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Risk Factors for the Development of Metabolic Syndrome in Obese Children and Adolescents

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SUMMARY

Introduction High prevalence of metabolic syndrome (MetS) in children and adolescents is a great concern of the modern society.

Objective Our aim was to determine the influence of previously investigated, but also and potentially novel risk factors for the development of metabolic syndrome in children and adolescents.

Methods Observational case-control clinical study was conducted involving children and adolescents with obesity/metabolic syndrome, treated on inpatient basis from January 2008 to January 2012 at the Pediatric Clinic of the Clinical Centre Kragujevac, Kragujevac, Serbia. The group of "cases" (n=28) included patients aged 10-16 years with the diagnosis of metabolic syndrome according to the International Diabetes Federation (IDF) criteria, while the control group included twice as many obese patients (n=56) matched to the compared group.

Results Presence of maternal gestational diabetes ($OR_{adjusted}$: 39.426; 95% CI: 1.822-853.271; p=0.019), and/or lack of breastfeeding in the first six months of life ($OR_{adjusted}$: 0.079; 95% CI: 0.009-0.716; p=0.024) were significant predictors for developing MetS. Also, microalbuminuria is associated with MetS in obese children and adolescents ($OR_{adjusted}$: 1.686; 95% CI: 1.188-2.393; p=0.003).

Conclusion Presence of maternal gestational diabetes and/or lack of infant breastfeeding are considered as relevant factors that may contribute to the increased risk of developing MetS syndrome, while microalbuminuria is frequently associated with MetS in obese children and adolescents.

Keywords: metabolic syndrome; child obesity; adolescent obesity; risk factors

INTRODUCTION

Metabolic syndrome (MetS) is a complex medical condition involving multiple interrelated factors that directly increase the risk of developing cardiovascular disease and type 2 diabetes mellitus, and includes abdominal obesity, dyslipidemia, glucose intolerance and hypertension [1]. Even though the current literature describes a wide range of cut-off criteria values used to define MetS in the pediatric population [2, 3, 4], the definition of the International Diabetes Federation (IDF) is generally accepted [5].

Obesity is considered one of the major components of MetS in the pediatric population. Rise in the prevalence of obesity in children and adolescents presents a global and severe problem of modern era, since excess weight is associated with various health problems in the pediatric population, and at the same time presents a significant risk factor for morbidity and mortality in adulthood [6].

Physical inactivity, inadequate and unhealthy diet and modern, "sedentary" lifestyle are the leading causes of the increase in childhood obesity, especially in developing countries [1]. According to the 2004 data of the International Obesity Task Force [7], 10% of schoolchildren aged 5 to 17 are overweight, and it is estimated that the prevalence of childhood obesity will continue to increase, as has been the case in recent years. In 2003/2004, percentage of obese children aged 2-19 in the USA was 17.1% [8]. It is interesting to note that among adolescents obesity is slightly higher in countries of Western and Southern Europe in comparison to Central and Northern Europe [9]. The prevalence of MetS varies not only depending on the population, but also the criteria defined for syndrome diagnosis. Cook et al. [3] estimated that the prevalence of the syndrome among youths aged 12 to 19 is 4.1%. According to the Bogalusa Heart Study [10], in the population aged 8-17 the prevalence is 3.6%. However, there is consensus that it is significantly higher in obese children [2].

Certain circumstances, beginning with birth (or even earlier), are linked to obesity and glycemic disorders, or MetS. The presence of maternal gestational diabetes [11], low/high birth weight [12], certain kinds of diet of newborns [13], early rise in "fats" [14], genetic factors, growing up in an "obesogenic" environment and the impact of socio-economic factors [15] are only some of the factors that may contribute to the increased risk for the development of these disorders in children. Early identification of children at risk of MetS, and prevention of progression to type 2 diabetes mellitus and cardiovascular disease later in life, is of great importance for their future wellbeing.

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OBJECTIVE

The aim of our study was to further evaluate risk factors for the development of MetS in children and adolescents.

METHODS

The study was designed as an observational case-control clinical study involving children and adolescents of Serbian nationality with obesity/metabolic syndrome, treated on an inpatient basis from January 2008 to January 2012 at the Endocrine Department of the Pediatric Clinic at the Clinical Centre Kragujevac, Kragujevac, Serbia. The study was approved by the Ethics Committee of the Clinical Centre Kragujevac.

