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PEDIATRIC TYPE 2 DIABETES (PS ZEITLER, SECTION EDITOR)

Metabolic Syndrome in Children and Adolescents: a Critical Approach Considering the Interaction between Pubertal Stage and Insulin Resistance

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Abstract Pediatricians increasingly diagnose the metabolic syndrome (MetS) in recent years to describe cardiovascular risk and to guide management of the obese child. However, there is an ongoing discussion about how to define the MetS in childhood and adolescence. Since insulin resistance—the major driver of MetS—is influenced by pubertal stage, it is questionable to use definitions for MetS in children and adolescents that do not take into account pubertal status. A metabolic healthy status in prepubertal stage does not predict a metabolic healthy status during puberty. Furthermore, cardiovascular risk factors improve at the end of puberty without treatment. However, having a uniform internationally accepted definition of the MetS for children and adolescents would be very helpful for the description of populations in different studies. Therefore, the concept of MetS has to be revisited under the influence of puberty stage.

Keywords Puberty · Definition · Metabolic Syndrome · Intervention · Obesity

Introduction

The increasing prevalence of obesity in childhood and adolescence poses a growing problem [1]. Obese children tend not only to become obese adults [1] but obesity is associated with a wide range of serious complications already in childhood [2]. As in adulthood, obesity in childhood contributes to an increased prevalence of cardiovascular risk factors, such as hypertension, hypertriglyceridemia, low HDL-cholesterol, and impaired glucose metabolism [2–6]. The prevalence of these abnormalities is increasing in a parallel manner with the degree of overweight (Table 1). Obese children and adults without cardiovascular risk factors have been classified as metabolic healthy obese (MHO) [7–9]. A total of 6 % to 40 % of obese adults [10, 11] and 6 % to 36 % of obese children [8, 12–14] are metabolically healthy.

The clustering of obesity, hypertension, dyslipidemia, and impaired glucose tolerance is associated with atherosclerosis and cardiovascular diseases (CVD) leading to increased mortality [15–19]. Based on this observation, the concept of the metabolic syndrome (MetS) was developed [17]. The concept of MetS means that the clustering of risk factors is predictive for CVD above and beyond the risk associated with its individual components [15, 17, 20].

Definition of MetS in Children and Adolescents

There is an ongoing discussion concerning the definition of MetS in children and adults [20, 21]. Multiple definitions of the MetS have been proposed for children based on definitions in adults [22] agreeing on the essential components—obesity, hypertension, dyslipidemia, and distributed glucose metabolism—but differing in the details (Table 2) [23–26]. Today, the IDF definition is the most frequently used definition of MetS [22, 26].

Pediatricians increasingly diagnose the MetS to describe cardiovascular risk [24] and to guide the management of the obese child. For example, the rationale to treat MHO humans has been questioned since there is no evidence for increased mortality [12–14]. On the other hand, it has been suggested to

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Table 1 Prevalence of cardiovascular risk factors in 26,008 Caucasian children

	Normal- weight (BMI > 10th - <90th percentile)	Overweight (BMI 90th - <97th percentile)	Obese (BMI 97th - <99.5th percentile)	Extreme obese (BMI ≥99.5th percentile)
Hypertension	5 %	7 %	12 %	26 %
HDL-cholesterol <0.91 mmol/L	2 %	4 %	10 %	15 %
Triglycerides >1.7 mmol/L	8 %	10 %	14 %	16 %
Impaired fasting glucose	1 %	1 %	1 %	4 %
Impaired glucose tolerance	0 %	5 %	6 %	8 %
Type 2 diabetes mellitus	0 %	0.1 %	0.2 %	0.4 %
Clustering of cardiovascular risk factors	0 %	5 %	10 %	15 %

Data from [3].

treat intensively patients with MetS, including with drugs and bariatric surgery [12–14]. However, before basing treatment recommendations on the concepts of MetS and MHO, some shortcomings of their definitions in children and adolescents have to be kept in mind, which will be discussed in the following. The limitation of these concepts are apparent since pediatric studies in obese children report a wide range of prevalence of MetS of 30 % to 72 % [12–14, 20] and MHO of 6 % to 36 % [8, 12–14], independent of body mass index (BMI). This suggests that further important factors influence the prevalence of MetS.

