DOI: 10.70949/pramed202502003M

STANDARD AND ADVANCED METHODS FOR DIAGNOSIS OF METABOLIC SYNDROME AND ITS COMORBIDITIES IN CHILDREN

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SUMMARY

The metabolic syndrome (MS) is a clinical entity of substantial heterogeneity, represented by the combination of obesity (especially central obesity), insulin resistance, impaired glucose tolerance, atherogenic dyslipidemia (high triglyceride levels and low levels of HDL-cholesterol (HDL-C)), and hypertension. Childhood obesity has become more common as a result of urbanization, bad diets, and more sedentary lifestyles
The incidence of metabolic syndrome is ten times higher in children with obesity, and a special risk factor is the presence of obesity in the pediatric population, the classification of metabolic syndrome is based on standards set by the International Diabetes Federation (IDF).
Our goal is to summarize the diagnostic procedure of metabolic syndrome as well as comorbidity based on conventional methods and modern imaging procedures by analyzing the published papers.

Keywords: obesity, children, visceral fat tissue, Metabolic syndrome, Body Mass Index, diagnosis, comorbidities, insulin resistance

SRPSKI

STANDARDNE I NAPREDNE METODE ZA DIJAGNOSTIKU METABOLIČKOG SINDROMA I NJEGOVIH KOMORBIDITETA U DECE

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SAŽETAK

Metabolički sindrom (MS) je klinički entitet nastao kombinacijom razliciitih patofizioloških poremećaja: gojaznosti (posebno centralne gojaznosti), insulinske rezistencije, poremećene tolerancije glukoze, aterogene dislipidemije (visoki nivoi triglicerida i niski nivoi HDL- holesterola (HDL-C)) i hipertenzije.
Incidenca metaboličkog sindroma je deset puta veća kod dece sa gojaznošću, a poseban faktor rizika je prisustvo gojaznosti u detinjstvu. Klasifikacija metaboličkog sindroma zasniva se na standardima koje je postavila Međunarodna federacija za dijabetes (IDF).
Naš cilj je da analizom objavljenih radova sumiramo dijagnostičku proceduru metaboličkog sindroma kao i komorbiditeta na osnovu konvencionalnih metoda i savremenih imidžing tehnika.

Ključne reči: gojaznost, deca, visceralno masno tkivo, metabolički sindrom, Indeks Telesne Mase, komorbiditeti, insulinska rezistencija

INTRODUCTION

The International Diabetes Society (1,2) has defined Metabolic syndrome (MS) as "a cluster of the cardiovascular risk factors" - diabetes or elevated fasting plasma glucose, abdominal obesity, high cholesterol and high blood pressure."
As the proportion of the population with obesity continues to rise, the prevalence of metabolic syndrome is increasing in both children and adolescents. Elevated triglycerides (TG), altered glucose metabolism, reduced high-density lipoprotein cholesterol (HDL-C), and elevated blood pressure and adiposity are the main risk factors (3,4). They are primarily caused by insulin resistance, leading to diabetes mellitus, hepatic steatosis, polycystic ovary syndrome, and obstructive sleep apnea.