The group of "cases" included 28 patients during the study period aged 10 to 16 years with the diagnosis of MetS according to the IDF criteria [5]. The control group included 56 obese patients (obesity was defined as waist circumference ≥90th percentile for age and sex, according to Yugoslav standards [16]), randomly selected from the source population, matched to cases by gender, age and comorbidity (allergic rhinitis, asthma or epilepsy). Written informed consent was obtained from the parents of the participants, and an oral consent from each child.

In order to properly identify the risk factors and potential confounders for the development of MetS in children and adolescents, the following variables were monitored and analyzed in the study: patient's basic characteristics and clinical parameters/signs on admission (age, gender, comorbidities, waist circumference, body weight, height, BMI, blood pressure, heart rate, presence/absence of *Acanthosis nigricans*); basic blood chemistry panel (blood glucose, urea, creatinine, uric acid, alkaline phosphatase, direct bilirubin, total bilirubin, C-reactive protein, lipid profile (cholesterol, HDL, LDL, triglycerides), ALT, AST, GGT, HbA1c); fasting blood glucose levels, and levels at 120 minutes after glucose load, or fasting insulin levels and levels at 120 minutes (oral glucose tolerance test - OGTT with insulin levels); homeostatic indices of insulin sensitivity: HOMA and QUICKI; morning cortisol levels; microalbuminuria - in the quantitative urinalysis (24-hour urine).

The parent-related variables determined by the questionnaire were as follows: body weight, height, parental BMI; mother's pregnancy (controlled, special-care, use of medications in pregnancy, smoking, specific diseases such as gestational diabetes, pregnancy-induced hypertension, etc.); the presence of significant co-morbidities (assessing the existence of chronic diseases in the child's parents and immediate family); socioeconomic living conditions, family living area (rural/urban); level of parental education; birth order of children in the family; family diet (type of food, regularity of meals); smoking (active/passive); physical activity ("sedentary" lifestyle); existence of stressogenic family events (divorce, loss of a close person, loss of job, change of residence...); family attitude towards obesity.

The child-related variables that were determined by interviewing parents and children, were the following: birth weight, APGAR score; diet during the first months of life (breast/formula milk); physical activity/"sedentary" lifestyle; significant child comorbidity (existence of chronic diseases); significant co-medication in children (chronic drug therapy); diet – types of food, regularity of meals.

Patients from both groups underwent clinical examination on admission to hospital. Height and weight were measured without the subjects wearing shoes or heavy outer clothing. Standing height was measured to the nearest 0.1 cm and weight to the nearest 0.1 kg. Waist circumference was measured at the level of the narrowest point between the lower costal border and the illiac crest with non-stretchable measuring tape (produced by local Serbian manufacturer) while the patient exhaled slightly. While the patients were sitting, relaxed for more than 10 minutes, blood pressure (BP) was measured twice (each measurement 5 minutes apart), and the final BP was presented as the mean value of these measurements. *Acanthosis nigricans* was diagnosed by a dermatologist independent from the investigators. Blood chemistry was performed in the Laboratory Diagnostics Department of the Clinical Centre Kragujevac (according to standard operating procedure for laboratory diagnostics at the Clinical Centre Kragujevac), while the remaining components of the clinical study were conducted at the Pediatric Clinic of the Clinical Centre Kragujevac, pursuant to applicable hospital protocols.

HOMA index (Homeostasis Model Assessment) was calculated using a formula suggested by Matthews et al. [17]: (Gly0(mmol/L)×Ins0(μIU/mL)/22.5. On the other hand, the QUICKI index (Quantitative Insulin Sensitivity Check Index) was based on a logarithmic transformation model: 1/log(Ins0(μIU/mL))+log(Gly0(mg/dL)) [18]. To calculate the index, a conversion of glycemic units from mmol/L into mg/dL with the mathematical formula: mg/dL=mmol/L×18.0182, was used.

For continuous variables, the significance of differences in cases of normal data distribution was tested by parametric tests (Student's t test), whereas in the case of irregular data distribution non-parametric tests were used (Mann-Whitney U test). For categorical variables, Pearson's χ^2 test was used to assess the significance of differences. The difference in the compared data was considered statistically significant if the probability of the null hypothesis was less than 5% ($p<0.05$). The variables which turned out to be significant predictors/markers of the followed outcome of interest after the univariate logistic analysis were included in multivariate binary logistic regression. The SPSS statistical software was used for all calculations (SPSS Inc, version 18, Chicago, IL, USA).

