Novel Insights in the Metabolic Syndrome in Childhood and Adolescence

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Abstract

Metabolic syndrome (MetS) is recognized as an escalating major health risk in adults as well as in children and adolescents. Its prevalence ranges from 6 to 39% depending on the applied definition criteria. To date, there is no consensus on a MetS definition for children and adolescents. However, most authors agree on essential components such as glucose intolerance, central obesity, hypertension, and dyslipidemia; each representing a risk for cardiovascular disease. Recently, associations between MetS and non-alcoholic fatty liver disease, hyperuricemia, and sleep disturbances have emerged. Biomarkers like adipocytokines are a subject of current research as they are implicated in the pathogenesis of the MetS. Epigenetics and gestational programming, especially the role of microRNA, comprise a novel, rapidly developing and promising research focus on the topic of MetS. MicroRNAs are increasingly valued for potential roles in the diagnosis, stratification, and therapeutics of MetS. Early detection of risk factors, screening for metabolic disturbances, and the identification of new therapies are major aims to reduce morbidity and mortality related to MetS. Dietary modification and physical activity are currently the only adopted treatment approaches. Pharmacological therapies and bariatric surgery are still contradictory and, therefore, are only recommended in selected high-risk cases.

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Introduction

During the last 20 years, the proportion of overweight and obese children and adolescents has significantly increased across most countries. Although the prevalence of obesity at a young age has stabilized or even slightly declined in some countries, the number of adolescents with obesity is still increasing [1]. In 2006, the German Children and Adolescent Health Survey (KIGGS) estimated that 15% of all children and adolescents between the ages of 3 and 17 years were overweight, and 6.3% were obese. More recent studies confirm the same trend [2].

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Table 1. Diagnostic criteria for the metabolic syndrome in children and adolescents

Authors [Ref.], year	Criteria for MetS (3 or more criteria fulfilled?)
Cook et al. [24], 2003	WC ≥90th pct., SBP or DBP ≥90th pct., TG ≥1.24 mmol/L or HDL-C ≤1.03 mmol/L, fasting glucose ≥6.11 mmol/L
Cruz and Goran [105], 2004	WC >90th pct., BP ≥90th pct., TG ≥90th pct. or HDL-C ≤10th pct., glucose intolerance (ADA criteria)
Weiss et al. [106], 2004	BMI *z*-score ≥2.0, BP >95th pct., HDL-C <5th pct., TG >95th pct., glucose intolerance (ADA criteria)
Viner et al. [107], 2005	BMI ≥95th pct., SBP ≥95th pct., TG ≥11.69 mmol/L or HDL-C ≤0.91 mmol/L or total cholesterol ≥95th pct., insulin ≥104.2 pmol/L or fasting glucose ≥5.55 mmol/L
Zimmet et al. (IDF) [108], 2007	WC ≥90th pct., SBP ≥130 mm Hg or DBP ≥85 mm Hg, TG ≥1.69 mmol/L or HDL-C ≤1.03 mmol/L, fasting glucose ≥5.55 mmol/L
de Ferranti et al. [109], 2004	WC >75th pct., BP >90th pct., TG ≥1.1 mmol/L, HDL-C <1.17 mmol/L (girls), HDL-C <1.3 mmol/L (boys), fasting glucose ≥6.1 mmol/L
Ahrens et al. [12], 2014	Monitoring level (action level) WC ≥90th (95th) pct., SBP/DBP ≥90th (95th) pct., TG ≥90th (95th) pct. or HDL-C ≤10th (5th) pct., HOMA-IR ≥90th (95th) pct. or fasting glucose ≥90 (95th) pct.

MetS is defined if 3 or more of the abovementioned criteria are fulfilled. MetS, metabolic syndrome; WC, waist circumference; pct., percentile; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure; ADA, American Diabetes Association; HOMA-IR, homeostatic model assessment of insulin resistance.

This epidemic of childhood obesity is responsible for the occurrence of metabolic diseases, previously confined to obese adults [3]. Obesity represents a major cardio-metabolic risk and is strongly linked to co-morbidities such as hypertension, hyperlipidemia, hyperinsulinemia, type 2 diabetes, and non-alcoholic fatty liver disease (NAFLD) [4]. The constellation of these morbidities is commonly known as the metabolic syndrome (MetS) [4]. Several epidemiological studies reported that MetS is not only a simple cluster of several metabolic complications related to the presence of adipose tissue, but it is also an important risk factor to develop cardiovascular diseases [5]. Multiple meta-analyses calculated that MetS is associated with a 2-fold increase in cardiovascular outcomes and a 1.5-fold increase in all-cause mortality [6].

During the last years, there has been a big scientific interest in the definition of the criteria for MetS in children as well as in adults. A lot of uncertainty exists regarding the diagnosis of MetS in the pediatric population, mainly due to the different and conflicting definitions proposed. Herein, we give a brief overview of the main diagnostic criteria of MetS in children and adolescents (Table 1). We aim to focus the attention on some new concepts in terms of MetS in children and adolescents spanning from the definition to the diagnosis.