The definition of MS in children and adolescents remains unclear due to the absence of gold standard diagnostic criteria of MS for the pediatric population.
Some of the diagnostic criteria used by studies include the International Diabetes Federation (IDF) criteria, the World Health Organization criteria, the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria modified for age, the de Ferranti et al. the Weiss et al., and the Cruz and Goran criteria (3,4,5).
Prevalence of MS among the children (6,7) ranges from 0.2% to 38.9%, according to different studies. The prevalence was considerably higher in the overweight (11.9%) and obese (29.2%) population.
In a systematic review of 85 studies in children (8), the median prevalence of metabolic syndrome in whole populations was 3.3% (range 0–19.2%), and in overweight children it was Dyslipidemia linked to metabolic syndrome can also accelerate the atherosclerotic process (16,17, 18).
Dyslipidemia is defined as increased free fatty acid flow, elevated triglyceride levels, decreased high density lipoprotein (HDL) cholesterol values, increased low-density lipoprotein (LDL) cholesterol, and increased apolipoprotein (apo) B. Overproduction of very low-density lipoprotein (VLDL) / apo B-100, reduced catabolism of apo B-containing particles, and increased catabolism of HDL-apo / A-I particles may all contribute to dyslipidemia in MS patients (18,19). The major problem in the genesis of MS is related to the adipose tissue's failure to convert free fatty acids to triglycerides (inadequate esterification).
Under conditions of insulin resistance, the antilipolytic effect of insulin on adipose tissue is weak (20), increasing plasma free fatty acid levels. Insulin resistance lowers LDL receptor expression and raises hepatic cholesterol production and VLDL secretion.
The increased hepatic cholesterol production in people with MS results in non-decrease in the breakdown of triglyceride leftovers in the postprandial state. Abnormal postprandial lipemia has been detected in individuals with coronary heart disease and other disorders linked to an increased cardiovascular risk. (9,21)
Increased plasma uric acid has been thought to possess antioxidant properties (22). However, uric acid's harmful effects include an inhibitory influence on nitric oxide (NO) generation, platelet aggregation, and pro-inflammatory action. It has been claimed that hyperuricemia may predict the onset of metabolic syndrome, diabetes, hypertension, renal disease, and cardiovascular disease.

PURPOSE

In the last decade and a half, several novel methods and biochemical parameters have emerged in the diagnosis of obesity and metabolic syndrome: ultrasonography (US), bioelectrical impedance analyzer, computed tomography (CT), magnetic resonance (MRI), magnetic resonance spectroscopy (MRS), positron emission tomography (PET), 8F-fluorodeoxyglucose (FDG) PET, Dual-Energy x-ray Absorptiometry (D However, traditional markers such as BMI, WC, fasting glucose, arterial blood pressure, and hyperlipidemia are still used to define metabolic syndrome. In this study, we evaluated at whether innovative approaches outperformed established ones in predicting metabolic syndrome and associated comorbidities.

RESULT

Obesity is diagnosed based on body mass index (BMI). Children with a BMI ≥95th percentile for gender and age are considered obese, and those with BMI ≥85th percentile and <95th percentile - overweight. Additionally, visceral fat accumulation (23), independent of the degree of obesity, is strongly associated with both childhood metabolic syndrome and cardiovascular diseases later in life.

Waist circumference (WC) is used to define central obesity. The World Health Organization and the International Diabetes Federation (24) suggest measuring WC in the horizontal plane midway between the lowest ribs and the iliac crest (Table 2).(25)
Our research (26) on a sample of 60 obese children aged 2 to 17 years revealed that waist circumference is a criterion that exhibits a strong relation with BMI, LDL-cholesterol and insulin levels, as well as with subcutaneous fat thickness (measured in the subscapular area).
In the pediatric population, emphasis should be given to history on the course of pregnancy, with a focus on the child's birth weight (SGA, children with birth weight defined as small for gestational age). Many studies (27,28) have examined the increased risk of obesity and metabolic syndrome in SGA children later in life; however, neither the proportion of SGA in childhood obesity nor the prevalence of obesity in SGA is known. In a Belarusian (29) birth cohort study, 8.9 percent of participants were born SGA and made up a minor proportion of those who were overweight or obese when compared to those born big for gestational age.

