METABOLIC SYNDROME IN PAEDIATRIC POPULATION: IS IT TIME TO THINK BACK ON DIAGNOSIS CRITERIA?

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ABSTRACT

Metabolic syndrome (MetS) represents an emerging disease in the paediatric population; it is characterised by a cluster of cardiometabolic abnormalities, including visceral obesity, dyslipidaemia, hypertension, and Type 2 diabetes mellitus, that directly increase the risk of developing cardiovascular disease and diabetes. Currently, several definitions of MetS are available in the paediatric setting, causing confusion and discrepancy in the identification of these patients. Moreover, in recent years, several other comorbidities, besides those traditionally used to define MetS, which are also linked to the disease have been identified, making its definition even more difficult. Among these, mainly non-alcoholic fatty liver disease and obstructive sleep disorders have been strictly linked to MetS. In this review, we discuss the importance to re-evaluate diagnostic criteria for MetS, in order to uniformly define this disease in children, considering also the inclusion of the other emerging clinical features.

Keywords: Metabolic syndrome, non-alcoholic fatty liver disease, obesity, children, cardiovascular risk.

INTRODUCTION

Childhood obesity and its metabolic complications are rapidly emerging as one of the greatest challenges of the 21st century. The epidemic spread of obesity in the last 20 years has in fact led, in a paediatric setting, to the appearance of diseases previously considered a prerogative of adulthood, such as metabolic syndrome (MetS) and Type 2 diabetes mellitus (T2DM). MetS, described for the first time in the 1988 by Reaven, is characterised by a cluster of metabolic abnormalities comprising insulin resistance (IR), dyslipidaemia, visceral obesity, and hypertension, associated with an enhanced cardiovascular risk in adulthood.[1] Although the pathophysiological mechanism underlying the development of MetS is still only partially understood, the most widely accepted hypothesis identifies IR and excessive production of free fatty acids as the key components in the development of this disease.[2] In the paediatric population an important role in the pathogenesis of MetS is played by intrauterine events and factors that emerge during the early years of development. In fact, the presence of maternal gestational diabetes, low birth weight, and infant feeding practices contribute to enhance the future risk of MetS. Other factors are socio-economic or environmental (an obesogenic environment, for example), similar to adults.

In the last decade, many criteria have been proposed by the various scientific societies in an attempt to define MetS in children, changing the diagnostic criteria of the adults and using them to diagnose children and adolescents. The major limitation to the application of these criteria is represented by the fact that many of them (body mass index [BMI], waist circumference, blood pressure, and lipid profile) are continuous age-dependent variables. In fact, although several authors have applied the diagnostic criteria of adults to the paediatric population, inserting specific numerical cut-offs expressed in percentiles, the effects have led to great diversity in the results of various epidemiological studies. More importantly, none of the MetS definitions consider the influences of growth and puberty, for instance, physiological insulin resistance in puberty, changes in fat and fat-free mass, and changes in sex steroid secretion.[3]

Until now more than 40 definitions for childhood MetS have been proposed, most based on adaptations of adult criteria.[4] Several studies have clearly demonstrated that the prevalence of MetS in the paediatric age group may vary widely using different definitions, ranging from 2.2% to 52.1% among different studies.[5] Table 1 displays three of the most commonly used definitions for MetS in the paediatric population.

Despite the diversity of such data, it is clear that there is an increased prevalence of MetS among obese children and that, in this population, the prevalence of MetS increases with the increase of the degree of obesity. Recent data (International Obesity Taskforce) reported that around 150 million school-aged children and 50 million children are overweight and obese, respectively, with consequent early and long-term obesity-related comorbidities, including MetS. The health consequences of childhood obesity and MetS are wide-ranging, as obesity appears to be on the causal pathway of every major chronic disease.[2] Several studies have, in fact, reported that the metabolic alterations related to obesity and MetS are multisystemic and include other organs in addition to the best-known targets of MetS, changing the actual scenario of paediatric MetS (Figure 1). Recently, other abnormalities, such as chronic proinflammatory and prothrombotic states, non-alcoholic fatty liver disease (NAFLD), and sleep apnoea have been added to the entity of the syndrome, making its definition even more complex and raising doubts about the accuracy of the metabolic features considered as criteria for the diagnosis of MetS.[4]

Table 1: Criteria for the diagnosis of metabolic syndrome (MetS) in children.

