Metabolic syndrome: comparison of diagnosis criteria

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Abstract

Objective: To propose a new criterion for the diagnosis of metabolic syndrome (MS) in adolescents and to check its consistency with those proposed by Jolliffe and Janssen and by the International Diabetes Federation (IDF).

Method: This is a cross-sectional study of 80 obese adolescents aged 14 to 19 years. Anthropometric (weight, height, and waist circumference) and laboratory (fasting triglycerides, HDLc, glucose, and insulin) parameters, as well as blood pressure were evaluated. The HOMA-IR index was used to characterize insulin resistance, and the presence of steatosis was assessed by hepatic ultrasound. Agreement analyses across the three criteria were made using the kappa coefficient.

Results: The prevalence of MS was 13.5, 15, and 25% for IDF and Jolliffe and Janssen's criteria and the proposed method, respectively. A nearly perfect agreement between Jolliffe and Janssen's and IDF (kappa = 0.94) criteria and a moderate agreement between the new criteria and the previous two (kappa = 0.46 and 0.41, respectively) were observed.

Conclusions: The highest prevalence of MS was observed with the criterion proposed in this study, which included steatosis and insulin resistance as parameters, thus being able to diagnose a larger number of adolescents at metabolic risk.

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Introduction

Metabolic syndrome (MS) is defined as a combination of clinical factors that include hypertension, dyslipidemias, glucose metabolic disorders, and obesity (especially abdominal), with intra-abdominal fat deposition. MS constitutes a group of risk factors for the development of cardiovascular diseases (CVD).^{1,2}

The prevalence of MS among children and adolescents has increased concomitantly with the number of cases of obesity and its comorbidities.³ Data from the National Health and Nutrition Examination Survey (NHANES) III (1988-1992) and NHANES (1999-2000) show an increase in the prevalence of MS from 4.2 to 6.4% in the population of U.S.

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adolescents.4 A study of obese children and adolescents found an MS prevalence of 38.7 and 49.7% among those with moderate and severe obesity, respectively.5

The prevalence of MS varies widely across several studies, and that is due to the different diagnostic criteria used. Reinehr et al.6 compared the prevalence of MS in children and adolescents using eight different definitions. The prevalence ranged from 6 to 39%, and only 2% met all the proposed criteria, thus underscoring the necessity for standardization of diagnostic criteria.

Several criteria for the diagnosis of MS in children and adolescents have already been proposed,5,7-9 but no consensus exists in the literature about the most appropriate one. The constant physiological changes in metabolism and in body composition, which occur in these age groups, hinder the adoption of specific cutoff points for the parameters used in this diagnosis. In addition, there is a paucity of long-term follow-up studies with children and adolescents that associate these values with future morbidities. The criterion for the diagnosis of MS in children and adolescents should include parameters that contemplate early-onset metabolic disorders in these individuals.

Weiss et al.⁵ noted that insulin resistance (IR) was an independent factor for the diagnosis of MS in overweight children and adolescents and that the prevalence of MS increased as IR worsened.

The gold standard for measurement of IR is the euglycemic hyperinsulinemic clamp; however, it is not used in clinical practice. 10 The HOMA-IR (homeostasis model assessment - insulin resistance) index can be used as an alternative method for IR assessment as it has a good correlation with the euglycemic hyperinsulinemic clamp.¹¹

Chan et al. 12 conducted a systematic literature review and propose that non-alcoholic fatty liver disease (NAFLD) be acknowledged as a component of MS given that it is implicated in the context of risk factors for the development of type 2 diabetes mellitus and early-onset CVD. Musso et al.13 observed a positive correlation between IR and NAFLD and also suggested including NAFLD as diagnostic criteria for MS. D'Ádamo et al. 14 carried out a cross-sectional study with 100 obese prepubertal children and found a prevalence of 52% for hepatic steatosis. Obese children with steatosis, when compared with the control group of normal-weight children and with obese children without steatosis, had higher HOMA-IR indices, which suggests an association between IR and steatosis. Sartorio et al. 15 assessed obese children and adolescents and detected steatosis in 44% of them, and in their study, HOMA-IR was also higher among obese individuals with steatosis, compared with obese children and adolescents without steatosis.

Notwithstanding the difficulty in diagnosing MS, it is of paramount importance that children and adolescents that fulfill the criteria for this diagnosis be identified, as

they are at greater metabolic risk and should therefore be properly monitored.