Definition and Prevalence of the MetS in Children and Adolescents

The concept of MetS emerged in 1988, when Gerald Reaven, an American endocrinologist, defined this condition for the first time in obese adults as "a link between insulin resistance, hypertension, dyslipidemia, impaired glucose tolerance and other metabolic abnormalities associated with the risk for atherosclerotic and cardiovascular diseases" [7]. Since then, the concept of MetS rapidly spread in the medical community, though our understanding of the pathophysiology of its development is still limited and the sets of the specific metabolic parameters considered for the definition remain controversial. However, all diagnostic criteria agreed on the essential components: glucose intolerance, central obesity, hypertension, and dyslipidemia.

Several authors considered the necessity of having an adapted definition for MetS in children and adolescents. To obtain definitions for the pediatric population, the well-known age- and sex-dependent anthropometric, metabolic, and cardiovascular parameters need to be considered. Therefore, it is important to employ age- and sex-specific cutoffs as reference values. Since 2003, several definitions for pediatric MetS have been proposed

(Table 1). In 2007, Reinehr et al. [8] compared different MetS definitions in a cohort of 1,205 children and adolescents. The prevalence of MetS differed significantly (ranged from 6 to 39%) depending on the definition criteria applied. In accordance with these definitions, only 2% of the children fulfilled the criteria of MetS. Despite these variations in prevalence reflecting the different MetS definitions, all studies confirmed that the prevalence of MetS in children and adolescents has increased, paralleling the epidemics of obesity in this age group.

Most of the recent MetS definitions have limitations. For instance, during recent years, associations between MetS and NAFLD, hyperuricemia, sleep apnea, and several other potential biomarkers, useful for early identification of patients with a higher cardiometabolic risk, have been described. However, these are still not considered when MetS is defined. Furthermore, it has been described that many of the metabolic and cardiovascular complications of obesity were already detectable in prepubertal children [9–11]. Therefore, MetS definition must be extended to prepubertal children, which is not currently the case. A promising new approach was applied by Ahrens et al. [12], who developed a quantitative MetS score using z-score standardized values for all different parameters. Furthermore, to help pediatricians to stratify children who need strict monitoring and those who merit an urgent intervention, the authors proposed two different cutoffs for the different parameters included in the score. Current data about the rate of MetS in the pediatric population and the track of MetS from childhood to adulthood should lead to a wider application of screening and intervention programs.

Additional Components of the MetS in Children and Adolescents

In addition to the traditional components, NAFLD, hyperuricemia, and sleep disturbances have been frequently discussed as additional components of MetS. Several recent studies identified these derangements as strong risks for metabolic impairment and as early signs of cardiovascular diseases in adults as well as in children. The pathophysiological mechanisms of these mentioned conditions are mainly characterized by the effects of obesity and insulin resistance on different organs.

Non-Alcoholic Fatty Liver Disease

During the last decade, studies have shown that in parallel with the increased prevalence of obesity in the pediatric population, NAFLD has become the most common form of hepatic disease during childhood [13]. In fact, its prevalence has more than doubled over the past 20 years [14]. The overall prevalence in children has reached approximately 10%, including up to 17% in teenagers and 40–70% among obese children and adolescents [15]. The development of NAFLD is strongly influenced by age, sex, race, and ethnicity [13, 14, 16]. Different epidemiological studies reported that NAFLD appears twice as often in boys than in girls [17]. In adults, it is more prevalent in American Hispanics (45%) compared to Caucasians (33%) or African Americans (24%) [18]. The physiologic hepatic lipid content is about 5 %. Therefore, fat infiltration higher than 5% in the liver, confirmed by liver histology and in the absence of excessive alcohol intake, viral, autoimmune, or drug-induced liver disease, is defined as hepatic steatosis [19, 20]. NAFLD encompasses a large spectrum of conditions ranging from simple hepatic steatosis to steatohepatitis (NASH) with or without fibrosis. NASH could deteriorate to hepatic cirrhosis or other related complications like hepatocellular carcinoma and portal hypertension [21]. However, only a minority of the affected patients progress to NASH and cirrhosis, suggesting an important interplay between genetic predisposition and environmental factors. Early theories for the pathogenesis of NAFLD and NASH were based on a so-called "two hit hypothesis" [22]. The "first hit," hepatic triglyceride accumulation, or steatosis, increases the susceptibility of the liver to injury mediated by the "second hit." The "second hit" includes inflammatory cytokines/adipokines, mitochondrial dysfunction, and oxidative stress, which lead to steatohepatitis and/or fibrosis. More recent studies suggest that the "two hit hypothesis" may be an oversimplification of the underlying pathogenic mechanisms. Therefore, it is more appropriate to consider a "multiple hits hypothesis," which accounts for additional factors that undoubtedly play important roles in the pathogenesis of NAFLD. Lipotoxicity, adipocytokines, altered mitochondrial permeability, uric acid, endogenous alcohol production, stellate cell activation, gut-derived microbiome, trace elements, the ghrelin-ghrelin O-acetyltransferase system, vitamin D metabolism, or obstructive sleep apnea (OSA) syndrome have all been reported to interact with persistent liver injury, yet their roles in the development of NASH are not completely understood [15, 23]. NAFLD and MetS are strongly related, such that NAFLD has been described as the hepatic manifestation of MetS [24–26] with insulin resistance being the driver of pathogenesis. A recent study reported that 66% of the investigated children with biopsy-proven NAFLD had MetS.

