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Metabolic Syndrome: Criteria for Diagnosing in Children and Adolescents

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Abstract

Metabolic Syndrome (MS) is defined as a group of risk factors related to insulin resistance and its highest prevalence is found in obese individuals. The first observations concerning MS occurred in the 1920s, contributing to a surge of new associations between hyperglycemia and obesity. As of 1979, there was a greater understanding of one of its components: insulin resistance. The prevalence of MS varies according to the diagnostic criterion used, mainly for children and adolescents among which its prevalence has increased considerably. The principle criteria used in diagnosing the pediatric population are the International Diabetes Federation (IDF), National Cholesterol Education Program and Adult Treatment Panel III (NCEP-ATP III), World Health Organization (WHO) and I Prevention Directive against Atherosclerosis in Infancy and Adolescence, and due to their differences, the prevalence of the syndrome varies according to the diagnostic criterion used. Nevertheless, many points should be taken into consideration in choosing a criterion, such as sample size, age, applicability, risk factors to be considered and available resources. In this context, efficiency and applicability are advantages in distinct criteria.

Keywords: Metabolic syndrome; Children; Adolescent

Introduction

Currently, obesity is seen as an epidemic of global proportion [1] and is associated with the increase of risk for many diseases and premature death [2]. Its interaction with other systemic and metabolic diseases increases organic disturbances significantly [3]. Among the several pathologies which are associated with obesity, Metabolic Syndrome (MS) has attracted the attention of health specialists.

Recent studies revealed that population sets which contain a greater number of MS are those formed by obese individuals [3-5] and this metabolic disturbance is present in developed countries as well as developing countries, with a high rate of prevalence among the adult population e increasing prevalence in the pediatric population [6,7].

Historical Aspects and Definition

MS has been observed since the 19th Century, receiving several names down through the years [8]. The first observations related to the syndrome occurred in the 1920s [9]. In 1923, Swedish doctor Eskil Kylin observed the association between hyperglycemia, obesity and the uric acid in the joints, known as gout, in hypertensive individuals [10].

In 1965, Avogaro et al. [11] described the metabolic aspects of obesity and mentioned a syndrome called plurimetabolic [11]. However, since 1979 there was greater understanding concerning an important component of MS, which is the Insulin Resistance (IR) [12,13]. In 1980, MS was called Syndrome X by Reaven, and since the studies of Reaven and Hoffman the involvement of IR and hyperinsulinemia in hypertension [14,15] etiology was verified.

Reaven also discussed the relationship of IR to the concentration of Free Fatty Acids (FFA) and progressed in the hypothesis that IR was a central mechanism in MS [16]. Finally, in a classic article published on the subject in 1988, this author proposed that a collection of diverse risk factors, connected by a common link could compose the syndrome which was then called MS [17].

After clarifying the boundaries which characterize MS, he went on to define it as a collection of risk factors of metabolic origin that appears to be directly related to the development of atherosclerosis and cardiovascular disease [18-20]. Among these risk factors are unfavorable lipid profile, hypertension, elevated plasmatic glucose, pro-thrombotic states, pro-inflammatory [21] and obesity, mainly abdominal [22].

Epidemiology

The prevalence of MS has increased drastically in the last years, transforming it into an event of global proportions, similar to the obesity proportions. As such, there is believed to be a connection between MS and obesity [21]. The confirmation of this suspicion may be exemplified in a study which says that approximately 60% of participants with moderate obese (BMI of approximately 35 kg/m^2) presented MS, although less than 6% of normal-weight adults met the criteria for the metabolic syndrome, affirming that normal-weight population may also met the criteria for MS [23].

Evidences indicate between 20 and 30% of the adult population can be diagnosed with MS [21]. In the United States, the prevalence of overweight children and adolescents is 6.8% and obesity is 28.7% and in the pediatric population of Brazil, Ferreira (2007) revealed the prevalence of MS to be 17.3% in obese children aged 7 to 10.

