

Review

Metabolic syndrome in children: current issues and South Asian perspective

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Abstract

Objective: The objective of this review is to discuss definition, determinants, and management issues of the metabolic syndrome in children with a focus on South Asians.

Methods: The literature search was done using the PubMed search engine (National Library of Medicine, Bethesda, MD, USA). Manual searches for other important references and medical databases were also done.

Results: There is a need for an integrated definition of the metabolic syndrome in children and adolescents, taking cognizance of the ethnic-specific variations. Obesity and body fat patterning are important determinants of insulin resistance and the metabolic syndrome in children and ethnic variations in these parameters are seen. Excess body fat and thicker truncal subcutaneous fat are important predisposing factors for development of insulin resistance in South Asian children. Because the metabolic syndrome tracks into adulthood, its manifestations need to be recognized early for prevention of diabetes and coronary heart disease. Therapeutic lifestyle changes, maintenance of high levels of physical activity and normal weight are most important strategies; pharmacologic therapy for individual components of the metabolic syndrome is occasionally needed.

Conclusion: The metabolic syndrome in children is an important clinical marker of diabetes and coronary heart disease in adults. In view of the rapid increase in the metabolic syndrome in most populations, high-risk screening and effective public-intervention educational programs are urgently needed. © 2007 Elsevier Inc. All rights reserved.

Keywords:

Metabolic syndrome; Insulin resistance; Diabetes; Asian Indians; Obesity; Truncal subcutaneous fat

Introduction

The metabolic syndrome (insulin resistance syndrome, syndrome X) has been defined as a constellation of major risk factors, including obesity, high fasting triacylglycerols, low levels of high-density lipoprotein cholesterol (HDL-C), elevated fasting plasma insulin, impaired glucose tolerance, and hypertension. These factors tend to cluster together in

many individuals and appear to be associated with each other, suggesting a common etiology [1–3]. In adults, the metabolic syndrome has been reported to predispose to an increased risk for type 2 diabetes mellitus (T2DM) and coronary heart disease (CHD) [4,5], with significant therapeutic implications. The National Cholesterol Education Program, Adult Treatment Panel III (NCEP, ATP III) has also recognized the clustering of these major CHD risk factors as a secondary target of risk-reduction therapy [6]. Although the metabolic syndrome has been studied extensively in adults, much less is known about it in children and young individuals. Further, because childhood metabolic syndrome likely tracks into adulthood, early identification may help target interventions to improve future cardiovascular risk [7].

This review is an attempt to discuss emerging areas of

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the metabolic syndrome in children and adolescents, highlighting the various facets of the syndrome and focusing on South Asian populations. We have specifically discussed the metabolic syndrome in South Asian children because these populations have an ethnic susceptibility to develop various cardiovascular risk factors and the metabolic syndrome. The literature search was done using the keywords “insulin resistance, or the metabolic syndrome, or obesity or cardiovascular risk factors in children, or adolescents or young individuals, and in Asian Indians or South Asians” from the medical search engine PubMed (National Library of Medicine, Bethesda, MD, USA). Manual searches for other important references and medical databases were also done. An important objective of review is to discuss definition, determinants, and management issues of the metabolic syndrome in children and less emphasis has been placed on pathophysiologic issues.

Definition and prevalence

There is lack of consensus on the definition of the metabolic syndrome in children, which is mostly defined in various populations using different criteria and cutoff points. In the Quebec Family Cohort Study [8], skinfold measurements and mean blood pressure were used as the most important variables, whereas in the Taipei Children Heart Study [9], a population distribution for cutoff points in a Taiwanese population was used. In a Hungarian study [10], the metabolic syndrome was defined by more extreme lipid cutoff points, body fat measurement instead of waist circumference, and 24-h blood pressure monitoring. A pediatric definition was proposed by de Ferranti et al. [11] by extrapolating the adult definition based closely on the more inclusive NCEP, ATP III adult criteria [6], considering the effects of age, gender, and puberty. A modified version of the NCEP, ATP III definition of the metabolic syndrome was used by Cook et al. [12] and Duncan et al. [7] to analyze the prevalence of the metabolic syndrome in adolescents from cross-sectional data available from the Third National Health and Nutrition Survey 1988–1994 and 1999–2002, respectively (Table 1). Lambert et al. [13] used other parameters with different cutoff points to define the metabolic syndrome in children (Table 1). We recently reported the prevalence of the metabolic syndrome in Asian Indian adolescents using population-specific cutoff points of various parameters, such as body mass index (BMI), waist circumference, and fasting hyperinsulinemia, alone or in combination (with the prevalence differing accordingly) [14]. The recent International Diabetes Federation (IDF) definition of the metabolic syndrome for children includes waist circumference as a mandatory criterion and two or more cutoffs for other risk variables [15] (Table 1).