More specifically, 63% had hypertriglyceridemia, 45% had low HDL-cholesterol, 40% suffered from hypertension, and 10% presented an impaired glucose tolerance. In addition, an association between the histologic severity of the disease and some components of MetS has been reported [27]. Despite recent advances in the understanding of pediatric NAFLD, the natural history and the consequences of this condition are still unclear [28].

Hyperuricemia: The Role of Fructose and Uric Acid in MetS

Uric acid is the end-product of the purine metabolism in humans. High ingestion of purine sources or a high intake of fructose are directly related to an increase of serum urate [29] which can cause gout and urolithiasis. Hyperuricemia has also been implicated in the pathophysiology of hypertension, chronic kidney disease, congestive heart failure, type 2 diabetes, and atherosclerosis. In our contemporary world, the intake of added sugars has increased and fructose represents the major component of these sugars. A key difference between glucose and fructose is their initial metabolism. Fructose is phosphorylated to fructose-1-phosphate, inducing intracellular phosphate depletion. This lower intracellular phosphate reserve inactivates adenosine monophosphate deaminase, which converts adenosine monophosphate into inosine monophosphate and inosine and to uric acid. Intracellular uric acid is then secreted into circulation [30]. Stanhope et al. [31] compared the effects of fructose- and glucose-sweetened beverage consumption in overweight and obese adults and they noted that dietary fructose increases hepatic de novo lipogenesis, promotes dyslipidemia, decreases insulin sensitivity, and increases visceral adiposity. Many studies described correlations between serum uric acid levels, MetS, and several of its components in children and adolescents [32–34]. For instance, every 1 kg/m^2 increment in BMI is associated with a 5.74 μmol/L increase of serum uric acid levels [35]. These results were further supported by Jones et al. [36], Pan et al. [37], and Viazzi et al. [38]. Moreover, carotid intima media thickness, a well-established cardiovascular risk factor, is significantly related to uric acid levels [39]. Two distinct mechanisms were proposed to explain this link. First, hyperuricemia can induce endothelial dysfunction via insulin-stimulated nitric oxidative-induced vasodilation. This theory suggests a bidirectional causal effect between hyperuricemia and hyperinsulinemia. The second hypothesis considers the role of xanthine, produced in the reactive oxygen species reaction, which contributes to oxidative and inflammatory alterations in adipocytes [29].

Lanaspa et al. [30] described that intracellular uric acid can induce inflammatory effects and oxidative stress in adipocytes and in vascular cells. It is noteworthy that, apart from its pro-oxidative effect, uric acid also plays an essential role in humans as the major extracellular antioxidant of blood [29]. Data regarding the association between uric acid and NAFLD are still inconsistent [34, 40, 41]. Uric acid is not yet included in the diagnostic criteria of MetS, though it is an important parameter from the pathophysiological point of view [26] and should be considered as additional diagnosis parameter [33].

Sleep Restriction, Sleep Architecture, OSA, and Cardiometabolic Risk in Children

There is increasing recognition that disturbances of sleep are risk factors for obesity and cardiometabolic disturbances [42]. The associations between sleep parameters and metabolic risk factors are more conflicting in children and adolescents compared to adults. Nonetheless, chronic short sleep duration (less than 8 h) in children and adolescents as well as poor or insufficient sleep quality are associated with elements of MetS such as increased blood pressure, probably driven by blunting of the usual nocturnal dip in blood pressure, or insulin resistance in children independent of obesity [43]. A recent study revealed that acute sleep restriction increases dietary intake in preschool-aged children [44, 45]. In addition, Wang et al. [45] demonstrated that both short and overlong sleep duration are associated with a higher risk of overweight/obesity in preschool-aged children and with an impairment of their lipid profile. Detailed pathophysiological pathways for these associations are unknown at present, but leptin levels and different compositions of diets seem to play a role [42].

OSA is a very common condition among obese adults and children. OSA is characterized by repetitive pharyngeal narrowing and closure during sleep [46], snoring, and frequent nocturnal awakenings [15], leading to recurrent oxyhemoglobin desaturation, sleep fragmentation, and hypercapnia [42]. It is well recognized that obesity and specific fat depots (upper airway, tongue, and abdominal adipose deposition) predispose to OSA. Moreover, OSA may also predispose to obesity due to daytime somnolence, decreased activity, and decreased sleep duration, as well as due to neurohumoral changes, such as resistance to the anorexigenic hormone leptin. OSA is associated with MetS in children and adolescents. A study reported that MetS is present in 16% of children without OSA, but in 59% of those with OSA. Likewise, all single components of MetS are associated with OSA [42].

