Review Article

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Definition and early diagnosis of metabolic syndrome in children

Abstract: With this review, we aim to focus the attention on some established as well as new concepts for the metabolic syndrome (MetS) in children and adolescents spanning from definition to recommendations for the diagnostic approach. Even though there is no international commonly used definition of the metabolic syndrome in children and adolescents, all definitions include obesity as precondition for the development of MetS even in children. Obesity is one of the major cardiometabolic risk factors and it is strongly linked to other metabolic diseases like hyperlipidemia, hyperinsulinemia as well as hypertension. The metabolic syndrome is commonly known as a constellation of the mentioned morbidities. Pediatricians and researchers agree that early diagnosis and early interventions of the MetS are important to improve the prevention of cardiovascular disease and type 2 diabetes in adulthood. However, this requires appropriate screening tools for children and adolescents at risk for the MetS and its comorbidities. Due to controversies regarding the definition of MetS and the lack of consensus thresholds for the single components in children and adolescents, there is no internationally accepted diagnostic pathway for MetS available. However, several consensus statements and national guidelines for the assessment of obesity and its comorbidities in children and adolescents are available. Obesity seems to be the driving factor for the development of the other risk factors of MetS. In order to avoid conflicts concerning the definition of overweight and obesity, we recommend using the WHO definition of overweight (one standard deviation body mass index for age and sex and obesity; two standard deviations body mass index for age and sex) in children and adolescents.

Keywords: adipocytes; childhood obesity; endocrinology; gastrointestinal; metabolic syndrome; NAFLD; obese; overweight; PHTS; PTEN.

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Introduction

Even though there is no international commonly used definition of metabolic syndrome (MetS) in children and adolescents, all available definitions include obesity as precondition for the development of MetS, even in children. In most countries, the prevalence of overweight and obese children and adolescents has been increasing over the last 20 years [1]. In recent years, the prevalence of obesity at younger ages has appeared to stabilize or even gently decline in some countries, but the proportion of obese adolescents is still increasing [2]. The German Children and Adolescents Health Survey (KIGGS) reported that up to 6.3% of children and adolescents between 3 and 17 years were obese and up to 15% were overweight [3]. These data were also confirmed in more recent studies [2]. Obesity is a major cardiometabolic risk factor and is strongly linked to other metabolic diseases like hyperlipidemia, hyperinsulinemia, and hypertension; MetS is commonly known as a constellation of these morbidities [4]. However, MetS is not only a cluster of several metabolic complications related to the presence of adipose tissue, it is also an important risk factor for the development of cardiovascular diseases [5]. MetS significantly increases cardiovascular disease (CVD) and other causes of mortality by 1.5–2-fold in both adults and pediatric age groups [4, 6, 7]. There is also evidence that older obese children and adolescents are more likely to develop type 2 diabetes and cardiovascular disease [8]. Furthermore, the increasing prevalence of MetS in the pediatric obese age group is significantly predisposing for the development of metabolic diseases in adulthood [4, 9]. This emphasizes the requirement of identifying signs of MetS at an early stage in order to start an intervention.

Definition and prevalence of MetS in children and adolescents

In 1988, Gerald Reaven, an American endocrinologist, introduced the concept of Syndrome X, which was later renamed as MetS [10]. He defined this condition in obese adults as "a link between insulin resistance (IR), hypertension, dyslipidemia, impaired glucose tolerance and other metabolic abnormalities associated with the risk for atherosclerotic and cardiovascular disease" [11]. In the following years, MetS emerged as a public health problem worldwide, as well as a clinical dilemma [12]. The understanding of the pathophysiology of its development is still incomplete, so the composition of specific (metabolic) parameters for the definition remains controversial. However, most of the commonly used definitions agree on the following essential components: central obesity, impaired glucose tolerance, dyslipidemia, and hypertension.

There is a great need for a specific definition of MetS for both children and adolescents. Several definitions for pediatric MetS have been published since 2003 (Table 1). Dichotomous as well as continuous approaches for the definition have been proposed [13–16]. However, at present, there is still no international consensus for a widely accepted definition. One of the first definitions of MetS in children was published by Cook et al. in 2003. The authors defined pediatric MetS as combination of at least three of the following markers: waist circumference (WC) >90th percentile (using NHANES III data), blood pressure >90th percentile, fasting glucose >110 mg/dL, triglycerides >110 mg/dL, and HDL cholesterol <40 mg/dL [14]. These criteria were slightly modified the following year by de Ferranti et al., by using the same parameters but less stringent cut-offs for waist circumference (75th instead of 90th percentile), triglycerides (100 instead of 110 mg/dL), and HDL cholesterol (50 instead of 40 mg/dL) [15].

The International Diabetes Federation (IDF) published a consensus definition in 2007. In this, they agreed that children from the age of 10 years fulfilled the criteria of MetS if they had at least three of the following risk factors: high WC, high blood pressure, IR, and dyslipidemia [16]. The IDF recommended to use different cut-offs for the parameters based on the age group. For children between 10 and 15 years, the following cut-offs were stated: WC >90th percentile, systolic blood pressure >130 mmHg or diastolic blood pressure >85 mmHg, triglycerides >150 mg/dL, and HDL cholesterol <40 mg/dL. For adolescents older than 15 years, the IDF recommended the same criteria for the diagnosis of MetS as used in adults: central obesity (ethnicity specific cut-offs for waist circumference) and at

Table 1: Diagnostic criteria for metabolic syndrome in children and adolescents. Adapted from Bussler et al. [34].