Despite the need, there are several difficulties involved in establishing a universally accepted definition of the metabolic syndrome in children. Importantly, despite several years of research and numerous attempts, the definition of

the metabolic syndrome in adults is also not universally accepted [16–19]. The problem primarily relates to the development of ethnic-specific criteria of obesity and other parameters of the metabolic syndrome. Cole et al. [20] attempted to define obesity by internationally acceptable cutoff points of BMI. These investigators further recommended that the 99th percentile of percentage body fat from skinfold thicknesses should be taken as standard for classifying obesity in children [21]. These studies may help in defining obesity worldwide and would be one method to help develop a more universally acceptable definition of the metabolic syndrome in children.

Defining the metabolic syndrome based on different criteria or by extrapolation of the adult definition to a pediatric population has its limitations, and the prevalence rates have been reported to differ. Goodman et al. [22] investigated the prevalence of the metabolic syndrome among Black, White Caucasian, and Hispanic adolescents by using NCEP, ATP III and World Health Organization (WHO) definitions and reported that agreement between definitions was poor. Among obese teenagers, the prevalence rates were 19.5% and 38.9% according to NCEP, ATP III and WHO definitions, respectively. The non-White teens were more likely to have the metabolic syndrome by WHO criteria compared with White teens (Fig. 1) [22]. Rodriguez-Moran et al. [23] used yet another definition including additional parameters (family history of obesity, T2DM, hypertension, and birth weight) and reported a high prevalence of the metabolic syndrome with the use of the new definition compared with the NCEP, ATP III and WHO definitions [23]. Similarly, Golley et al. [24] concluded that the prevalence of the metabolic syndrome depends strongly on the definition chosen. For example, a changing prevalence in the metabolic syndrome was reported by Cook et al. [12] and de Ferranti et al. [11] using different definitions in children 12–19 y of age in the same population sample of the Third National Health and Nutrition Survey. Further, the prevalence estimates are higher if plasma insulin is included in the definition and pediatric-specific cutoff points for metabolic indicators are used [24]. In a recent study in Asian Indian adolescents, we showed that by application of NCEP, ATP III criteria with appropriate percentile cutoff points for Asian Indian adolescents, the metabolic syndrome was identified in only 0.8% of subjects [14]. Inclusion of BMI in addition to waist circumference in the definition resulted in an increase in the prevalence of the metabolic syndrome to 4.3%. Further, with inclusion of fasting hyperinsulinemia as an additional criterion, the prevalence of the metabolic syndrome increased to 4.2% (from 0.8%) in the modified NCEP, ATP III definition, to 5.2% (from 0.9%) when BMI was substituted for waist circumference, and to 10.2% (from 4.3%) when BMI and waist circumference were included [14]. Our data suggested that fasting hyperinsulinemia, being an early biochemical surrogate of insulin resistance, may be included as an additional defining criterion of the metabolic syndrome in young Asian Indians. Apart from fasting insulin