The Role of Adipocytokines in the Pathogenesis of Metabolic Disturbances

For decades, white adipose tissue was considered as a passive storage organ; however, it is now widely recognized as an important endocrine organ. It secretes several hundreds of different factors, collectively termed adipocytokines. This includes classical hormones (such as leptin), growth factors (e.g., insulin-like growth factor-1 and platelet-derived growth factor), inflammatory mediators, enzymes, and metabolites (such as fatty acids). Thus, white adipose tissue is in permanent crosstalk influencing other organ systems through the production of these adipocytokines [47]. Altered levels of adipocytokines have been demonstrated as a common feature not only in obesity, but also in NAFLD and MetS in children and adolescents [48, 49]. Apart from that, adipocytokines have been described to play a role in growth, reproduction, bone metabolism, immune response, cancer development, and many other important biological processes [48].

In the following sections, we give a brief overview of the main adipocytokines and emphasize on their involvement in the pathogenesis of metabolic disturbances. Table 2 summarizes the current knowledge on adipocytokines in association with childhood obesity and its complications.

Selection of Relevant Adipocytokines

Leptin acts as an afferent satiety signal affecting central circuits in the hypothalamus, thereby suppressing food intake and stimulating energy expenditure. Thus, leptin plays a major role in the control of body fat stores through coordinated regulation of feeding behaviour, metabolism, autonomic nervous system, and body energy balance. Furthermore, recent studies also revealed a peripheral effect of leptin, partly mediated by interactions with other peripherally acting hormones such as insulin. Elevated circulating levels of leptin were described in obese children due to the enlarged fat mass. These children fail to reduce their food intake in response to the increased endogenous leptin. This paradox of response is regarded as a condition of relative leptin resistance [50, 51]. Peripheral leptin resistance (particularly in skeletal muscle) is also linked to insulin resistance and the development of NAFLD and MetS in children [48]. Interestingly, Josefson et al. [52] demonstrated that high maternal leptin levels identify neonates with increased adiposity. However, most studies suggest that leptin and its soluble receptor may be more important in states of energy deficiency than in energy excess and MetS [53].

Much more promising with respect to counteracting the MetS is the adipocytokine adiponectin. It is perceived as the strongest predictor for MetS in adults and children [54]. In contrast to most adipocytokines, it exerts profound beneficial actions as an anti-atherogenic, -diabetogenic, -inflammatory, and -proliferative molecule and thereby protects against the development of type 2 diabetes and cardiovascular disease [53]. Adiponectin acts as an insulin sensitizer with anti-inflammatory and antioxidative properties, which are mediated by the inhibition of tumor necrosis factor alpha (TNFα) and superoxide radical generation. Low plasma adiponectin levels in children and adolescents are linked to obesity, insulin resistance, type 2 diabetes, higher systolic blood pressure, other markers of cardiovascular disease, and an increased risk of malignancies [48, 51, 55].

Resistin impacts on insulin sensitivity and was discussed as a new link between obesity and insulin resistance [48, 50, 56], although its role in the development of insulin resistance, type 2 diabetes, and MetS is still controversial [48]. However, studies confirmed that resistin is implicated in inflammatory processes such as atherosclerosis [50, 51, 57].

Chemerin acts through a chemoattractant protein which binds chemokine-like receptor 1 (CMKLR1), which is localized in adipocytes, endothelial cells, and inflammatory cells. It is implicated in adipogenesis, glucose and lipid metabolism [48, 58], with a possible link to increased fat mass and an early atherogenic risk profile in obese children [59]. Chemerin was found to be increased in obese and diabetic individuals, especially in obese children with vitamin D deficiency. It is significantly correlated with markers of metabolic and cardiovascular abnormalities, inflammation, and endothelial dysfunction [58]. Recently, significantly elevated chemerin levels were noted in children with NAFLD which facilitated the identification of individuals with steatosis [60].

Circulating nicotinamide phosphoribosyltransferase (NAMPT) levels and single nucleotide polymorphisms (SNP) of the *NAMPT* gene are inconsistently linked to obesity. NAMPT influences glucose metabolism via its role in the regulation of glucose-stimulated insulin secretion in pancreatic β-cells [61–63]. NAMPT is significantly associated with several anthropometric parameters (BMI, waist circumference, and hip circumference) [64], components of MetS, and inflammation [48] in children. While Kotnik et al. [48] found no association between NAMPT and insulin resistance, Salama et al. [64] demonstrated a significant link between NAMPT and an impaired homeostatic model assessment for insulin resistance (HOMA-IR).

