Metabolic syndrome: identifying the risk factors

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Abstract

Objectives: To discuss the metabolic syndrome and identify its risk factors, including in the pediatric age group.

Sources: Indexed review articles.

Summary of the findings: The metabolic syndrome is characterized by insulin resistance and the presence of risk factors for cardiovascular diseases and diabetes mellitus type 2. Consensus has not yet been reached on its diagnostic criteria. This review presents diagnostic criteria defined by the American Heart Association (US National Cholesterol Education Program), the American Association of Clinical Endocrinologists, the World Health Organization and the International Diabetes Federation and discusses the possibilities of applying them to children. Pathophysiologic features of the syndrome are also covered, principally those related to the perinatal period and childhood.

Conclusions: The metabolic syndrome is being diagnosed with ever greater frequency, principally during adolescence. Lifestyle changes, such as to diet and level of physical activity are fundamental to prevention. Treatment with medication and, in extreme cases, with surgery should also be considered, depending on severity and age.

J Pediatr (Rio J). 2007;83(5 Suppl):S204-208: Metabolic syndrome, diabetes mellitus, cardiovascular risk, dyslipidemia.

Metabolic syndrome: definitions

Metabolic syndrome is characterized by insulin resistance and the presence of risk factors for cardiovascular diseases and diabetes mellitus type 2.[1] During the 1980s, Reaven,[2] observed that dyslipidemia, arterial hypertension and hyperglycemia were very often found in combination in a single patient and that they indicated increased cardiovascular risk; a condition he named Syndrome X. Since then, many different definitions of metabolic syndrome have emerged. Consensus has not yet been reached on the diagnostic criteria for metabolic syndrome. Table 1 below compares the criteria from the leading institutions that have released publications on the subject.

In addition to these criteria, which are used to diagnose the metabolic syndrome, other metabolic abnormalities, such as increased fibrinogen and plasminogen activity factor, hyperuricemia, increased C-reactive protein, hyperhomocysteinemia, increased TNF-α expression and reduced adiponectin levels, are frequently present.[1]

There is no definition of the metabolic syndrome in childhood that is accepted by the entire scientific community.[1]

Cook et al.[3] adapted the NCEP criteria and proposed a definition of pediatric metabolic syndrome based on the presence of three out of the following criteria: waist circumference greater than or equal to the 90th percentile, fasting glycemia greater than or equal to 110 mg/dL, triglycerides greater than or equal to 110 mg/dL, HDL-cholesterol less than 40 mg/dL and arterial blood pressure greater than or equal to the 90th percentile. Furthermore, measurement of waist circumference in children is not standardized. Some authors have standardized measurements by age and define measurements above the 90th percentile as elevated.[4]

Pathophysiology

Epidemiological studies suggest that there is a relationship between low birth weight, especially in small for gestational age infants, and developing metabolic syndrome in adulthood. According to the World Health Organization,[5] low birth weight is the term that should be used to describe infants born weighing less than 2,500 grams. The definition of small for gestational age (SGA), has greater scope and takes into consideration weight and length, according to sex and gestational age.[6] Infants born below -2 standard deviations are

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Table 1 - Definitions of metabolic syndrome

IDF	NCEP	WHO	AACE
Diagnosed if glycemia is abnormal and 2 further criteria are present	Diagnosed if 3 out of 5 criteria are present	Diagnosed if glycemia is abnormal and 2 further criteria are present	Indicates risk factors
Fasting glycemia 100-125 mg/dL or DM2	Glycemia 110-125 mg/dL	Glucose intolerance, DM2 or insulin-resistance due to HOMA-IR	Fasting glycemia 110-125 mg/dL or > 140 mg/dL 2 hours after oral GTT
WC ≥ 94 cm MWC ≥ 80 cm W	WC > 102 cm MWC > 88 cm W	BMI > 30 and HWR > 0.9 M and > 0.85 W	BMI ≥ 25 and WC >102 cm M and WC > 88 cm W
Tg ≥ 150 mg/dL or HDL< 40 M and < 50 W	Tg ≥ 150 mg/dL or HDL< 40 M and < 50 W	Tg ≥ 150 mg/dL or HDL< 35 M and < 39 W	Tg ≥ 150 mg/dL or HDL< 40 M and < 50 W
On treatment for SAH or BP ≥ 130x85 mmHg	BP ≥ 130x85 mmHg	On treatment for SAH or BP ≥ 160x90 mmHg	BP ≥ 130x85 mmHg
		Microalbuminuria ≥ 20 mcg/min	