Authors [Ref.], year	Criteria for metabolic syndrome (three or more criteria fulfilled?)
Cook et al. [14], 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 et al. [83], 2004	WC >90th pct., BP ≥90th pct., TG ≥90th pct. or HDL-C ≤10th pct., glucose intolerance (ADA criteria)
Weiss et al. [84], 2004	BMI z-score ≥2.0, BP >95th pct., HDL-C <5th pct., TG >95th pct., glucose intolerance (ADA criteria)
de Ferranti et al. [15], 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
Viner et al. [85], 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
Zimmer et al. (IDF) [16], 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
Ahrens et al. [13], 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 three or more of the abovementioned criteria are fulfilled. ADA, American Diabetes Association; BP, blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; MetS, metabolic syndrome; pct., percentile; SBP, systolic blood pressure; TG, triglycerides; WC, waist circumference.

least two or more of the following parameters: raised blood pressure (systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or treatment of previously diagnosed hypertension), raised fasting plasma glucose (> 100 mg/dL or previously diagnosed type 2 diabetes), raised triglycerides (> 150 mg/dL, or specific treatment for this lipid abnormality) or reduced HDL cholesterol (< 50 mg/dL in females, < 40 mg/dL in males or specific treatment for this lipid abnormality) [16, 17].

However, this consensus definition also stated that children under 10 years should not be diagnosed with MetS. This was explained by the absence of age-specific reference values for MetS components for this age group [16]. In 2014, Ahrens et al. published a promising new approach, proposing a quantitative MetS score using age- and gender-specific anthropometric and metabolic parameters in children between 2 and 11 years [13]. The

underlying data for these reference values were obtained from the Identification and Prevention of Dietary and Lifestyle-induced Health Effects in Children and Infants study, carried out from 2006 to 2012 [18–21]. To help physicians to stratify children at risk, this scoring system recommends a strict monitoring level at or above the 90th percentile, and for those at or above the 95th percentile, there is a need for urgent intervention [13]. If the definition of Ahrens et al. is used, the prevalence of MetS in preschool children is 3.4% and, therefore, higher compared to previous definitions [22]. These results were consistent with those of a Spanish cross-sectional study, published in 2011, which showed a MetS rate of 8–32% in prepubertal and 9.7–41.2% in pubertal children, depending on the definition used [23]. In addition, Reinehr et al. compared different definitions of the MetS in a cohort of 1,205 children and adolescents and found a wide range of the prevalences spanning from 6 to 39% [24].

The racial and ethnic distribution of MetS in children and adolescents is similar to that seen in adults, with the highest prevalence in Mexican Americans, followed by non-Hispanic whites and non-Hispanic blacks (12.9, 10.9, and 2.9%, respectively). Native Americans may be the ethnic group at greatest risk for MetS, as illustrated by a population-based study of Canadian Native (Oji-Cree) children and adolescents (10–19 years). This study reported a 19% prevalence rate (defined by ATP III criteria) [25].

However, in several factor analyses, no significant differences between boys and girls and among racial or ethnic subgroups were found regarding factor loadings of measured variables [26].

Complex pathophysiology

The pathophysiology of MetS is complex and not yet fully understood. The World Health Organization hypothesizes that IR is the key and driving factor in the development of MetS. In states of IR, metabolic dysfunction across several organs occurs, creating the observed interplay of several concurrent metabolic abnormalities. It is widely accepted that obesity and the concomitant development of inflammation are the major components of IR. Other reviews show the up-to-date understanding of the pathophysiology in more detail comprising the role of lipid partitioning and inflammation, adipose tissue IR and free fatty acid flux, muscle IR and glucose intolerance, hepatic IR and fasting dyslipidemia, intestinal IR and postprandial dyslipidemia [27].

Many researchers performed confirmatory factor analyses of cardiometabolic risk factor clustering to uncover relationships among many variables. This allows numerous intercorrelated variables to be condensed into a smaller set of dimensions in order to elucidate the structure of the MetS. However, the findings are not consistent. In adults, most studies favor multiple-factor models (two-, three-, or four-factor models) supporting a multifactorial pathophysiology and etiology of MetS [28–30]. Previous factor analyses could not sustain a single common factor hypothesis, either because this underlying factor in the pathogenesis does not exist or because of misleading statistical methods, as Pladevall et al. [30] assume. However, Pladevall et al. were able to show that IR, mean arterial pressure, triglyceride-to-HDL ratio, and WC cluster together. This supports the concept that one single causal factor may underlie the different components of MetS [30].

