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Metabolic syndrome in obese adolescents: what is enough?☆

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A B S T R A C T

Objective: To study the agreement among three distinct criteria for metabolic syndrome (MS) adapted to adolescents, and to identify associated factors for MS.
Methods: Cross-sectional study with 65 obese subjects aged 10 to 18 years, attended to at the Outpatient Clinic for Obese Children and Adolescents at the Clinical Hospital of the Universidade Estadual de Campinas (Unicamp). MS was defined using the criteria of the World Health Organization (WHO), the International Diabetes Federation (IDF), and the Adult Treatment Panel III (ATP III). Clinical, anthropometrical, and laboratorial data were associated to MS.
Results: From the 65 subjects, none had MS according to the WHO criteria, while 18 were diagnosed with MS (27.6%) according to the IDF, and 19 (29.2%) according to the ATP III. Agreement between IDF and ATP III was excellent (kappa 81%). In this study, puberty and triglycerides levels showed significant statistical difference when comparing subjects with and without MS, the first for ATP III ($p = 0.03$), and the second for IDF ($p = 0.005$) and ATP III ($p = 0.001$) criteria.
Conclusion: The WHO criteria does not seem to be adequate for adolescents. IDF and ATP III criteria had an excellent agreement. Puberty and triglycerides were associated with MS.

Palavras-chave:
Síndrome metabólica
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Síndrome metabólica em adolescentes obesos: o que é suficiente?

R E S U M O

Objetivo: Avaliar a correlação de três critérios de síndrome metabólica (SM) para adolescentes e identificar fatores associados.
Métodos: Estudo transversal com 65 pacientes obesos entre 10 e 18 anos do Ambulatório de Crianças e Adolescentes Obesos do HC-Unicamp. SM foi definida de acordo com a Organização Mundial da Saúde (OMS), International Diabetes Federation (IDF) e Adult Treatment Panel III (ATP III). Buscaram-se fatores associados a SM em dados clínicos, antropométricos e laboratoriais.
Resultados: Dos 65 pacientes, nenhum foi diagnosticado como SM pela OMS, sendo 18 (27.6%) pelo IDF e 19 (29.2%) pelo ATP III. A correlação entre IDF e ATP III foi excelente

☆Study conducted at the Outpatient Clinic for Obese Children and Adolescents, Universidade Estadual de Campinas, Campinas, SP, Brazil
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(kappa 81%). Neste estudo, a puberdade e os triglicérides apresentaram diferença estatisticamente significativa entre pacientes com e sem SM, sendo a primeira para o ATP III (p = 0.03) e o segundo para IDF (p = 0.005) e ATPIII (p = 0.001).
Conclusão: O critério da OMS não parece ser adequado para adolescentes. Há correlação excelente entre os critérios do IDF e ATP III. Puberdade e triglicérides foram fatores associados à SM.

Introduction

The childhood obesity epidemic is followed closely by early onset of diseases once just observed in adults, such as diabetes mellitus type 2, high blood pressure, impaired lipid profile, and cardiovascular diseases.[1–3] The clustering of risk factors for these diseases is called metabolic syndrome (MS), which is highly prevalent in adults nowadays, and has serious consequences on life expectancy.[4–8]

The diagnosis of MS in the pediatric field still has not reached a consensus in the literature, since it is difficult to define reference levels for several components such as insulin resistance and lipid levels according to age.[6,8–11] MS diagnosis aims to detect patients at risk for cardiovascular and metabolic diseases, allowing the development of a preventive measures and treatment when needed.[10]

The first MS criteria was presented in 1998 by the World Health Organization (WHO), with emphasis on risk factors for diabetes mellitus type 2.[12] In 2001, the Adult Treatment Panel III (ATP III) presented an MS definition focused on cardiovascular diseases.[13] Finally, in 2007, the International Diabetes Federation (IDF) developed a criteria that addressed to children aged 10 and older.[14]

Longitudinal studies have demonstrated that adults presenting MS started their health problems during childhood, thus justifying the investigation of MS risk factors in children.[15,16]