AACE = American College of Endocrinology/American Association of Clinical Endocrinologists; BMI = Body mass index; BP = arterial blood pressure; DM2 = diabetes mellitus type 2; GTT = oral glucose tolerance test; HOMA = homeostasis model assessment; HWR = hip:waist ratio; IDF = International Diabetes Federation; M = men; NCEP = US National Cholesterol Education Program; SAH = systemic arterial hypertension; Tg = triglycerides; W = women; WC = waist circumference; WHO = World Health Organization.

defined as SGA, which makes it easier to identify in newborns who have been affected by some degree of fetal suffering. It is estimated that 2.3% to 10% of newborn infants are SGA. The majority of these children manage to attain normal growth within the first 2 years of life, known as catch-up growth. Being SGA brings with it a risk of metabolic syndrome in adulthood, especially for those children who recover rapidly soon after birth. In contrast, absence of catch-up growth is a cause of short stature and many psychological consequences during adolescence and adulthood.[7]
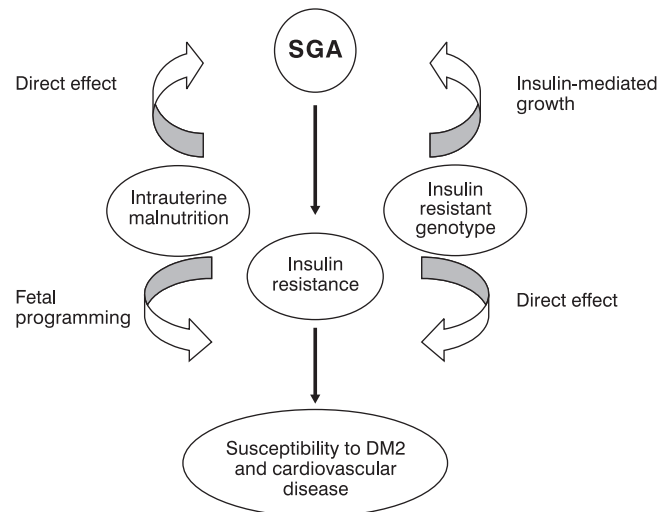
The causative mechanisms of the relationship between SGA and the metabolic syndrome remain obscure, but, currently, the hypothesis of fetal programming, by which fetal adaptation to exposure to nutrient scarcity results in a failure to adapt to exposure to an abundance of nutrients, is widely accepted.[8,9] This hypothesis, also known as the Barker Hypothesis,[10] postulates that certain structures of the organs have their functions programmed during embryonic and fetal life. This programming will determine the balance (set point) of adult physiological and metabolic responses.[8] Barker et al. found that the prevalence of insulin resistance at 50 years of age was 10 times greater among individuals who had been born weighing less than 2.5 kg.

In contrast, Neel[11] and Hattersley & Tooke,[12] have offered a different hypothesis for the emergence of metabolic syndrome in adulthood. For these authors, insulin resistance is determined genetically and the insulin resistant genotype is the factor that determines low birth weight, glucose intolerance and arterial hypertension. The criticism that some authors[7] have made of the work by Barker et al. is that the weight assessed was that achieved by 1 year of age and not at birth. Furthermore, since ultrasound was not used to assess gestational age, it is possible that some individuals classified as low weight were merely premature, and not SGA. Other authors have been unable to reproduce Barker's results and, therefore, further studies are needed.[7] It is imperative that these studies employ standardized methods to assess gestational age, such as ultrasound.[7] Figure 1 summarizes these theories.

