UNSOLICITED REVIEW

Cardiovascular Therapeutics

Metabolic Syndrome: Bridging the Gap from Childhood to Adulthood

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SUMMARY

Childhood and adolescence are particularly vulnerable periods of life to the effects of cardiometabolic risk and later development of atherosclerosis, hypertension, and diabetes mellitus. Developing countries with limited resources suffer most heavily from the consequences of cardiometabolic risk in children and its future implications to the global health burden. A better understanding of mechanisms leading to cardiometabolic risk in early life may lead to more effective prevention and intervention strategies to reduce metabolic stress in children and later disease. Longitudinal "tracking" studies of cardiometabolic risk in children provide a tremendous global resource to direct prevention strategies for cardiovascular disease. In this review, we will summarize the pathophysiology, existing definitions for cardiometabolic risk components in children. Screening and identifying children and adolescents of high cardiometabolic risk and encouraging them and their families through healthy lifestyle changes should be implemented to as a global public health strategy.

Introduction

Metabolic syndrome (MetS) is a complex disorder with a tremendous impact and socioeconomic burden on global health. It is defined as clustering of risk factors that directly increase the risk for cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) [1]. It is crucial to note that MetS starts early in childhood [2,3]. More importantly, developing countries with limited resources suffer most heavily from the consequences of MetS and its future implications to the global health burden [4].

MetS in children implicates the early start of dyslipidemia, high blood pressure, and obesity in childhood which will confer substantial risk for future CVD in adulthood [5]. As a consequence, efforts for combating future CVD should be directed to prevent MetS and lifelong exposure to cardiometabolic risk in children. Acknowledging the potential implications for public health, screening for cardiovascular risk factors in children is now recommended by American Academy of Pediatrics (AAP) [6], American Heart Association (AHA) [7], and National Heart, Lung, and Blood Institute [8].

Therefore, early prevention strategies beginning in childhood is the most logical step to reduce the future cardiovascular morbidity and mortality. In this review, we will summarize the pathophysiology and existing definitions for MetS in children.

Longitudinal "Tracking" Studies of Cardiometabolic Risk in Children

Although MetS was originally described in adults [1], the clustering of cardiometabolic risk factors starts at a young age [2]. Autopsy studies reveal that atherosclerosis is evident early in life and the degree of atherosclerosis in children associates with the presence of cardiometabolic risk factors in childhood [9]. Bogalusa Heart Study (BHS) [10] and Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Study [11] clearly demonstrate that high blood pressure and dyslipidemia in children associate with a higher prevalence of premature atherosclerosis. Hence, metabolic or cardiometabolic syndrome in children and adolescents is defined as the clustering of the risk factors associated with CVD early in life [12]. MetS prevalence, ethnic distribution, existing definitions, prevention strategies, and therapeutic options have been the subject of intense clinical research.

BHS, a long and detailed study of a biracial population of children, has focused on understanding the early natural history of CVD [10]. BHS bridges the gap between the childhood and adulthood in understanding the evolution of cardiometabolic risk. This study demonstrates that major risk factors for vascular disease such as high blood pressure or cholesterol, cigarette smoking, unhealthy diet, inactivity, poor social status, or limited access to medical care can in fact be modifiable. BHS has been

ongoing for over 35 years, along with other long-term international pediatric studies, namely Muscatine Study, the Cardiovascular Risk in Young Finns Study, and Childhood Determinants of Adult Health study (Australia). The lessons we learned provide a tremendous global resource to direct prevention strategies for CVD [5,13]. These studies are now linked as an international consortium to emphasize the importance of prevention and public health practice beginning in kindergarten. International Childhood Cardiovascular Cohort (iC3) Consortium examines the association in noninstitutionalized individuals of risk factors such as cholesterol, body mass index (BMI), and systolic blood pressure at different childhood age groups and their "tracking" into adulthood [14].

Puberty, Sexual Maturation, and Cardiometabolic Risk

Controversies still exist in screening children and adolescents for cardiovascular risk factors [8]. Body fat distribution, blood pressure, and lipids are all affected by puberty and normal growth. Normally, lean body and fat mass increase during the transition from late childhood to adolescence, so it is necessary to use childhood percentages at ages during growth. Fat distribution changes by gender, age, and ethnicity [15]. The percentage of body fat increases strikingly through adolescence especially in black females [16]. It is known that physiological hormonal changes in puberty leading to increased fat mass, androgen levels, and decreased sex hormone-binding globulin (SHBG) levels promote "normal" insulin resistance [17]. In obese children, MetS prevalence is remarkably higher than in normal weight children in all pubertal stages [3].

