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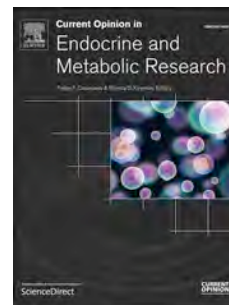
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METABOLIC SYNDROME BEFORE PUBERTY: MYTH OR REALITY?

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Abstract

Metabolic syndrome is defined as a cluster of alterations related with insulin resistance (obesity, dyslipidemia, hypertension and impaired glucose metabolism), which are associated with a higher risk of cardiovascular disease in adults. Several definitions have been proposed for older children and adolescents. However, no definitions have been made according to pubertal status, and those in prepubertal state have not received attention enough, despite there are data suggesting the early presence of risk factors. The new insights concerning healthy and unhealthy metabolic status or the addition of novel metabolic risk biomarkers, may contribute to the knowledge about the development of metabolic syndrome in children. This manuscript reviews the available evidence on metabolic syndrome during childhood, focusing on the prepubertal period.

Keywords: Metabolic syndrome. Insulin resistance. Pubertal status.

Introduction

Metabolic syndrome (MetS) is defined as a cluster of cardiometabolic risk factors (obesity, dyslipidemia, elevated blood pressure and impaired glucose metabolism) which are associated with a higher risk of cardiovascular disease (CVD) and type 2 diabetes mellitus in adults. The pathophysiological basis of MetS is not yet completely understood, but central obesity and insulin resistance (IR) seem causative factors. There are several definitions for adults that share most of the variables, while using different cut-off values(1). Similarly, there are many definitions proposed for children and adolescents, but there is no consensus definition yet. These definitions agree on defining MetS in older children and adolescents, since puberty is well-known as a critical lapse for IR(2). However, the diagnosis of MetS in prepubertal children is still an uncertain concept. Some limitations are related with the unavailability of population-specific cut-off points for the variables used in the definition, which should be established with control groups with the same characteristics of ethnicity, age, sex, and pubertal stage, and also with the absence of longitudinal studies.

During puberty, physiological insulin resistance takes place, however, there are data that suggest an increase of metabolic risk if obesity exists, although the transition from middle to late puberty seems to reverse it(3). The clinical utility of the diagnosis of MetS in childhood lies in the recognition of those subjects with the highest risk of developing CVD, at short and /or long term. Strategies to prevent or treat MetS only make sense if the diagnosis remains stable during the transition from childhood to adolescence. This follow-up has been studied mainly from adolescence to adulthood, showing contradictory results. In this context, there is little evidence on how cardiometabolic risk factors or MetS change during the transition from the prepubertal stage to older ages.

Definition of metabolic syndrome in children

More than 40 different MetS definitions have been published for children and adolescents(4). Most of them were based on the National Cholesterol Educational Program (NCEP) definition for adolescents aged 12 to 19 years (Table 1). This definition is based on the fulfillment of 3 out of 5 risk factors: waist circumference (WC) $\geq 90^{\text{th}}$ percentile (age and sex specific), fasting plasma triglycerides (TG) ≥ 110 mg/dL, high density lipoprotein-cholesterol (HDL-c) ≤ 40 mg/dL, fasting plasma glucose (FPG) ≥ 110 mg/dL and blood pressure (BP) $\geq 90^{\text{th}}$ percentile (age and sex specific)(5).

In 2007, the International Diabetes Federation (IDF) proposed a specific definition for children and adolescents, recognizing that MetS parameters change with age and pubertal development. It included children over 10 years, arguing MetS cannot be diagnosed as an entity in younger children, although those with obesity should be encouraged to lose weight in order to prevent the development of IR or other complications(6). They established the same criteria and cut-off points used for adults. Since then, most authors investigating MetS, unified children and adolescents with different pubertal stages, using the same criteria (usually, IDF- and NCEP-adapted or modified definitions coming from adults) for all individuals, despite none of these definitions were especially made according to pubertal status (table 1).