RESULTS

In regard to the basic characteristics of patients in both the MetS study group and the obese control group, a significant difference between the study groups in body weight

(84.29±21.85 vs. 76.34±14.03 kg, p=0.047), waist circumference (95.46±9.58 vs. 91.04±8.41 cm, p=0.033), systolic blood pressure (134.11±14.60 vs. 128.39±8.26 mmHg, p=0.024) and diastolic blood pressure (83.57±11.21 vs. 78.84±9.63 mmHg, p=0.048) was identified using the Student's t test, while χ^2 test was used to determine the frequency of *Acanthosis nigricans* (35.7% vs. 10.7%, p=0.006) (Table 1). Regarding the age (12.93±1.96 vs.12.43±2.07 years), BMI (31.77±4.93 vs. 30.14±3.06 kg/m^2), heart rate (86.79±11.24 vs. 82.84±8.61 per minute), and the frequency of female subjects (57.1% vs. 53.6%), no statistical difference between the groups was observed (p>0.05).

A detailed analysis of blood chemistry panel in both groups using the Student's t test showed a significant difference between the MetS group and the group of obese patients in serum uric acid (356.32±32.70 vs. 340.98±32.30 umol/L, p=0.044), glycosylated hemoglobin A1c (5.55±0.69 vs. 5.24±0.54 %, p=0.030) and GGT (22.39±10.64 vs.18.37±6.99 U/L, p=0.041). Since irregular distribution of data related to the levels of AST and ALT was found, the difference between the compared groups in AST values (27.50±17.68 vs. 24.71±9.97 U/L, p>0.05) and in ALT values (26.04±20.30 vs. 19.93±11.04 U/L, p=0.020) was tested by the Mann Whitney U test. Student's t test showed significant difference in the values of total cholesterol (5.02±1.43 vs. 4.54±0.66 mmol/L, p=0.035), LDL (3.33±1.25 vs. 2.78±0.74 mmol/L, p=0.013) and a highly significant difference in the compared values of HDL (0.94±0.34 vs. 1.31±0.18 mmol/L, p<0.001), and triglycerides (1.95±1.10 vs. 1.12±0.42 mmol/L, p<0.001). Statistical difference between the observed groups was not detected (p>0.05) in values of urea (4.50±1.22 vs. 4.26±1.06 mmol/L), creatinine (69.39±18.03 vs. 62.45±16.83 umol/L), alkaline phosphatase (195.43±63.89 vs. 204.96±44.20 U/L), direct bilirubin (1.73±0.83 vs. 1.85±0.87 umol/L), total bilirubin (13.21±3.20 vs. 14.45±3.46 umol/L) and CRP (3.83±1.73 vs. 3.23±1.29 mg/l), which were mainly within reference ranges.

Comparison of cortisol values measured at 8 am and 4 pm, (within assessment of characteristic endocrine glands functions) using the Student's t-test identified the statistically significant difference in morning cortisol (measured at 8am) between the group with MetS and obese group (472.04±129.53 vs. 412.39±118.51 nmol/L, p=0.038), while this difference was not observed for 4pm values (243.21±74.36 vs. 217.14±54.72 nmol/L, p>0.05).

Regarding the comparison of differences in 24-hours microalbuminuria, significantly higher values were detected in the group of patients with MetS (7.04±4.96 vs. 3.05±1.81 mg/L, p<0.001).

Using the Student's t-test, the analysis of blood glucose and insulin values during OGTT showed a statistically significant difference between the study groups in blood glucose values at 120 minutes (6.93±1.18 vs. 6.38±0.93 mmol/L, p=0.023), but not in the values of fasting glucose (4.66±0.71 vs. 4.43±0.51 mmol/L, p>0.05). From the standpoint of statistical approach to fasting blood insulin levels and levels at 120 minutes, it was determined that the values of monitored parameters in both typical observation time points during OGTT were significantly higher in MetS patients (20.28±7.02 vs. 14.95±3.77 μIU/mL, p<0.001 and 140.41±49.98 vs. 100.45±39.76 μIU/mL, p<0.001). Using the Student's t-test, a highly significant difference was found when comparing the homeostatic indices of insulin sensitivity, HOMA (4.25±1.81 vs. 2.97±0.95, p<0.001) and QUICKI (0.312±0.013 vs. 0.327±0.014, p<0.001).