Table 2. Adipocytokines in alphabetic order – associations with childhood obesity and its complications

Adipokines	Origin	Biological/pathological function	Results in obese children	Authors [Ref.]
Adiponectin	Adipocytes	Antiatherogenic, antidiabetogenic, anti-inflammatory/proliferative/oxidative effects	↓ Serum levels Association with IR, T2D, MetS, and CVD ↑ Risk of malignancies	Kotnik et al. [48] Balagopal et al. [51] Körner et al. [53]
A-FABP (adipocyte-fatty acid-binding protein)	Adipocytes, dendritic cells and macrophages	Cytoplasmic lipid carrier, role in the maintenance of glucose and lipid homeostasis	↑ Serum levels Association with insulin, BMI, WC, TG, HOMA-IR (girls), HDL-C, hsCRP, leptin (boys), impaired glucose tolerance (both sexes)	Not confirmed by all authors Barraco et al. [58] Khalyfa et al. [83] Reinehr et al. [110]
Chemerin	Adipocytes and hepatocytes	Implication in adipogenesis, glucose and lipid metabolism, acts through chemokine like receptor 1, which is localized in adipocytes, endothelial and inflammatory cells	↑ Serum levels in obese and diabetic children Association with IR, inflammation, endothelium dysfunction, CVD, and NAFLD	Kotnik et al. [48] Barraco et al. [58] Klusek-Oksiuta et al. [60]
FGF-21 (fibroblast growth factor-21)	Hepatocytes and adipocytes	↑ Lipolysis in WAT and ketogenesis in the liver ↑ Hepatic glycogen production ↓ Gluconeogenesis ↑ Insulin signalling Amelioration of dyslipidemia, thermogenic	↑ Serum levels with increasing hepatic fat content independently of obesity, visceral fat content, and IR Association with cytokeratin 18	Not confirmed by all authors Barraco et al. [58] Zhang et al. [65]
hsCRP	Hepatocytes and adipocytes	Nonspecific acute-phase reactant Marker of low-grade inflammation	↑ Serum levels	Not confirmed by all authors Körner et al. [53] de Luca and Olefsky [66] Zhang et al. [111]
IL-6, IL-8	Adipocytes and macrophages	Proinflammatory	↑ Serum levels	de Luca and Olefsky [66] Gallistl et al. [70] Straczkowski et. al. [71] Roytblat et al. [69]
Leptin	Adipocytes and other cells	↓ Food intake ↑ Energy expenditure	↑ Serum levels Relative leptin resistance in obese children Association with IR, NAFLD, and MetS	Kotnik et al. [48] Körner et al. [50, 53] Balagopal et al. [51]
Lipocalin-2	Neutrophils and adipocytes	Possible independent risk factor for IR and hyperglycemia in obese children	↑ Serum levels Association with SBP, glucose, insulin, TG, HOMA-IR, HDL-C, hsCRP, uric acid	Not confirmed by all authors Barraco et al. [58] Akelma et al. [112]
NAMPT (visfatin, pre-B-cell colony-enhancing factor 1)	Adipocytes	Binding of the insulin receptor, possible insulin-mimetic effects ↓ Blood glucose ↑ Insulin sensitivity ↑ Vascular smooth cell maturation	Association with BMI, WC, HC, HOMA-IR, and low-grade inflammation	Not confirmed by all authors Kotnik et al. [48] Fukuhara et al. [61] van der Veer et al. [62] Garten et al. [63] Salama et al. [64]
Omentin-1	Visceral adipocytes and other cells	↑ Transduction of the insulin signal (enhancing insulin-stimulated glucose transport)	Controversial results: ↑ ↓ ↔ serum levels in obese children or those with MetS	Barraco et al. [58] Catli et al. [113] Prats-Puig et al. [114]
RBP4 (retinol binding protein 4)	Adipocytes	Interaction with glucose transporter 4 (GLUT 4) Mediation of IR and T2D	↑ Serum levels Association with IR, and several components of MetS, independently of BMI Possible involvement in atherosclerosis and CVD	Not confirmed by all authors Kotnik et al. [48] Balagopal et al. [51] Körner et al. [53] Reinehr et al. [115] Janke et al. [116]

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Table 2 (continued)

Adipokines	Origin	Biological/pathological function	Results in obese children	Authors [Ref.]
Resistin	Macrophages and other cells	Proinflammatory effects Antagonizing effect on insulin action ↓ Insulin sensitivity ↓ Insulin-stimulated glucose uptake	Controversial results: association with IR, T2D, and MetS, possible involvement in atherosclerosis	Not confirmed by all authors Kotnik et al. [48] Körner et al. [50] Balagopal et al. [51] Steppan et al. [57]
TNFα	Monocytes, macrophages, adipocytes	Interaction with insulin signalling pathways ↓ Expression of insulin receptor and GLUT4 genes ↓ Insulin-stimulated glucose uptake	↑ Serum levels	Körner et al. [53] Dixon et al. [68] Hotamisligil et al. [67]
Vaspin (visceral adipose tissue derived serpin)	Visceral, periadventitial, and epicardial adipocytes, vascular smooth muscle cells	Associations with CVD, glucose metabolism, and insulin sensitivity Linking mechanisms not entirely understood	↑ Serum levels Association with insulin, IR, T2D, weight, BMI, DBP, TG, negatively associated with adiponectin, SBP, impaired endothelial function	Barraco et al. [58] Blüher [117]