The aim of the present study is to propose a new diagnostic criterion for MS in obese adolescents and to check its consistency with those criteria proposed by Jolliffe & Janssen⁸ and by the International Diabetes Federation (IDF).9

Methods

This is a cross-sectional study, conducted with male and female obese adolescents [body mass index (BMI) > P95], aged between 14 and 19 years, enrolled in four public schools belonging to the same region, in the city of São Paulo, Brazil. Adolescents with acute or chronic diseases, those being treated for weight loss, as well as pregnant or lactating adolescents, were excluded from the study. The study protocol was approved by the Research Ethics Committee of Universidade Federal de São Paulo (UNIFESP), and the data were collected only after a consent form was signed by all participating adolescents and their legal guardians.

Of 2,330 adolescents, 150 (6.43%) were diagnosed as obese. Among these, 26 (17.33%) met the exclusion criteria described above. Of the 124 remaining adolescents, 42 (33.87%) refused to take part in the study, and two (1.61%) quit the study during laboratory data collection. The final sample consisted of 80 obese adolescents (64.5% of the initial sample). When the mean BMI values of the analyzed sample, stratified by age and sex, were compared with the mean BMI values of the 44 adolescents who did not participate in the study, no statistically significant differences were found between groups, indicating that losses to follow-up did not generate a selection bias. Likewise, the proportions in relation to age, sex and pubertal development were maintained.

A Kratos® digital scale (model Linea) and a portable Alturaexata® anthropometer, placed on a flat and sturdy surface, were used for the measurement of weight and height, respectively. Waist circumference (WC) was measured from the midpoint between the lowest rib and the iliac crest, using a nonstretch measuring tape. Blood pressure check and the diagnosis of hypertension followed the recommendations established by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. 16 Blood samples were collected by venipuncture after a 12-hour fasting period, and conventional laboratory techniques were used to determine glucose and insulin levels and the lipid profile. The cutoff points suggested by the American Heart Association (AHA)¹⁷ were considered for the lipid profile. The HOMA-IR, used for the classification of IR, was obtained by multiplying the fasting plasma insulin level (μ U/mL) by the fasting glucose level (mmol/L) and by dividing the result

by 22.5. 18 Levels greater than 3.43 were considered to be indicative signs of IR. 19

A hepatic ultrasound, using LOGIC 400 PRO-GE, was performed by the same radiologists. Steatosis was classified as mild, moderate or severe, according to Saverymutu et al. 20

The proposed method for the diagnosis of MS took into consideration the presence of three or more of the following components: WC (90 cm for boys and 80 cm for girls) – as suggested by the IDF²¹ for the South American population, as there is no specific curve for Brazil and all adolescents had pubertal development ≥ 4 , according to Tanner's criteria, hypertension, 16 hypertriglyceridemia and/or reduction in HDLc (high density lipoprotein cholesterol), 17 IR assessed by HOMA-IR 19 and steatosis. 20 Table 1 shows the parameters and the respective cutoff points, according to different criteria.

Descriptive statistics [mean, standard deviation and 95% confidence interval (95%CI)] was used for sample characterization, and the kappa coefficient was used to analyze agreement across the three diagnostic criteria for MS. The statistical analyses were made using Stata 10.0.²²

Results

Of 80 adolescents, 33 (41.25%) were male. Mean age was 15,96 years, and mean BMI was 32.53 kg/m² (Table 2). Male adolescents had a higher weight (97.46 vs. 88.81 kg; p = 0.006) and height (174.05 vs. 164.45 cm; p = 0.000) than female adolescents, but there

was no significant difference in BMI (p = 0.526). No significant difference was noted between mean levels of WC (p = 0.098), diastolic blood pressure (p = 0.336), triglycerides (p = 0.589), HDLc (p = 0.164) and HOMA (p = 0.28), in terms of sex, except for systolic blood pressure (p = 0.040). Steatosis was detected in 16.88% of the study population (Table 2), and was more frequent among male individuals (18.18 vs. 15.91%).

The prevalence of MS varied according to the criterion used: 13.75% in the IDF criterion; 15% in the Jolliffe & Janssen's criterion, and 25% in the proposed method.