Both sex hormone and SHBG levels have important effects on high-density lipoprotein–cholesterol (HDL-C) levels and insulin resistance among children and adolescents [18]. With puberty, a rising level of estrogen occurs for girls and a sharp increase in androgen is noted for boys. While SHBG levels decrease in both gender (more pronounced for boys), free androgen index and free estradiol index levels increase with puberty [19]. Elevated testosterone is associated with MetS in adolescent girls [20] while low SHBG levels and hyperandrogenism have proven to be predictive of the development of MetS in girls [21]. We have recently reported that estradiol associated negatively with HDL-C levels and positively with homeostasis model assessment–insulin resistance (HOMA-IR) index among prepubertal boys. In contrast, a negative correlation occurs between androgen index and HDL-C levels, while SHBG levels were associated positively with HDL-C levels and negatively with HOMA-IR index among girls [18]. Hepatic lipase may be a logical link to explain the profound decrease in HDL-C after puberty. Hepatic lipase modulates HDL-C metabolism through its triglyceride hydrolase and phospholipase activities and lowers the plasma HDL-C levels [22]. Sex hormones (particularly androgens) regulate hepatic lipase mass and activity. Observations indicate that low SHBG levels after puberty increase the free androgen levels, and androgens are known to enhance HDL-C catabolism by increasing hepatic lipase activity [23].

Anthropometric Criteria of Cardiometabolic Risk

Although BMI is a good and often utilized measure of cardiometabolic risk in children, there are limitations with BMI as the sole anthropometric assessment. The main consideration is that BMI is not a measure of fat distribution and may underestimate excess fat. Further, there is big difference in childhood BMI. Therefore to define obesity on the basis of BMI, age- and sex-specific cutoff points should be utilized.

Thus, additional anthropometric indices are needed to estimate the fat distribution among children. As with IDF definition, an increase in waist circumference defines central obesity, while waist-to-hip ratio indicates abdominal obesity and correlates well with MetS risk criteria [24] as does waist-to-height ratio (waist/height: WHtR) [25]. Waist circumference percentiles in a population are influenced by the population's ethnicity. More importantly, adequate percentile information in a locally representative sample may not be available particularly for developing countries. Alternative and readily available anthropometric criteria are needed particularly in these populations. WHtR is reported as another anthropometric index of fat distribution in children; therefore, an increased WHtR is associated with higher metabolic risk in children [25]. Combining high waist circumference ($\geq$ 90th percentile) and WHtR ($\geq$ 0.5), representing central adiposity, can predict a 3.8 fold increase in CVD risk [26]. Waist circumference increases with age, but WHtR seems not to be affected by age; with 0.5 as a good cut-point, WHtR is suggested as the best indicator of central adiposity in both genders of adolescents [27]. Another anthropometric index, skin fold thickness, also correlates with cardiovascular risk among children [28] with some variations at different sites. Subscapular skin fold thickness is associated with central abdominal fatness.

Screening for High Blood Pressure in Children

BHS demonstrates that the number of cardiovascular risk factors correlates with the severity of asymptomatic coronary and aortic atherosclerosis in young individuals [10]. To prevent future cardiovascular devastating events, each component of the syndrome must be identified as early as possible. Early diagnosis and treatment for hypertension [29] and dyslipidemia have the potential to reduce teenagers' risk of developing CVD in adulthood [7,30]. Assessment of structure/function measures of the vasculature by simple noninvasive methods can identify early vascular damage in young asymptomatic subjects. Pulse wave velocity, central aortic pressure, and augmentation index are among modern and novel measures of cardiovascular assessment among children [31]. BHS reports that cardiovascular risk factors influence adversely measures of both structure and function of the vasculature to varying degrees in young subjects, with small artery compliance showing maximum variance [32].

Children with systolic blood pressure above the age- and gender-specific criterion values are at increased risk of hypertension and the MetS later in life [33]. Blood pressure has increased over the past decade among children and adolescents especially in

the developing countries [34]. This increase is partially attributable to an increased prevalence of obesity [35]. Pharmacological management is reserved for individuals with hypertension who do not respond to behavioral changes, and/or have additional cardiovascular risk factors such as diabetes [36] or even prediabetes [37].