Table 1
Adult and proposed pediatric definitions of the metabolic syndrome

Metabolic syndrome variables	Adult definition*	Proposed pediatric cutoffs					
		de Ferranti et al. [11]	Duncan et al. [7]	Cook et al. [12]	Lambert et al. [13] [†]	Vikram et al. [14] [‡]	Zimmet et al. [15]**
Hypertriglyceridemia	≥1.65 mmol/L	75th (male) and 85th (female) percentiles ≥1.1 mmol/L	≥1.24 mmol/L	≥90th percentile ≥1.24 mmol/L	≥75th percentile (1.08 mmol/L for boys and 1.18 mmol/L for girls)	>90th percentile >1.60 mmol/L	≥1.7 mmol/L
Low HDL	<1.04 mmol/L (men), <1.3 mmol/L (women)	<40th percentile HDL <1.3 mmol/L (boys 15–19 y old, <1.17 mmol/L)	≤10th percentile HDL ≤1.04 mmol/L	≤1.04 mmol/L	≤25th percentile (1.00 mmol/L for boys, 1.18 mmol/L for girls)	≤10th percentile HDL ≤1.04 mmol/L for males and females [#]	<1.03 mmol/L
High fasting blood glucose	≥6.1 mmol/L	≥6.1 mmol/L	≥6.1 mmol/L	≥6.1 mmol/L	75th percentile ≥6.1 and ≤7.0 mmol/L	≥6.1 mmol/L	≥5.6 mmol/L
Central obesity (waist circumference)	>102 cm (men), >88 cm (women)	>75th percentile for age and gender, 72nd (male), 53rd (female)	≥90th percentile for age and sex	≥90th percentile for age and sex	≥85th percentile	>90th percentile (male >80 cm, female >74 cm) [#]	≥90th percentile, or adult cutoff if lower
Hypertension	SBP/DBP ≥130/≥80 mmHg	>90th percentile for age, gender, and height	≥90th percentile for age, gender, and height	≥90th percentile for age, sex, and height	≥75th percentile	SBP or DBP ≥90th percentile	SBP/DBP ≥130/≥85 mmHg
Fasting hyperinsulinemia	NI	NI	NI	NI	≥75th percentile (boys 50.7 pmol/L, girls 62.76 pmol/L)	>20 μU/mL (145 pmol/L)	NI
Prevalence rates	Variable	9.2%	NA	4.2%	14%	0.8% [§] , 4.3% , 10.2% [¶]	NR

DBP, diastolic blood pressure; HDL, high-density lipoprotein; NA, not available; NI, not included; SBP, systolic blood pressure; NR, not researched

* National Cholesterol Education Program, Adult Treatment Panel III. To convert Système International to conventional units, divide millimoles per liter by 0.0113 for triacylglycerols, 0.0259 for HDL, and 0.0555 for glucose.

[†] Cutoff points for 16-y-old subjects.

[‡] Study done in 14- to 18-y-old adolescents.

[§] According to the National Cholesterol Education Program, Adult Treatment Panel III definition.

^{||} National Cholesterol Education Program, Adult Treatment Panel III and body mass index.

[¶] National Cholesterol Education Program, Adult Treatment Panel III, body mass index, and fasting insulin.

[#] Cutoff points for the >90th percentile for waist circumference and the 10th percentile for HDL have been based on cutoff points used by Cook et al. [12].

** International Diabetes Federation definition, 2007; valid for children 10–16 y old (waist circumference with at least two other risk factors mentioned); for children <6 y old, insufficient data; for children 6–10 y old, waist circumference ≥90th percentile; for those >16 y old, current International Diabetes Federation criteria for identification of the metabolic syndrome in adults [15].

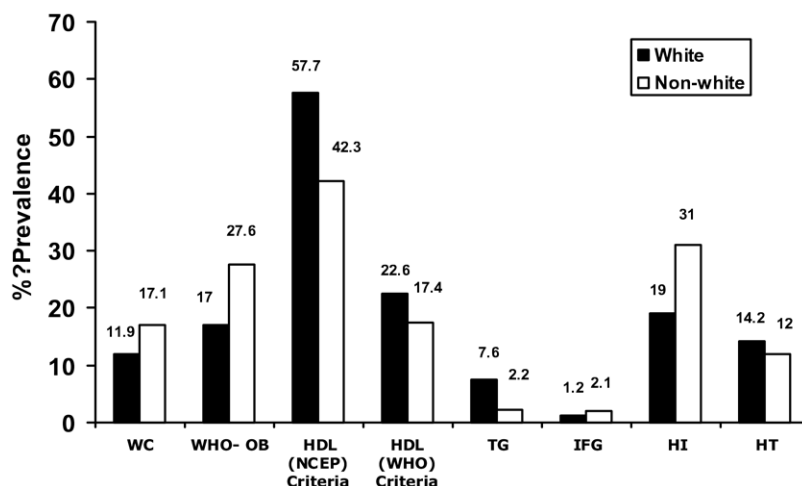


Fig. 1. Differences in the prevalence of the metabolic syndrome in White and non-White children 12–19 y of age using WHO criteria. Adapted from Goodman et al. [22]. HDL, high-density lipoprotein cholesterol; HI, hyperinsulinemia; HT, hypertension; IFG, impaired fasting glucose; NCEP, National Cholesterol Education Program; TG, serum triacylglycerols; WC, waist circumference; WHO-OB, World Health Organization–defined central obesity.

levels, insulin resistance could also be measured by other surrogate markers, the Homeostatic Model of Assessment [25] and QUICK indexes [26]; however, utility of these research investigations need to be researched further in children.