Parameters	Diagnostic criteria for MetS			
	International Diabetes Federation (IDF)*		National Cholesterol Education Program/ Adult Trial Panel III°	American Heart Association (AHA)^
Age	10-16 years	>16 years	12-19 years	12-19 years
Waist circumference	≥90th percentile (or adult cut-off if lower)	In Caucasian population ≥90 cm	≥90th percentile for age and sex	≥90th percentile for age, sex, and ethnicity
Triglycerides	≥150 mg/dl (≥1.7 mmol/l)	≥150 mg/dl (1.7 mmol/l) or specific treatment for this lipid abnormality	>110 mg/dl (1.24 mmol/l)	≥110 mg/dl (1.24 mmol/l)
HDL cholesterol	<40 mg/dl (≤1.3 mmol/l)	<40 mg/dl (1.03 mmol/l) in males <50 mg/dl (1.29 mmol/l) in females or specific treatment for this lipid abnormality	<40 mg/dl (1.03 mmol/l)	≤10th percentile for race and sex
Fasting glucose	>100 mg/dl (5.6 mmol/l)	>100 mg/dl (5.6 mmol/l) or known T2DM	>110 mg/dl (6.1 mmol/l)	≥100 mg/dl (5.6 mmol/l)
Blood pressure (BP)	Systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg	Systolic BP ≥130 or diastolic BP ≥85 mmHg or treatment of previously diagnosed hypertension	Systolic or diastolic above the 90th percentile (age, gender, and height-specific)	≥90th percentile for age, sex, and height

HDL: high density lipoprotein; T2DM: Type 2 diabetes mellitus.
* For the diagnosis of MetS, three of the five criteria must be present.
° For the diagnosis of MetS the presence of three or more of the criteria is required.
^ For the diagnosis of MetS, central obesity and two of four other components must be present.