Influence Factor on Prevalence of MetS

Insulin resistance is a key mechanism in the development of MetS [15, 27]. It is related to all cardiovascular risk factors summarized in the MetS [15]. Body fat amount and distribution, as well as physical activity, are related to insulin resistance. Accordingly, weight loss and increase in physical activity improve insulin resistance and MetS [15, 28–39]. Children with MetS were reported to have lower physical activity compared with MHO children [8, 12–14]. The association between body fat, physical activity, and insulin resistance is mediated by several adipocytokines, such as leptin [40], adiponectin [40], retinol binding protein [41], and visfatin [42], hepatokines, such as fibroblast growth factor (FGF)-21, fetuin [43, 44], and sex hormone binding globulin (SHBG) [45], as well as hormones secreted by the muscle, such as irisin [46]. Furthermore, obesity is regarded as a low-grade chronic inflammation, further contributing to insulin resistance because inflammation increases insulin resistance through multiple pathways [47]. Disturbed secretion of adipocytokines and inflammatory markers could be observed, particularly in mesenterial fat [40, 47]. Therefore, it is not surprising that some studies in children and adolescents reported a stronger correlation between waist circumference and insulin resistance compared with the correlation between BMI and insulin resistance [8, 12–14].

Furthermore, genetic background is an important influence factor for presence of MetS in obese children. For example, Hispanic, African, and Asian children demonstrated higher frequencies of MetS compared with non-Hispanic White children [23, 24]. Interestingly, children of these affected ethnicities have a greater insulin resistance compared with non-Hispanic White children [48, 49].

Most importantly, pubertal stage has been identified as a major influence factor on cardiovascular risk markers that are components of MetS. Cardiovascular risk factors deteriorated at onset of puberty and improved in late puberty in a longitudinal study of 287 untreated obese non-Hispanic White children (53 % female, mean age 11.4 years, mean BMI 28.2 kg/m^2) [50]. In a further longitudinal study, early puberty in obese Afro-Caribbean girls was associated with increased blood pressure and higher fasting glucose [51]. We confirmed the relationship between puberty and cardiovascular risk factors in a larger longitudinally study based on 2017 obese non-Hispanic White children (mean age 11.6 ± 2.8 years, 45.0 % male, 41.6 % prepubertal, mean BMI 28.5 ± 5.3 kg/m^2) [52••]. In this study, entering into puberty was associated with deteriorations of blood pressure, lipids, and glucose levels (Fig. 1), whereas transition from mid to late puberty was associated with improvement of these factors, independent of changes of weight status. These findings match well with previous cross-sectional studies demonstrating a relationship between cardiovascular risk factors and pubertal stage [53•, 54–56]. Accordingly, Ferranti and Cook reported a 3- to 5-fold higher prevalence of the MetS in pubertal adolescents compared with prepubertal children [25, 57]. Pinhas-Hamiel and colleagues reported an increase of lipid and insulin levels during puberty [55]. Furthermore, impaired glucose tolerance and impaired fasting glucose are more frequent in pubertal obese adolescents compared with prepubertal children [58] and normalize at end of puberty [59].

Table 2 Proposed definitions of the Metabolic Syndrome in children and adolescents

Cook et al [25] ≥3 of 5 criteria:	Ferranti et al [57] ≥3 of 5 criteria:	Viner et al [23] ≥3 of 4 criteria:	Weiss et al [24] ≥3 of 5 criteria:	IDF [26] WC > 90th percentile + ≥2 criteria
WC > 90th percentile for age and gender	WC > 75th percentile for age and gender	BMI > 95th percentile for age and gender	BMI > 97th percentile for age and gender	
BP > 90th percentile	BP > 90th percentile	Systolic BP > 95th percentile	BP > 95th percentile	Sys RR > 130 or dias RR > 85
Triglycerides ≥110 mg/dL	Triglycerides ≥100 mg/dL		triglycerides > 110 mg/dL	Triglycerides > 150 mg/dL
HDL-cholesterol <40 mg/dL	Female: HDL- cholesterol <50 mg/dL Male: HDL- cholesterol <45 mg/dL	1 of 3 criteria: Triglycerides ≥150 mg/dL HDL- cholesterol < 35 mg/dL Total cholesterol > 95th percentile	HDL-chol. < 40 mg/dl	HDL-chol. < 40 mg/dl
Impaired fasting glucose	Impaired fasting glucose	1 of 3 criteria: impaired fasting glucose impaired glucose tolerance fasting insulin: ≥ 15 mU/L prepubertal ≥ 30 mU/L pubertal ≥ 20 mU/L late/postpubertal	impaired glucose tolerance	impaired fasting glucose

BP blood pressure, *WC* waist circumference.