The differences between these definitions are based on their specific thresholds, which are usually expressed as percentiles for each component, generally based on population-specific reference values. On one hand, variations are due to sex and age (or even height or ethnicity), anthropometry (body mass index or waist circumference), as well as metabolic (lipids and glucose/insulin metabolism) and cardiovascular (blood

pressure) parameters. On the other hand, puberty has been shown to influence the mentioned components, being a crucial period for IR, and therefore, for cardiovascular risk factors and the development of MetS(7). In fact, IR promotes a fast pancreatic beta cell deterioration in adolescents with a pre-diabetes status, where a type 2 diabetes earlier than adults(8). However, there are not always age- and sex-specific reference values for some of these parameters in children, nor particular considerations for MetS diagnosis according to pubertal status, despite there are well-known differences in cardiometabolic risk factors and MetS diagnosis along the pubertal stages(3,7,9).

The above-mentioned NCEP and IDF adapted definitions were made for older children and adolescents, with ages probably included during the peri- and post-pubertal periods. In this context, the IDEFICS study proposed a new definition of MetS in early childhood (most of them in prepubertal stage), with age- and sex-specific values for each risk factor, based on 18745 European children aged 2-10.9 years(10). This definition still requires for the fulfillment of at least 3 out of 5 risk factors, establishing different levels of monitoring for these children in relation to the risk of disease.

Continuous MetS score and metabolic status

However, this original MetS construct has been questioned for several reasons. On one hand, the fulfillment of each MetS criteria is dichotomous (yes/no), while their variables are continuous. Some authors have proposed the diagnosis of MetS as a continuum, arguing the traditional definition was not sensitive enough(11). A MetS score, built by adding the different z-scores of each risk factor, allows to measure metabolic risk (higher z-scores imply higher metabolic risk). However, the MetS score also presents some limitations. First, there is no unified statistical method for calculating this score (z-scores, factor analysis, principal components analysis and confirmatory factor analysis

have been reported). Second, these methods are sample-specific and, therefore, MetS scores cannot be compared between studies unless demographic characteristics, distribution of data, and measures of central tendency and variability were similar between samples(11,12). In this context, Vukovic *et al.*(13) have proposed a new MetS score that simplifies previous statistical methods. It was called “Pediatric siMS” based on the definition by Soldatovic *et al.*(14) for adult population, although it used the IDF definition of MetS for children (over 10 years). The validity of these various methods for predicting MetS in children have been reported to be high and similar between them(12).

On the other hand, the distinction between metabolically healthy(MHO) or unhealthy (MUO) children with obesity is particularly focused on those children who display a healthy cardiometabolic profile without other MetS associated factors (15). Given the lack of consensus on the MH definition during the past years, the assessment and interpretation of cardiometabolic risk has been challenging and complicated by the large number of definitions. Recently, Damanhoury *et al.*(16) have proposed a consensus definition of MH obesity which needs the accomplishment of all these criteria: BMI-SDS $>+2$ SD (according to the WHO growth charts), HDL-c > 40 mg/dL (or > 1.03 mmol/l), TG ≤ 150 mg/dL (or ≤ 1.7 mmol/l), SBP and DBP ≤ 90 th percentile, and a measurement of glycemia. However, the authors did not reach a consensus regarding the measurement of glycemia nor its cut-off value, and the pubertal status was not considered either.

Based on these issues, the American Academy of Pediatrics has recently recommended to focus on metabolic and cardiovascular risk factors independently, instead of defining MetS in children (17). Thus, beyond the definition used, population-reference values (age- and sex-specific) for each MetS component have been

increasingly reported to aid in the identification of these cardiometabolic risk factors in prepubertal children(18–22).