IR, insulin resistance; T2D, type 2 diabetes; MetS, metabolic syndrome; CVD, cardiovascular disease; BMI, body mass index; WC, waist circumference; TG, triglycerides; HOMA-IR, homeostasis model assessment of insulin resistance; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitive C-reactive protein; NAFLD, non-alcoholic fatty liver disease; WAT, white adipose tissue; HC, hip circumference; IL, interleukin; TNFα, tumor necrosis factor alpha; GLUT4, glucose transporter 4; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Fibroblast growth factor-21 (FGF-21) is preferentially released by the liver and, to a minor extent, by white and brown adipose tissues. FGF-21 possesses thermogenic, antihyperglycemic, and antihyperlipidemic effects. In vitro and animal studies revealed that it stimulates lipolysis in the white adipose tissue and ketogenesis in the liver, improves insulin signaling and hepatic glycogen production, and reduces gluconeogenesis. In addition, FGF-21 can ameliorate dyslipidemia [58, 65] and enhance the "browning" of the white adipose tissue. FGF-21 serum levels increase with hepatic fat content, independently of obesity development, and visceral fat as well as with hepatic or adipocyte insulin resistance. Interestingly, FGF-21 is positively correlated with cytokeratin 18, a novel reliable marker of cellular apoptosis [58].

Apart from these well-studied adipocytokines, a large number of additional adipokines emerged during the last years, including adipocyte-fatty acid-binding protein (A-FABP), retinol binding protein 4 (RBP4), lipocalin-2, omentin-1, and vaspin [48, 58, 64] (Table 2). Some of these may be promising biomarkers in the context of metabolic disturbances.

Inflammatory Cytokines
In obesity, several pathological alterations of white adipose tissue ensue. Both hyperplastic and hypertrophic growth of adipocytes can be observed with diameters exceeding the maximal diffusion rate of oxygen. It is supposed that local hypoxia, cell death, and macrophage infiltration occur consequently and lead to an altered adipokine secretion profile with an upregulation of inflammatory factors, which contribute to the chronic low-grade inflammation observed in obesity [47]. This low-grade inflammation might underlie, at least in part, the clustering of cardiovascular risk factors [53]. High-sensitive C-reactive protein (hsCRP), a nonspecific acute-phase reactant, is a good marker for low-grade inflammation and is commonly elevated in obese children and those with insulin-resistant states [66]. Most studies in children do not conclusively confirm that hsCRP is associated with insulin resistance or metabolic risk, especially when analyses are corrected for BMI [53]. Other major players in inflammation are TNFα, interleukin 6 (IL-6), interleukin 8 (IL-8), and resistin. In particular, studies regarding TNFα presented controversial results. Some studies reported a significantly elevated expression of adipose tissue TNFα in human obesity and demonstrated strong correlations with levels of hyperinsulinemia, while others noted a decrease in obese prepubertal children [53, 67, 68]. IL-6 and IL-8 are elevated in obese children [69–71] and were reported in various diabetic and insulin resistance states [66]. Moreover, IL-6 was significantly as-

sociated with elevated systolic blood pressure [72]. Free fatty acids, elevated in overnutrition and obesity, can directly activate proinflammatory responses in vascular endothelial cells, adipocytes and myeloid-derived cells, and therefore contribute to the development of systemic inflammation [66].

Several adipocytokines and inflammatory cytokines have recently been identified, with significant positive (leptin, chemerin, vaspin, TNFα, IL-6, and IL-8) or negative (adiponectin) associations with metabolic risk factors. Some of these might be considered as pathophysiological factors linking obesity and its complications such as insulin resistance and NAFLD. However, data on other adipocytokines and their role in metabolism remain controversial and partly unknown, especially regarding their role in childhood (resistin, NAMPT, FGF-21, A-FABP, RBP4, lipocalin-2, omentin-1, hsCRP). Indeed, they warrant future investigations.

The Role of Epigenetics and Developmental Programming in the MetS

Epigenetic mechanisms are emerging as mediators linking early environmental exposures during pregnancy with programmed changes in gene expression that alter offspring growth and development [73]. Recent studies revealed that epigenetic mechanisms may account for a majority of MetS initiation [74]. Low and high birth weight results in an increased risk for childhood and adult obesity. Importantly, maternal obesity during pregnancy or increased weight gain in pregnancy is associated with higher-weight newborns and an increased risk of obesity and diabetes in later life [74]. The concept of "gestational programming" signifies that the nutritional, hormonal, and metabolic environment (as well as stress, lower physical activity, and endocrine disruptors) provided by the mother alters organ structure, cellular responses and gene expression that ultimately impacts metabolism and physiology of her offspring [75]. These epigenetic alterations are mediated by DNA methylation, histone modifications, chromatin remodelling, and/or regulatory feedback by microRNAs. Apart from the extrinsic processes resulting from the maternal phenotype and the associated nutrient alterations occurring within each pregnancy, epigenetic inheritance may also occur by somatic cells or the germ line involving maternal and paternal lineages [73]. Although the exact mechanisms are still unclear, new important insights in the field (e.g., microRNA) have been published.