The reason for the changing MetS prevalence during puberty lies likely in the worsening of insulin resistance during puberty. Entry into puberty is characterized by a physiologic ~30 % reduction of insulin sensitivity that is reversed at post-puberty [60•, 61–63]. These changes are parallel to the changes of cardiovascular risk factors during puberty [52••, 53•, 64]. In a longitudinal study in 253 overweight Hispanic youth, insulin sensitivity decreased in both sexes in early puberty with a recovery in late puberty [65••]. In non-Hispanic White children, the same changes in insulin sensitivity during puberty have been reported [66]. A rise of insulin resistance has been reported prior to puberty when adrenarche starts [67, 68•]. Moreover, it has been reported that insulin resistance increases during puberty in obese children more than in normal-weight children [54, 64]. Finally, it is well-known that glucose metabolism frequently deteriorates during puberty in children suffering from type 1 diabetes mellitus and improves at end of puberty [69]. Besides treatment nonadherence, increased insulin resistance may contribute to this problem in adolescents with type 1 diabetes mellitus [69].

The reasons for changes in insulin resistance during puberty are not well understood. Puberty has an effect on fat oxidation rates during exercise in overweight and normal-weight girls, resulting in increased insulin resistance [70]. A temporal relationship between insulin sensitivity and the pubertal decline in physical activity in peripubertal Hispanic and African American females has been reported [71]. Ethnicity also seems to influence the relationship between insulin sensitivity and puberty [48]. This points toward genetic factors modulating the impact of puberty on insulin sensitivity [49]. Concentrations of sex hormones, adipocytokines, and inflammatory cytokines change dramatically during pubertal development, making an influence on insulin resistance and MetS probable [45, 72••]. Adiponectin concentrations had been negatively correlated to many cardiovascular risk factors and decrease with onset of puberty in males [42]. Also, the adipokines, visfatin and vispin, as well as their changes during puberty, have been reported to be associated with cardiovascular risk factors [42, 73]. Serum retinol binding protein 4 is another adipocytokine that is related to adiposity, pubertal development, and cardiovascular risk factors [41]. However, another study reported no relationship between retinol binding protein 4 levels and insulin resistance during puberty [74]. Additionally, osteocalcin, which is a link between skeleton, obesity, and insulin resistance, was also linked to puberty [75]. Furthermore, fetuin-A, a hepatocytokine that is related to MetS and fatty liver disease in obese children, changed during puberty [43]. SHGB levels predict insulin sensitivity, disposition index, and cardiovascular risk during puberty [76]. However, the observed relationships between adipocytokines and insulin resistance were only weak in longitudinal studies during puberty, suggesting further important influence factors [74].