Screening for Dyslipidemia in Children

Population-based data from National Health and Nutrition Examination Survey (NHANES) III (1988–1994) indicate that the mean age-specific values for total cholesterol peak just before puberty and decrease thereafter [38] and girls have significantly higher mean total cholesterol and low-density lipoprotein–cholesterol (LDL-C) than boys. The LDL-C then progressively rises into adulthood, yet HDL-C, high in childhood (around 65 mg/dL), dramatically decreases during puberty in Caucasian males to reach a nadir around 16 years to remain at the adult level, around 45 mg/dL.

AHA and National Heart, Lung, and Blood Institute recommend targeted screening of children with other risk factors (i.e., diabetes) family history of CVD, diabetes, and/or dyslipidemia [8,30]. Overweight children belong to a special risk category and need cholesterol screening regardless of family history or other risk factors. Children and adolescents with very high-risk hyperlipidemia may require lipid-lowering drug therapy, particularly those with familial hypercholesterolemia [8,30].

Data from BHS, Young Finns Study, and Childhood Determinants of Adult Health Study found that adolescents with elevated LDL-C had an increased risk of high carotid intima media thickness (cIMT) as LDL-C increased into adulthood. Children and adolescents with persistent low HDL-C and with low HDL-C that normalize by adulthood have an increased risk of high cIMT [13]. Low HDL-C levels may become a major concern particularly for developing countries [39]. Thus, non-HDL cholesterol and Apo B are likely to be better parameters than LDL-C to assess cardiometabolic risk among children [40]. BHS examines clustering of long-term rates of change in MetS variables (BMI, HOMA-IR, ratio of triglyceride to HDL-C and mean arterial pressure) from childhood to adulthood. Cardiometabolic risk variables coexist in terms not only of their levels in childhood and adulthood but also of long-term rates of change [41]. Thus, the goal is to identify children at increased cardiometabolic risk as early as possible. Table 1 shows criteria with potential utility to identify children at high risk universally.

Table 1 Criteria with potential utility to identify children at high risk universally

Waist circumference ≥90th percentile
Waist/height ratio >0.5
Body mass index >90th percentile
Fasting plasma glucose ≥86 mg/dL
Triglycerides >75th percentile
High-density lipoprotein cholesterol <25th percentile
Systolic or diastolic blood pressure >75th percentile
Positive family history for diabetes mellitus or metabolic syndrome

Predictors of Prediabetes and Diabetes

It has been known that T2DM has a strong familial component and risk factors of T2DM are expressed at relatively young age in those with parental diabetes [42]. Sixteen-year-old follow-up from BHS reported that race, sex, and parental history of diabetes predict the early onset of T2DM [43]. Incidence of onset of diabetes was found to be greater in black-versus-white females and baseline parental history of diabetes was significantly associated with T2DM in age onset group 18–29. Further, BHS indicates that the earlier onset of diabetes is associated with parental history (mother) of diabetes. This is before other morbidities compound the diagnosis and may be due to attrition of beta cells occur over time [43]. It is of interest in these studies a fasting glucose value of 86 mg/dL was found as a cut-point of being potentially abnormal (Table 1) [44]. Obesity was the most consistent predictor of the MetS from adulthood, preceding the onset of high insulin levels [45].

Ethnic and Population Contrasts

Ethnic and racial differences exist in criteria, definition, and prevalence of MetS in adolescents between populations [46]. Recently, AHA published heart disease statistics. According to the report, in United States, among children 2 to 19 years of age, 31.7% are overweight or obese and 16.9% are obese. Mexican American boys or girls and African American girls are disproportionately affected [47]. Approximately 30% of overweight children have the MetS and nine of 10 have at least one feature of the syndrome [48].

It has been shown that differences exist in the criteria, definition, and prevalence of MetS in children and adolescents between populations [49]. For example, data from NHANES III (1988-1994) revealed that non-Hispanic African American children and adolescents aged 4-19 years old had significantly higher mean total cholesterol, LDL-C, and HDL-C levels [38] but lower MetS prevalence compared to non-Hispanic white and Mexican American children and adolescents [50]. Subsequently, NHANES (1999–2004) indicated that prevalence of the MetS increased with age, and was higher among boys than girls. The highest prevalence was observed among Mexican American adolescents aged between 12 and 17 years [51]. More recently, NHANES (1999-2008) showed that girls had higher insulin levels than boys, and non-Hispanic African American and Hispanics had higher insulin levels than non-Hispanic whites [52].