There are comparably inconsistent results for pediatric populations. Li et al. [31] found a one-factor model most suitable for their data with excellent goodness-of-fit indices, and overall estimates of factor loadings, for the total sample of 0.76, 0.46, 0.81, and 0.42 for WC, triglycerides, fasting insulin, and systolic blood pressure, respectively. In contrast to that, Bahar et al. [32] proposed a two-factor model with a blood pressure factor and an adiposity/lipid factor, which have been consistent from childhood to adolescence. Kelishadi et al. [33] loaded three factors: lipids, adiposity, and blood pressure that accounted for 87.4–90.8% of the variance and Khader et al. extracted four factors in their analysis (adiposity, blood pressure, lipids, and blood glucose), with the adiposity factor accounting for the largest proportion of the total variance in the four groups [26].

Unlike Li et al., Bahar et al., Kelishadi et al., and Khader et al. concluded that multiple factor models were a better data fit than a one-factor model [26, 31–33]. Therefore, their studies are supportive of the concept of MetS consisting of several distinct but intercorrelated entities.

Regarding the pathophysiology of MetS, the factor analyses performed so far have not been conclusive due to the inconsistency in the findings proposed by the studies.

The use of different measures for one variable or multiple measures to account for the same trait (fasting glucose and fasting insulin to represent IR) might contribute to the inconsistencies, because these highly correlated measures will cluster together under a separate factor instead of loading on a common factor [30]. Currently, most studies favor models with the core components of MetS, which account for a large proportion of the variance. However, the pathogenic roles of additional components like leptin or uric acid need to be explored further [30].

Other associations of MetS with several obesity-related disorders

Apart from the traditional cluster of metabolic disorders, there are other abnormalities which are often discussed as further components of MetS.

Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is been considered as an additional component of MetS, even in children and adolescents. Hepatic steatosis is defined by a hepatic lipid infiltration higher than 5%, confirmed by liver histology and in absence of excessive alcohol intake, viral, autoimmune, or drug-induced liver disease. NAFLD encompasses a large spectrum of conditions ranging from simple hepatic steatosis to steatohepatitis with or without fibrosis. Steatohepatitis can deteriorate into hepatic cirrhosis with other related complications such as hepatocellular carcinoma and portal hypertension. NAFLD and MetS are strongly related, such that NAFLD has been described as the hepatic manifestation of MetS, with IR as the driver of pathogenesis. A recent study reported that 66% of the investigated children with biopsy-proven NAFLD had MetS. In addition, an association between the histology severity of the disease and some components of the MetS has been reported [34]. Liver biopsy remains the gold standard for the definitive diagnosis of NAFLD and is the only test that can reliably distinguish between simple steatosis and NASH. Due to its invasive nature and high cost, liver biopsy is not proposed as a screening procedure. Accurate non-invasive imaging techniques to diagnose and monitor NAFLD are being developed but all show marked limitations. Ultrasound scans are safe, but unable to quantify steatosis or fibrosis; MRI could enable rapid, reproducible measurements of steatosis and fibrosis, but is not yet cost-effective. Fibroscan has the potential to become a diagnostic feature, but yet it is not suitable for widespread use in these patients. Anthropometric, demographic, clinical, and laboratory features may offer a clue to identify those at risk of NAFLD, and acanthosis nigricans and increased WC are warning signals. Increased alanine-aminotransferase levels in combination with liver ultrasound are an indicator for fatty liver disease, but normal alanine-aminotransferase levels do not exclude liver steatosis, fibrosis, or cirrhosis. However, increased serum alanine-aminotransferase and γ-glutamyltransferase levels raise the suspicion of NAFLD in children at risk of more severe disease [35]. Studies based mainly on elevated ALAT levels (>35–40 IU/L) in obese children and adolescents have identified a prevalence of NAFLD of 14–23% [36–39].

The intestinal microbiome seems to also play a crucial role in the development of NAFLD. In a recent study, it was shown that obese children with small intestinal bacterial overgrowth had an increased risk for developing NAFLD [40].

Liver enzymes should be measured and age- and sex-specific percentiles should be used for evaluation [41].

Sleep disturbances

Sleep disturbances seem to be a risk factor for, as well as a consequence of, obesity. It has been reported that chronic short sleep duration and insufficient sleep quality in children and adolescents are associated with elements of MetS, such as hypertension or IR, independent of obesity. Acute sleep restriction increases dietary intake in pre-school-aged children. Both short and overlong sleep duration are associated with overweight and obesity in pre-school-aged children. Obstructive sleep apnea (OSA) is characterized by repetitive pharyngeal narrowing and closure during sleep, snoring, and frequent nocturnal awakenings, leading to recurrent oxyhemoglobin desaturation, sleep fragmentation, and hypercapnia. Obesity and specific fat depots predispose to OSA. OSA itself may predispose to obesity due to daytime somnolence, decreased activity, and decreased sleep duration. A study reported that MetS is present in 16% of children without OSA, but present in 59% of those with OSA. Likewise, all single components of MetS are associated with OSA [34]. Sleep disturbances can be assessed using structured sleep questionnaires, sleep diaries, or polysomnography [42].