MicroRNAs (miRNA, miR), small non-coding RNA molecules containing about 22 nucleotides, are found in many organisms and mainly function in the downregulation of gene expression. They have emerged as key regulators of metabolism [76]. MiRNA were established as biomarkers for several diseases and are commonly studied in the context of metabolic disease [47, 77, 78]. Recently, various miRNAs associated with obesity or its complications were identified; a few examples will be further discussed. Several miRNA species, like miR-130 or miR-27b, regulate adipogenic differentiation by targeting the expression of peroxisome proliferator-activated receptor gamma (PPARγ), the master regulator of adipogenesis [47]. Along the same line, miR-125b-5p, which is upregulated during human adipogenesis, downregulates the antiadipogenic matrix metalloproteinase 11 and directly inhibits adipogenesis itself [79]. Zhang et al. [76] demonstrated that overexpression of miR-378 apparently prevents and treats obesity by activating the muscle pyruvate-phosphoenolpyruvate futile cycle and enhancing lipolysis in adipose tissue. In addition, Jiang et al. [80] revealed that miR-378 expression in human adipocytes is induced by adipokines (IL-6, TNFα, leptin, and free fatty acids). Recent experiments provided evidence that obesity induces overexpression of miR-143, which inhibits insulin-stimulated AKT activation leading to impairment of glucose metabolism [81]. MiR-29a, which is upregulated in skeletal muscles of intrauterine growth-restricted rats, can suppress PPARδ and leads to reduced insulin-dependent glucose uptake and ATP production. MiR-29a overexpression also causes a decrease in the levels of glucose transporter 4 (GLUT 4) and may contribute to development of insulin resistance [82]. A large number of miRNAs were identified as intrinsic in the pathogenesis of insulin resistance by affecting pancreatic β-cell development, insulin biosynthesis, insulin secretion, or by interacting with insulin signaling pathways [81]. In addition, several miRNAs proved to be associated with endothelial dysfunction [83], serum lipid level alterations [78, 84, 85], inflammation [86], and other additional markers of metabolic dysfunction in children [85]. Interestingly, some miRNAs are enriched in the hypothalamus, suggesting a primary role in the hypothalamic regulation of energy intake, expenditure, and body weight control [87]. Although there are still many challenges and drawbacks, miRNAs are an exciting, novel, rapidly developing, and promising research field. They have the potential for employment in the diagnosis, stratification, and therapeutics in the context of metabolic disease [47].
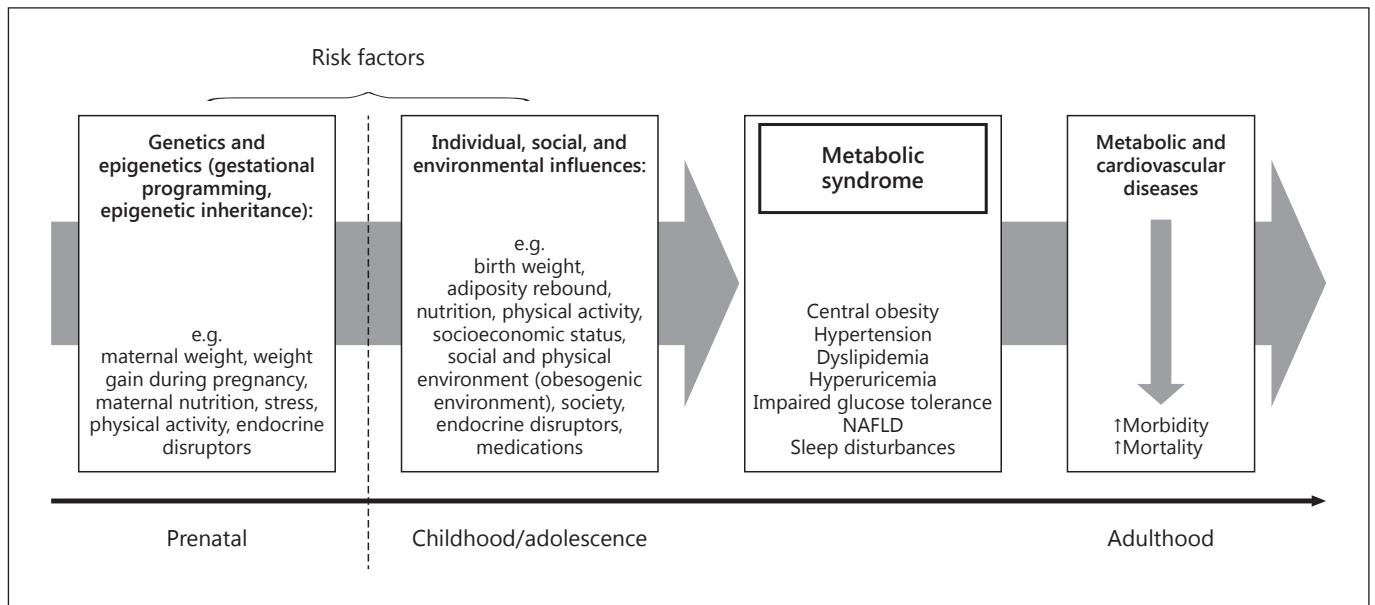
Fig. 1. Risk factors and consequences of the metabolic syndrome. NAFLD, non-alcoholic fatty liver disease.