The prevalence of MS varies depending on the diagnostic criteria used, since different health organizations develop different ways to diagnose MS, not counting other factors which can influence its rise, such as ethnicity and age [5,24]. A study performed on the American population, verified the prevalence of MS to be 22% in adults, 42% in individuals between 60 and 69 years [25], suggesting that age appears to have an influence on the development of MS.

According to a European study DECODE (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) there is a significant increase in death by all causes and cardiovascular complications in individuals with MS [26]. Similar data has been presented in studies using the British, Scandinavian, and American population [27-30].

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Current Criteria for Diagnosing Metabolic Syndrome

Criteria used for each one of the risk factors which characterize MS are referred to, mainly, in regards to their etiology, clinical importance of the diagnosis and physiopathological mechanisms involved in MS [31] and consequently there is no consensus in regards to MS diagnosis.

Due to this variety of diagnostic criteria, there are difficulties in establishing what the global prevalence of MS is. Each criteria takes into consideration different risk factors, our different reference values, and studies show that the same sample evaluated by different criteria can present a wide variation in regards to prevalence [32].

Grundy [21] in a review study collected the data regarding the prevalence of MS in populations in different regions in the world and used different criteria, showing the high prevalence of MS in the global population, and the difference in prevalence in the same populations when using different criteria.

The numbers presented by Grundy [21] can be observed in Table 1, in which is presented studies performed throughout Europe, in Table 2, studies in Asian populations and in Table 3, studies in Latin America.

The situation is even more complex when dealing with children and adolescents, because of the lack of consensus about the MS diagnosis in infancy that could be accepted by the whole scientific community.

Different criteria currently used for the parameters related to metabolic syndrome were published in varied well-known organizations in the area of health. In 1999, the World Health Organization (WHO) published their definition of MS [11] and two years later the National Cholesterol Education Program and Adult Treatment Panel III (NCEP-ATP III) [33] in the United States also published their own criteria.

In Brazil, the 1st Brazilian Guidelines for Metabolic Syndrome Diagnosis and Treatment [34], published in 2004 by the Brazilian Hypertension Society based on the definition proposed by NCEP-ATP III [33]. The following year, the Brazilian Cardiology Society proposed the I Guideline for Prevention of Atherosclerosis in Infancy and Adolescence [35] thereby providing reference values of the same components present in former directives, regarding MS, but specific for children and adolescents.

Aiming to standardize the MS diagnostic criteria for children and adolescents, the International Diabetes Federation (IDF) [36] in 2007 also released a definition according to age groups, thus establishing values which could be used for anthropometric delineation, pressure and sanguinary biochemicals, to be applied to children and adolescents between 10 and 19 years [35]. Children under the age of 6 were excluded from definition, not having sufficient data for this age group. IDF does not recommend the diagnosis of MS in children under the age of ten, however it suggests monitoring the abdominal circumference and following the other risk factors in case there is family history with MS, Diabetes Mellitus type 2, dyslipidemia, heart disease, hypertension and/or obesity.

In this criteria, for youth between 10 and 16 years of age, the reference values are the same as proposed by adults, with the exception of waist circumference whose percentiles rather than absolute values have been used to compensate for varying degrees of development and ethnicity, being considered as having excess of central fat the ones who present a circumference greater than 90th percentile. It is important to clarify that for all the age groups, central obesity is an essential condition to diagnose MS, in other words, the diagnosis requires the presence of central obesity plus two or more of the other risk factors. The reason to the using of waist circumference as a central obesity measure in IDF criteria is the impractical determination of insulin resistance in clinical practice and its strong

