

Predictive values of metabolic syndrome in children

Research Article

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Abstract: Metabolic syndrome is a clinical term encompassing risk factors (obesity, insulin resistance, dyslipidemia and hypertension), which yield an increased risk for the development of diabetes mellitus type 2 and cardiovascular disorders in adolescence. Two sets of criteria for diagnosing metabolic syndrome were applied, the criteria for adults, specifically adapted for children, and the criteria defined by the International Diabetes Federation (IDF). A reliability analysis was conducted; sensitivity (SE), specificity (SP), positive predictive value (PPV) and negative predictive value (NPV) of applying certain criteria of both definitions of metabolic syndrome. Metabolic syndrome in adolescents was diagnosed much more frequently using the specific criteria (41%) in comparison to the IDF criteria (22%). Using the specific criteria for children and adolescents, it was established that the HDL cholesterol was the most specific and had the largest PPV. Using the IDF criteria for diagnosing metabolic syndrome, the reliability analysis established that the highest PPV was recorded with the elevated level of triglycerides. The specific criteria have been found to be more efficient in diagnosing metabolic syndrome in adolescents. The highest predictive value was displayed by dyslipidemic disorders, hypertriglyceridemia and hypo HDL cholesterolemia.

Keywords: Metabolic syndrome • Children • Predictive value

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1. Introduction

Metabolic syndrome is a clinical term, encompassing many risk factors, such as obesity, insulin resistance, dyslipidemia and hypertension, which yield an increased risk of the development of diabetes mellitus type 2, early atherosclerosis, cerebrovascular and cardiovascular disorders in adolescence. The prevalence of metabolic syndrome is increasing and is directly related to the obesity rate among children. Obesity and accompanying metabolic complications have aroused great interest among researchers over the past eighty years. It was Gerald M. Reaven who in 1988 described metabolic syndrome as syndrome X and pointed out the importance of insulin resistance for the occurrence of atherosclerosis and its connection with obesity, dyslipidemia and diabetes [1]. The IDF consensus group suggested the currently valid definition of metabolic syndrome for adults

in 2005 [2], i.e. in 2007 for children and adults [3]. Many studies reveal that the diagnosis of metabolic syndrome in children was set using the criteria for adults, which had been specifically adapted and modified for children. It was demonstrated that applying the criteria specific for children led to a significantly higher percentage of diagnosed metabolic syndrome in children [4-10].

The previous century saw intensive discussions about the danger of combined effects of several risk factors, while over the past few years the analysis of predictive values of metabolic syndrome has become a topical and important subject of numerous researches [11-16]. Since certain risk factors of metabolic syndrome have higher sensitivity and lower specificity, i.e. their predictive values differ, an ideal solution should be found for identifying children with an increased risk of developing the metabolic syndrome, cardiovascular diseases or type 2 diabetes in adolescents. It is

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understood that patients with one risk factor should be tested for other factors and individual factors should be treated aggressively. Regardless of the definition of the metabolic syndrome, it is vital to emphasise the risk factors, since they inevitably lead to obesity complications, while metabolic syndrome is widely spread, but insufficiently well recognised and treated [17,18].

The aim of the research was to analyse the criteria for diagnosing the metabolic syndrome and predictive values of the metabolic syndrome in overweight and obese children and adolescents in Vojvodina.

2. Material and Methods

The research has been conducted as a cross study analysis of children and adolescents under 18, treated and controlled for overweight and obesity at the Department of Endocrinology, Diabetes and Metabolism Disorders and the Endocrinology Clinic of the Institute for child and youth health care of Vojvodina in Novi Sad between 2004 and 2008. The sample comprised 206 patients, divided into two groups, depending on the body mass index (BMI): overweight patients (BMI 85-95 percentiles) and obese patients (BMI over 95 percentiles). Each group was further divided according to their age: children up to 10 years of age (including those aged 10) and adolescents between 11 and 18 years of age (our institute treats patients under and including 18 years of age). The research included the analysis of the following criteria: BMI, waist circumference, blood pressure, triglycerides, HDL cholesterol, glycemia and insulinemia during the oral glucose tolerance test (OGTT). Two sets of criteria for diagnosing metabolic syndrome were applied: the criteria for adults, specifically adapted for children [19,20], and the criteria defined by the International Diabetes Federation (IDF) for children and adolescents [3].