MS criteria for children and adolescents usually are an adaptation of the adult criteria. In the search for an alternative, criteria have been developed specifically for the pediatric group, such as the use of a continuous score from childhood until adulthood,[7] and a proposal considering components which are early risk factors, such as birth weight and family history.[17]

Of the MS components, insulin resistance is believed to have a central role on metabolic dysfunction, leading to problems such as hyperlipidemia, hepatic steatosis, and atherosclerosis, which may progress to cardiovascular diseases and diabetes mellitus type 2.[18,19]

Obese children and adolescents frequently present insulin resistance as a consequence of a primary reduction in insulin sensitivity and a subsequent increase in production.[19]

Reference levels for insulin resistance are still not determined for pediatric and adolescents patients, but they are known to be influenced by ethnicity and puberty.[20,21] The Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), a relation between fasting glucose and insulin, has been recognized as the most sensitive and specific method for measuring insulin resistance.[20]

The present study aimed to evaluate the prevalence of MS and the agreement between three distinct definitions (WHO, IDF, ATP III). In addition, the study aimed to individually analyze associated clinical and laboratorial factors of obese adolescents on follow-up at an outpatient clinic from a tertiary university hospital.

Methods

This is cross-sectional study; data was collected between April, 2005 and January, 2010 from 150 subjects who presented consecutively at the Outpatient Clinic for Obese Children and Adolescents at the Clinical Hospital of the Universidade Estadual de Campinas (Unicamp). Selected subjects presented age between 10 and 18 and obesity (body mass index [BMI] > 95th percentile).[22] Exclusion criteria were impaired neurological development (which could be related to a genetic syndrome), hepatic or kidney dysfunction, and endocrine diseases such as hypothyroidism.

Data was collected from patients' history (age, gender, family-reported age since excessive weight gain started), physical examination (pubertal development, presence of acanthosis nigricans, blood pressure), anthropometrical measures (weight, height, abdominal circumference), and laboratory analysis. Puberty was determined when Tanner stage ≥ 2.[23] Weight and height measures were obtained as described by Cameron,[24] from which BMI was calculated. Abdominal circumference was obtained according to Freedman's methods,[25] and McCarthy's curves were used as reference.[26]

Blood pressure was measured according to the guidelines of the Second Task Force on Blood Pressure Control in Children. High blood pressure (BP) was considered if systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) ≥ 95th percentile, according to age, gender, and height percentile.[27]

Serum fasting glucose, insulin, triglycerides (TGC), total-cholesterol, high-density lipoprotein- (HDL) cholesterol, and low-density lipoprotein- (LDL)cholesterol concentrations were measured using the methodology established by the Clinical Pathology Laboratory of Unicamp. HOMA-IR was calculated by the formula: fasting glucose (mg/dL) x fasting insulin (μU/mL) /405.[28]

Considering the lipid reference levels used by IDF for children, the MS definitions by WHO and ATP III were adapted using the

same levels: TGC were considered abnormal when ≥ 150 mg/dL, and HDL-cholesterol when < 40 mg/dL, for both genders.

To adapt the WHO criteria for children, it was decided to keep the proportionality of what is proposed for adults: glucose levels unchanged, BMI value for children when defines obesity and blood pressure that characterize hypertension. The waist to hip ratio was changed for waist circumference, and microalbuminuria was not evaluated (Box 1).

On the ATP III criteria, the proportionality was also kept: no change on glucose levels, blood pressure levels for pre-hypertension (between the 90th and 95th percentiles). Waist circumference was normal when < 95th percentile for age and gender. No adaptation was made for IDF III (Box 1).

Box 1 – Adapted metabolic syndrome criteria.

Adapted metabolic syndrome definition from the World Health Organization

Patient must have at least one of the following:

- Diabetes mellitus – fasting glucose ≥ 126mg/dL or 2h after 75g glucose challenge ≥ 200mg/dL
- Impaired glucose tolerance – fasting glucose < 126mg/dL and 2h after 75g glucose challenge ≥ 140mg/dL and < 200mg/dL
- Impaired fasting glucose – fasting glucose ≥ 110mg/dL and < 126mg/dL and 2h after 75g glucose challenge < 140mg/dL
- Insulin resistance – under hyperinsulinemic, euglycemic conditions, glucose uptake below lowest quartile for background population under investigation.