Country	Population	Age(N)	Criteria	MS Prevalence (% of the population)		
				Men	Women	Total
France	Men and Women	35-64 (3359)	NCEP	3,0	16,9	-
France	Men	50-59 (10 592)	NCEP IDF WHO	29,7 38,9 35,5	- - -	- - -
Germany	Men and Women	(4816 men and 2315 women)	NCEP	23,5	17,6	-
Holland	Adult men and women	50-75 (1364)	NCEP WHO	19,0 26,0	32,0 26,0	- -
Italy	Men and Women	45-64 (1877)	NCEP	24,1	23,1	22,2
Italy	Men and Women	40-79 (888)	NCEP WHO	- -	- -	17,8 34,1
Italy	Men and Women	≥19 (2100)	NCEP	15,0	18,0	-
Italy	Men and Women	65-84 (5632)	NCEP	29,9*	55,2*	-
Spain	Men and Women	35-64 (2540)	NCEP IDF	27,7	33,6	-
Portugal	Men and Women	18-90 (1436)	NCEP	19,1	21,0	23,9
Greece	Men and Women	Adults (9669)	NCEP IDF	- -	- -	24,5 43,4
Croatia	Men and Women	18-88 (996)	NCEP	-	-	34,0
United Kingdom	Men and Women	60-79 (3589)	NCEP IDF WHO	- - -	29,8 47,5 20,9	-

NCEP = US National Cholesterol Education Program - Adult Treatment Panel III; IDF = International Diabetes Federation;
WHO = World Health Organization. *Subgroup with diabetes, 64.9% of the men and 87.1% of the women have Metabolic Syndrome according to NCEP

Table 1: Metabolic Syndrome prevalence in Europe.

Country	Population	Age (N)	Criteria	MS Prevalence (% of the population)		
				Men	Women	Total
India	Men and Women	20-70 (26 001)	NCEP IDF WHO	- - -	- - -	25,8 18,3 23,0
India	Men and Women	>20 (1123)	NCEP	22,9	39,9	31,6
India	Men and Women	20-75 (475)	NCEP	-	-	41,1
Thailand	Men and Women	≥35 (404)	NCEP	-	-	18,0
Thailand	Men and Women	20-70 (1383)	NCEP	15,7	11,7	12,8
Singapore	Men and Women	adults (3954)	NCEP	14,1	12,3	-
China	Men and Women	20-90 (16342)	NCEP with BMI ≥ 25 Kg/m²	15,7	10,2	13,2
China	Men and Women	18-66 (1513)	NCEP IDF WHO NCEP	-	-	9,6 7,4 13,4 5,8
China	Men and Women	25-64 (18630)	NCEP modified for asians IDF	- -	- -	9,5 8,5
China	Men and Women	50-85 (10362)	NCEP IDF	- -	- -	8,5 15,7 25,8
China	Men and Women with DMT2	>30 (1039)	NCEP IDF WHO	- - -	- - -	55,7 50,0 70,0
China	Men and Women with DMT2	19-95 (3589)	NCEP	23,9	12,8	16,8
Japan	Men and Women	19-88 (8144)	NCEP	19,0	7,0	-
Japan	Men and Women	30-79 (6985)	NCEP	30,2	10,3	-
Japan	Men and Women	>40 (11941)	Three or more metabolic risk factors	-	-	14,9

NCEP = US National Cholesterol Education Program - Adult Treatment Panel III; IDF = International Diabetes Federation; WHO = World Health Organization: DMT2 = Diabetes Mellitus type 2; BMI = body mass index.

Table 2: Metabolic Syndrome Prevalence in Asia.

Country	Population	Age (N)	Criteria	MS Prevalence (% of the population)		
				Men	Women	Total
Brazil	Men and Women of Asian Origin	30-60 (721)	NCEP modified for Asians	-	-	53
Brazil	Men and Women of Asian Origin	40-79 (151)	NCEP	36,9	38,8	
Brazil	Adults	(385)	WHO	39,7	58,7	
Brazil	Men and Women of Asian Origin	(479)	NCEP modified for Asians	49,8	43,0	
Brazil	Girls being or not being overweight	12-19 (388)	Three or more risk factors		Normal Weight 14% Overweight 21,4%	
Mexico	Men and Women	20-69 (2158)	NCEP WHO			26,6 13,6
Venezuela	Hispanic Men and Women	≥ 20 (3108)	NCEP			35,3

NCEP = US National Cholesterol Education Program - Adult Treatment Panel III; IDF = International Diabetes Federation; WHO = World Health Organization.