Body weight, (BW). Body Mass Index - as well as arterial blood pressure should be obtained during physical examination. While waist circumference is considered indicative of visceral adiposity (30), the lack of pediatric reference range data precludes its use in the routine evaluation for childhood obesity.
Visceral adiposity can also be estimated using waist to hip ratio and magnetic resonance imaging. Alternatively, waist to height ratio is used in children. A ratio of 0.6 or more is indicative of increased risk for metabolic syndrome (31) and cardiovascular diseases.
Signs of MS comorbidities, such as acanthosis nigricans (indicative of insulin resistance) and genu valga should be registered during the examination. Polycystic ovaries (with hypertrichosis, menstrual cycle irregularities, acne, and so on) in girls may be the first symptom of insulin resistance and MS complications.
Biochemical parameters including liver function indexes and a fasting lipid profile should be obtained. Lipids and HDL lipid profile should be measured in overweight children between the ages of 2–8 and repeated between 12 - 16. The presence (32) of high triglycerides – low HDL cholesterol profile is highly suggestive of insulin resistance.
Non-HDL-C represents the total of highly atherogenic lipoprotein particles, computed as TC minus HDL-C. Recent guidelines advocate universal lipid screening with nonfasting non-HDL-C testing in all youth aged 9–11 and 17–21.
Hypertriglyceridemia can be diagnosed if TG level is ≥100 mg/dL (1.69 mmol/L) in children (<10 year) or ≥130 mg/dL (1.47mmol/l) in adolescents (10–19 year) based on an average of two fasting measurements (33)
The American Diabetes Association (ADA), has advised an oral glucose tolerance test as screening for type 2 diabetes, every 3 years from the age of 10 or from the start of puberty in the context of the presence of any two of the following features: a family history of T2D, high risk ethnicity, signs of insulin resistance, or associated diseases (hypertension, dyslipidemia, polycystic ovarian disease, or being born small for gestational age) or maternal history of diabetes or gestational diabetes affecting the overweight child.
According to guidelines of the ADA, prediabetes can be diagnosed by one of three laboratory values: (1) elevated fasting glucose of 100 to 125 mg/dL (5.6–6.9 mmol/L) or (2) elevated glucose at 2 hours during an oral glucose tolerance test, 140 to 199 mg/dL (7.8–11.0 mmol/L) or (3) hemoglobin A1C (HbA1C) level between 5.7% and 6.4% (39–46 mmol/mol. Puberty, which is linked to a considerable rise in insulin resistance and may play a role in the development of T2DM, is one factor that exacerbates prediabetes in adolescence (34).
The link between BMI/WC, hyperinsulinemia and blood pressure was discovered in children as young as four years old.

Obesity is commonly associated with non-alcoholic fatty liver disease, elevated alanine transaminase (ALT) levels as well as other liver function abnormalities (35). Features of metabolic syndrome are not only highly prevalent in patients with Nonalcoholic Fatty Liver Disease (NAFLD) but components of MS also increase the risk of developing NAFLD. In the majority of patients, NAFLD is commonly associated with metabolic comorbidities such as obesity, diabetes mellitus, and dyslipidemia. The most prevalent and well-established risk factor for NAFLD is obesity (excessive body mass index and visceral obesity). In actuality, NAFLD is linked to the full spectrum of obesity, from overweight to obese to very obese (36). The majority (>95%) of patients with severe obesity undergoing bariatric surgery will have NAFLD.

NASPGHAN (North American Society For Pediatric Gastroenterology, Hepatology & Nutrition) guidelines recommend ALT as the best screening test for NAFLD in children. These guidelines propose an ALT ≥ 80 U/L on initial screening or ALT greater than or equal to twice the upper limit of normal (ALT ≥ 44 U/L for females and ALT ≥ 52 U/L for males) on repeated screening as an indication for further evaluation. As demonstrated in the SAFETY study, for the general population including children with obesity, the 95th percentile for ALT was 26.0 U/L in females and 37.2 U/L in males. However, the diagnosis of NAFLD should not be made solely based on ALT (37), despite the fact that it may be an important screening tool.

ALT and MS components (visceral fat, body mass index, waist circumference, percentage body fat, blood pressure, elevated blood glucose, and lipid profiles) were significantly correlated, according to a study by Elizondo-Montemayor et al (38). The best indicator of a high ALT was waist circumference.

Liver function tests (serum alanine and aspartate aminotransferases) is advised biannually starting from 10 years of age in obese children or those overweight with risk factors.