Cardiometabolic risk factors in prepubertal children

There is evidence of the existence of cardiometabolic risk factors in peri- and post-pubertal children(23), but less efforts have been made on finding out if these alterations are already present at prepubertal stage. Unfortunately, the pubertal status is not always specified in studies with younger children, which usually only report age ranges, limiting the extent of the conclusions for the prepubertal population. However, there are several reports suggesting the early existence of these cardiometabolic risk factors during the prepubertal period(9,24,25).

The use of the various definitions of MetS, and of those referring to MH or MU status, brings back wide differences in the estimated prevalence of cardiometabolic risk factors in prepubertal children. Most recent studies applying different definitions in their samples, show a significant variability in this prevalence(10,24,26). Olza *et al.*(24) used seven different definitions of MetS for children and adolescents on a sample of 478 prepubertal children with obesity, and found a prevalence of MetS ranging from 8.3% to 34.2% depending on the definition (5,6,27–31).

The prevalence of MetS found by the IDEFICS definition among 12,319 children (mostly prepubertal), 951 of which had obesity, was higher than with others(5,6,30), with the lowest one found for the IDF definition (0.4% for total population)(10). In contrast to previous definitions, they found that the proportion of children exceeding the cut-off of each component was similar, with no component showing a lower prevalence. Dyslipidemia and increased WC were the components

found to have the higher likelihood to classify a child as with MetS according to the other compared definitions.

In another study with 622 prepubertal children with obesity (5-10.9 years), the prevalence of MUO (defined as: obesity and at least one another metabolic risk criteria of each definition) varied from 14 to 70%, using eight different classifications (26). Five definitions were based on classical MetS components (3,6,10,24,32) and three included homeostatic model assessment- IR (HOMA-IR) cut-offs (24,32,33). Those of Olza *et al.* (24) and Ahrens *et al.* (10) showed the highest prevalence, and IDF (6) and those based on HOMA-IR the lowest ones.

There is a recent study that analyzes cardiometabolic risk factors in 1409 children with obesity (mean 9.7 (2.2-17.9) years) and classified them according to pubertal status and age in four groups (Group 1, prepubertal < 6 years; Group 2, prepubertal > 6 years; Group 3, pubertal stages II-III; Group 4, pubertal, stages IV-IV). They reported a prevalence of MHO (defined as obesity without any other risk factor: BP, glycemia, insulinemia, glycemia and insulinemia after an oral glucose tolerance test (OGTT), HOMA-IR, total cholesterol, HDL-c, LDL-c and TG) of 59.8% for group 1, and nearly 30% on the other three groups. For groups 1 and 2, the prevalence of the following cardiometabolic risk factors were, respectively: hypertension in 5.9 and 12.9%, abnormal HOMA-IR in 19.8% and 49.9%, or dyslipidemia in 20.6 and 36.1% (9). In conclusion, it seems that cardiometabolic risk factors are present in prepubertal children regardless of the definition (MetS, MH or MU status) used (Table 1).

Other non-traditional cardiometabolic risk factors

Some other cardiovascular and metabolic biomarkers associated with higher cardiometabolic risk, both in adults and children(1), are not included in the MetS traditional framework, although they could help modulate the diagnosis. These parameters have been reported to be involved in the IR state or the proinflammatory status, at the first steps of MetS development.

The adipose tissue constitutes an endocrine organ that secretes several factors, as proinflammatory cytokines (e.g. tumor necrosis factor- α and interleukins) and adipokines (e.g. adiponectin and leptin), that are related to the cardiometabolic risk profile(1). Plasma leptin concentrations have been found to be increased in prepubertal children with IR(34), and associated with high BMI and fat mass, as well as with other MetS factors and continuous MetS scores(25,26,35). Conversely, adiponectin plasma levels seem to be low in prepubertal children with overweight/obesity compared with those with normal-weight (26,35–37). The leptin/adiponectin ratio has been also studied as a cardiometabolic risk marker, and found higher in those prepubertal children with higher BMI and BMI z-scores, and with other MetS factors(35). Other adipokines such as resistin, irisin, visfatin, retinol-binding protein 4 or S100A4 protein have also been found to be associated with cardiometabolic risk in prepubertal children(26,36–42). For all of these new factors, despite the attempts of establishing a unique cut-off value, the use of age- and sex-specific values and its percentiles should be more appropriate(43,44), as those reported for classical cardiometabolic risk factors(10).