Recent Standards in the Diagnosis, Therapy, and Prevention of the MetS and Its Complications

A conspicuous number of recent studies support the notion that an early diagnosis and a successful treatment represent the first steps to reduce morbidity and mortality related to MetS [88–90]. The individual's risk for the development of MetS is influenced by genetics and epigenetics (gestational programming and epigenetic inheritance) and is associated with weight status at birth and early adiposity rebound [91–93]. Independently of these predisposing conditions, overnutrition, low physical activity, social and physical environment, society, and endocrine disruptors strongly influence the development towards metabolic disturbances (Fig. 1). The identification of high-risk children will facilitate the implementation of adequate screening programs for MetS and its single components at an early stage of life. This screening should include measurements of BMI and waist circumference, blood pressure, lipid profile, serum glucose, and an oral glucose tolerance test, if indicated [94]. It is necessary to interpret each obtained value according to referenced cutoffs specific for age, gender, and race. Although different guidelines have proposed several treatment approaches for MetS during the last decade, there is no specific treatment at the present time. However, all these guidelines converge on the importance of lifestyle

changes, characterized by a nutritional program, appropriate for age, and regular physical activity [95, 96]. Some studies reported that even in the absence of weight loss, lifestyle interventions can have positive effects on the components of the MetS [97]. Other evidence points out that improvements in the atherogenic profile and insulin resistance are only achieved if the BMI-SDS decreases by at least 0.5 over a 1-year period [98]. Experience informs us that lifestyle modifications are not easy to obtain in clinical practice and are usually insufficient to gain the target value of individual conditions. This fact justifies the use of pharmacological interventions capable to control blood pressure, dyslipidemia, glucose metabolism impairment, and other abnormalities related to the MetS. However, at the moment, there is still limited experience on the use of pharmacological interventions in the pediatric population with MetS. Different studies reported that metformin can improve insulin sensitivity and BMI in nondiabetic obese adolescents with a clinical phenotype of normoglycemia and hyperinsulinemia [99–101]. However, a limited effect of metformin on weight and insulin sensitivity was found in another larger study of obese, insulin-resistant adolescents [102]. Therefore, the use of this drug is still debatable and several authors consider it as an adjunct to the lifestyle programs in selected cases. In terms of dyslipidemia and hypertension, both statins and antihypertensive drugs should be considered

in selected cases. Due to the absence of consistent safety and efficacy data, there is a common agreement to limit the use of these drugs to children and adolescents who are at a very high risk with failure to respond to lifestyle modifications [88]. Bariatric surgery is one of the most promising and efficient procedures to treat obesity and obesity-related complications in adults as well as children and adolescents [103]. These surgeries produce long-lasting weight loss and improvement in many obesity-related conditions such as type 2 diabetes, hypertension, obstructive sleep apnea syndrome, and NAFLD [104]. Although these surgical interventions improve weight loss, physical health, and psychosocial outcomes, limited knowledge is available regarding the long-term outcomes in children and adolescents. Considering all these aspects, a recent guideline underlines that weight loss surgery should only be considered under exceptional circumstances for obese children, and that these children must be physically mature and have failed 6 months of multidisciplinary lifestyle interventions [1034]. Although several approaches for the treatment of MetS are available at the moment, it is obvious that further controlled trials, specific for the pediatric populations, are required to better assess their efficacy in order to tackle obesity, insulin resistance, and other conditions correlated to MetS.

Conclusion

During the last years, there has been a surge in the number of publications addressing the dimensions and relevance of MetS in children and adolescents. However, different challenges are still faced on this condition. First, the definition of pediatric MetS, and its clinical utility remains a subject of ongoing debate. The possibility to add new MetS components (NAFLD, hyperuricemia, sleep disturbance) to the standard definition represents one of the "hot topics" in this field. The second open question in terms of MetS is represented by the possibility to use new biomarkers capable of promptly identifying the individuals affected by MetS. MiRNAs have emerged as a new and valid tool not only for the diagnosis and stratification of this condition, but also as a potential therapeutic target. In the meantime, the search for more effective childhood obesity prevention and treatment interventions continues apace. Diet and physical activity represent the current milestones of MetS treatment. However, during the last years, contemporary therapeutic approaches have been experimented in order to optimise the management approach to these patients.

Disclosure Statement

The authors confirm that there is no conflict of interest.

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