We previously observed that Turkish children had lower BMI compared to age and gender-matched African American and Caucasian children of Bogalusa. Despite their lower BMI, Turkish children paradoxically displayed higher triglyceride and lower HDL-C levels [39]. African American children and adolescents had higher prevalence of obesity and high blood pressure compared to their white counterparts. Further, they displayed a lower prevalence of MetS due to their lower triglyceride and higher HDL-C levels [12]. The SEARCH for Diabetes in Youth Study showed that non-Hispanic whites had the highest prevalence of diabetes mellitus in the 0- to 9-year-old group. Among 10- to 19-year-old youth, black youth and non-Hispanic white youth demonstrated the highest prevalences of diabetes, followed by American Indian youth, Hispanic youth, and Asian/Pacific Islander youth [53].

Investigators from Japan and Australia have compared their cohort with BHS population in an attempt to explain the coronary artery disease mortality differences in these countries. The finding of a higher HDL-C in Japanese children than in BHS cohort is thought to contribute to the lower coronary artery disease mortality in Japanese population [54]. Results from BHS indicate that white male subjects have a significantly higher prevalence of prediabetes than white female subjects. With respect to diabetes, white male-versus-white female subjects and black female-versus-white female subjects have significantly higher prevalence. Male-versus-female subjects with prediabetes and black-versus-white subjects with diabetes have a significantly higher prevalence [37,55]. Furthermore, African American children show a higher degree of clustering of long-term rates of change in MetS risk variables than observed in whites [41].

Physical activity and eating habits not only differ among populations but also change during puberty–adolescence transition which negatively influences the body fat distribution, blood pressure, and lipid levels [56].

Existing Definitions for Metabolic Syndrome in Youth

Due to an alarming increase in childhood obesity over the past two decades, MetS in children and adolescents have recently become a major public health problem [57]. Yet, there is still no consensus regarding the criteria and the definition of MetS in children. Secular and temporal changes of cardiovascular risk factors as well as population differences further complicate the diagnosis of MetS in children [58].

In 1999, BHS established the limits for LDL-C, glycemia, insulin, HDL-C and waist circumference in children and adolescents [59]. Later, a modified National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III) [60] definition had been used by Cook et al. They suggested criteria including waist circumference ≥90th percentile, triglyceride ≥110 mg/dL, HDL-C ≤ 40 mg/dL, fasting plasma glucose (FPG) ≥ 110 mg/dL and blood pressure ≥ 90th percentile. The presence of ≥3 criteria defined the MetS in children [61]. Following the initial attempts, Ferranti et al. used lower cutoff points regarding the waist circumference and lipid levels and thus reported a higher prevalence of MetS among children than previous studies [50].

Other groups suggested that MetS in children must be defined on the basis of BMI levels rather than the waist circumference which displayed important racial variations [62]. Therefore, Weiss et al. defined obesity by BMI *Z* score of ≥2 [3]. As body proportions normally change during pubertal development and may vary among children of different race and ethnic groups, to overcome these variations, age- and sex-specific cutoff points of BMI are provided to assess the overweight and obesity status in children [63]. These cutoff points of BMI associate with cardiovascular risk factors in an international population [64]. Centers for Disease Control and Prevention (CDC) [65] adjusted BMI curves for age and sex. Since then, these curves have been widely used [66].

Large-scale studies provide age- and sex-specific percentiles for lipid levels in children of different populations [67]. As age- and sex-specific lipid percentiles are not available in many populations, several studies utilized National Heart Lung and Blood Institute Growth and Health Study (NGHS) as the reference population [67,68]. For instance, triglyceride ≥90th and HDL-C ≤ 10th percentile levels of NGHS were considered as risk determinants of MetS [21]. Weiss et al. used lipid levels adjusted for age, sex, and race or ethnic group [3]. Not surprisingly, different prevalences of MetS in children and adolescents have been reported, ranging from 3 to 11% according to the selected definition [3,50,61].

In 2007, a consensus report was published by the International Diabetes Federation (IDF) group. The report included definitions with cutoff points fixed for blood pressure, lipids and glycemia, and waist circumference points assessed by percentiles [69]. The IDF definition considers abdominal obesity (waist circumference ≥90th percentile of locally representative sample) as a prerequisite for MetS. Children were divided into three age groups. As there is lack of data for children under 6 years of age, the first group consists of children aged 6–10 years old. In this group, the cutoff points of metabolic and blood pressure variables were not well