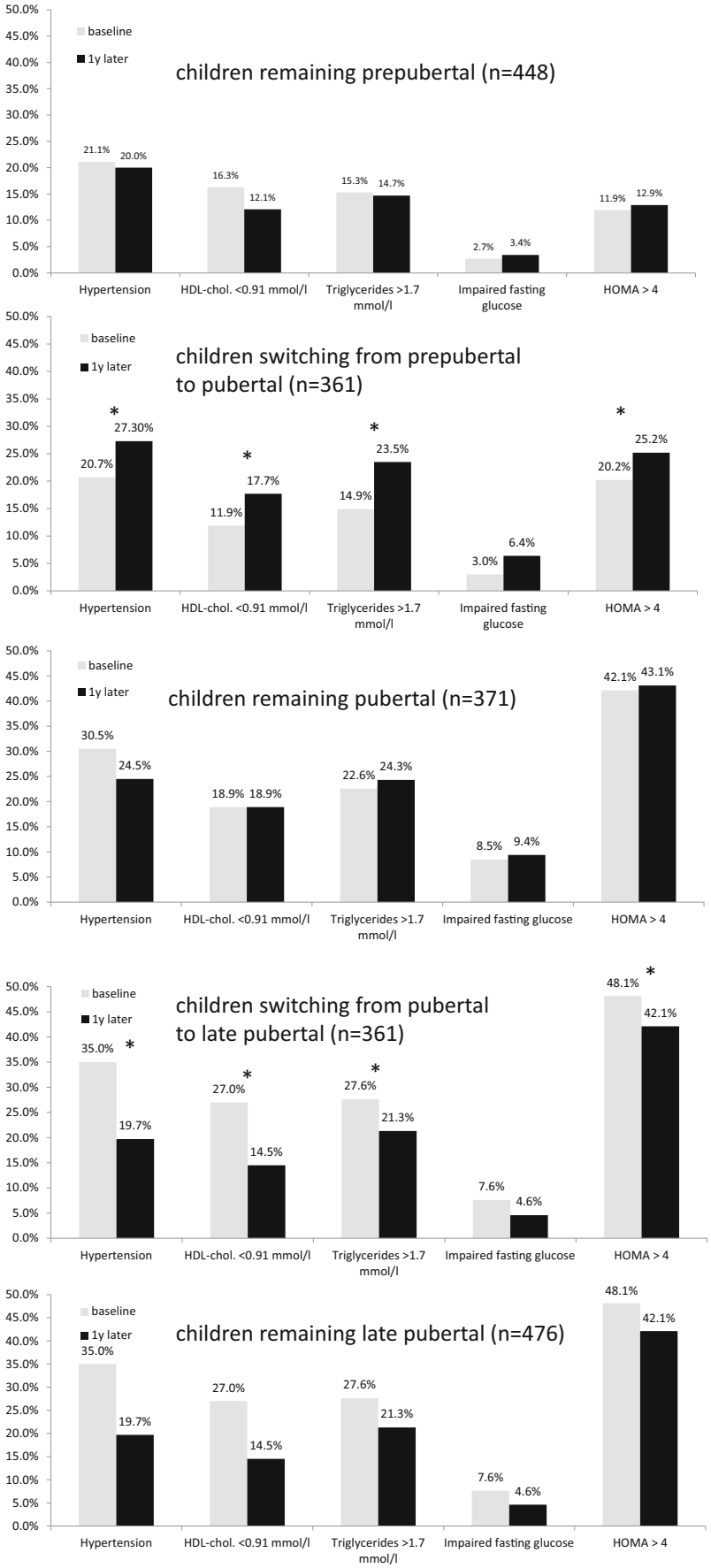

Fig. 1 Changes of cardiovascular risk factors in the time period of 1 year in 2017 obese children without intervention separated to pubertal stage. (Data from [52••]);*: significant difference between baseline and 1 year later; chol.: cholesterol

Interestingly, puberty is also influenced by insulin resistance. In mouse models, an interaction between insulin and leptin signaling was reported during the peripubertal period in the neurons responsible for pubertal development [77]. Furthermore, a study in obese children reported an advanced onset of puberty after metformin, a drug to decrease insulin resistance [78]. Therefore, there seems to be a bidirectional interaction between insulin resistance and puberty.

Resulting Shortcomings in the Concept of MetS in Children and Adolescents

Since puberty is an important influence on insulin resistance, a definition of MetS without considering the puberty stage leads to misconceptions. For example, the impact of puberty on insulin resistance may explain the wide range of MetS prevalence reported in obese children [12–14, 20]. Furthermore, some surprising findings in the literature concerning the MetS in children can probably be attributed to the influence of puberty. The missing effect of metformin on cardiovascular risk factors in some randomized controlled trials may be explained by the fact that children in the untreated control group move from mid- to late puberty, as the age ranges of these studies suggest [79, 80]. Furthermore, the low predictive value of impaired glucose tolerance for development of type 2 diabetes and the high conversion rate (66 % to 75 %) back to normal glucose tolerance in adolescents in contrast to adults, where the rate of conversion from impaired glucose tolerance to type 2 diabetes in 5 years is reported to be 30 % [81, 82], may also be attributed to the fact that many adolescents in the longitudinal studies move from mid to late or postpubertal stage [83, 84].

Due to the relationship between puberty and cardiovascular risk factors, different cut-off points specific for prepubertal, pubertal, and postpubertal children and adolescents might be necessary. But the whole concept of using recommended cut-off points for the various risk factors in the definition of the MetS represents a major concern since the cut-offs imply that the values above the specified thresholds are associated with an excess risk, despite the fact that the rationale for the different cut-off points has never been delineated in children and adolescents [20]. Moreover, the artificial dichotomization of continuous variables such as lipids, waist circumference, and blood pressure values seems debatable since dichotomization leads to an unnecessary loss of information [85]. In fact, the relationships are not even linear, which opens up the question of how risk in this conglomeration of the "syndrome" might be weighted more appropriately.