Even though prevalence rates vary depending on diverse criteria used in the pediatric age group, and despite a lack of uniform definition, various investigators have convincingly shown that the metabolic syndrome develops and is highly prevalent during childhood, particularly in obese children [7,27]. Importantly, the prevalence of the metabolic syndrome in obese adolescents has shown an increase from 4.2% to 6.4% during the previous decade [7]. In young Asian Indian patients with premature CHD, a high prevalence of hypertension, obesity, impaired glucose tolerance, hyperinsulinemia, and dyslipidemia has been reported by us, suggesting a fully developed metabolic syndrome [7,28]. Overall, high prevalence of excess body fat (in particular truncal body fat in the subcutaneous location), hypertriglyceridemia, and insulin resistance beginning at a young age have been consistently recorded in Asian Indians irrespective of their geographic locations [29–32].

In view of the high and increasing prevalence of obesity and T2DM in children and adolescents, there is an urgent need to establish internationally acceptable criteria for the metabolic syndrome; however, it has been debated that the ethnic differences in obesity and metabolic parameters should be considered in the definition. It needs to be researched further whether any ethnic-specific cutoff points of anthropometry or other parameters need to be employed while creating a universal definition of the metabolic syndrome in children, similar to the recent IDF definition of the metabolic syndrome in adults [33]. The resolution of this dilemma would greatly affect the preventive and management strategies in tackling the disorder early and will have positive therapeutic implications. In the recent IDF definition of the metabolic syndrome in children (10–16 y; Table 1) [15],

no ethnic difference in parameters has been accounted for, and its clinical utility and advantages over other proposed definitions need to be researched.

Pathophysiology

The underlying pathophysiology of the metabolic syndrome is not adequately understood, but insulin resistance plays an important role in the background of genetic predisposition. Clearly, obesity is the central factor in the pathogenesis of insulin resistance. Other associated factors such as hypertension, dyslipidemia, and subclinical inflammation are more likely to be consequences of insulin resistance rather than play any substantive role in the pathophysiology of the metabolic syndrome in children. Detailed discussion on the pathophysiology of the metabolic syndrome is available for reference [34–38]. Interestingly, apart from these factors, there is evidence that non-alcoholic fatty liver disease (NAFLD) may play a critical role in the determination of hepatic insulin resistance [39–41]. Further, polycystic ovarian syndrome (PCOS) is being increasingly recognized as a condition closely associated with the metabolic syndrome. However, apart from PCOS, the clinical significance of other conditions in children remains poorly investigated. An interplay of genetics and environmental factors, best seen in migrant populations, is involved in the etiopathogenesis of the metabolic syndrome [42].

Obesity, body fat patterning, and lipodystrophy

Childhood obesity is a major risk factor for insulin resistance and the metabolic syndrome in children and adults. About one-third of overweight or obese children and adolescents exhibit features of the metabolic syndrome [43].

The prevalence of the metabolic syndrome in children increases with obesity and has been reported to be as high as 22.5–52.8% in obese children and 10–25% in obese adolescents [44]. Prevalence of the metabolic syndrome reaches as high as 50% in severely obese youngsters. Each half-unit increase in BMI stepwise increases the risk of the metabolic syndrome in overweight subjects [10]. An overweight profile during childhood and adolescence is significantly associated with insulin resistance, dyslipidemia, and elevated blood pressure in young adulthood [45]. Obese children and adolescents of different ethnicities (Whites, Blacks, and Asians) were found to have abnormal glucose homeostasis (46%), fasting hyperinsulinemia (40%), impaired fasting glucose (0.8%), impaired glucose tolerance (11%), dyslipidemia (30%), and hypertension (32%) [46]. Further, in Asian Indian children, we recently reported that age- and gender-adjusted odds ratios for development of T2DM was 86.4 (95% confidence interval 17.0–438.5) in children who had a high waist-to-hip circumference ratio and a family history of T2DM in a first-degree relative [47].

The phenotype of obesity is not similar in all ethnic groups. Compared with White Caucasians, adult Asian Indians have lower BMI, waist circumference, and muscle mass [48,49]. Further, in adult South Asians, hyperglycemia, hypertriglyceridemia, and hypertension appear at lower levels of BMI (<25 kg/m²) and at waist circumference levels otherwise considered to be “normal” [50]. Such ethnic differences in anthropometry also have been reported for children [51–54]. Higher adiposity, related to insulin resistance and other cardiovascular risk factors, and metabolic derangements have been detected in South Asian children than in White children in the United Kingdom [55].

