rosett J, et al. The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999-2004). Arch Intern Med. 2008;168:1617-24.
24. Meigs JB, Wilson PW, Fox CS, Vasan RS, Nathan DM, Sullivan LM, et al. Body mass index, metabolic syndrome, and risk of type 2 diabetes or cardiovascular disease. J Clin Endocrinol Metab. 2006;91:2906-12.
25. D'Adamo E, Cali AM, Weiss R, Santoro N, Pierpont B, Northrup V, et al. Central role of fatty liver in the pathogenesis of insulin resistance in obese adolescents. Diabetes Care. 2010;33:1817-22.

26. Stefan N, Kantartzis K, Machann J, Schick F, Thamer C, Rittig K, et al. Identification and characterization of metabolically benign obesity in humans. Arch Intern Med. 2008;168:1609-16.
27. Marini MA, Succurro E, Frontoni S, Hribal ML, Andreozzi F, Lauro R, et al. Metabolically healthy but obese women have an intermediate cardiovascular risk profile between healthy nonobese women and obese insulin-resistant women. Diabetes Care. 2007;30:2145-7.
28. Shin MJ, Hyun YJ, Kim OY, Kim JY, Jang Y, Lee JH. Weight loss effect on inflammation and LDL oxidation in metabolically healthy but obese (MHO) individuals: low inflammation and LDL oxidation in MHO women. Int J Obes (Lond). 2006;30:1529-34.
29. Brochu M, Tchernof A, Dionne IJ, Sites CK, Eltabbakh GH, Sims EA, et al. What are the physical characteristics associated with a normal metabolic profile despite a high level of obesity in postmenopausal women? J Clin Endocrinol Metab. 2001;86:1020-5.
30. Bouhours-Nouet N, Dufresne S, de Casson FB, Mathieu E, Douay O, Gatelais F, et al. High birth weight and early postnatal weight gain protect obese children and adolescents from truncal adiposity and insulin resistance: metabolically healthy but obese subjects? Diabetes Care. 2008;31:1031-6.
31. Eckel RH. Insulin resistance: an adaptation for weight maintenance. Lancet. 1992;340:1452-3.
32. Arnlov J, Ingelsson E, Sundstrom J, Lind L. Impact of body mass index and the metabolic syndrome on the risk of cardiovascular disease and death in middle-aged men. Circulation. 2010;121:230-6.
33. Karelis AD, Messier V, Brochu M, Rabasa-Lhoret R. Metabolically healthy but obese women: effect of an energy-restricted diet. Diabetologia. 2008;51:1752-4.