The metabolic syndrome is characterized by low-grade inflammation. C-reactive protein (CRP), an inflammatory biomarker often increased in children with MS, is also an independent predictor of future cardiovascular events. Tumor necrosis factor (TNF), interleukin 6 (IL-6), interleukin 8 (IL-8), and resistin are other important actors in inflammation linked to diabetes and insulin resistance (39). Concentrations of anti-inflammatory cytokines (IL-10), ghrelin, adiponectin, and antioxidant factors (PON-1) are decreased in MS, and the decreases correlated with specific disorders within the cluster. Recent studies point to causal relationship between uric acid and insulin resistance (40).

Metabolic syndrome is associated with an increased risk of cardiovascular disease (CDC) and type 2 diabetes mellitus. Carotid intima–media thickness and lumen diameters were increased in children with MS as compared to children without MS. The correlation between Carotid Intima-Media Thickness (CIMT) and waist circumference (WC) in adolescents has been proven, and the association between BMI and CIMT is supported by Iannuzzi et al (41) and White et al who observed that obese children had a larger CIMT than children with a healthy BMI.

Imaging studies

Ultrasonography (US), computed tomography (CT), and magnetic resonance (MR) imaging may assess the subcutaneous adipose and visceral abdominal tissue (VAT).

Ultrasonography have been used to measure VAT, intra-abdominal fat thickness and abdominal fat index (ratio of the thicknesses of the pre-peritoneal and subcutaneous abdominal fat). Computed tomography can even more accurately assess VAT. Subcutaneous fat thickness was defined as the measurement from the skin-fat interface to the linea alba, and visceral fat thickness (VFT) was defined as the thickness from the linea alba to the aorta. Computed tomography (CT) and dual X-ray absorptiometry (DXA) are well-established techniques used in clinical and scientific research to evaluate abdominal adipose tissue compartments.

Several studies (42) utilized positron emission tomography (PET) for assessing insulin resistance. 8F-fluorodeoxyglucose (FDG) PET imaging revealed insulin-stimulated FDG uptake in skeletal muscle as well as glucose absorption throughout the body.

Dual-energy x-ray absorptiometry is the imaging modality used to quantify adipose tissue (DXA). DXA detects fat, lean mass, and bone mineral content by measuring the attenuation of two X-ray photon energies with minimal radiation exposure (1mSv/scan16), short scanning time (5–13 minutes), high precision, and cheap cost. 17 A bioelectrical impedance analyzer can be applied to measure fat mass, muscle mass and fat-to-muscle ratio. DEXA body composition analysis is quick and easy, and the patient experiences little discomfort or radiation exposure. These characteristics promoted the use of DEXA in clinical settings and studies to accurately measure body fat.

Although hepatic biopsy represents golden standard in fatty liver diagnosis, it is rarely used comparing to ultrasound and aminotransferase levels.

Several MR methods can also be used for imaging abdominal obesity. Magnetic Resonance offers the advantage of no radiation exposure but has been used less frequently due to higher cost. Magnetic resonance spectroscopy (MRS) using carbon (13C) is ideally suited for the research purposes, e.g., studies of metabolism due to the extensive range of compounds that can be detected and the ability to attribute signals to the different carbon atoms within individual molecules (43).

An ECG, ECG-stress test, stress echocardiography, stress single-photon emission computed tomography, or myocardial perfusion imaging should be performed to evaluate any symptoms of myocardial ischemia, arrhythmias, and hypertension associated with structural heart disease (Table 3) (44).

Comorbidity in the Metabolic syndrome

Obesity / metabolic syndrome leads to numerous early complications (45,46) such as persistent low-level inflammation (47,39), hypertension (48) and left ventricular hypertrophy.

The Framingham Heart Study states that the risk of heart failure was doubled with obesity (49). The central risk factor concerning the MS in adolescence is juvenile obesity. Numerous studies (50,51) have demonstrated that vascular alterations associated with this syndrome result in much more prevalent strokes, dementia, and Alzheimer's disease.