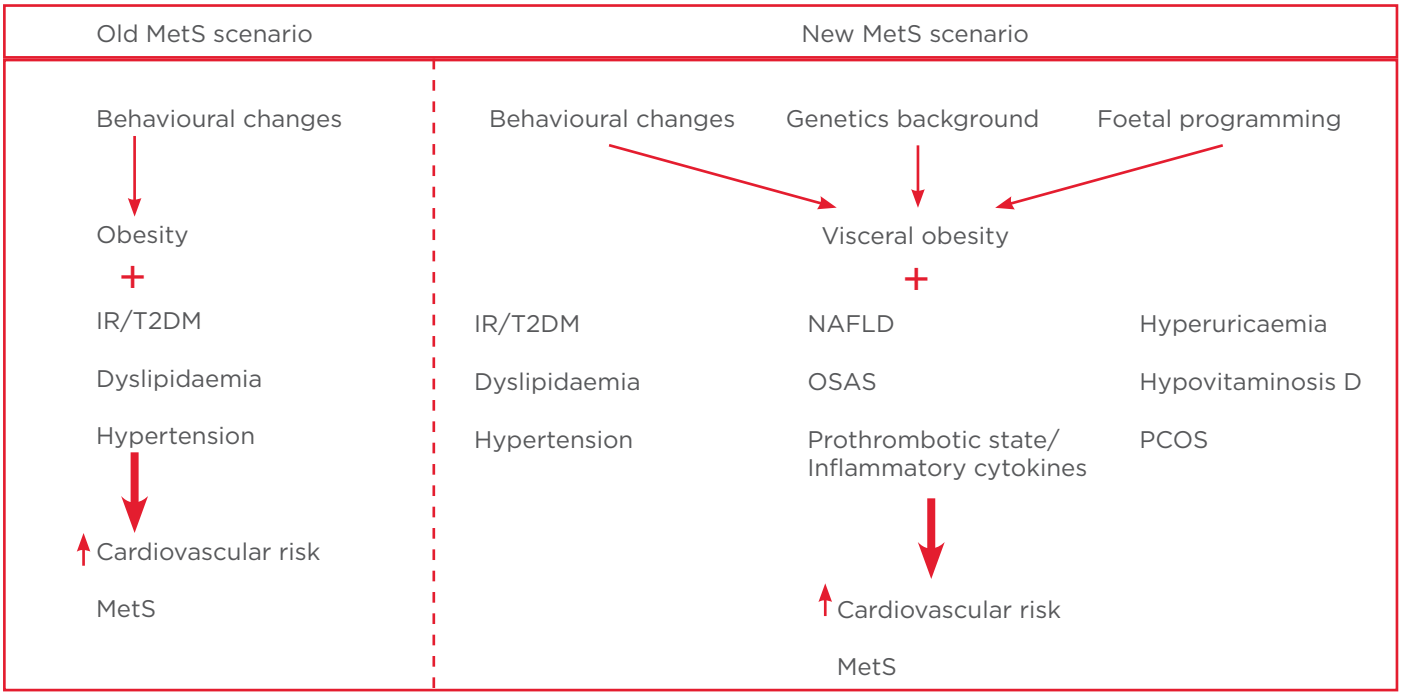

Figure 1: The evolving scenario of metabolic syndrome (MetS) in children.
T2DM: Type 2 diabetes mellitus; PCOS: polycystic ovary syndrome; NAFLD: non-alcoholic fatty liver disease; OSAS: obstructive sleep apnoea syndrome; IR: insulin resistance.

The primary management for MetS is healthy lifestyle promotion, which includes moderate calorie restriction with changes in dietary composition, reducing saturated fat and increasing fibre, which is associated with a moderate intensification in daily physical activity. Unfortunately, because lifestyle changes are difficult to obtain and maintain for children and their families, drug treatments are crucial to prevent the progression of severe organ damage. In the present review, we discuss the importance of establishing clear criteria to define MetS, highlighting the latest research, which extends the metabolic features of MetS to other clinical manifestations, suggesting the need for a re-evaluation of the actual criteria for the diagnosis of paediatric MetS.

NAFLD

The term 'non-alcoholic fatty liver disease' includes a spectrum of liver disease, ranging from simple fat accumulation in the hepatocytes, called simple steatosis, to various degrees of liver inflammation and fibrosis, and even cirrhosis (non-alcoholic steatohepatitis [NASH]).[6] In the last decade, many advances have been made in the understanding of pathogenesis, the clinical implications, and the treatment of this liver disease in children. Unfortunately, because of a scarcity of data regarding long-term follow up, the prognosis of paediatric NAFLD is still doubtful.[7] NAFLD in children displays the same basic morphological lesions observed in their adult counterparts, but the pattern of distribution of these lesions is frequently different. Three distinct histological types were traditionally identified: Type 1 NASH, characterised by steatosis with ballooning degeneration and/or perisinusoidal fibrosis, without portal involvement; Type 2 NASH, characterised by steatosis with portal inflammation and/or fibrosis, in the absence of ballooning degeneration or perisinusoidal involvement; and a NASH overlap type, in which characteristics from both types were present. Most paediatric subjects have Type 2 NASH, which is more likely to be associated with advanced fibrosis.