Table 3: Metabolic Syndrome Prevalence in Latin America.

correlation with waist circumference. In the IDF criterion for adolescents older than 16, reference values developed for adults should be used [36].

Furthermore, recent studies has shown that obese children and adolescents, with higher intra-abdominal fat are more prone to develop MS and non alcoholic fatty liver disease than those with higher values of subcutaneous fat, independent of possible confounding variables. It may be explained by the endocrine function of the adipose tissue (adipokines production), causing inflammatory process and insulin resistance, especially visceral adipose tissue, which has particularities related to higher lipolysis and higher release of adipokines [37].

Among the cited criteria, the most used are that from WHO and that of NCEP-ATP III and some differences among them are observed. The definition from WHO requires evaluation of resistance to insulin or the alteration of the glucose metabolism. On the other hand, the definition from NCEP-ATP III does not require the measuring of resistance to insulin, facilitating its use in epidemiological studies [38].

Risk Factors	IDF [36]	WHO [44]	NCEP [33]	I DPAIA [35]
Age	10 to <16 years		12 to 19 years	
MS Diagnosis	Obesity plus 2 or more RF	3 or more RF	3 or more RF	
Obesity	WC ≥ 90th percentile or adult cut-off if lower	BMI>95th percentile	WC ≥ 90th percentile	BMI>85th percentile according to sex and age
Glycemic homeostasis	Fasting glucose ≥ 5.6 mmol/L (100 mg/dL) or known Diabetes Mellitus type2	• Hyperinsulinemia prepubertal >15 mU/L;(31) (stage 1 Tanner) pubertal>30 mU/L; (31) (stages 2-4 Tanner) Post-pubertal ≥ 20 mU/L (stage 5 Tanner) • Fasting glucose ≥ 6.1 mM/L • Glucose intolerance • Γlucose at 120 min ≥ 7.8 mM/L	Fasting glucose ≥ 110 mg/dL	Plasma Insulin >15 um/L
Elevated Arterial Pressure	Systolic BP ≥ 130 mmHg o r Diastolic BP ≥ 85 mmHg	SBP>95th percentile for age, sex and stature NHBPEP [46]	SBP/DBP ≥ 90th percentile for age and sex and stature NHBPEP [45]	SBP and/or DBP in >90th and >95th percentiles or always that BP >120/80 mmHg
Dyslipidemia	• TG ≥1.7 mmol/L (150 mg/dL) • HDL <1.03 mmol/L (40 mg/dL)	• TG >105 mg/dL for< 10 years >13 6mg/dL for ≥ 10 years • HDL <35 mg/dL • TC>95th percentile	• TG ≥110 mg/dL • HDL ≤ 40 mg/dL	TC < 150 mg/dL LDL <100 mg/dL HDL ≥ 45 mg/dL TG <100 mg/dL

MS = metabolic syndrome; RF = risk factors; IDF = International Diabetes Federation; WHO = World Health Organization; NCEP = National Cholesterol Education Program - Adult Treatment Panel III; I DPAIA = Guidelines for the Prevention of Atherosclerosis in Childhood and Adolescence, BMI = body mass index, WC = waist circumference, TC= total cholesterol; TG = triglycerides, HDL = high density lipoprotein, SBP = systolic blood pressure, DBP = diastolic blood pressure; mm Hg = millimeters of mercury; mg/dL = milligrams per deciliter; mM / L = millimoles per liter

Table 4: Diagnostic Criteria for Metabolic Syndrome adapted for children and adolescents proposed by IDF, WHO, NCEP and I DPAID.