Table 1. Basic patient characteristics, typical blood chemistry profile of subjects and the values of glucose tolerance test with insulin levels by groups

Parameter/sign	Metabolic syndrome (n=28)	Obese group (n=56)	Test value; p value
Weight (kg)	84.29±21.85	76.34±14.03	t=2.019; p=0.047
Waist circumference (cm)	95.46±9.58	91.04±8.41	t=2.171; p=0.033
Systolic pressure (mmHg)	134.11±14.60	128.39±8.26	t=2.293; p=0.024
Diastolic pressure (mmHg)	83.57±11.21	78.84±9.63	t=2.009; p=0.048
Acanthosis nigricans (n, %)	10 (35.7)	6 (10.7)	χ^2=7.566; p=0.006
Uric acid (umol/L)	356.32±32.70	340.98±32.30	t=2.043; p=0.044
ALT (U/L)	26.04±20.30	19.93±11.04	Z=-2.332; p=0.020
GGT (U/L)	22.39±10.64	18.37±6.99	t=2.073; p=0.041
HbA1c (%)	5.55±0.69	5.24±0.54	t=2.211; p=0.030
Total cholesterol (mmol/L)	5.02±1.43	4.54±0.66	t=2.138; p=0.035
HDL (mmol/L)	0.94±0.34	1.31±0.18	t=-6.505; p<0.001
LDL (mmol/L)	3.33±1.25	2.78±0.74	t=2.540; p=0.013
Triglycerides (mmol/L)	1.95±1.10	1.12±0.42	t=4.980; p<0.001
Cortisol – 8 AM (nmol/L)	472.04±129.53	412.39±118.51	t=2.108; p=0.038
Microalbuminuria (mg/L)	7.04±4.96	3.05±1.81	t=5.363, p<0.001
Blood glucose 120 minutes (mmol/L)	6.93±1.18	6.38±0.93	t=2.317; p=0.023
Fasting blood insulin (μIU/mL)	20.28±7.02	14.95±3.77	t=4.534; p<0.001
Blood insulin 120 minutes (μIU/mL)	140.41±49.98	100.45±39.76	t=3.979; p<0.001
HOMA	4.25±1.81	2.97±0.95	t=4.278; p<0.001
QUICKI	0.312±0.013	0.327±0.014	t=-4.797; p<0.001

The data represent mean ± standard deviation (SD), or n/frequency. Only significant factors are presented for the sake of clarity.

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Parent-related risk factors

A detailed analysis of parents' characteristics led to an interesting discovery – the Student's t test showed higher maternal body weight in the group of children and adolescents diagnosed with MetS (81.36±11.85 vs. 77.07±6.81 kg, p=0.038), as well as mothers' BMI (29.34±4.33 vs. 27.25±3.42 kg/m^2, p=0.018), and fathers' BMI (32.42±5.99 vs. 30.25±2.62 kg/m^2, p=0.023) (Table 2). The values of fathers' body weight did not differ significantly among the MetS group and the group of obese patients (102.25±16.83 vs. 97.29±7.84 kg, p>0.05).

There was also statistically significant difference in the presence of elevated cholesterol/triglyceride levels (abnormal lipid profile values) (82.1% vs. 58.9%, p=0.033), and the frequency of patients' parents with type 2 diabetes (67.9% vs. 44.6%, p=0.045) among the subjects in the group of patients with MetS and obese control group.

With respect to the family history of obesity (92.9% vs 78.6%), arterial hypertension (92.9% vs. 80.4%), asthma (25.0% vs. 32.1%), and psychiatric illnesses (7.1% vs. 1.8%), as well as the regularity of meals (42.9% vs. 58.9%), frequency of spicy/fatty foods intake (89.3% vs. 82.1%), carbonated beverage intake (71.4% vs. 55.4%), regularity of fruit and raw vegetables in the diet (35.7% vs. 46.4%), existence of smokers in the family (92.9% vs. 76.8%) and parents' physical activity (7.1% vs. 8.9%), no significant differences were found between the group of children with MetS and the obese group (p>0.05).