The physical examinations included the following: measuring body weight (W) in kilograms, height (H) in centimetres using a Harpenden stadiometer, waist circumference (WC) in centimetres using a non-elastic tape at the navel level and body mass index (BMI) -defined as the individual's body weight divided by the square of his or her height in meters (kg/m^2). The arterial pressure was measured with standard auscultation sphygmomanometer, using mercury manometer and appropriate cuffs. The results obtained were compared against the nomograms [21], and the entry criterion for diagnosing the metabolic syndrome was existence of supranormal pressure (> 95 percentiles for sex/age), systolic, diastolic or both.

A laboratory analysis of triglycerides and HDL cholesterol within the lipid status was conducted using a method of enzyme colorimetric test (Roche/Hitachi 902 analyser) after the patients had been deprived of food for 12 hours. The standard 2-hour OGTT was conducted after the patients had been deprived of food for 12 hours with 1.75 g/kg glucose orally (maximum 75g). Venous blood samples for plasma glycaemia and insulinemia analysis were taken every 30 minutes during 120 minutes of the test. The laboratory analysis of glycaemia was conducted using the hexokinase method (Roche/Hitachi 902 analyser), while the analysis of insulinemia was conducted using the immunometric method (ADIVA Centaur XP analyser). The glycaemia values during the OGTT were analysed using the criteria of the America Diabetes Association [22]. Fasting glucose disorder is defined as having values ≥ 5.6 mmol/l, but < 7 mmol/l; glucose tolerance disorder is defined as having values between 7.8 and 11 mmol/l in 2nd hour of the OGTT; diabetes is defined with fasting glucose values ≥ 7 mmol/l or ≥ 11.1 mmol/l in 2nd hour of the OGTT. The insulinemia values were assessed basally, in the first and second hour of the OGTT [23]. Based on the OGTT, the entry criteria for a pathological result of the OGTT, i.e. a disorder in carbohydrate metabolism, were hyperglycaemia, glucose tolerance disorder, hyperinsulinemia, insulin resistance or diabetes (dichotomy applied: positive/negative results).

A control group was not established, since there is nomograms for all patients, related to sex and age and determined using a large sample of children. The following nomograms were used: body mass index [24], waist circumference [25], blood pressure [21], HDL cholesterol and triglyceride values [26].

The criteria for diagnosing the metabolic syndrome in adults, specifically adapted for children, were applied [19,20]: the metabolic syndrome is diagnosed if three or more of the following are present: body mass index (BMI) > 97 percentiles for sex/age, arterial pressure > 95 percentiles for sex/age, serum triglycerides > 95 percentiles for sex/age, HDL cholesterol < 5 percentiles for sex/age, pathological result of the OGTT – carbohydrate metabolism disorder (hyperglycaemia, glucose tolerance disorder, hyperinsulinemia, insulin resistance or diabetes).

Another set of criteria [3] were also applied for diagnosing the metabolic syndrome, those prescribed by the International Diabetes Federation (IDF); in children aged 10-16, the metabolic syndrome is diagnosed if the waist circumference is ≥ 90 percentiles (or applying the criteria for adults, if they are more strict), accompanied by two or more of the following parameters: triglycerides ≥ 1.7 mmol/l, HDL cholesterol < 1.03 mmol/l, elevated

Table 1. Frequency of criteria of both definitions in adolescents diagnosed with the metabolic syndrome.

Metabolic syndrome	Specific criteria		Criteria IDF	
	frequency	%	frequency	%
BMI > 97p / WC ≥ 90p	56	88.89	34	100
BP > 95p / ≥130/85 mmHg	54	85.71	30	88.23
HDL cholesterol < 5p / ≤ 1.03 mmol/l	6	25.40	24	70.58
TG > 95p / ≥ 1.7 mmol/l	38	60.32	18	52.94
abnormal OGTT / FPG ≥ 5.6 mmol/l	57	90.48	3	8.82

IDF: International Diabetes Federation; BMI: body mass index; WC: waist circumference; BP: blood pressure; HDL cholesterol: high density lipoprotein cholesterol; TG: triglycerides; OGTT: oral glucose tolerance test; FPG: fasting plasma glucose; p: percentile.

arterial pressure (systolic ≥ 130 mmHg, diastolic ≥ 85 mmHg), fasting glucose ≥ 5.6 mmol/l. The metabolic syndrome was not diagnosed in children under 10 and additional tests were conducted only in case of positive family medical history. In case of children over 16, the criteria for adults were applied.