And any two or more of the following:

- Waist circumference > 95th percentile26 and/or BMI > 95th percentile;[22]
- Triglycerides ≥ 150mg/dL and/or HDL cholesterol < 40 mg/dL;
- Blood pressure ≥ 95th percentile;[27]

Adapted metabolic syndrome definition from the Adult Treatment Panel III

Any three of the following:

- Fasting glucose ≥ 110 mg/dL;
- Waist circumference > 95th percentile;[26]
- Triglycerides ≥ 150mg/dL;
- HDL cholesterol < 40mg/dL;
- Blood pressure between 90th and 95th percentiles;[27]

Metabolic syndrome definition from the International Diabetes Federation

Age 6 to younger than 10 years: cannot be diagnosed; 16 years or older: adult criteria.

From 10 to 16 years old:

- Obligatory component: abdominal circumference ≥ 90th percentile for age[26]
- Presence of two or more:
- Triglycerides ≥ 150 mg/dL
- HDL cholesterol < 40 mg/dL
- Systolic blood pressure ≥ 130 mmHg or diastolic ≥ 85 mmHg[27]
- Fasting glucose ≥ 100 mg/dL

BMI, body mass index; HDL, high-density lipoprotein.

In this study, an individual analysis of clinical and laboratorial factors related to the presence of MS was proposed, including those used by different MS criteria.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 16.0 (SPSS Inc. – Chicago, IL, USA). The agreement between MS definitions was obtained by the kappa test. The chi-squared test, Fisher's exact test, and and Student's *t*-test were used to compare groups and risk factors. Significant levels were considered when $p < 0.05$.[29]

This study was approved by the Ethics Committee of the Medical Sciences Faculty of Unicamp (number 711/2009), and an informed consent was obtained from all subjects and their parents.

Results

Of the 65 subjects selected, none fulfilled the adapted WHO criteria for MS. Using adapted IDF and ATP III criteria, 18 (27.6%) and 19 (29.2%) were identified with MS, respectively. The overall kappa value for these two definitions was 81% (Table 1).

Table 1 – Agreement between metabolic syndrome diagnosis by IDF and ATP III.

	IDF		kappa
	Yes	No	
ATP III			81%
Yes	16	3	
No	2	44	

IDF, International Diabetes Federation; ATP III, Adult Treatment Panel III; kappa – kappa test.

Gender (IDF: p = 0.30; ATP III: p = 0.46) (Table 2), age (medians over 11.5 years; IDF: p = 0.613; ATP III: p = 0.93), family-reported age when the excessive weight gain started (medians over 4 years old; IDF: p = 0.79; ATP III: p = 0.38), and years of obesity (medians over 6.8 years; IDF: p = 0.31; ATP III: p = 0.82) were not statistically different for MS by both criteria (Table 3).

Elevated BMI results (median over 32 kg/m^2; IDF: p = 0.68; ATP III: p = 0.85), BMI z scores (median over +2.3; IDF: p = 0.31; ATP III: p = 0.09), and waist circumference (median over 101.7 cm; IDF: p = 0.48; ATP III: p = 0.23) were found for all patients, but with no statistically difference to MS by IDF and ATP III adapted criteria (Table 3).

The presence of puberty was statistically different for MS according to ATP III adapted criteria (p = 0.03), and close to a significant level according to IDF criteria (p = 0.06). Acanthosis nigricans (IDF: p = 0.10; ATP III: p = 0.58) was not considered an associated factor for MS by both criteria (Table 2). Also, no statistically significant difference was found when evaluating glucose metabolism using fasting glucose (IDF: p = 0.81; ATP III: p = 0.53), insulin (IDF: p = 0.07; ATP III: p = 0.13), and HOMA-IR (IDF: p = 0.09; ATP III: p = 0.14). Medians for fasting

Table 2 – Analysis of gender, puberty, and acanthosis nigricans as risk factors for metabolic syndrome by IDF and ATP III criteria.