Body fat patterning appears to be important for the genesis of metabolic perturbations in South Asians. In adult South Asians, subcutaneous body fat is thicker than in White Caucasians [30,43,48,56,57]. Further, in Asian Indians with a higher degree of insulin resistance, subcutaneous fat was the only body composition feature different from White Caucasians [48]. We compared anthropometry and body fat patterning of postpubertal children of three ethnic groups (White Caucasians, Blacks, and Asian Indians) and reported that Asian Indian children had greater subcutane-

ous adipose tissue in the truncal area compared with other ethnic groups (Table 2) [28]. We also observed that a high prevalence of insulin resistance in urban Asian Indian adolescents was associated with excess body fat, abdominal adiposity, and excess truncal subcutaneous fat [58]. We recently observed that subjects with increased subscapular skinfold thickness had higher odds of developing fasting hyperinsulinemia than those with a large waist circumference [58].

Importantly, truncal subcutaneous fat has not been highlighted adequately as an important correlate of insulin resistance and the metabolic syndrome in adults and children. Considering these data, it is important that clinical evaluation and management strategies in Asian Indians should take in account an abnormal body composition profile in childhood [43,59,60]. Because the manifestations of such body composition seems to occur as early in life as birth, genetic and *in utero* or early-life adverse environmental events have been implicated. Poor nutrition in a mother leading to low birth weight may have the potential to interfere with the development of key organ systems involved in metabolic regulation. Due to some as yet unknown mechanism, body composition is also affected, which may become worse with accelerated velocity of growth and “catch-up” childhood obesity [61,62]. Hence, management should ensure good antenatal nutrition, balanced nutrition to the child, and avoidance of childhood obesity, particularly truncal adiposity.

Excess body fat deposition is not always the cause of insulin resistance, which can occur in individuals with loss or lack of body fat. Lipodystrophies are rare disorders of adipose tissue characterized by selective loss of body fat, which may be generalized or regional. These disorders can be genetic or acquired. Among the genetic lipodystrophies, congenital generalized lipodystrophy, caused by mutations in 1-acylglycerol-3-phosphate O-acyltransferase 2 (*AGPAT2*) and Berardinelli-Seip congenital lipodystrophy-2 (*BSCL2*) genes, manifest at birth [63]. The affected patients develop insulin resistance, diabetes mellitus, hyperlipidemia, and hepatic steatosis early in life [64,65]. Familial partial lipodystrophies, caused by defects in the lamin A/C (*LMNA*) and peroxisome proliferator-activated receptor- γ (*PPARG*) genes, occur at the time of

Table 2
Comparisons of anthropometry and body fat patterning of postpubertal children of three ethnic groups*

Skinfold thickness (mm)	Male [†]			Female [†]		
	Whites (n = 384)	Blacks (n = 174)	Asian Indians (n = 155)	Whites (n = 431)	Blacks (n = 253)	Asian Indians (n = 95)
Triceps	10.4 ± 6.5	11.7 ± 7.9	13.8 ± 7.0*§	15.0 ± 7.4	17.3 ± 8.9	16.0 ± 4.6
Subscapular	11.0 ± 7.5	12.2 ± 7.9	15.7 ± 9.8*§	14.4 ± 8.0	17.7 ± 9.8	17.6 ± 7.4 [‡]

* Data are presented as mean ± SD. Adapted from Misra et al. [43]. Data for White and Black children were taken from quoted references and compared with our data.

[†] For White and Black children, data are from Mensah et al. [162] (mean age 15.3 ± 2.3 y) and Park et al. [163] (age range 13–17 y), respectively, for Asian Indian children (age range 14–18 y).

[‡] P < 0.05, White versus Asian Indian children.

[§] P < 0.05, Black versus Asian Indian children.

puberty or later. In these patients, subcutaneous adipose tissue is gradually lost from the extremities and variably from the trunk, and excess fat may get deposited resulting in a double chin, excess supraclavicular fat, and a “cushingoid appearance.” These patients may have severe insulin resistance and metabolic perturbations and almost 50% of them develop diabetes [64,65]. These rare adipose tissue disorders must be considered whenever phenotype suggests so, or there is early development of severe insulin resistance and its consequences [64,65].