Size at birth is fundamentally dependent on placental function and duration of pregnancy. The placenta is the point of interchange between the maternal and fetal metabolisms and regulates fetal growth by means of the secretion and metabolism of growth hormones, such as IGF (insulin growth factor), and of glucocorticoids.[7]

A variety of situations, such as malnutrition, infection, maternal arterial hypertension, gestation or diabetes, inflammation and hypoxia are responsible for exposing the fetus to adipokines, cytokines and growth factors and to hypersecretion of corticoids, hyperinsulinemia, hyperleptinemia and IGF-axis abnormalities.[13] This environment causes changes to metabolism, the immune system, the vascular system, hemodynamics, the renal system and growth. Some authors believe that increased oxidative stress suffered in these situations is directly related to modulation of genes related to the action of insulin and modulation of arterial blood pressure, and, therefore, may be one of the mechanisms behind the emergence of the metabolic syndrome in adulthood.[14] Infants born at high weights are also at increased risk of metabolic syndrome, although for low birth weight babies the risk is much greater. There are currently several ongoing prospective and

Adapted from Murphy et al.[7]

Figure 1 - Hypotheses to explain the relationship between SGA and metabolic syndrome

randomized studies attempting to prevent oxidative stress during gestation.[14]

In pregnancies where uterine growth is restricted, there is increased placental vascular resistance, which in turn increases afterload on the fetal heart, which may impact on fetal programming for cardiovascular disease. A deficiency in the action of the placental enzyme 11βHSD 2 (hydroxysteroid dehydrogenase type 2) provokes increased exposure to maternal cortisol, which may program the fetus for arterial hypertension and metabolic diseases. The placenta functions as a sensor of nutritional status, regulating nutrient transport in accordance with supply. This is why the placenta plays a fundamental role in fetal programming. Changes to the maternal compartment can cause mitigation of placental genes, increasing oxidative stress and modifying placental function.[15]

Newborn infants subjected to a hyperinsulinemic uterine environment also exhibit an increased risk of developing metabolic syndrome in adulthood. Boney et al.[16] assessed the development of metabolic syndrome in individuals who were large for gestational age (LGA) and appropriate for gestational age (AGA). The study followed-up 84 children in the LGA group and 95 in the AGA group, at ages 6, 7, 9 and 11 years, the mothers of whom did or did not have a history of gestational diabetes. The children were subdivided into four groups: LGA with control mothers, LGA with mothers with gestational DM, AGA with control mothers and AGA with mothers with gestational DM. Anthropometric and biometric measurements were taken at 6, 7, 9 and 11 years. Metabolic syndrome was defined based on presence of obesity (BMI > 85th percentile), systolic or diastolic arterial blood pressure above the

95th percentile, fasting glycemia above 110 mg/dL and postprandial glycemia above 140 mg/dL, triglycerides above the 95th percentile by age and HDL-cholesterol below the 5th percentile by age. The prevalence of more than two components of the metabolic syndrome at any given time was 50% for LGA group/mothers with gestational DM, 29% for LGA group/control mothers, 21% for AGA group/mothers with gestational DM and 18% for AGA group/control mothers. The status of LGA and maternal obesity, individually, doubled the risk of developing metabolic syndrome. The risk of developing metabolic syndrome did not differ between the LGA and AGA groups, but was increased in the LGA group with mothers with gestational DM.

More recently, some authors hypothesize that one important determinant of the emergence of metabolic syndrome in adulthood is rapid weight gain, especially fat, during the postnatal period, which is very common among SGAs with catch-up growth. From this fact it can be concluded that the Barker hypothesis could be applied to the postnatal period.[6]

Accumulation of adipose tissues, particularly in the abdominal region, is fundamental to triggering off the metabolic syndrome. There is an association between adipose tissue and the principal inflammatory cells, leading to an increase in production of inflammatory mediators and increased liberation of free fatty acids, the effects of which are felt both in the Langerhans beta islet cells and their receptors and also in the vascular wall. Studies with children and adolescents have confirmed that these phenomena begin early on.[17]

Metabolic syndrome in the pediatric age group

According to the NCEP diagnostic criteria, the prevalence of metabolic syndrome among American adults was 6.7% for

the age group from 20 to 29 years, 43.5% for 60 to 69 years and 42% among those more than 70 years old.[18] Although it is more common among the elderly, the incidence rate of metabolic syndrome at earlier ages has been increasing, especially due to lifestyle changes and the increase in obesity.[19] The prevalence of metabolic syndrome among American adolescents is 4.8%, varying depending on age, sex, ethnic origin, social strata and presence of obesity.[20]