	IDF				ATP III			
	Yes	No	Total	p	Yes	No	Total	p
Gender								
Female	22	11	33	0.30[a]	22	11	33	0.46[a]
Male	25	7	32		24	8	32	
Puberty								
Yes	30	14	44	0.06[b]	28	16	44	0.03[b,c]
No	13	1	14		13	1	14	
AN								
Yes	31	8	39	0.10[a]	28	11	39	0.58[a]
No	10	7	17		12	5	17	

IDF, International Diabetes Federation; ATP III, Adult Treatment Panel III; AN, acanthosis nigricans.
[a]Chi-squared test;
[b]Fisher's exact test;
[c]significance: $p > 0.05$.

insulin levels were in the upper level (medians over 19 mg/dL, reference for adults up to 20 mg/dL) for subjects with and without MS (Table 3).

Blood pressure analysis was made based on medians of systolic and diastolic blood pressure. The SBP did not show statistically significant difference for MS (IDF: $p = 0.31$; ATP III: $p = 0.47$), as well as the DBP measures (IDF: $p = 0.40$; ATP III: $p = 0.68$) (Table 3).

When evaluating lipid profile results, there was no statistically significant difference between groups for total cholesterol (IDF: $p = 0.31$; ATP III: $p = 0.72$), HDL (IDF: 0.34; ATP III: $p = 0.23$), and LDL-cholesterol (IDF: $p = 0.38$; ATP III: $p = 0.63$) levels. Statistically significant differences for TGC levels were found between obese children with and without MS, using both adapted ATP III and IDF definitions. Children evaluated for MS by IDF presented median TGC levels of 172.44 mg/dL ('Yes' group) and 96.68 mg/dL ('No' group), $p = 0.005$. Under the ATP III adapted criteria median TGC levels were 163 mg/dL ('Yes' group) and 98.93 mg/dL ('No' group), $p = 0.001$ (Table 3).

Discussion

Despite the controversy on the need of MS criteria for children and adolescents, this study shows MS prevalence on the selected subjects using three different criteria from world-recognized organizations.

None of the patients fulfilled the adapted WHO criteria because they did not present a dysfunctional glucose metabolism, considered essential for the classification. Other studies have showed an MS prevalence ranging from 5.2%[10] to 39%,[30] depending on the adaptations made, but none of these studies kept impaired glucose or insulin level as an obligatory criteria. Based on the data found, it appears that the WHO criteria is not a very useful definition for the pediatric population, as it considers the presence of impaired glucose metabolism, a dysfunction known to happen later in life. Patients were probably classified as not having MS as consequence of lack of time to develop the impaired laboratory findings. With adapted IDF and ATP III = criteria, the prevalence found was 27.6% and 29.2%, respectively. When compared with studies based on the same criteria and obese pediatric population, the data are similar, ranging between 31%[30] and 31.9%[21] for IDF and 25.8%[10] and 28.7%[1] for ATP III.

The agreement between these two criteria was excellent (kappa test 81%). Unfortunately, they are not comparable to other references, since the criteria used were distinct (ATP III and Weiss, kappa test 53%),[31] and the selected population was not the same: adolescents evaluated using two adult criteria, kappa 41%.[32]

Many studies have shown that child and adolescent obesity continues into adulthood,[1] and also has a positive association with adult cardiovascular and metabolic diseases.[33] Although MS is defined as a cluster of risk factors for cardiovascular and metabolic diseases,[1] in this study MS associated factors were considered individually, from clinical characteristics to laboratorial findings, including those that are usually employed to define several MS criteria, such as waist circumference, blood pressure, fasting glucose, and lipid profile.

Younger children are expected to present lower prevalence of MS and less risk factors than older children and adolescents. This may happen as a consequence of a time-related exposure to factors such as hypercaloric diets and sedentary lifestyle.[4] On the contrary, the present study could not find an association between MS defined by IDF and ATP III's adapted criteria related to age, family-reported age when excessive weight gain started, and years of obesity.

In the same way, there was no association between gender and MS in both criteria. Conflicting data exist on this subject, since there are publications showing higher frequencies of MS in males,[1] others showing a slightly higher prevalence in females or, as in the present work, showing no significant difference according to gender.[31]

When considering anthropometric data, BMI and BMI z scores, the patients included in this study did not present these components as associated factors for MS. However, it is an important fact that the medians for all patients were extremely high (BMI over 32 kg/m^2, and BMI SD scores over +2.3).