Review and comparison of mothers' pregnancy-related data for children and adolescents in both study groups with respect to special-care pregnancy and application of tocolytic agents, showed a significantly higher frequency in the group with MetS (53.6% vs. 30.9%, p=0.045). Gestational diabetes was identified as a significant pathology in pregnancy, confirmed by the statistically significant difference within the studied groups (25.0% vs. 8.9%, p=0.047). In addition, there was a statistically significant difference regarding certain harmful habits of mothers during pregnancy, such as smoking (57.1% vs. 32.1%, p=0.028). In respect to the presence of pregnancy-induced hypertension (28.6% vs. 12.5%), no significant difference in the prevalence of pathophysiological phenomenon in mothers of children and adolescents in the observed groups was found (p>0.05).

The existence of a stressogenic family event (divorce of parents, loss of a close person, loss of job, change of residence), a significant risk factor for many diseases, was more prominent in children in the study group versus the control group (53.6% vs. 30.4%, p=0.039). In terms of socio-economic, demographic and other relevant factors related to the family setting, neither significant difference regarding rural/urban area of residence (urban - 64.3% vs. 60.7%), adequate, economic living conditions (57.1% vs. 66.1%), university education (at least one) of the parents (17.9% vs. 25.0%), "positive" family attitude toward obesity (50.0% vs. 42.9%) nor frequency of firstbornness (71.4% vs. 55.4%) were found between the observed groups of participants in the study (p>0.05).

Table 2. Characteristics of parents, children and families

Risk factors	Metabolic syndrome (n=28)	Obese group (n=56)	Test value; p value
Mother's weight (kg)	81.36±11.85	77.07±6.81	t=2.105; p=0.038
Mother's BMI (kg/m^2)	29.34±4.33	27.25±3.42	t=2.414; p=0.018
Father's BMI (kg/m^2)	32.42±5.99	30.25±2.62	t=2.313; p=0.023
Family history of elevated cholesterol/ triglyceride levels	23 (82.1%)	33 (58.9%)	χ^2=4.527; p=0.033
Family history of type 2 diabetes mellitus	19 (67.9%)	25 (44.6%)	χ^2=4.033; p=0.045
Special-care pregnancy	15 (53.6%)	17 (30.9%)	χ^2=4.022; p=0.045
Gestational diabetes	7 (25.0%)	5 (8.9%)	χ^2=3.938; p=0.047
Mother smoked during pregnancy	16 (57.1%)	18 (32.1%)	χ^2=4.842; p=0.028
Family history of stressogenic event	15 (53.6%)	17 (30.4%)	χ^2=4.266; p=0.039
Breastfeeding during first 6 months of life	9 (32.1%)	34 (60.7%)	χ^2=6.099; p=0.014

The data represent the mean ± standard deviation (SD), or n/frequency. Only significant factors are presented for the sake of clarity.

Child-related risk factors as determined by surveying parents/child

Analyzing both perinatal data and general characteristics of interest related to children and adolescents in the observed groups, a significant difference between the MetS group and the group of obese patients was found regarding breastfeeding (natural food) in the first 6 months of life (32.1% vs. 60.7%, p=0.014) (Table 2), while no such difference was determined in body weight at birth (3416.07±270.13 vs. 3335.36±613.98 g) and APGAR scores (8.86±0.59 vs. 9.08±0.57) of children participating in the study (p>0.05).

It is interesting to note that between the children and adolescents with MetS and the obese children no difference in physical activity (14.3% vs. 19.6%), regularity of meals (three meals and two snacks) (25.0% vs. 39.3%), diets based on spicy/fatty foods (92.9% vs. 96.4%), i.e. based on the snacks and sweets (96.4% vs. 94.6%), regular presence of fruit and raw vegetables in the diet (28.6% vs. 41.1%), and consumption of soft drinks (64.3% vs. 67.9%) was found (p>0.05).