With regards to the pathogenetic mechanisms that lead to the development of NAFLD in children, multiple metabolic factors, mainly IR, visceral obesity, and dyslipidaemia, interact with each other, creating a network of metabolic derangements involved in both the development and progression of liver damage. It is easy to note the close overlap between the principal pathogenetic factors of MetS and NAFLD, for which fatty liver is now

widely considered as the hepatic manifestation of MetS. In recent years, genome-wide association studies have identified some single-nucleotide polymorphisms, associated with the feature of MetS[8] and NAFLD/NASH, in children.[9] More recently, in addition to well-known environmental factors, emerging studies have reported a possible common genetic susceptibility pattern for NAFLD and MetS.[10] 1 year ago, Xu et al.[11] reported that the rs1800849 variant of the *UCP3* gene is associated with MetS components and increased risk of NAFLD in obese Chinese. Moreover, recent evidence strongly suggests not only a relationship between NAFLD and MetS in obese children, adolescents, and adults, but also the key role exerted by liver fat deposition in the pathogenesis of MetS.[12] Clinically, several studies reported a strict association between these two entities[13] and a case-control study of 300 overweight/obese children (150 with biopsy-proven NAFLD and 150 without) reported that the presence of MetS traits increased 5-times the odds of having NAFLD, compared to age-matched obese children without MetS.[14] Further cross-sectional studies conducted on different ethnic groups have supported the connection between NAFLD and MetS in the paediatric population. Kelishadi et al.[15] have, in fact, reported that in 1,107 Iranian subjects (aged 6–18 years), central obesity may be used as a predictor of NAFLD, assessed by ultrasound and levels of alanine aminotransferase (ALT). It has also been reported that in obese Chinese children, the overlap between NAFLD and MetS may be found in 84.61% of cases.[16]

All these data reinforced the idea that NAFLD represents the hepatic involvement of MetS, and suggested the possible role of NAFLD in the development of metabolic complications during life. In this regard, several studies in the last few years have demonstrated an association between NAFLD and structural or functional cardiovascular abnormalities, including myocardial IR, alterated cardiac energy metabolism, and abnormal left ventricular (LV) structure, independently of cardiovascular risk and metabolic risk factors.[17] Interestingly, Pacifico et al.[18] have recently demonstrated that obese children with NAFLD exhibit features of early LV diastolic and systolic dysfunction compared to obese patients without NAFLD, and that children with more severe liver histology (NASH) have worse cardiac dysfunction. Considering the emerging long-term effects of MetS and NAFLD on cancer and cardiovascular disease (CVD) development, the understanding of the interplay between these two entities may help to identify and promptly treat this high-risk population. Moreover, a prompt intervention on these subclinical abnormalities may be important because treatment to reverse the process is most likely to be effective earlier in the disease.

Lifestyle modification remains the first-line therapy for paediatric NAFLD, but it is usually difficult to achieve. Therefore, in the last decade, based on new knowledge in terms of risk factors and pathogenesis of NAFLD, several studies have evaluated the effects of different molecules, such as insulin-sensitisers, antioxidants, and cytoprotective agents in the treatment of paediatric fatty liver. Metformin, among insulin-sensitiser agents, and vitamin E, such as antioxidants, are the principal drugs evaluated in children with NAFLD. The results of studies conducted in children reported divergent results; recently, the American TONIC trial[19] reported that metformin and vitamin E, either alone or in association, have little effect in reducing serum ALT levels, with partial effects, mainly for vitamin E, on liver histology (hepatocyte ballooning). Furthermore, among the new pharmacological studies for NAFLD, the effect of treatment with docosahexaenoic acid (DHA) requires particular attention. It has been demonstrated that in children with NAFLD, DHA supplementation ameliorates liver fat content, insulin sensitivity index, serum ALT, and triglycerides levels.[7] Other interesting approaches are actually ongoing in NAFLD animal models or in adults. Among these, nuclear receptors are very interesting agents which act to regulate the expression of specific genes controlling a broad range of cellular and metabolic functions. The most studied are the peroxisome proliferator-activated receptors, involved in the activation of hepatic stellate cells, and the farnesoid X receptor, also implicated in the pathogenesis of NAFLD.[7]