The connection between asthma and obesity has long been noticed, (52) as well as immune system dysregulation. Non-alcoholic liver disease, cholecystitis (53,54), as well as pancreatitis, gastroesophageal reflux, and esophageal adenocarcinomas are many times more common in overweight individuals.

Obesity is one of the leading causes of osteoarthritis. It affects the knee and hand joints (55).

The risk of polycystic ovary syndrome (PCOS) is increased with obesity (56) with more serious PCO phenotype. Obese children are frequently subjected to societal condemnation and stigma (57) resulting in social isolation and depression, with girls facing more prejudice.

Conclusion

Metabolic syndrome is common in this child population, particularly among children who are overweight or obese. Preventing this disorder requires lifestyle changes, eating habits correction, and consistent physical activity.

New biomarkers, in addition to standard clinical and biochemical measurements, allow for the rapid and accurate diagnosis of pediatric metabolic syndrome.

Table 1: International Diabetes Federation (IDF) criteria for Metabolic syndrome in children (13)

Variables	IDF definition age <10 years	IDF definition ages 10–16 years	Cook *et al.*
Defining criteria	Cannot be diagnosed in the age group	Central obesity plus at least 2 out of 4 criteria	≥3 criteria
Central obesity		WC ≥90th percentile or adult cut-off if lower	WC ≥90th percentile
Hypertension		SBP ≥130 mmHg or DBP ≥85 mmHg or treatment with anti-hypertensive medication	BP ≥90th percentile
Hypertriglyceridemia		TG ≥150 mg/dL	TG ≥110 mg/dL
Low HDL		HDL <40 mg/dL	HDL ≤40 mg/dL
Impaired glucose		FPG ≥100 mg/dL or known T2DM	FPG ≥110 mg/dL

Table 2: Waist circumference reference values in boys and girls presented by percentile classification (27)

Age (years)	BOY (cm)		GIRL (cm)	
	50th Percentile	90th percentile	50th Percentile	90th percentile
10	63.7	77.7	62.5	75.5
11	65.8	81.1	64.4	78.3
12	67.9	84.5	66.3	81.2
13	70.0	87.9	68.2	84.1
14	72.1	91.3	70.1	86.9
15	74.1	94.7	74.1	89.8
16	76.2	98.1	73.9	92.7
17	78.3	101.5	75.8	95.5
18	80.4	104.9	77.7	98.4

Table 3: Diagnostic parameters of metabolic syndrome in children

PROCEDURE	PARAMETERS	RISK FACTORS
History	- gestational age - birth weight - eating habits - parental weight	SGA (small for gestational age) obesity or overweight parents
Anthropometric measurements	- Body weight - Body height - Waist circumference (WC) - BMI (kg/m²) - BMI/WC	Overweight or obesity abdominal obesity
Clinical examination	- Acanthosis nigricans - Signs of hyperandrogenism - Musculoskeletal deformities - blood pressure	- systolic blood pressure of ≥130 mmHg or a diastolic blood pressure of ≥ 85 mmHg;
Biochemical test	- Glycemia - OGTT and insulinemia, HbA1c - lipid profile (HDL, triglyceride, LDL) - Alanine aminotransferase (ALT)	impaired fasting glucose -triglycerides ≥ 1.47 mmol/L, and low values of high-density lipoprotein < 1.03 mmol/L The 95th percentile for ALT was 26.0 U/L in females and 37.2 U/L in males
Biomarkers	- CRP, IL-6, TNF-α markers of pro-oxidant status (OxLDL, uric acid) prothrombic factors (PAI-1)	

Table 4. Radiological diagnostic procedures of metabolic syndrome in children

Imaging studies	Ultrasonography (US)
	Bioelectrical impedance analyzer
	Computed Tomography (CT), Magnetic Resonance (MRI)
	Magnetic Resonance Spectroscopy (MRS)
	Positron Emission Tomography (PET)
	8F-fluorodeoxyglucose (FDG) PET
	Dual-Energy x-ray Absorptiometry (DXA)

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