The effect of metabolic impairment has also been observed through several biomarkers that reflect the low-grade inflammatory status (C-reactive protein, TNF- α , IL-6, IL-8), vascular damage (sE-selectin, sICAM-1, sVCAM-1) and risk of CVD (Active-PAI-1, PAI-1, myeloperoxidase), both in children(25,26,36,37) and adults(1). The circulating concentration of these molecules have been found to be higher in

prepubertal children with higher BMI(36,37), higher waist-to-height ratio(37), higher scores of continuous MetS(25) and MU status(26).

The apolipoproteins have been studied as markers of dyslipidemia and predictors of atherosclerosis in adults. The apo A1 is an anti-atherogenic particle, which is the main protein of HDL. In turn, the apo B is a pro-atherogenic particle included in several lipid fractions such as LDL. The ratio apo B/A1 represents the lipid profile and has been shown to be consistently higher in prepubertal children with higher metabolic risk (with a positive correlation with the number of MetS factors) and to be positively associated with BMI(45,46). Moreover, apo B levels seemed to track better than other markers of dyslipidemia in the transition from childhood to adolescence, showing the importance of its determination in children for the prediction of future cardiovascular risk (47).

Another consequence of the mentioned metabolic derangement is the non-alcoholic fatty liver disease (NAFLD), as the hepatic manifestation of an IR state and the most common cause of chronic hepatic disease in childhood. In this context, alanine aminotransferase (ALT), previously related to IR and NAFLD in adults with MetS(48), has been found increased in obese prepubertal children compared with their normal-weight peers, and positively correlated with MetS and impaired insulin sensitivity (HOMA-IR > 97.5th percentile)(49). Fetuin-A, an hepatokine related to hepatic insulin function, has been also associated with IR and other metabolic risk factors (z-scores BMI, blood pressure and dyslipidemia) in prepubertal children(50). Other biomarkers such as vifastin, cytokeratin 18 or pentraxin-3 have been proposed for the non-invasive assessment of NAFLD in children(41,51,52).

Last, elevated levels of serum uric acid have also been associated with higher BMI and other MetS factors (higher blood pressure and TG, and low HDL-c), as well as

with IR, markers of endothelial damage, and carotid intima-media thickness in prepubertal children (53–55).

To study these non-classical risk factors may be useful to demonstrate the presence of cardiometabolic derangements and to improve the ability to diagnose subjects with a worse metabolic profile and a higher risk of CVD. However, nowadays most of them are exclusively investigated for research purposes.

Conclusion

The consensus definition of MetS in pediatric population has not been reached yet, but recently proposals may improve the diagnosis of MetS, especially in prepubertal children. The application of continuous MetS scores or the measurement of novel biomarkers may also contribute to determine the cardiometabolic risk of children in both research and clinical settings. Beyond the chosen definition, it could be adequate for future studies to focus on the grouping of cardiometabolic risk factors, without trying to define MetS in children. Despite the debate regarding the stability of the MetS construct from childhood to adolescence, there is enough evidence of the influence of individual risk factors on its development, especially obesity, on the risk of future CVD. Hence, longitudinal studies and strategies for fighting against them from the beginning of childhood should be continued.

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Declaration of interest

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* of special interest

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Table 1. Authors' Criteria used for the diagnosis of metabolic syndrome in prepubertal children.