OBSTRUCTIVE SLEEP DISORDERS

Obstructive sleep apnoea syndrome (OSAS) is characterised by episodes of chronic intermittent hypoxia and sleep fragmentation and, in obese adults, it has been considered as a respiratory manifestation of the MetS.[20] In fact, according to the International Diabetes Federation Recommendations,[21] adults with OSAS should also be evaluated for cardiovascular disorders and, conversely, the possibility of OSAS should be considered in all patients with diabetes and MetS. Concomitantly with the emerging epidemic of

obesity in childhood, studies evaluating the prevalence of OSAS in children have shown a substantial increase with obesity, such that, for each increase of 1 kg/m^2 of BMI above the mean in children, the risk of OSAS increases by 12%.[22]

OSAS, by exposing children to recurrent intermittent hypoxaemia or oxidative stress, may amplify the adverse effects of adiposity on systemic inflammation and metabolic features associated with vascular disease and diabetes.[23] In fact, emerging data have demonstrated that OSAS leads to a pattern of cardiovascular and metabolic alterations, similar to obesity, due to the production of reactive oxygen species secondary to chronic intermittent hypoxaemia and oxidative stress. These observations suggest that OSAS may exacerbate the deleterious metabolic effects of overweight in adults and children. In fact, children with OSAS have higher levels of blood pressure, C-reactive protein and increased IR, as well as LV hypertrophy,[24] suggesting that childhood OSAS may also increase the risk of developing severe chronic cardiovascular and metabolic conditions.[25,26] Moreover, recently, Nobili et al.[27] have demonstrated a strict association between presence and severity of NASH and OSAS in children with fatty liver, independent of IR and visceral obesity. A growing number of experimental studies have reported an interesting interplay between OSAS and NASH pathogenesis, based on the induction, by hypoxia, of hepatic triglyceride accumulation, inflammation, and fibrosis. On the basis of recent advances concerning the relationship between OSAS and NASH, it has been suggested that children with NAFLD should be routinely screened for OSAS. Further studies are needed to better define the real impact of hypoxaemia correction by OSAS treatment on laboratory, ultrasonography, and histological features of NAFLD, and on metabolic impairments.[27]

HYPERURICAEMIA

Although the serum uric acid (UA) level is not included in any definition of MetS, several studies have shown strong associations between UA levels and MetS or its components.[28,29] In particular, increased serum UA levels are associated with a risk of CVD or renal disease in adulthood.[30,31] The pathogenesis of the association between hyperuricaemia and MetS is not fully understood, but IR is thought to play a pivotal role. In fact, the excess insulin concentrations increase sodium and UA reabsorption by the kidney partially explained this association. Hyperuricaemia, in turn, reduces nitric oxide bioavailability, which is essential for insulin action. Therefore, UA seems to be involved itself in IR pathogenesis, inducing a vicious cycle that is associated with the onset of some components of the MetS.[32]

To date, there is little information regarding this relationship in the paediatric population, both due to the difficult definition of MetS in children and the age-dependent reference values for UA.[33] Recently, in a cohort of 148 Hispanic children with overweight/obesity a prevalence of hyperuricaemia of 53% has been reported, and in the group of patients with hyperuricaemia worse metabolic parameters have been reported, such as higher waist circumference, blood pressure, and Homeostasis Model Assessment index. In this study, the level of UA-associated with less favourable metabolic features in obese children was 5.4 mg/dl.[34] According to these results, subsequent studies reported a strict association between high UA levels and MetS.[35] Pacifico et al.[36] demonstrated an independent association between UA concentrations and the presence of MetS in 120 obese children, and in this study increased UA levels were also associated with carotid atherosclerosis. Recent evidence suggests, in fact, an important pro-atherogenic effect of UA since many studies have associated serum UA concentrations with increased oxidative stress, endothelial dysfunction, inflammation, and hyperinsulinaemia. Therefore, hyperuricaemia should be considered in the scenario of MetS as an independent risk factor causing an increased cardiovascular risk in the paediatric setting also.