Parents and children had been informed about the nature and rationale behind the research and had signed consent for the relevant data to be included in the research. The ethical committee of the Institute had also approved the research before it commenced.

Adequate statistical data processing was conducted after the research. Attributive (binary) and numerical variables were analysed using the standard procedures of descriptive statistics. The descriptive statistics methods were used to determine the central tendency (the mean) and dispersion (standard deviation) with numerical values (age), i.e. frequency and relative relations (percentage) with attributive values (criteria for diagnosing the metabolic syndrome). The comparative statistics methods were then used to compare certain pairs of traits, encompassing a z-test for establishing the difference between the ratios of certain pairs of attributive values. A statistical test of the difference between proportions was used to test the hypothesis that the metabolic syndrome was diagnosed significantly more often by applying the specific criteria for children and adolescents than by applying the International Diabetes Federation criteria. In all the tests applied, the results with significance level of 95% ($p < 0.05$) were interpreted and statistically significant, while those with significance level of 99% ($p < 0.01$) were interpreted as highly significant. In order to estimate the reliability of certain parameters, the following indicators were determined: sensitivity (SE), specificity (SP), positive predictive value (PPV) and negative predictive value (NPV).

3. Results

Among the 206 children included in the research, the body mass index (BMI) suggested that 153 of them (74%) were obese and 53 (26%) overweight. There were 155 (75%) adolescents and 51 (25%) children. The sample comprised (50.5%) boys and 102 (49.5%) girls. Among the adolescents, 30.3% (47) were overweight and 69.7% (108) obese, while among the children there were 11.7% (6) overweight and 88.2% (45) obese. The youngest child encompassed by the research was 4, while the average age of the patients was 12.06 ± 3.42 years.

A comparative analysis of the criteria in both definitions was conducted on a group of adolescents ($n=155$); by applying the specific criteria, the metabolic syndrome was diagnosed with 41% of adolescents, while the application of the International Diabetes Federation criteria saw the metabolic syndrome diagnosed with 22% of adolescents. A proportion difference test showed that the metabolic syndrome was diagnosed significantly more often by applying the specific criteria for children and adolescents than by applying the International Diabetes Federation criteria, i.e. the application of the specific criteria for children and adolescents is more efficient in terms of the number of diagnosed cases ($p < 0.01$). The criteria for diagnosing the metabolic syndrome of both definitions were analysed in the group of adolescent diagnosed with the metabolic syndrome (Table 1).

Applying the specific criteria for diagnosing the metabolic syndrome in children and adolescents on the whole sample, yielded the following results: metabolic syndrome was diagnosed with 38% of the patients, i.e. with 9% of the overweight, 48% of the obese or with 29% of children and 41% of adolescents. Applying the International Diabetes Federation criteria for children and adolescents, the metabolic syndrome was diagnosed with 17% of all patients, i.e. with 4% of the overweight, 22% of the obese and 22% of adolescents.

Table 2. Reliability analysis of specific criteria of the metabolic syndrome in children and adolescents.

	SE	SP	PPV	NPV
BMI > 97p	0.91	0.44	0.5	0.89
BP > 95p	0.87	0.79	0.72	0.91
HDL cholesterol < 5p	0.23	0.95	0.75	0.67
TG > 95p	0.55	0.83	0.66	0.75
abnormal OGTT	0.88	0.77	0.7	0.92

MS: Metabolic syndrome; BMI: body mass index; BP: blood pressure; HDL cholesterol: high density lipoprotein cholesterol; TG: triglycerides; OGTT: oral glucose tolerance test; p: percentile; SE: sensitivity; SP: specificity; PPV: positive predictive value; NPV: negative predictive value.....

Table 3. Reliability analysis of the International Diabetes Federation criteria for diagnosing the metabolic syndrome in adolescents.