Table 2 - Descriptive statistics of anthropometric, clinical and laboratory parameters of the assessed adolescents

Mean ± SD	95%CI
15.96±1.13	15.71-16.21
92.38±14.23	89.21-95.55
168.41±8.04	166.62-170.20
32.53±4.27	31.58-33.48
100.14±9.66	97.88-102.29
115.23±11.49	112.68-117.79
70.01±8.81	68.04-71.97
86.67±40.75	77.60-95.74
47.87±9.25	45.81-49.93
3.37±2.19	2.88-3.86
16.88	-
	15.96±1.13 92.38±14.23 168.41±8.04 32.53±4.27 100.14±9.66 115.23±11.49 70.01±8.81 86.67±40.75 47.87±9.25 3.37±2.19

95%CI = 95% confidence interval; BMI = body mass index; DBP = diastolic blood pressure; HOMA-IR = homeostasis model assessment – insulin resistance; SBP = systolic blood pressure; SD = standard deviation; WC = waist circumference.

Table 1 - Parameters and cutoff points according to different criteria

Classification			
IDF	Jollife & Janssen ⁸	Proposed method	
	Cutoff point according to age and sex		
90 cm		90 cm	
80 cm		80 cm	
	Cutoff point according to age and sex	According to AAP	
≥ 130			
≥ 85			
> 150	Cutoff po int according to age and sex	> 150 according to AHA	
	Cutoff point according to age and sex	< 35 according to AHA	
< 40			
< 50			
> 100	> 100	-	
-	-	> 3.43	
_	_	steatosis	
	90 cm 80 cm ≥ 130 ≥ 85 > 150 < 40 < 50	IDF Cutoff point according to age and sex 90 cm 80 cm Cutoff point according to age and sex ≥ 130 ≥ 85 > 150 Cutoff po int according to age and sex Cutoff po int according to age and sex Cutoff point according to age and sex Cutoff point according to age and sex < 40 < 50	

Agreement as to the diagnosis of MS was nearly perfect according to IDF and Jolliffe & Janssen's criteria (kappa = 0.94; p < 0.001). The 11 adolescents diagnosed with MS according to Jolliffe & Janssen's criterion were also diagnosed by the IDF criterion, whereas only one case was diagnosed only by Jolliffe & Janssen's criterion. Note that the 68 cases not diagnosed by the IDF criterion were not diagnosed by Jolliffe & Janssen's criterion.

Agreement as to the diagnosis of MS by the IDF criterion and by the proposed method was moderate (kappa = 0.41; p < 0.001) (Table 3). Among the 20 diagnoses of MS by the proposed method, eight had a perfect match, whereas 12 cases were diagnosed by the proposed method only. The 12 adolescents diagnosed by the proposed method had IR, and only one had abnormal glucose levels (103 mg/dL).

Table 3 -Number and percentage of patients according to the agreement between the proposed method and IDF

	II		
Proposed method	Without MS	With MS	Total
	n (%)	n (%)	n (%)
Without MS	57 (95)	3 (5)	60 (100)
With MS	12 (60)	8 (40)	20 (100)
Total	69 (86.25)	11 (13.75)	80 (100)

IDF = International Diabetes Federation - Zimmet et al.9; kappa = 0.41 (p < 0.001); MS = metabolic syndrome.

Likewise, when the data obtained by Jolliffe & Janssen's criterion and by the proposed method were compared, diagnosis showed moderate agreement (kappa = 0.46; p < 0.001) (Table 4). Jolliffe & Janssen's criterion established the diagnosis separately in three adolescents, whereas the proposed method diagnosed MS in 11. The 11 cases diagnosed by the proposed method had IR. The three adolescents diagnosed with MS by IDF and Jolliffe & Janssen's criteria, but not by the proposed method, were the same.

Table 4 -Number and percentage of patients according to the agreement between the proposed method and Jollife & Janssen's criterion

	Jollife &		
Proposed method	Without MS n (%)	With MS n (%)	Total n (%)
Without SM	57 (95)	3 (5)	60 (100)
With SM	11 (55)	9 (45)	20 (100)
Total	68 (85)	12 (15)	80 (100)

Jollife & Janssen⁸; kappa = 0.46 (p < 0.001); MS = metabolic syndrome.

Among all adolescents diagnosed with IR, 70% had normal fasting glucose levels.

The hepatic ultrasound results revealed steatosis in 13 adolescents, seven of whom belonged to the group diagnosed with MS. It should be highlighted that five out of these seven adolescents were diagnosed with MS by the proposed method only, whereas the remaining two were diagnosed by the three criteria. Significant difference was observed in mean HOMA-IR indices when the presence or absence of steatosis was considered (4.68 vs. 3.05; p = 0.001). The mean HOMA-IR index was significantly higher in the presence of steatosis.