Table 2 Criteria for metabolic syndrome in children

	De Ferrati	Weiss	Cook	BHS
	≥3 risk criteria below			At least one measure of obesity and ≥3 risk criteria
Waist circumference Waist-to-height ratio or BMI	Waist circumference ≥75%	BMI *z* score ≥ 2.0	Waist circumference ≥ 90%	WHtR > 0.5 or BMI > 75% or Waist > 90%
FPG or OGTT(mg/dL)	FPG ≥ 110	140–200 at 2 h	FPG ≥ 110	FPG ≥ 100
Triglycerides (mg/dL)	≥100	>95%	≥110	≥100 mg/dL or >75%
HDL-C (mg/dL)	<50(F), <45(M)	<5th p	≤40	<25%
Blood pressure	>90%	>95%	≥90%	BP > 75% or SBP ≥ 115 mmHg or DBP ≥ 75 mmHg

%, percentile; F, female; M, male; Waist, waist circumference; BMI, body mass index; WHtR, waist-to-height ratio; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; BHS, Bogalusa Heart Study.

defined. An increased central adiposity (waist circumference ≥ 90th percentile) was considered to be the prerequisite for MetS. IDF definition consists of abdominal obesity and 2 or more clinical features including high blood pressure, hypertriglyceridemia, low HDL-C, and elevated FPG. More research and data are needed for children younger than 10 years of age.

Waist circumference percentiles in a population are influenced by the population's ethnicity. More importantly, adequate percentile information in a locally representative sample may not be available particularly for developing countries. Therefore, alternative and readily available anthropometric criteria are needed. Waist circumference ≥90th percentile and waist-to-hip ratio >0.5 are used as an index of central obesity for children between 10 and 16 ages. We recommend that fasting glucose ≥86 mg/dL [44], triglyceride ≥100 mg/dL, HDL-C < 45 mg/dL, and blood pressure ≥115 mmHg systolic or ≥75 mmHg diastolic can be considered as abnormal values for children (Table 1). Similarly, for adolescents over 16 years of age, criteria can be modified as FPG ≥ 100 mg/dL or known T2DM, triglyceride ≥100 mg/dL or specific treatment for high triglyceride, HDL-C < 45 mg/dL for males and <50 mg/dL for females, or specific treatment for low HDL-C and systolic blood pressure ≥115 mmHg or diastolic blood pressure ≥75 mmHg or treatment of previously diagnosed hypertension. Although IDF definition is the most widely used definition, it comes with several limitations. Controversies exist related to the criteria, phenotype, and ethnicity of MetS in children and adolescents.

Modified NCEP and IDF definitions are proposed. By a simplified approach, risk criteria (BMI, blood pressure, triglyceride, and FPG) can be defined as ≥ 75th percentile range of the specific population (≤25th percentile for HDL-C). For modified NCEP definition, 3 of 5 components diagnosed the syndrome while elevated BMI plus any 2 of the remaining 4 is needed for modified IDF definition [5,70]. We recommend in addition to remainder, WHtR > 0.5 should be considered as an index of central obesity [27].

Most recently, we proposed the following criteria for MetS in children:

1. Risk factors (available population data: NHANES [71], BHS [72], Muscatine study [73], Finnish Youth [74]) greater than 75th percentiles (<25th percentile for HDL-C)
2. Positive family history, especially important as predictor of diabetes [55].
3. Obesity, dyslipidemia (triglyceride ≥100 mg/dL, HDL-C < 45 mg/dL), hypertension (systolic blood pressure ≥115 mmHg or diastolic blood pressure ≥75 mmHg) hyperinsulinemia, FPG ≥ 100 mg/dL.

According to our definition, 3 or more risk factors should be present but including at least 1 measure of obesity (e.g., BMI, WHtR, waist circumference). Table 2 shows different suggested criteria for MetS definition. Future prospective studies are needed to test the standard definition and ethnic variations of MetS in children and adolescents.

Limitations

The current review aims to summarize current understanding on the definition of MetS in children and comes with several limitations. Secular trends in blood pressure, obesity, and lipid levels among children and adolescents have been a subject of interest in several studies from developed countries. Most study findings are population specific, and it is hard to prove that the selected study populations are representative of all children. Ethnic differences exist in the criteria, definition, and prevalence of MetS in adolescents between populations. Most of the data reviewed comes from the United States or Western Europe. One definition cannot fit various populations around the world. MetS is a complex trait likely to be caused by the nonlinear interactions of numerous genetic and environmental risk pathways.

Conclusion

Clustering of risk factors starts atherosclerosis early in life. MetS in children and its many consequences including T2DM and CVD present serious threats to the current and future health of youth. Screening and identifying children and adolescents for cardiovascular risk and encouraging them and their families through healthy lifestyle changes should be implemented to as a global strategy.

Conflicts of Interest

The authors declare no conflict of interest.

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