	SE	SP	PPV	NPV
WC ≥ 90p	1	0.43	0.33	1
BP ≥ 130/85 mmHg	0.88	0.67	0.43	0.95
HDL cholesterol ≤ 1.03 mmol/l	0.71	0.87	0.60	0.91
TG ≥ 1.7 mmol/l	0.53	0.91	0.62	0.87
FPG ≥ 5.6 mmol/l	0.09	0.98	0.60	0.79

WC: Waist circumference; BP: blood pressure; HDL cholesterol: high density lipoprotein cholesterol; TG: triglycerides; FPG: fasting plasma glucose; p: percentile; SE: sensitivity; SP: specificity; PPV: positive predictive value; NPV: negative predictive value.....

A reliability analysis was conducted; sensitivity-SE, specificity-SP, positive predictive value-PPV, negative predictive value -NPV of certain specific criteria for diagnosing the metabolic syndrome in children and adolescents and among the International Diabetes Federation criteria for diagnosing the metabolic syndrome (Table 2,3).

4. Discussion

Obesity in children is the leading problem today, with all the risks of developing metabolic complications, diabetes and cardiovascular diseases in adolescence and early adulthood. Research shows that the metabolic syndrome prevalence is increasing and that it is directly related to the obesity level in children, hence the need for investigating obesity in children, establishing the risk factors of metabolic syndrome and quantifying the problem, so that it could be prevented, monitored and treated.

By applying the specific criteria in this research, the metabolic syndrome was diagnosed with 41% of adolescents, while the application of the International Diabetes Federation criteria saw the metabolic syndrome diagnosed with 22% of adolescents. Metabolic syndrome in children and adolescents was diagnosed much more frequently using the specific criteria in comparison to the International Diabetes Federation criteria, which is why the former are much more efficient for diagnosing metabolic syndrome. Other researchers used the criteria for adults recommended by the World

Health Organisation (WHO) and the criteria suggested by the experts from the National Cholesterol Education Program – Adult Treatment Panel (NECP-ATP) and confirmed the metabolic syndrome in 12.2 and 13.7% of obese children, whereas in the same group of children the application of the specific criteria for children diagnosed the metabolic syndrome in 31% of obese children [20]. The International Diabetes Federation criteria and definitions for diagnosing metabolic syndrome in children and adolescents were inspired by the definition of criteria for adults, simplified and made insufficiently specific for the age in question. This definition does not include children under 6, those under ten cannot be diagnosed with metabolic syndrome, but if the family medical history is positive, the children need to be monitored and advised to change the style of living and reduce their body weight. The fact that 29% of children were diagnosed with metabolic syndrome using the specific criteria shows that obesity and early metabolic changes pose a great problem among children today and that there has been a shift in the age affected by the problem of obesity. In case of children older than 16, the criteria for adults are applied and percentile curves are used only for waist circumference. Age characteristics and development specificities emphasise the importance of applying percentile curves and other criteria in order to achieve better efficiency in the number of diagnosed cases. It is because all these reasons that we choose to apply the specific criteria for diagnosing the metabolic syndrome in children and adolescents in our daily work.

All adolescents with metabolic syndrome had a waist circumference ≥ 90 percentiles; 89 % of the patients had

a BMI > 97 percentiles; arterial pressure > 95 percentiles was recorded with 86% of the patients; arterial pressure $\geq 130/85$ mmHg was recorded in 88% of adolescents; 25% of the patients had an HDL cholesterol < 5 percentiles; HDL cholesterol $\leq 1,03$ mmol/l (adolescents >16 years of age according to the criteria for adults) was recorded with 71% of adolescents; serum triglycerides > 95 percentiles were recorded with 60% of the patients; triglycerides $\geq 1,7$ mmol/l were recorded in 53% of adolescents; pathological result of the OGTT was recorded with 90% of the patients; fasting glucose $\geq 5,6$ mmol/l was recorded in 9% of adolescents (Table 1). In this research, the criteria for obesity, body mass index and waist circumference were confirmed in similar percentages by applying both definitions. The specific criteria for lower values of HDL cholesterol are stricter, so more children and adolescents were identified using the International Diabetes Federation criteria. Elevated serum triglycerides are significantly more present when the specific criteria for diagnosing the metabolic syndrome in children and adolescents are applied. The high percentage of pathological results of the OGTT testifies to the existence of disorder in the carbohydrate metabolism, despite maintaining regular levels of fasting glucose.