Multivariate analysis (logistic regression)

The results of logistic regression model are shown in Table 3. The multivariate binary logistic regression model, excluding the parameters typical for IDF definition of MetS in children and adolescents, showed a significant association between the development of MetS and microalbuminuria ($OR_{adjusted}$: 1.686; 95%CI: 1.188-2.393; p=0.003) and

Table 3. Multivariate analysis of risk factors for the development of metabolic syndrome in children and adolescents

Risk factors	B	OR	95% CI		p
			Lower value	Upper value	
Microalbuminuria	0.522	1.686	1.188	2.393	0.003
Gestational diabetes	3.674	39.426	1.822	853.271	0.019
Breastfeeding during the first 6 months of life	-2.537	0.079	0.009	0.716	0.024

Only significant factors are presented for the sake of clarity.
B – coefficient of logistic regression analysis; OR – odds ratio; CI – confidence interval

maternal gestational diabetes ($OR_{adjusted}$: 39.426; 95%CI: 1.822-853.271; p=0.019), or breastfeeding during the first 6 months of life ($OR_{adjusted}$: 0.079; 95%CI: 0.009-0.716; p=0.024), while all the other potentially significant predictors/markers after univariate logistic analysis of the study groups as mother's BMI and weight, father's BMI, child/adolescent cortisol levels at 8AM, levels of ALT, GGT, uric acid, LDL, family history of elevated cholesterol/triglyceride levels, family history of type 2 diabetes mellitus, special-care pregnancy, maternal smoking during pregnancy, family history of stressogenic event were not predictive; Hosmer-Lemeshow Goodness-of-Fit Test for the conducted logistic regression model: χ^2=2.043, df=8, p=0.980.

DISCUSSION

Whether a patient meets the criteria for the development of MetS may be adequately determined by observing the patient's medical history, physical examination and laboratory assessments. Globally, obesity in the pediatric population has been one of the major concerns of the modern era, and the increase in MetS prevalence is directly related to the degree of obesity in children and adolescents.

After analysis of risk factors for MetS development in children and adolescents, our study showed that the frequency of gestational diabetes in mothers of children and adolescents with MetS versus mothers of the obese study subjects was significantly higher. Specifically, the presence of maternal gestational diabetes was observed to be one of the factors that may contribute to the increased risk of obesity and type 2 diabetes in children [11], and recent research supports the development of MetS in children born to diabetic mothers as "large for gestational age" [19].

It should be noted that our study demonstrated that breastfeeding during the first months of life was clearly more prevalent in the obese children versus the children with MetS. Opinions on the correlation between the type of diet in the infant period and its repercussions on the development of obesity in later life are controversial. In the past, a dominant hypothesis was that during the first year of life the total number of adipocytes was completed, and that hypercellular obesity developed during this period carried a higher risk of persistent obesity [20]. Today, the assumption that the duration of obesity and not the age at which it develops represents the crucial factor in determining the number of adipocytes is considered more likely [21, 22]. De Armas et al. [23], in their research which was based on the estimated correlation of breastfeeding and prevalence of obesity, i.e. development of MetS in obese children and adolescents, have demonstrated that breastfeeding longer than three months was associated with a lower degree of obesity, smaller waist circumference and significantly fewer potential complications associated with MetS in childhood and adolescence, and that as many as 64% of children with a complete picture of MetS were fed using formula milk. The assumption that nutrition mode in early childhood may influence the development of obesity in adulthood [24] is not uncommon either. Artificial nutrition, in fact, stimulates postnatal growth and subsequently a more intensive development of obesity in overweight children and adolescents, while in turn, breastfeeding is correlated with a slower pace of growth. Higher protein content in formula milk vs. breast milk is considered a significant factor influencing the rapid growth in the neonatal period. On the other hand, breastfeeding protects children from developing obesity by decreasing plasma insulin, significantly reducing fat reserves, and preventing early development of adipocytes [24].

Although gestational diabetes and maternal diet in the first months of life stand out as the leading risk factors for the development of MetS in the pediatric population, the univariate analysis used in the study showed that factors such as increased maternal body weight, mother's and father's body mass index, increased cholesterol/triglyceride levels, presence of diabetes mellitus type 2 and stressogenic family events, smoking during pregnancy, and special-care pregnancy may be considered the valid predisposing factors, review and analysis of which shall allow for timely and appropriate diagnostic approach to MetS in vulnerable children and adolescents, the attitude further supported by the results of numerous other studies [15, 21, 25, 26, 27].