Hyperuricemia

Uric acid is the end-product of the purine metabolism in humans. High ingestion of purine sources or high intake of fructose (the major component of added sugars) is directly related to an increase in serum urate, which can cause gout and urolithiasis. Hyperuricemia has also been shown to be implicated in the pathophysiology of hypertension, chronic kidney disease (CKD), congestive heart failure, type 2 diabetes, and atherosclerosis. Correlations between hyperuricemia, MetS, and several of its components have been described for children and adolescents. For instance, every 1 kg/m² increment in body mass index (BMI) is associated with 5.74 μmol/L increase in serum uric acid

levels. Moreover, carotid intima media thickness, a well-established cardiovascular risk factor, is significantly related to uric acid levels [34]. In a recent study, it was proposed that serum levels of uric acid can be used as an indicator of unhealthy obesity in youth, where lower levels of uric acid indicate a lower risk and higher levels suggest a higher risk of metabolic unhealthy obesity [43]. Uric acid levels should be measured to assess for hyperuricemia.

Chronic kidney disease

Studies have confirmed that obesity and MetS are associated with an increased risk of CKD and microalbuminuria [44, 45]. Higher multivariate-adjusted odds ratios of CKD and microalbuminuria were found in adult participants with MetS compared to those without. Additional, higher odd ratios were reported with an increasing number of components of MetS present in participants [45]. However, controversially, the risk for CKD extends to those who are metabolically healthy, indicating that obesity *per se* contributes to CKD independently of MetS. Recent developments in the pathophysiology of obesity-related kidney disease indicate that chronic inflammation and abnormal lipid metabolism contribute to kidney cell injury. Children with severe obesity have increased prevalence of early kidney abnormalities, including albuminuria, decreased kidney function, and elevated biomarkers of early kidney injury [44]. For the assessment of CKD, the following can be used: eGFR (mL/min/$1.73\,m^2$) = $39.8 \times [ht/Cr]0.456 \times [1.8/CysC]0.418 \times [30/BUN]$ $0.079 \times [1.076]male \times [ht/1.4]0.179$ where ht = height in meters, Cr = serum creatinine in mg/dL, CysC = serum cystatin C in mg/dL, and BUN = blood urea nitrogen in mg/dL (patel), microalbumin or cystatin C levels [46].

Polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women. It is associated with significant morbidity including impaired reproductive health, psychosocial dysfunction, MetS, cardiovascular disease, and increased cancer risk. There are still controversies about underlying etiopathogenesis, diagnostic criteria, and recommendations for PCOS in adolescents. Accepted etiologic theories include disordered neuroendocrine gonadotropin secretion, hyperandrogenism, IR, and hyperinsulinemia or a combination thereof. Diagnostic criteria mainly include menstrual irregularity, androgen excess (e.g., clinically presenting as hirsutism or acne),

and polycystic ovary morphology. In addition to the above-mentioned metabolic disturbances, overweight and obesity are commonly found in adolescents with PCOS [47].

The diagnostic criteria for PCOS in adolescents include abnormal uterine bleeding pattern (abnormal for age or gynecologic age, persistent symptoms for 1–2 years) and evidence of hyperandrogenism (persistent testosterone elevation above adult norms, moderate-severe hirsutism, moderate-severe inflammatory acne vulgaris) [48].

Metabolic healthy obese (MHO) and metabolic unhealthy obese (MUO)

A new subtype of the classification of obesity has been proposed distinguishing between a metabolic healthy phenotype and metabolic unhealthy phenotype in obese individuals. In general, MHO describes obese individuals with the absence of any metabolic disorders including type 2 diabetes, dyslipidemia, and hypertension. However, as for MetS, there is no commonly accepted definition for MHO available, especially in children [49]. Because of this, prevalences vary from 3 to 80% according to the definition applied [50–52]. To address this issue, in 2018, Damanhoury et al. conducted a published review to identify definitions of MHO and establish a consensus-based definition for children, using a Delphi process [51]. Experts agreed on applying the WHO BMI-for-age to assess weight status, using MHO and MUO as the terms to describe children at relatively low and high cardiometabolic health risk, and including HDL-C (>40 mg/dL or >1.03 mmol/L), triglycerides (≤150 mg/dL or ≤1.7 mmol/L), and blood pressure (SBP and DBP ≤90th percentile) in the definition, but without including fasting glucose.

In support of the concept of MHO, it is not only the amount of fat which determines the development of cardiometabolic disturbances, but independently of the BMI, age and sex, increased visceral fat accumulation, inflammation in visceral adipose tissue and adipose tissue dysfunction mediate IR and may contribute to unhealthy obesity [49]. Based on current understanding and available data, it seems plausible that visceral fat and especially intrahepatic fat is the underlying driver for IR and inflammation. As in adults, the absence of hepatic steatosis seems to be a strong predictor of MHO, even after adjusting for WC or BMI *z*-score [52]. Studies suggest that maintained insulin sensitivity may be the key mechanism underlying healthy obesity, because it was observed that as long as insulin sensitivity was preserved the number of other comorbid disorders was low. However, these

increased significantly with the presence of IR in obese individuals [49, 53].