Discussion

The prevalence of MS in children and adolescents varies widely in the literature due to the different diagnostic criteria used.6,23,24 Most of these criteria stem from criteria used for adults; thus, abnormal results that have a low frequency in children and adolescents, such as abnormal glucose levels, may be included in the requirements for this diagnosis.

In the present study, the prevalence of MS varied according to the criterion used: 13.75% for the IDF criterion, 15% for Jolliffe & Janssen's criterion and 25% for the proposed method. Other authors, who compared the prevalence of MS using different criteria, also found variation in prevalence rates.^{23,24}

The large agreement in MS prevalence between Jolliffe & Janssen's and IDF criteria can be explained by the use of the same parameters, but of different cutoff points. The proposed method showed moderate agreement with Jolliffe & Janssen's and IDF criteria, but it diagnosed MS in a higher rate of adolescents, which may be explained by the replacement of glucose with IR (30 adolescents with IR, and only nine with glucose levels ≥ 100 mg/dL). Weiss et al.5 stress that fasting glucose levels go up at a later stage of MS in children and adolescents. In this study, the cutoff point for IR suggested by Cuartero¹⁹ was used, due to the physiological IR observed in adolescents. Invitti et al.²⁵ considered IR as one of the parameters for the definition of MS in obese children and found prevalence of this syndrome in 23.3%, a rate that is quite close to that observed in the proposed method (25%). Ferreira et al.²⁶ conducted a cross-sectional study with 52 obese children aged 7 to 10 years and found MS in 10% of boys and in 25% of girls. They also noted that the higher the HOMA-IR, the higher the number of cardiovascular risk factors. Likewise, Caranti et al., 27 in a comparative study with obese Brazilian and Italian adolescents, detected differences between the two populations in terms of MS prevalence: 23.6% for Brazilian and 16.5% for Italian adolescents. HOMA-IR was the parameter with the highest frequency of abnormal results in both groups and was the highest one among Brazilian adolescents.

The cutoff points for hypertension were different across the three criteria used in this study. The IDF criterion, with higher cutoff points and without stratification by age, sex and height, diagnosed hypertension in a smaller number of adolescents (8%) than did Jolliffe & Janssen's criterion (13.75%) and the proposed method (23.75%).

There was a higher prevalence of abnormal results for HDLc when Jolliffe & Janssen's criterion was used, with higher cutoff points than the other two criteria. The proposed method was based on values recommended by AHA, 17 regarded as risk factors for CVD. Triglycerides showed abnormal levels in seven adolescents, with discordant results in only one of the three criteria. Sinaiko et al., 28 in a longitudinal study with adolescents aged 11 to 14 years, found higher triglyceride and lower HDLc levels in the IR group, characterized by euglycemic hyperinsulinemic clamp, than those observed in this study.

Some authors regard the presence of steatosis as hepatic manifestation of IR. 13,15 In the study undertaken by Schwimmer et al., 29 children and adolescents with NAFLD had higher absolute levels for cardiovascular risk markers, in addition to higher frequency of MS. Vitola et al.³⁰ observed reduction in intrahepatic triglycerides in magnetic resonance, as well as improvement in insulin sensitivity in obese adolescents after a weight management program. In the present study, hepatic steatosis was detected by ultrasound, which can be easily performed; however, according to Saadeh et al., 31 this exam detects abnormalities only after hepatic parenchyma involvement is greater than 33%, which is revealed by biopsy. Steatosis was found in 13 adolescents, and was associated with IR in seven, suggesting that it should be investigated in the presence of IR. Its inclusion in the diagnosis of MS may allow for the identification of individuals at higher metabolic risk.

Conclusions

The prevalence of MS varied according to the diagnostic criterion used. The higher prevalence was detected by the method proposed in the present study, which included IR and hepatic steatosis among its parameters, thus being able to diagnose a larger number of adolescents at metabolic risk. The proposed method diagnosed more MS cases than the other two criteria because it used IR instead of glucose level as parameter for glucose metabolic findings. Glucose tends to show abnormal levels at a later stage of MS in children and adolescents.

It is important to identify children and adolescents who meet the criteria for the diagnosis of MS, as these individuals are at higher metabolic risk and should therefore be properly monitored. The persistence of these findings may favor the development of type 2 diabetes mellitus and of CVD in adulthood.

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