Metabolic syndrome during childhood

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Key words

Metabolic syndrome · Childhood · Overweight · Obesity · Type 2 diabetes · Paediatrics

Introduction

Obesity has become a global health problem and has been described as an epidemic. This obesity crisis also affects the child and adolescent populations, causing metabolic conditions which were only found in the adult population.

Overweightness and obesity have been shown to be associated with a wide range of chronic conditions, such as type 2 diabetes mellitus (T2DM), cardiovascular diseases (CVDs), and certain types of cancer (Al-Hamad & Raman, 2017) . The increased prevalence of overweightness and obesity has a major impact on the morbidity and mortality rates of the general population.

There is evidence that obesity is associated with metabolic syndrome (MS): a cluster of cardiovascular risk factors whose definition and diagnostic criteria in adults have varied in recent decades until a consensus was reached, which included the presence of three of the five proposed criteria (Alberti et al., 2009):

1. Elevated waist circumference according to population studies.
2. Systolic blood pressure greater than or equal to 130 mm Hg and/or diastolic blood pressure greater than or equal to 85 mm Hg; alternatively, antihypertensive drug treatment.
3. Fasting blood glucose levels greater than or equal to 100 mg/dL or treatment for hyperglycaemia.
4. Triglyceride levels greater than or equal to 150 mg/dL or drug treatment for hypertriglyceridaemia.
5. HDL levels lower than 40 mg/dL in males and lower than 50 mg/dL in females.

However, although there is consensus regarding the definition and diagnostic criteria of MS in adults, these criteria are not yet established for diagnosis in child and adolescent populations. Defining MS at these ages is even more complex due to racial and pubertal differences and the absence of cardiovascular events at these ages (DeBoer & Gurka, 2017; Maynard et al., 2001) .

In order to establish a definition of MS in children and young adolescents, reference values should be used based on sex, age, ethnicity, and maturation (Weiss, Bremer, & Lustig, 2013).

Depending on the different diagnostic criteria applied, the prevalence of MS has been reported to range between 6% and 39%. Despite this wide variability, all studies confirm that the prevalence of MS in children and adolescents has increased at the same time as the obesity epidemic (Bussler et al., 2017).

Despite the aforementioned difficulties, most authors agree on the essential defining components of this syndrome during childhood: glucose intolerance, central obesity, hypertension, and dyslipidaemia (Table 1) (Burguete-García, Valdés-Villalpando, & Cruz, 2014; Cook, Weitzman, Auinger, Nguyen, & Dietz, 2003; García García, 2015).

Table 1. METABOLIC SYNDROME CRITERIA IN CHILDREN AND ADOLESCENTS						
	AHA[a]	IDF[b]			ATP III[c]	WHO[d]
Age (years)	12-19	6-9	10-15	>15	12-19	
Waist circumference (WC) or BMI	Percentile ≥ 90th for age, sex, or ethnicity	Percentile ≥ 90th for age	Percentile ≥ 90th for age	Criteria for adults	WC p > 90 or BMI p > 85	BMI ≥ 95 for age or sex
Blood pressure (mm Hg)	Percentile > 90th for age, sex, and height	MS diagnosis is not contemplated	SBP ≥ 130 or DBP ≥ 85		SBP or DBP percentile > 90th	SBP *p* > 95 for age, sex, or height
Triglycerides	≥ 110		≥ 150		> 110 or p > 95	< 10 years old: > 105 ≥ 10 years old: > 136
HDL (mg/dL)	Percentile ≤10th for ethnicity or sex		≤ 40		< 40 or p < 5	< 35
Glucose homeostasis (mg/dL)	Fasting blood glucose ≥ 100		Fasting blood glucose ≥ 100 or reported 2TDM		Basal glucose > 100	Fasting hyperinsulinaemia or glucose intolerance
Total cholesterol						Percentile > 95th

AHA, American Heart Association; IDF, International Diabetes Federation; ATP III, Adult Treatment Panel III; WHO, World Health Organization; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; MS, metabolic syndrome; T2DM, type 2 diabetes mellitus.
[a] Three of the five criteria must be met for diagnosis.
[b] Central obesity (WC) and two of the remaining four criteria must be met for diagnosis.
[c] Three of the five criteria must be met for diagnosis.
[d] Three or more of the criteria must be met for diagnosis.

Additional components

In addition to the traditional components, recent associations have also been found between MS and non-alcoholic fatty liver disease, hyperuricaemia, sleeping disorders, vitamin D deficiency, thyroid dysfunction, polycystic ovary syndrome, and the existence of a chronic low-grade pro-inflammatory state in adults as well as in children and adolescents (Al-Hamad & Raman, 2017; Thompson et al., 2016).