The relevance of distinguishing between MHO and MUO was also shown in the longitudinal Bogalusa Heart study by Li et al., which showed that participants with the MHO phenotype during childhood were more likely to retain MHO status in adulthood [54]. Despite the fact that the level of obesity and fat mass was still markedly increased in childhood and in adulthood, this group of MHO individuals (both, during childhood and in adulthood) showed a cardiometabolic profile generally comparable to that of non-obese children and non-obese adults. In addition, carotid intima-media thickness did not differ in adulthood between former MHO children and former non-obese children. These results are of significant importance, since they show that the MHO phenotype—if it starts in childhood and may be preserved into adulthood—may have a very favorable cardiometabolic risk profile, which is comparable to normal weight individuals of comparable age [54].

Even more important, there is increasing body of evidence showing that the metabolic profile of MHO individuals is almost indistinguishable from that of lean individuals [52]. However, although there is evidence showing differences in the metabolic profile of obese children and adolescents with effects for their future health and, therefore, consequences for interventions, there are also studies questioning the benign nature of MHO [55, 56].

Di Bonito et al. showed that despite the absence of traditional cardiometabolic risk factors, the prevalence of hepatic steatosis and left ventricular hypertrophy progressively increased across BMI categories (overweight, obesity, morbid obesity) [55]. Concluding that the MHO phenotype does not represent a "benign" condition in youth, Shaharyar et al. also suggested that MHO phenotype may not be benign, because, in their study cohort, they could show that, contrary to the name "metabolic healthy", metabolic abnormalities were found in the MHO group as compared to the normal weight metabolically healthy group. In particular, the prevalence of elevated CRP (≥3 mg/dL) and hepatic steatosis differed between the groups [56].

Critical appraisal of MetS in children and adolescents

Currently, there is still an ongoing debate on whether MetS should be defined/diagnosed in the pediatric age group,

and if defined, which definition should be used [16, 57, 58]. One of the key problems is that MetS is highly unstable throughout childhood and puberty [58].

The American Diabetes Association and the European Association for the Study of Diabetes published a joint statement raising questions about whether the components of MetS, as defined above, warrant classification as a true "syndrome" [59]. The arguments raised include: the lack of clarity for the definition; the inclusion of multiple different phenotypes within MetS, with indications for differing treatment strategies; a lack of a consistent evidence base for setting the thresholds for the various components in the definitions; the unclear pathogenesis; and not including other risk factors for CVD in the definition, such as inflammatory markers.

The lack of a consensus on a MetS definition for children leads to varying prevalences and challenges in comparing different studies with each other. Furthermore, the concept of MHO and MUO as a subtype of classification of obesity adds further confusion to the MetS definition.

One subject under discussion is the anthropometric indicator for central obesity and its cut-off. While the IDF definition [17] and several other authors have included and proposed WC as the best marker for central obesity [34], experts such as Damanhoury et al. have proposed to use BMI instead [51]. Other anthropometric indicators, such as body fat discriminators in children and adolescents, are available, for example, waist-to-hip ratio, waist-to-height ratio, neck circumference, hip circumference, or skinfold thickness [60–62]. In a systemic review and meta-analysis, Alves Junior et al. found that BMI, waist circumference (WC), and waist-to-hip ratio are excellent body fat discriminators in both sexes and these indicators can all be used by health professionals to asses body fat in children and adolescents, with some limitations [60]. However, Brambilla et al. proposed that WC is a good predictor for visceral adipose tissue, while BMI is suitable for subcutaneous adipose tissue [63].

One major difference between the proposed definitions of MetS is the variability in the definition of IR. This is in part because insulin concentrations change physiologically during puberty, making it difficult to interpret them in adolescents, and fasting insulin levels are limited by great intra- and interindividual variability. Another reason is that serum insulin concentrations are only an indirect parameter of IR. A very accurate assessment of IR requires a complicated and invasive test and is, therefore, impractical for clinicians. Simple tools such as fasting glucose, however, show only weak correlation with continuously measured blood glucose. Impaired glucose tolerance from the oral glucose tolerance test (OGTT) shows a better

association with continuously measured blood glucose but has a low reproducibility. HbA1c may be a better parameter, since it demonstrates the best correlation with continuous glucose measurements [64].

For the pediatric population, the concept of MetS is even more difficult to define due to the physiological changes throughout their growth and development, and the lack of cardiovascular events [4]. In one study of 1,098 adolescents, as many as half of the adolescents initially classified as having MetS lost this diagnosis during the three-year observation period, while others acquired the diagnosis [65]. This observation that 50% or even more of the formerly MetS-positive subjects in pediatric cohorts can become MetS-negative over time was also confirmed in one short-term study (about 3-week follow-up) [66] and one long-term study (about 9-year follow-up) [67]. Puberty seems to be an important influencing factor for cardiovascular risk markers which are components of MetS. This is probably due to a physiological reduction of insulin sensitivity (up to 30%); these changes are reversed at post pubertal stages and are parallel to the changes in cardiovascular risk factors during puberty [64]. However, the increase in IR during puberty has been reported to be more severe in obese as compared to normal-weight children. Since puberty has an important influence on insulin resistance, Reinehr et al. claim that a definition of MetS without considering the stage of puberty leads to misconceptions [64].