Combinations of several metabolic syndrome risk factors and individual predictive importance of certain components have been topics of many researches, aiming at identifying, at an early age, children who run a risk of developing cardiovascular diseases and type 2 diabetes in early adulthood [27]. Some questions arise, such as whether a combination of metabolic syndrome risk factors carries more important or greater risk than individual components, whether each of the aforementioned factors carries a risk of developing cardiovascular diseases and whether they should be treated accordingly. Many analyses of sensitivity, specificity and positive predictive values for various definitions of metabolic syndrome have shown that a combination of the metabolic syndrome risk factors is more significant than individual components in the development of metabolic syndrome [11-13]. There are not many researches examining the metabolic syndrome predictive values in children.

A reliability analysis of all metabolic syndrome risk factors has shown that, when the specific criteria for children and adolescents are applied, body mass index (BMI) is the most sensitive factor, HDL cholesterol the most specific and the least sensitive, with the greatest positive predictive value, while pathological results of the OGTT have the highest negative predictive value. A reliability analysis of all metabolic syndrome risk factors has shown that, when the International Diabetes

Federation criteria are applied, waist circumference is the most sensitive factor and has the highest negative predictive value, fasting glucose is the most specific and the least sensitive factor, while triglycerides have the highest positive predictive value. An analysis of both sets of criteria leads to a conclusion that a dyslipidemic disorder in metabolic syndrome, hypertriglyceridemia and hypo HDL cholesterolemia has the highest metabolic syndrome predictive value.

Only a few research works examined the predictive values of metabolic syndrome among children, which is why we had decided to conduct this research in order to show which metabolic syndrome component had the highest predictive value. The factors predisposing the metabolic syndrome in adults have been examined. Certain components of the metabolic syndrome have been analysed and their practical value in confirming or ruling out the metabolic syndrome in adults. Hypertriglyceridemia in men and hypo HDL cholesterolemia in women had the highest positive predictive value, thus proving to be strong metabolic syndrome predictors [14]. Another research, also dealing with adults, has shown that fasting hyperglycaemia and hypertriglyceridemia had high metabolic syndrome positive predictive values. Increased waist circumference and lower HDL cholesterol had high negative predictive value [15]. A study conducted in China analysed which of the metabolic syndrome components was best at predicting the syndrome and central obesity and dyslipidemic disorders proved to have the highest positive predictive value [16].

The dyslipidemic atherogenic profile of the metabolic syndrome includes elevated levels of serum triglycerides, lower levels of HDL cholesterol, accompanied by small and dense LDL particles. The changes occur as a consequence of lipoprotein metabolism disorder, while increased release of free fat acids from adipocytes and increased synthesis of triglycerides in liver are the foundation of the development of lipid disorders in the metabolic syndrome. Hypertriglyceridemia accompanied by altered LDL particles could perform atherogenic influence, by increasing the penetration in the *intima media* and lowering the antioxidant capacity, while dyslipidemia is noted as the main mediator of atherosclerosis in metabolic syndrome. Obesity, development of insulin resistance and dyslipidemia in children lead to atherogenesis, hypertension and manifestations of other components of the metabolic syndrome, while dyslipidemic disorders, hypertriglyceridemia and lower levels of HDL cholesterol have displayed strong predictive values. The central role of dyslipidemic disorders in the metabolic syndrome pathogenesis and their high predictive value are of great

importance in timely detection of children bearing the risk of developing the metabolic syndrome and the prevention process.

There is a dilemma whether a diagnosis of metabolic syndrome provides more useful information about the risk of cardiovascular diseases than individual components [28].

The research has shown that it is necessary for obese children and adolescents to undergo screening of other components of metabolic syndrome and further detailed testing of fat and carbohydrate metabolism, as well as the consequences of their homeostasis disorders. Naturally, with patients who have one risk factor confirmed, tests should be conducted for other factors and individual factors should be treated aggressively.

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5. Conclusions

The existence of metabolic syndrome in adolescents has been confirmed much more frequently using the specific criteria than the International Diabetes Federation criteria, which is why the specific criteria have been found more efficient in diagnosing metabolic syndrome in adolescents. The highest predictive value was displayed by dyslipidemic disorders, hypertriglyceridemia and hypo HDL cholesterolemia.

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