Non-alcoholic fatty liver disease. In recent decades, its increased rates, together with increased obesity rates, have turned this clinical entity into the most common liver disease in the child population, with its prevalence doubling in the past 20 years. Although the specific role of MS in the pathogenesis of non-alcoholic fatty liver disease is unknown, there are numerous factors associated with its development: lipotoxicity, adipocytokines, uric acid, and vitamin D metabolism, among others. Its severity may range from simple hepatic steatosis to steatohepatitis with or without fibrosis. Some authors describe non-alcoholic fatty liver disease as the hepatic manifestation of MS, with insulin resistance being the main component of its pathogenesis (Atabek, Eklioglu, & Akyürek, 2014; Lonardo, Ballestri, Marchesini, Angulo, & Loria, 2015; Pacifico et al., 2011).

Hyperuricaemia and fructose. The high intake of sources of purine and large amounts of fructose is associated with an increase in serum urate. Nowadays, the Western pattern diet, with its high content in added sugars, is becoming globalised, with fructose being the principal component of these sugars. Some models have

shown that fructose-rich diets are associated with increased energy intake, decreased basal metabolic expenditure, excessive fat deposits, and insulin resistance, which suggests that they also play an important role in the obesity and T2DM epidemics.
Hyperuricaemia is associated with the physiopathology of arterial hypertension, T2DM, chronic kidney disease, and atherosclerosis, among others. Although hyperuricaemia is not among the diagnostic criteria of MS, it should be considered as an additional parameter in high-risk patients (Bussler et al., 2017; Weiss et al., 2013) .

Sleeping disorders. Short sleep duration on a regular basis (recommendations range between 9-12 hours for children aged 6-12 years old and between 8-10 hours for adolescents aged 13-18 years old) and insufficient or poor quality sleep in children and adolescents are related to elements associated with MS, such as increased blood pressure and insulin resistance, regardless of obesity.
In turn, obstructive sleep apnoea predisposes individuals to obesity due to daytime sleepiness or decreased activity. While little is known about the mechanisms that lead to this relationship between sleep and obesity, especially among children, there are reasons to suspect that increased stress and the irregular activity of hormones such as cortisol or leptin may play a significant role (Hart et al., 2013; Koren & Taveras, 2018).

Pathogenesis of MS

Insulin resistance

The combination of hypertension, dyslipidaemia, T2DM, and CVDs in adults suggests the existence of a common antecedent in the pathogenesis of MS, with the presence of insulin resistance being the most widely accepted.
Obesity favours the occurrence of this clinical entity due to the secretion of multiple substances from visceral fat: leptin, adiponectin, resistin...
Insulin resistance may be defined as a diminished response of tissues to insulin-mediated cellular actions, with reduced glucose metabolism in response to physiologically normal insulin levels (Ho, Garnett, & Baur, 2014; Serra et al., 2007).

Adipocytokines

Far from having only the function of storing energy, fat tissue is also an important endocrine organ. Adipocytes secrete several hormones that regulate lipid and glucose homeostasis. These proteins are generally called adipocytokines or adipokines because of their protein structure, which is similar to cytokines. These biomarkers are currently being studied for their involvement in the pathogenesis of MS.
Leptin. Leptin acts as a satiety regulator, with anorexigenic characteristics. It has been shown to be related to the degree of obesity, playing an important role in the control of fat distribution. Leptin probably plays an important role in high energy metabolism periods, such as puberty, ovulation, or pregnancy.
Adiponectin. Unlike most adipocytokines, adiponectin levels decrease with obesity. Adiponectin has anti-atherogenic, anti-diabetic, and anti-inflammatory functions, thus protecting against the development of T2DM or CVDs.
Adiponectin concentrations are inversely related to the degree of obesity, insulin resistance, and visceral adiposity. In turn, weight loss increases adiponectin levels.
Inflammatory cytokines. A growing body of evidence indicates that obesity is associated with a chronic low-grade pro-inflammatory state. In obese children and adolescents, there are higher levels of concentration of systemic markers of inflammation such as C-reactive protein (CRP), interleukin-6 (IL-6), or tumour necrosis factor-alpha (TNF), affecting glucose metabolism through interactions with the expression of insulin receptors, among others (Bussler et al., 2017).

Epigenetics and gestational programming

Epigenetic mechanisms are understood as mediators, as they connect early exposure to the environment with changes in the expression of gene that can alter growth and development. The concept of gestational programming means that the nutritional, hormonal, and metabolic environment provided by the mother during pregnancy can alter the cellular responses and gene expression of the foetus which will ultimately impact its later metabolism and physiology.

Among the most important factors that can alter gene expression, the following have been identified:

- Low or excessive birth weight is associated with an increased risk of obesity in adulthood.
- Maternal obesity during pregnancy, or weight gain during pregnancy, is associated with heavier neonates and with an increased risk of obesity and diabetes in adulthood.
- Gestational diabetes or maternal smoking also predispose the foetus to an increased risk of obesity in adulthood.