Indeed, the use of rigid cut-off points in the definition of MetS reduces its prognostic value both in adults and children. Mente and colleagues reported an underestimation of myocardial infarction in adults using the dichotomous variable MetS instead of the continuous variables blood pressure or lipids [86]. Fadini et al, as well as Baldassare and colleagues reported no increased risk in MetS compared with the sum of its individual components based on carotid intima-media thickness (cIMT) measurements, a non-invasive reliable and predictive marker for early atherosclerotic changes [87, 88]. We have recently reported that the sum of the individual components of the different MetS definitions was superior to predict presence of increased cIMT in obese adolescents compared with the all or nothing variable occurrence of MetS [89]. Furthermore, adding the MetS indicator to the individual components added no further information to prediction of increased cIMT [89, 90]. Other studies also reported that pediatric definitions of MetS were not better at predicting increased cIMT compared with BMI alone [91]. However, in all these pediatric studies, the findings were not adapted for pubertal stage, possibly contributing to the negative results. In conclusion, up to now no outcome study in childhood has proven an increased mortality or morbidity in clustering of cardiovascular risk factors regardless of the definition of the MetS used compared with the cardiovascular risk factors themselves [20, 21].

Further Difficulties in the Definition of MetS in Children and Adolescents

The proposed definitions of the MetS in children and adolescents agree on the essential components—obesity, hypertension, dyslipidemia, and disturbed glucose metabolism—but differ in the details. This explains at least in part the large reported range of MetS prevalence rates (30 % to 72 %) [12–14, 20]. Only 9 % of obese children fulfilled all the suggested definitions of the MetS for children and adolescents in a large study with >1400 participants, demonstrating the problems of the inconsistency of the proposed definitions [20].

One major difference between the proposed definitions of MetS is the definition of insulin resistance. Insulin concentrations change physiologically during puberty [92], making it difficult to interpret them in adolescents. Furthermore, the values of fasting insulin levels are limited by the great intra- and interindividual variability [93]. Additionally, serum insulin concentrations are only a indirect parameter of insulin resistance [93]. An accurate assessment of insulin resistance requires a complicated test (eg, the hyperinsulinemic euglycemic clamp technique). Its application in children is invasive and impractical. Clinicians prefer simple tools, such as fasting glucose. However, fasting glucose showed only a weak correlation to continuously measured blood glucose [94]. Impaired glucose tolerance demonstrated a better association with continuously measured blood glucose [94]. However, the reproducibility of pathologic glucose concentrations in oral glucose tolerance tests is low [95]. HbA1c levels may be a better parameter to describe glucose metabolism, since it

demonstrates the best correlation to continuous glucose measurements [94].

Another important difference between pediatric definitions of MetS is the definition of obesity (Table 2). Some definitions are based on BMI, though it is well known that central obesity is the main driver of insulin resistance [40]. However, the interpretation of waist circumference depends not only on age but also on puberty stage. Published cut-offs of waist circumference percentiles for children are only adapted to age and gender but not to pubertal stage. They also seem not to be very specific since the majority of overweight children had waist circumferences above the proposed thresholds [20]. The new proposed waist to height ratio [96] may be a better predictor for MetS. However, longitudinal studies taking into account the effect of puberty are missing so far.

Conclusions

The reported prevalence of hypertension, dyslipidemia, and disturbed glucose metabolism in obese children and adolescents underlines the necessity for screening since most of these disorders are asymptomatic but related to later cardiovascular diseases. Indications for treatment, including antihypertensive, lipid- or glucose-lowering drugs, and bariatric surgery, should be based on weighting of the cardiovascular risk factors themselves, keeping in mind pubertal stage, rather than the dichotomous variable MetS. The proposed MetS definitions for children and adolescents have only low diagnostic accuracy and poor prognostic value. Since puberty influences the prevalence of components of the MetS, it is questionable to use definitions for MetS in adolescents not accounting for pubertal stage. A MHO in prepubertal stage does not predict a MHO status during puberty. This questions the concept that MHO children do not need an intensive treatment approach. On the other hand, if cardiovascular risk factors improve at the end of puberty, the need for intensive treatment approaches including drugs or bariatric surgery can be considered controversial in obese adolescents with MetS. Suffering from MetS during puberty does not predict that it will persist in young adulthood. The concept of MetS has to be revisited on the background of pubertal development. Having a uniform internationally accepted definition of the MetS for children and adolescents would be very helpful for the description of populations in different studies.

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Compliance with Ethics Guidelines

Conflict of Interest Thomas Reinehr declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent The data presented in this article are based on studies that have been approved by the ethics committee of the University of Witten/Herdecke, Germany and have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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moving from mid to late pubertal stage is related to an improvement of cardiovascular risk factors.

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