Table 3 – Distribution of median and standard deviation clinical and laboratorial data according to metabolic syndrome criteria by IDF and ATP III.

	IDF				ATP III			
	n	Median	SD	p	n	Median	SD	p
Age								
No	47	11.55	2.18	0.613	46	11.70	2.14	0.931
Yes	18	11.89	1.87		19	11.53	2.01	
Age of onset								
No	43	4.65	3.16	0.791	42	4.79	3.21	0.388
Yes	17	4.65	3.10		18	4.33	2.95	
Years of obesity								
No	43	6.86	3.23	0.318	42	6.88	3.41	0.826
Yes	17	7.11	3.83		18	7.05	3.40	
BMI								
No	47	32.34	6.36	0.689	46	32.71	6.52	0.859
Yes	18	33.32	5.64		19	32.38	5.27	
BMI z score								
No	36	2.35	0.28	0.315	34	2.35	0.27	0.091
Yes	13	2.38	0.33		15	2.36	0.34	
WC								
No	47	103.52	14.39	0.484	46	103.96	14.81	0.235
Yes	17	102.86	11.72		18	101.78	10.28	
Fasting glucose								
No	47	84.43	7.16	0.811	46	84.87	6.94	0.534
Yes	17	84.24	6.36		18	83.11	6.85	
Insulin								
No	41	19.13	15.51	0.077	41	19.07	15.33	0.133
Yes	15	19.11	7.71		15	19.28	8.68	
HOMA-IR								
No	41	4.15	3.81	0.092	41	4.16	3.79	0.143
Yes	15	3.98	1.61		15	3.96	1.74	
SBP								
No	47	116.94	15.56	0.311	46	116.87	15.44	0.478
Yes	18	119.17	12.86		19	119.21	13.36	
DBP								
No	47	77.06	9.65	0.404	46	77.43	9.87	0.682
Yes	18	77.50	10.88		19	76.58	10.28	
TGC								
No	47	96.68	34.46	0.005*	46	98.93	37.14	0.001*
Yes	18	172.44	64.4		19	163.00	67.77	
Total-cholesterol								
No	47	161.89	33.16	0.312	46	162.43	34.14	0.725
Yes	18	163.33	36.77		19	161.95	34.28	
HDL-cholesterol								
No	47	46.57	9.66	0.342	46	46.83	9.68	0.238
Yes	18	36.33	6.80		19	36.26	6.36	
LDL-cholesterol								
No	47	99.74	29.45	0.386	46	99.67	29.96	0.635
Yes	18	94.83	40.72		19	95.26	39.26	

IDF, International Diabetes Federation; ATP III, Adult Treatment Panel III; BMI, body mass index; WC, waist circumference; HOMA-IR, homeostatic model assessment for insulin resistance; SBP, systolic blood pressure; DBP, diastolic blood pressure; TGC, triglycerides; p, Student's *t*-test; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
*significance: $p > 0.05$.

Abdominal circumference measurements were also not identified as an associated factor for MS, but all patients presented elevated medians as well. Waist circumference is a well accepted marker for assessing risk of underlying pathologies in adults; however, in the pediatric field it is still not a widespread, compulsory part of the examination, even with references demonstrating the advantages and high sensitivity of this method in screening for patients at risk.[26,34]

The problem of relating MS criteria and reference values for children and adolescents is a recurrent subject,[8,11] and involves the unsolved question of the influence of the physiological changes of puberty. Puberty is a transition period with rapid changes occurring in metabolic systems including hormonal regulations, changes in body fat and its distribution, and reduction in insulin sensitivity.[35] This resistance leads to an increased insulin secretion, and when associated with obesity-related changes in glucose metabolism, could result in a increased risk for MS.[21,35] The present study has found that the presence of puberty was an associated factor for MS using ATP III's adapted criteria ($p = 0.03$) and an almost significant level for IDF's criteria ($p = 0.06$). But there are confounding factors that must be considered before establishing an association between puberty and MS, one of which would be the evaluation of insulin resistance.