Post-birth factors such as breastfeeding, weight gain in the first year of life, or the presence of adequate vitamin D levels would also be programming factors affecting the risk of obesity, MS, and diabetes in adults (Boney, Verma, Tucker, & Vohr, 2005; Crespo, Perera, Lodeiro, & Azuara, 2007; Cu et al., 2015; More et al., 2006).

The exact mechanisms by which this alteration in gene expression occurs are yet unknown. However, recent, important findings point to the role of microRNAs, which would act as key regulators of metabolism(Chang & Neu, 2015; Fischer-Posovszky et al., 2016; Stone, Schetzina, & Stuart, 2016).

Dietary factors and physical activity

While the main approach to obesity has always been focused on the total amount of calories ingested, there is increasing evidence to suggest that the quality of those calories plays a major role in the pathogenesis of MS.

Due to its higher energy density, high palatability, and easier storage, fat is considered to be more obesogenic than other macronutrients. However, multiple studies have shown that low-fat diets are no more effective than diets based on calorie restriction when the variable in question is long-term weight loss. These factors are compounded by the easy access to this type of low-cost and high-energy-density products, available even in school cafeterias, and by the use of advertising targeting the paediatric population.

The historical decline in fat consumption has been coupled with an increase in total calorie intake, mostly in the form of carbohydrates, such as added sugars. Among the products that provide the most calories in the form of carbohydrates are sugary drinks, whose consumption is directly related to the presence of adiposity and obesity (Seth & Sharma, 2013; Stone et al., 2016; Whitaker, Wright, Pepe, Seidel, & Dietz, 1997).

The decrease in physical activity is also one of the changes in lifestyle that have influenced the current situation of obesity in recent decades, i.e. the transition from outdoor activities to indoor leisure using electronic devices: television, video games, or the Internet (Gupta, Shah, Nayyar, & Misra, 2013).

Treatment

Early detection of risk factors, screening for metabolic disorders, and identifying new therapeutic measures are the main and most crucial objectives in order to reduce the morbidity and mortality rates linked to MS (Thompson et al., 2016).

Regardless of the role of genetics in MS, attention should be paid to predisposing factors such as insufficient physical activity, the social and physical environment, or the diet of the child or adolescent (Lama, 2006).

The identification of these factors should be used for screening high-risk patients, including the measuring of blood pressure, body mass index, waist circumference, lipid profile, and serum glucose.
Nowadays, there is no specific treatment available. However, all guidelines agree on the importance of life-style changes, which mainly consist of following a nutrition programme and doing regular physical exercise, with no focus on weight loss (Table 2) (García García, 2015; Gupta et al., 2013).

Table 2. Recommendations for eating and exercise habits.

- Eating with the family.
- Eating slowly and chewing properly.
- Restricting food and eating to the dining room and the meal times established.
- Avoiding sugary drinks and soft drinks.
- Reducing the intake of saturated fats and trans fats.
- Reducing the intake of simple carbohydrates (refined sugars), which have a high glycaemic index.
- Increasing the intake of fruits, vegetables, pulses (legumes), and wholegrain.
- Not using food as a reward, nor withdrawing it as a punishment.
- Avoiding eating while watching TV or using electronic devices.
- Taking walks in nearby parks.
- Using the stairs instead of the lift.
- Avoiding the use of screens before 2 years of age, and after reaching this age, using them only for up to 2 hours a day.
- Having breakfast every day.
- Avoid eating out, especially in fast food restaurants

There is little experience in the use of pharmacological measures in children and adolescents. Some studies suggest that metformin may improve insulin sensitivity and BMI in non-diabetic adolescents, although other studies contradict its effectiveness. Therefore, the use of this drug is still controversial. Other drugs proposed, but also lacking evidence to support them, would be lipolytics such as orlistat or sibutramine (Serra et al., 2007).
As a last resort and in individualised cases, some societies might consider surgical treatment such as bariatric surgery, with much stricter criteria for the paediatric population than for the adult population (Inge et al., 2004)

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Conclusions

MS is a complex clinical entity that has been shown to be correlated with obesity, while remaining a different entity from it. The fact that thin children may develop MS suggests that, even though obesity and age contribute to the development of this syndrome, they are unlikely to be onset factors of this syndrome.
The environment is more likely to be a major factor, even before birth, due to programming factors and epigenetics. Among the responsible factors in this environment, special emphasis should be placed on the global incorporation of the typical Western pattern diet.
An agreement is expected to be reached in the future on the definition of the diagnostic criteria at the paediatric age that would facilitate the better identification of patients.

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