Study	Population	Obesity	Blood pressure	Lipids	Glucose/Insulin
Cook <i>et al.</i> 2003(5)	White, black and Mexican-American 12-19 years Male and female	WC $\geq 90^{\text{th}}$ P	SBP or DBP $\geq 90^{\text{th}}$ P	TG ≥ 110 mg/dL HDL-c ≤ 40 mg/dL	FBG ≥ 110 mg/dL
de Ferranti <i>et al.</i> (2004)(27)	Mexican-American, non-Hispanic White/Black 12-19 years Male and female	WC $\geq 75^{\text{th}}$ P	SBP $\geq 90^{\text{th}}$ P	TG ≥ 110 mg/dL HDL-c ≤ 40 mg/dL	FBG ≥ 110 mg/dL
Weiss <i>et al.</i> (2004)(28)	White, Black and Hispanic 4-20 years Male and female	BMI $> 97^{\text{th}}$ P or z-score > 2	SBP or DBP $\geq 95^{\text{th}}$ P	TG $\geq 95^{\text{th}}$ P and HDL-c $\leq 5^{\text{th}}$ P for age, sex and race	OGTT > 140 and < 200 mg/dl at 2h
Cruz <i>et al.</i> (2004)(29)	Hispanic (Mexican-American, Central American, or mixed) 8-13 years Male and female	WC $\geq 90^{\text{th}}$ P	SBP or DBP $\geq 90^{\text{th}}$ P	TG $\geq 90^{\text{th}}$ P and HDL-c $\leq 10^{\text{th}}$ P for age, sex and race	OGTT at 120 min ≥ 140 and < 200 mg/dl
Viner <i>et</i>	White, Black, South	BMI $\geq 95^{\text{th}}$ P	SBP $\geq 95^{\text{th}}$ P	Any of the following:	Fasting

<i>al.</i> (2005)(30)	Asian, and other or mixed ethnicity 2-18 years Male and female			TG \geq 150 mg/dl, HDL-c <35mg/dl, or totalcholesterol \geq 95 th P	hyperinsulinemia (pre-pubertal \geq 15 mU/l,peri-pubertal (stages 2–4) \geq 30 mU/l andpost-pubertal \geq 20 mU/l), FBG \geq 110 mg/dl or OGGT at 120 min \geq 140 mg/dl
Ford <i>et al.</i> (2005)(31)	12-17 years Male and female	WC \geq 90 th P	SBP or DBP \geq 90 th P	TG \geq 110 mg/dL HDL-c \leq 40 mg/dL	FBG \geq 100 mg/dL
Zimmet <i>et al.</i> (2007)(6)	\geq 10 to \leq 16 years	WC \geq 90 th P	SBP \geq 130 or DBP \geq 85mmHg	TG \geq 150 mg/dL HDL-c <40 mg/dL	FBG \geq 100 mg/dL
Ahrens <i>et al.</i> (2014)(10)	European 2-11 years	WC \geq 90 th P	SBP or DBP \geq 90 th P	TG \geq 90 th P or HDL-c \leq 10 th P	HOMA-IR or FBG \geq 90 th P
Zhao <i>et al.</i> (2019)(23)	Asian 6-11 years	WHtR \geq 0.5	SBP or DBP \geq 90 th P	TG \geq 110 mg/dL HDL-c \leq 40 mg/dL	FBG \geq 110 mg/dL

Table modified from Olza *et al.*(24).

BMI: Body mass index; DBP: diastolic blood pressure; FBG: Fasting blood glucose; HDL-c: High density lipoprotein-cholesterol; HOMA-IR: homeostasis model assessment of insulin resistance; LDL-c: Low density lipoprotein-cholesterol; OGTT: Oral glucose tolerance test; SBP: systolic blood pressure; WC: Waist circumference; WHtR: waist-to-height ratio; TG: Tryglycerides.

Journal Pre-proof

Dear editors:

“METABOLIC SYNDROME BEFORE PUBERTY: MYTH OR REALITY?”

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Authors have no conflict of interest.

Looking forward to hearing from you.

Sincerely,

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