Insulin resistance is the pathophysiologic basis for the emergence of the metabolic syndrome. Some prospective studies, like the Cardiovascular Risk in Young Finns Study and the Bogalusa Heart Study have demonstrated that hyperinsulinemia and, in particular, childhood obesity, are risk factors for the metabolic syndrome and that early hyperinsulinemia precedes the emergence of the metabolic syndrome, even in childhood. Childhood obesity, defined as a BMI greater than the 95th percentile for age, after 3 years, exhibits an important association with obesity in adulthood, and its prevalence has tripled over the last 3 decades. Insulin resistance can be assessed in a variety of ways and, in clinical practice, insulinemia and the HOMA index (homeostasis model assessment) are widely used. However, these methods have not yet been standardized for children and adolescents. For example, Goran & Gower[21] established insulinemia cut-offs, according to puberty stage: 15 mcU/l for prepubescents, > 30 mcU/l for pubescents and > 20 mcU/l for postpubescents. Tresaco et al.[22] defined a cutoff of 3 on the HOMA-IR index, in Spanish children.

Glucose intolerance and insulin resistance are often found among obese children and adolescents. The individuals who are at greatest risk of developing diabetes mellitus type 2 those who are obese and those who have acanthosis nigricans and a family history. In general, after ten years of age, adolescents develop this type of diabetes, possibly because the hormonal changes of puberty contribute to exacerbation of the disease. Sinha et al.[23] diagnosed 4% of obese adolescents as having diabetes mellitus type 2. In general, diabetic patients exhibit other cardiovascular risk factors, such as arterial hypertension, present in 17 to 32%, hypertriglyceridemia, present in 4 to 32%, and sleep apnea, present in 6% of these patients.[24]

Studies like the Bogalusa Heart Study and the Muscatine Study have demonstrated that obesity in adolescents is correlated with a proatherogenic dyslipidemic profile, with increased LDL cholesterol, potentiating the cardiovascular risk, itself already elevated due to the obesity.[25]

Treatment

Weight loss has a major impact on the metabolic syndrome. Published data demonstrate that a reduction of 7% to 10% of initial weight is enough to provoke improvements in waist circumference, lipid profile and glycemia.[26]

It is of fundamental importance to treat childhood obesity, and, in order that this treatment is successful, it is fundamental to involve the child/adolescent, their family and their social environment, in order to encourage lifestyle changes.

Changes aimed at achieving healthy diet must be embarked on by the entire family, with the intention of increasing the consumption of fruit, vegetables, skimmed milk products and water, two fraction feeding and reduce consumption of fried food, pastries, sweets and processed meat products.

Promotion of physical activity, whether programmed or not, reducing the child's idle time, especially in front of the television and computer, is another crucial point. The entire family should also be involved in this process.

In pediatrics, pharmacological treatment of obesity should be restricted to cases that are most resistant to clinical treatment and of the greatest severity. In the United States, only sibutramine and orlistat have been approved, for use with children over 12 years of age.

Metformin is indicated for children with glucose intolerance or diabetes mellitus type 2. In these patients the drug has an anorexigenic effect, reducing glucose and insulin levels and improving the lipid profile.[27]

Hypertension and dyslipidemia should also be treated with lifestyle changes and drugs, depending on the severity of the case.

Bariatric surgery for the treatment of adolescent obesity is an extremely invasive procedure and it can only be indicated in extremely restricted circumstances in this age group. The American Pediatric Surgical Association Clinical Task Force on Bariatric Surgery recommends that adolescents may be candidates for the procedure if they have a BMI greater than 50, or greater than 40 and associated with comorbidities (sleep apnea, diabetes mellitus type 2), are at a minimum Tanner puberty stage of III, a multidisciplinary team has failed to achieve a response after at least 6 months' treatment, medical and psychological assessments have been completed, there are severe problems socializing, there is good family support and if they are over 13 years old and have the capacity to take informed decisions.[28]

In summary, treatment and prevention of childhood obesity have become a public health priority. Acquisition of excessive fat during the postnatal period is related to insulin resistance in adulthood and breastfeeding may prevent this obesity.[7] Appropriate nutrition and increase physical activity, while still in childhood, are, therefore, important elements in prevention of the metabolic syndrome and, consequently of cardiovascular diseases in adulthood.

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