Cook et al. Arch Pediatr Adolesc Med, 2003; 157, 821-7 [46]	de Ferranti et al. Circulation, 2004; 110, 2494-7 [47]	Cruz and Goran J Clin Endocrinol Metab, 2004; 89, 108-13 48]	Weiss et al. N Engl J Med, 2004; 350, 2362-74 [49]	Ford Diabetes Care, 2005; 28, 878-81 [50]
Presence of three or more criteria				
Fasting glucose ≥ 110 mg/dL	Fasting glucose ≥ 110 mg/dL	Glucose intolerance (ADAcriteria)	Glucose intolerance (ADAcriteria)	Fasting glucose ≥ 110 mg/dL
WC> 90th percentile (specific for age and sex, NHANES III)	WC>75th percentile (specific for age and sex, NHANES III)	WC>90th percentile (specific for age and sex, NHANES III)	BMI - Z Score ≥ 2 (specific for age and sex)	WC>90th percentile (specific for sex, NHANES III)
TG ≥ 110 mg/dL (specific for age and sex, NCEP)	TG ≥ 100 mg/dL	TG ≥ 90th percentile (specific for age and sex, NHANES III)	TG ≤ 95th percentile (specific for age and sex, ethnicity, NCHS)	TG ≥ 110 mg/dL (specific for age and sex, NCEP)
HDL <40 mg/dL (specific for age, NCEP)	HDL < 50 mg/dL	HDL ≤ 10th percentile (specific for age and sex, NHANES III)	HDL ≤ 5th percentile (specific for age and sex, ethnicity, NCHS)	HDL < 40 mg/dL (specific for age, NCEP)
BP ≥ 90th percentile (specific for age, sex and height NHBPEP) [46]	BP ≥ 90th percentile (specific for age, sex and height NHBPEP)[46]	BP ≥ 90th percentile (specific for age, sex and height NHBPEP) [46]	BP ≥ 95th percentile (specific for age, sex and height NHBPEP) [46]	BP ≥ 90th percentile (specific for age, sex and height NHBPEP) [46]

WC = waist circumference; NHANES III = Third National Health and Nutrition Examination Survey; TG = triglycerides; NCEP = US National Cholesterol Education Program; BP = blood pressure; ADA = American Diabetes Association; BMI = body mass index; NHBPEP = National High Blood Pressure Education Program; NCHS= National Center for Health Statistics; HDL = high density lipoprotein.

Table 5: Definitions for metabolic syndrome for children and adolescents adapted by various authors.

Comparative studies, using various diagnostic criteria of the metabolic syndrome for children and adolescents confirms the difference in prevalence and verifies that the one connected with WHO was the one which resulted in greater prevalence and consequently the one recommended because of the emphasis on glycemic homeostasis [32,39].

The prevalence of the syndrome in Brazil in children and obese adolescents can reach between 23% [40] to 39.1% [41]. The importance of identifying the risk factors and the forms of control and the treatment of MS in infancy and adolescence is because its presence in this phase of life remains, many years in "silence". Therefore, its identification can contribute to the prevention of chronic diseases and premature death. Currently, there already exist MS definitions for children and adolescents which use as one of the criteria the abdominal obesity [42,43].

In Table 4 there are presented the main parameters and their respective reference values which are applied to children and adolescents.

Some authors also adapted definitions proposed for adults to be applied on children and adolescents (Table 5).

Conclusion

The prevalence of MS has increased in the whole world's adult population and pediatric population, and defining its prevalence has been

an arduous task, due to the lack of consensus of its diagnostic criteria. When dealing with the ease in relation to its applicability and sensitivity, the criteria from the International Diabetes Federation can be considered the most advantageous. However, considering the efficacy of the diagnosis, the criteria which most emphasizes the characteristics of glycemic homeostasis, and consequently the main risk factor of MS, resistance to insulin, is the criteria from the World Health Organization for taking into consideration the risk factors like fasting glucose, hyperinsulinemia and glucose intolerance.

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