The interpretation of laboratory test results and anthropometric measurements in pediatrics is performed in the context of age- and sex-dependent dynamics, in order to reflect on physiological developments and dynamics, particularly in the first years of life and during puberty. To reflect inter- and intraindividual variation of measurements, clinical decision-making is generally guided by reference intervals [68]. The WHO recommended that reference intervals should be derived from a healthy cohort and be age-, sex-, and pubertal stage-related percentiles. However, the cut-offs for these reference intervals (specific centile) vary in different studies.

Another shortcoming in the concept of MetS is that the CVD risk associated with MetS has not been shown, in all studies, to be greater than the sum of its individual components [69]. Reinehr et al. and other authors have also reported that pediatric definitions of MetS were not any better at predicting increased carotid intima-media thickness than BMI alone [64].

The critical weakness of the current MetS construct is that treatment of the syndrome is no different from the treatment for each of its components. It is generally agreed that the presence of one component of MetS should lead to

the evaluation of other risk factors. Whether patient benefit is gained from diagnosing patients with a syndrome of such uncertain characteristics or predictive value remains an open question.

Early diagnosis of MetS in children and adolescents

Pediatricians and researchers agree that early diagnosis and early interventions for MetS are important to improve the prevention of CVD and type 2 diabetes in adulthood [70]. However, this requires an appropriate screening tool for children and adolescents at risk of MetS and its comorbidities.

The next chapter will look at the following questions:
(1) Who should be screened for MetS and its comorbidities?
(2) What should be screened for?
(3) How often should children and adolescents be screened?

Risk factors

In order to answer these questions, we have to define what is meant by "risk factors". There are two types of risk factors to be considered.

The first type of risk factor is the predisposition to develop components of MetS. These can be divided into immutable risk factors, which cannot be changed by the individual, and influenceable risk factors.

The second type of risk factor is the components of MetS itself, because they predispose toward the development of CVD and type 2 diabetes.

Predisposing risk factors for MetS

Immutable risk factors for the development of MetS include, for example, genetics; epigenetics, including gestational programming and epigenetic inheritance; maternal birth weight; maternal weight gain during pregnancy; maternal nutrition; stress; physical activity; endocrine disruptors during pregnancy; birth weight; or adiposity rebound [16, 57].

Risk factors which can be influenced by individuals or changes in society include, for example, nutrition; low physical activity; socioeconomic status; short duration of sleep; excessive screen time; tobacco smoke; endocrine disruptors; or medications [16, 57, 71, 72].

Predisposing risk factors for CVD and type 2 diabetes

The risk factors most studies agree on are the four major components of MetS: central obesity; hypertension; dyslipidemia; and impaired glucose tolerance. Additional risk factors for CVD and type 2 diabetes associated with the MetS are, for example, NAFLD; hyperuricemia; sleep disturbances; CKD and microalbuminuria; and polycystic ovary syndrome.

In the CARITALY Study Group, 3,088 overweight (OW)/obese (OB) youths were investigated; the prevalence of impaired fasting glucose was determined to be 3.2/3.3% in OW/OB, respectively, and impaired glucose tolerance was found in 4.6/5.0% (OW/OB). This study also showed a 2–11-fold increased risk of other metabolic comorbidities (including high LDL-c, non-HDL-C, Tg/HDL-c ratio, and low insulin sensitivity) for participants with an impaired glucose tolerance as compared to participants with a normal glucose tolerance. So, perhaps phenotyping prediabetes conditions using the OGTT should be done as part of prediction and prevention of cardiometabolic diseases in OW/OB youths from early childhood on. However, the efficacy needs to be verified in longitudinal clinical outcome studies [53].

How should these risk factors be assessed?

Predisposing risk factors

The predisposing risk factors for MetS should be kept in mind when taking the history of a patient. The presence of risk factors can encourage physicians to do further screening, especially if children are overweight or obese. However, lean children and adolescents cannot develop MetS, so they should not be screened or tested for this condition.

Due to controversies regarding the definition of MetS and the lack of consensus thresholds for the single components in children and adolescents, there is no international accepted diagnostic pathway for MetS available. However, several consensus statements and national guidelines for the assessment of obesity and its comorbidities in children and adolescents are available.

However, obesity seems to be the driving factor for the development of MetS. Therefore, applying obesity guidelines to assess MetS appears to be reasonable. The following screening pathway has been proposed, largely considering four guidelines from the USA, UK, and Germany.

The US Preventive Service Task Force states that although all children and adolescents are at risk for obesity and should be screened; there are children with several specific risk factors who need special attention. These risk factors include parental obesity, poor nutrition, maternal diabetes, maternal smoking, low levels of physical activity, sedentary behavior, inadequate sleep, low family income, gestational weight gain, maternal smoking, rapid infant growth, or certain racial/ethnic backgrounds. They recommend the measurement of BMI as screening test for obesity. For children and adolescents, age- and sex-specific percentiles for the BMI should be used. Obesity is defined by BMI ≥ 95th centile. According to the USPSTF, there is no evidence regarding appropriate screening intervals for obesity in children and adolescents. However, they recommend measuring BMI routinely during health maintenance visits [73].