Acanthosis nigricans is a clinical sign with strong relation to hyperinsulinemia risk. It is believed that this cutaneous finding can be prior to laboratorial changes such as impaired insulin, fasting glucose, or lipids levels, as well as the diagnosis of MS.[36,37] The presence of acanthosis nigricans in patients included in this study was not associated to MS.

Insulin has a central role on signaling body fat stores and energy homeostasis, and also in the clustering of cardiovascular risk factors. Insulin resistance is commonly associated with obesity, and HOMA-IR is a sensitive and specific method for its measurement.[20] The present study has also showed a tendency to associate MS with insulin (IDF: $p = 0.07$; ATP III: $p = 0.13$) and HOMA-IR (IDF: $p = 0.09$; ATP III: $p = 0.14$), although all groups had insulin medians at the upper reference level. It is hard to affirm whether the HOMA-IR medians found are within normal range, since several cut-off points have been proposed for children and adolescents.[18] It has been recently discussed that the MS diagnosis for pediatric patients is probably limited due to the dichotomization of the criteria chosen. Very often, obese children and adolescents present altered values that are not yet considered abnormal.

Besides acting as the central regulator of glucose, insulin also plays an important role on lipid homeostasis. It has long been known that there is a highly significant relation among insulin resistance, compensatory hyperinsulinemia, and hypertriglyceridemia.[6] Insulin has three main influences on lipids: it enhances triglyceride synthesis in liver and adipose tissues, it increases the breakdown of circulating lipoproteins by stimulating lipase activity in adipose tissue, and it suppresses lipolysis in adipose tissue and muscles.[20] The presence of obesity, visceral body fat, and insulin resistance, and the consequent finding of an impaired lipid profile is well known.[38] When analyzing the selected patients, there was indeed a significant difference on TGC levels between patients with and without MS on both criteria used (IDF: $p = 0.005$, ATP III: $p = 0.001$).

The finding of TGC as an associated factor for MS is congruent with the report by Morrison in a long follow-up study, where a significant association of high TGC retained from childhood to adulthood with young adult cardiovascular disease (CVD) was found. In that study, the authors speculate that the association of high TGC from childhood through adulthood with adult CVD could reflect the presence of a pediatric MS, a known predictor of adult CVD.[39]

The same did not occur with other lipids (total cholesterol, LDL-cholesterol, and HDL-cholesterol). These findings are in agreement with the described lipids' pathophysiology secondary to obesity. Over successive cohorts, an increase in TGC levels and a reduction in HDL-cholesterol levels has been observed as an initial finding. In contrast, total cholesterol, LDL-cholesterol, and glucose levels remained unchanged.[38]

The relation between high blood pressure, lipoprotein abnormalities, and insulin resistance is not completely understood; it appears to be more complex than any of the other components of metabolic syndrome.[6] Hypertension is a well-recognized CVD risk factor, but the understanding of its connection with insulin metabolism is under study. There is already evidence showing that patients with essential hypertension are insulin resistant and hyperinsulinemic;[6] a follow-up study has demonstrated that children with high blood pressure and TGC who retained these into adulthood were more likely to develop diabetes mellitus type 2.[39] Even with the theoretical connection between hypertension, insulin resistance, CVD and, in consequence, MS, the patients evaluated in this study did not present high blood pressure as an associated factor for MS.

The limitations of this study were its cross-sectional design, the relatively small number of patients that were classified by MS definitions, and also the fact that the adolescents included were referred to a tertiary university hospital, thus they were expected to be a homogenously severe obese group.

In summary, even with all discussion over MS criteria and its usefulness , this study found that the WHO criteria is probably not adequate for an early detection of adolescents with metabolic risk. However, there is a very good agreement between IDF and ATP III criteria in detecting the pediatric population with MS. In addition, TGC levels were able to identify adolescents that are clearly at risk for early-onset metabolic and cardiovascular diseases. Even when not fulfilling criteria for MS, these patients need strong preventive measures aimed at stopping obesity evolution and avoiding clustering health problems.[40]

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Conflict of interest

All authors declare to have no conflict of interest.

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