HYPOVITAMINOSIS D

Over the last decade, a growing body of observational data from several lines of scientific inquiry indicating a relationship of serum 1,25-dihydroxyvitamin D to chronic metabolic, cardiovascular, and neoplastic diseases has emerged.[37] Several evidences have demonstrated that vitamin D levels are important for optimal functioning of many organs and tissues throughout the body not related to calcium homeostasis.[37] Many evidences also reported an inverse association between fat accumulation and low vitamin D concentrations, ascribed not only to the sequestration of this fat-soluble vitamin in adipose tissue, but also to the negative effect of adipokines produced by adipocytes (i.e. leptin) on synthesis of the active form of vitamin D.[38,39]

In fact, low vitamin D levels have been linked with higher rates of MetS, hypertension, diabetes, myocardial infarction, peripheral arterial disease, and CVD.[37] As previously reported, although CVD events occur most frequently during or after the fifth decade of life, pathologic evidence suggests that precursors of CVD originate in childhood.[40] A significant association between vitamin D and cardiovascular risk factors in youth would suggest that the successful repletion of vitamin D has the potential to improve the cardiovascular risk profile during childhood and adolescence, and to lower the risk of developing CVD in adulthood. From these perspectives, in the last few years, several clinical paediatric trials using different dosage of vitamin D supplementation have been made in order to evaluate the metabolic effects of vitamin D repletion.[41] Moreover, a paediatric trial on the effect of vitamin not only on metabolic characteristics but also on histological features of NASH is now ongoing in the paediatric setting of Italy.[42] The now available results seem to demonstrate positive effects of vitamin D supplementation on metabolic impairments in children, but further studies are needed to identify the optimal dosage and timing of treatment.

CONCLUSION

In the last decade, following the epidemic trail of childhood obesity, an important increase in the prevalence of MetS has been observed in children and adolescents. Given the relatively recent occurrence of MetS in childhood, long-term follow-up studies are limited. However, it is conceivable that the metabolic derangement observed in obese children will have dramatic repercussions on their health earlier than that observed in adults, with a consequent worsening of the prognosis in terms of morbidity and mortality when they are still in youth.[43] Moreover, recent data reported that MetS and its consequences now represent the most part of healthcare expenditure in the United States.[44]

Despite the challenges and difficulties of clearly defining paediatric MetS, it is clear that the prevalence of the single component of MetS is increasing in paediatric settings and that these aspects identify youths at higher risk of developing metabolic impairments, and therefore CVD. In the recent years, several studies reported that MetS is actually associated with many clinical conditions besides CVD and T2DM, including chronic low-grade inflammation, oxidative stress, hyperuricemia, hypertension, dyslipidaemia, hyperandrogenism and polycystic ovary syndrome, NAFLD, OSAS, and certain forms of cancer.[45] Moreover, it has been reported that some of these, such as NAFLD and OSAS for their strict pathogenetic interplay with MetS, should be considered as the hepatic and respiratory manifestations of MetS, respectively. In fact, recent guidelines suggest screening patients with these conditions for MetS and vice versa. In our opinion, considering the close relationship between pathogenetic mechanisms of MetS, NAFLD, and OSAS, and the important and independent effect of these conditions on CVD and metabolic impairments, all actual definitions proposed for MetS in children are unsatisfactory. A careful revision of actual criteria for diagnosis of MetS, also including these emerging features of MetS, is needed. This revision could, in the near future, facilitate the development of specific screening programs for children. There is, in fact, a need for new and sensitive early screening methods that are able to provide a large amount of information about subjects at risk or who are presenting early signs of metabolic injuries. An early identification of these patients at higher risk could permit a prompt intervention in order to prevent or slow the progression of developing metabolic disorders in the initial stages of disease.

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