The American Academy of Pediatrics (AAP) defines overweight as weight-for-length > 95th percentile for age/sex for children under 2 years. For children older than 2 years, overweight is defined by a BMI between the 85th and 94th percentile for age and sex, and obesity as BMI > 95th percentile for age and sex. The AAP recommends screening for fasting lipids in any overweight or obese child. Overweight or obese children older than 10 years with risk factors for type 2 diabetes should be tested for alterations in fasting lipids, aspartate aminotransferase/alanine aminotransferase (AST/ALT), and fasting glucose. Type 2 diabetes risk factors include a family history of diabetes, high-risk racial/ethnic background (African American, Hispanic, Native American), polycystic ovarian syndrome, acanthosis nigricans, and CVD risk factors. If serum screenings are normal, they should be repeated every 2 years for children older than 10 years [74].

The National Clinical Guideline Centre in the UK published recommendations for the "Identification, assessment and management of overweight and obesity in children, young people and adults" in 2014. They also recommend using the age- and sex-specific BMI to estimate obesity in children and adolescents, but highlight that BMI is not a direct measure of obesity. They do not recommend WC and bioimpedance as a routine measure for screening. According to NICE, children should be assessed for comorbidities of obesity if their BMI is ≥ 98th centile. Investigations include blood pressure measurement, fasting lipid profile, HbA1$_c$, fasting insulin, fasting glucose levels and OGTT, liver function tests, and endocrine function tests. Furthermore, they also emphasize the importance of: increasing awareness about the disease in the child and

family; assessing family history; investigating psychosocial distress, such as low self-esteem, teasing, or bullying; determining lifestyle, environmental, social, and family factors that may contribute to being overweight or obese; investigating the willingness and motivation to change; growth and pubertal status; as well as medical problems and medication [75].

The German Adiposity in children and young adults work group proposed an approach for the assessment of overweight and obesity and its comorbidities in children and adolescents. The diagnostic has three main objectives: 1. Assessing the degree of obesity, 2. Excluding an underlying disease, 3. Evaluating the health risk and comorbidities (adapted approach flowchart: Figure 1, part 1 and 2). In the initial examination, the age- and sex-specific BMI or BMI-SDS should be used. For adolescents >15 years, age- and sex-specific WC can be used to account for the body-fat-distribution. If the BMI is below the 90th centile, children should be re-assessed after one year. If a child is overweight (BMI ≥ 90th centile), screening for health risk factors is recommend. This includes taking a detailed

medical and family history, assessing the ethnic/racial background, measuring blood pressure, and screening for signs of dyslipidemia or IR, for example, looking for the presence of acanthosis nigricans. Further investigations are needed if there is a BMI increase of >2.0 kg/m²/year, or if there is serious concern about the weight or any abnormality in the above-mentioned factors (see: Screening for health risk and comorbidities for obese).

Obese children (BMI>97th centile) should be screened for health risks and comorbidities. They should receive a detailed anamnesis and examination. Primary underlying diseases must be excluded (chronic diseases associated with immobility, microsomia, hypothalamic syndrome, craniopharyngioma, and medications [e.g., glucocorticoids, insulin, valproate, phenothiazine]). In every child blood pressure, HDL-/LDL-cholesterol, fasting triglycerides, liver enzymes (ALT/AST), and fasting glucose should be measured.

Depending on family history and clinical- and paraclinical presentation, AGA recommends screening for signs of polycystic ovary syndrome (PCOS), IR, type 2 diabetes, hyperuricemia, sleep disturbances, increased risk for
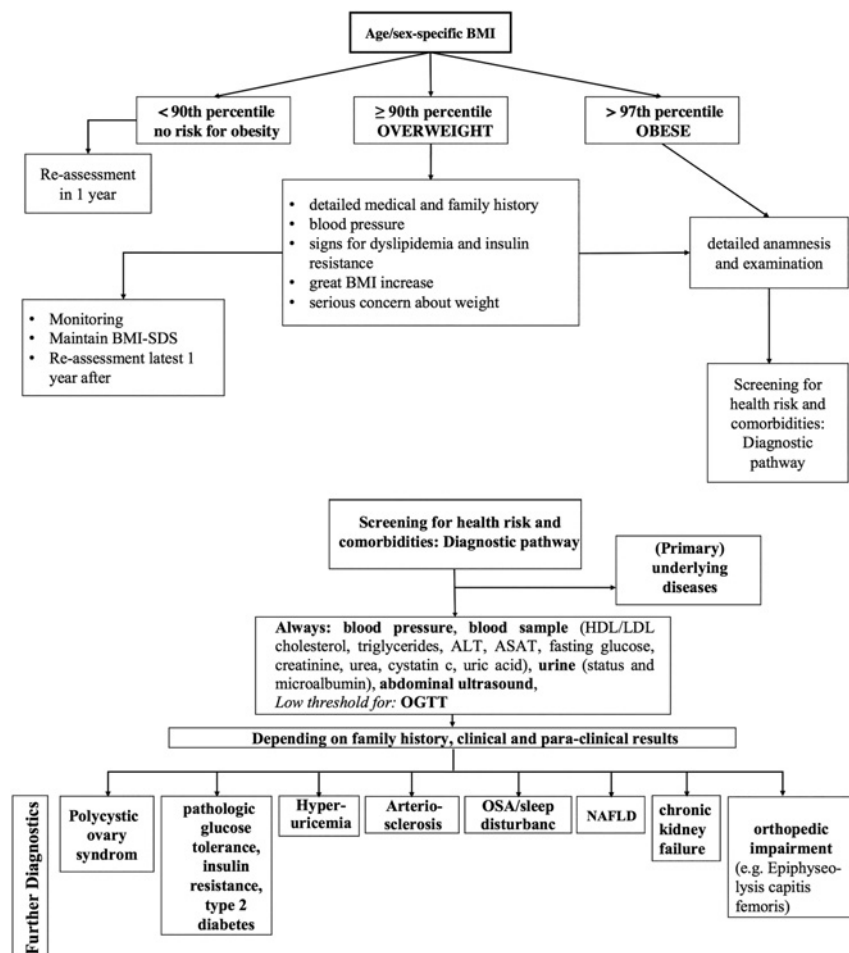