Cortisol is an adrenal cortex hormone involved in the regulation of many physiological functions of the body. Anagnostis et al. [28] stressed the importance of cortisol in the development of MetS. The increased activity of the hypothalamic-pituitary-adrenal axis was observed in patients with MetS, which may be due to the exposure to chronic stress or low birth weight. In addition, it is well-known that glucocorticoids help adipocyte differentiation and proliferation [29] and that their receptors are more dense in the visceral than in the subcutaneous adipose tissue [30], which in turn leads to the increased cortisol exposure contributing to the increased accumulation of fat in visceral depots. Also, Khani et al. [31] have shown that cortisol significantly influences stimulation of gluconeogenesis. Elevated cortisol levels that may occur within MetS contribute to increased gluconeogenesis in the liver and impaired glucose metabolism.

Even though cortisol levels in our study reached statistical significance in the analytical estimates, this early diagnostic marker for MetS diagnosis cannot be consid-

ered significant, since the confidence interval included the value of one.

The epidemiological study conducted by Sanad and Gharib [32], analyzing only obese children, found the microalbuminuria incidence of 14.7%. These children were found to have a higher waist circumference, increased blood pressure, high triglyceride levels, low HDL levels, insulin resistance and elevated fasting glucose compared to obese children with absence of albumin in urine. Although opinions on microalbuminuria as a component of MetS still differ greatly [33, 34], its significance in the field of MetS is supported by the fact that recent recommendations of WHO suggest that the disorder should be included in the definition of this pathophysiological syndrome [35].

Results of our research also support that microalbuminuria should be a part of this syndrome in obese children and adolescents.

Main limitation of our study was a relatively small study sample, collected from only one study site; therefore, local influences underlying the risk factors could not have been eliminated. Besides, the values of some of the variables were reported by the children and their parents, and could not have been double checked.

CONCLUSION

Based on our results, we could conclude that the presence of maternal gestational diabetes and/or lack of infant breastfeeding during the first months of life may contribute to the increased risk of developing MetS, while microalbuminuria is frequently associated with MetS in obese children and adolescents. Taking into account these factors, early identification of children and adolescents at risk of developing MetS may be improved, as well as the creation of preventive and timely strategies to prevent the occurrence of the syndrome or the development of potential complications (primarily cardiovascular diseases and diabetes mellitus type 2) in later life.

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Фактори ризика за развој метаболичког синдрома код гојазне деце и адолесцената

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КРАТАК САДРЖАЈ

Увод Висока преваленција метаболичког синдрома код деце и адолесцената општи је и забрињавајући проблем савременог друштва.

Циљ рада Циљ истраживања је био да се утврди утицај раније испитиваних и потенцијално нових фактора ризика на развој метаболичког синдрома код деце и адолесцената.

Методе рада Урађена је опсервациона клиничка студија испитивања случајева и контрола (енгл. *case-control study*) која је обухватила децу и адолесценте са гојазношћу, односно метаболичким синдромом, која су болнички лечена од јануара 2008. до јануара 2012. године у Педијатријској клиници Клиничког центра у Крагујевцу (Република Србија). Групу „случајева" чинило је 28 испитаника узраста од 10 до 16 година са дијагнозом метаболичког синдрома сходно критеријумима Међународне федерације за дијабетес (*International Diabetes Federation – IDF*), док је контролну групу испитаника чинило 56 гојазне деце и адолесцената сличних одлика и коморбидитета као компарирана група.

Резултати Заступљеност гестационог дијабетеса код мајке ($OR_{adjusted}$: 39,426; *95%CI*: 1,822–853,271; p=0,019) и/или изостанак дојења у првих шест месеци живота детета ($OR_{adjusted}$: 0,079; *95%CI*: 0,009–0,716; p=0,024) значајни су предиктори за развој метаболичког синдрома. С развојем метаболичког синдрома код гојазне деце и адолесцената удружена је и микроалбуминурија ($OR_{adjusted}$: 1,686; *95%CI*: 1,188–2,393; p=0,003).

Закључак Гестациони дијабетес мајке и/или изостанак дојења детета у првих шест месеци по његовом рођењу сматрају се релевантним факторима који могу допринети повећаном ризику за развој метаболичког синдрома. Микроалбуминурија је такође веома често удружена с развојем овог синдрома код гојазне деце и адолесцената.

Кључне речи: метаболички синдром; гојазност деце; гојазност адолесцената; фактори ризика

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