Figure 1: Part 1. Diagnostic approach: Flowchart to assess obesity and its comorbidities (MetS) in children and adolescents. Adapted from [76]. BMI-SDS: body mass index- standard deviation score. Part 2. Diagnostic approach: Flowchart to assess obesity and its comorbidities (MetS) in children and adolescents. Adapted from [76]. HDL: high-density lipoprotein, LDL: low-density lipoprotein, OSA: obstructive sleep apnea, NAFLD: non-alcoholic fatty liver disease.
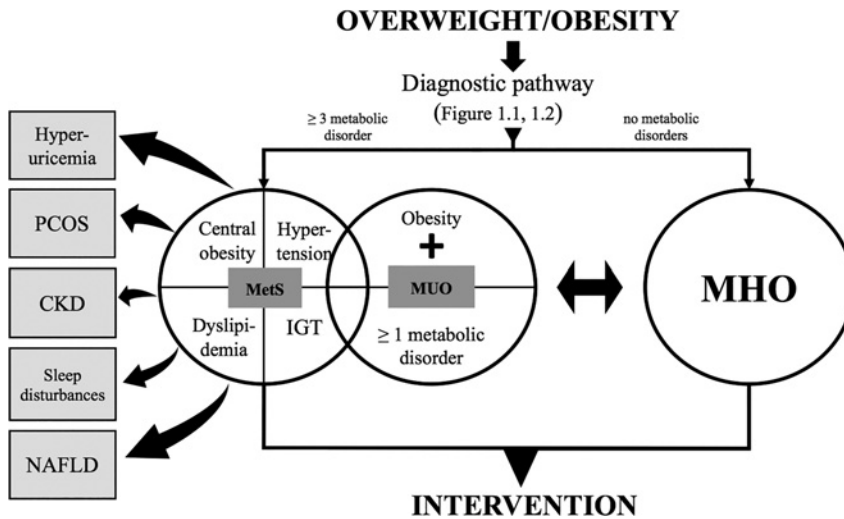
Figure 2: Diagnostic dilemma. Metabolic unhealthy obese (MUO) and metabolic healthy obese (MHO). CKD: chronic kidney disease, IGT: impaired glucose tolerance, METS: metabolic syndrome, MHO: metabolic healthy obese, MUO: metabolic unhealthy obese, NAFLD: non-alcoholic fatty liver disease, OGTT: oral glucose tolerance test, PCOS: polycystic ovary syndrome.

arteriosclerosis, or orthopedic problems [76]. Because of the association between metabolic disease and CKD, we like to recommend screening for signs of kidney impairment (creatinine, urea, microalbumin, cystatin c). Furthermore, the threshold for phenotyping prediabetes conditions by OGTT should be set low in overweight/obese youths, as a potential part of the prediction and prevention of cardiometabolic diseases [53]. These recommendations are summarized in Figure 1.

There is growing interest in inflammatory markers, adipocytokines, and microRNAs as potential future screening instruments [77–81], but they are not yet recommended as such [34].

Recommendations

It is known that an early diagnosis and successful treatment are the cornerstones for the reduction of morbidity and mortality related to MetS [82]. Regarding the discussed guidelines, we would like to recommend screening children for overweight and obesity and its comorbidities using clinical judgment and up-to-date reference values (age- and sex-related percentiles). In order to avoid conflicts concerning the definition of overweight and obesity, we recommend using the WHO definition of overweight (one standard deviation BMI for age and sex) and obesity (two standard deviations BMI for age and sex) in children and adolescents (last accessed 11.11.2019).

MetS is a complex cluster of disease, mainly concerning metabolic changes. However, psychological, social, or orthopedic implications related to MetS must also be considered. A diagnostic pathway (Figure 1, part 1 and 2) can help clinicians to screen for obesity and its comorbidities in children.

To date, there are no distinct therapeutic options for patients with different degrees of obesity or between MHO and MUO individuals. There is a growing body of evidence that MHO patients may not benefit from these therapeutic interventions in the way that MUO patients do. Perhaps different approaches for MUO and MHO are necessary [49]. Nevertheless, all obese patients in the pediatric field should be screened for potential need for interventions (Figures 1 and 2).

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