Insulin resistance

Insulin resistance is considered to be the central factor in the pathophysiology of the metabolic syndrome and dysglycemia [1]. Population-based data have suggested that the epidemic of pediatric obesity is being followed by an increase in T2DM [27]. Sinha et al. [66] reported impaired glucose tolerance in 25% and 21% of obese children and obese adolescents, respectively. Prevalence of the metabolic syndrome increased significantly with increasing insulin resistance after adjustments for ethnicity and the degree of obesity [10]. Furthermore, intrauterine exposure to hyperglycemia and size at birth have been recognized as risk factors for T2DM, and these findings have implications for perpetuating the cycle of obesity, insulin resistance, and their consequences in subsequent generations [67,68].

In postpubertal Asian Indian children, prevalence of fasting hyperinsulinemia is high (27%), being 22% in males and 36% in females [43]. This high prevalence of insulin resistance in Asian Indian children and young adults, who are undergoing “nutritional and lifestyle transitions” rapidly, is a worrisome feature taking cognizance of the enormous number of patients with T2DM in India [69,70]. The excessive insulin resistance in Asian Indians in part may be due to a primary metabolic defect because Asian Indians tend to develop severe insulin resistance even in the presence of an only mild increase of BMI or abdominal adiposity [50] and have greater insulin resistance even when BMI is matched with persons of other ethnic groups [48]. Importantly, a higher level of hyperinsulinemia was reported in Indian neonates, as recorded at birth, compared with White Caucasian neonates [56]. These issues need further research to develop a deeper understanding of the genetic mechanism, perinatal influences, and interaction with acquired factors, particularly fat accumulation, and may be helpful in explaining a predisposition to develop T2DM in Asian Indians.

A significant relation between fasting insulin, as an estimate of insulin resistance, and cardiovascular risk factors has been shown, but this was significantly influenced by body fatness in children [71]. The clustering of risk factors according to level of insulin sensitivity suggested that early-onset CHD is more likely to develop in children with the greatest degree of insulin resistance [71]. The Bogalusa

Heart Study provided rather robust evidence in this context. In this biracial cohort, elevated insulin levels persisted from childhood through young adulthood, resulting in a clinically significant cardiovascular risk factor profile in young adults [72]. This study provided evidence that hyperinsulinemia, once established in childhood, tracks through to adulthood, with adverse consequences.

Dyslipidemia and procoagulant factors

Dyslipidemia of the metabolic syndrome has been characterized by hypertriglyceridemia, low levels of HDL-C, and an increased presence of small, dense low-density lipoprotein cholesterol (LDL-C) and normal LDL-C levels. It is believed that such “atherogenic dyslipidemia” is associated with the metabolic syndrome and contributes to accelerated atherosclerosis [73]. Apart from abdominal adiposity, microalbuminuria, and deranged essential fatty acid metabolism, children with the metabolic syndrome have increased plasma levels of plasminogen activator inhibitor-1 and fibrinogen, which may contribute to hypercoagulability [35].

High serum triacylglycerol levels with other features of atherogenic dyslipidemia have been commonly found in urban Asian Indians residing in India and in migrant Asian Indians [74–76]. Prevalence of dyslipidemia in urban children has been reported to be: hypercholesterolemia, 13%; hypertriglyceridemia, 16%; and low levels of HDL-C, 10% [60]. Dyslipidemia in Asian Indians has been attributed to a multitude of factors, including physical inactivity [77], carbohydrate-rich diet, abnormal body composition, in particular excess truncal fat, increased intra-abdominal fat, and genetic predisposition [75,78,79]. Interestingly, nearly 70% of the adolescents studied by us in Delhi were physically inactive in the 10th and 12th classes, in which important academic examinations are held (A. Misra, unpublished data).

Hypertension

Hypertension probably is the weakest correlate of insulin resistance. Although increased blood pressure in childhood is the most powerful predictor of hypertension in adulthood, its significance in children in the overall context of the metabolic syndrome is as yet unknown. It has been postulated that hyperinsulinemia secondary to insulin resistance leads to increases in renal retention of sodium and in sympathetic activity, which causes elevation of blood pressure [80–82]. The mitogenic action of insulin may also cause smooth muscle hypertrophy leading to hypertension [83]. It has been also postulated that insulin resistance could be a marker for another, yet poorly understood pathologic process, and these features, however, are not mutually exclusive of each other [83].

Several investigators have reported the link between in-

sulin resistance and hypertension. A substantial percentage of hypertensive patients have insulin resistance and hyperinsulinemia [81,84]. Hypertension present in obese youngsters worsens with the degree of obesity [85]. Longitudinal studies of Pima Indian children have demonstrated that birth weight, exposure to diabetes *in utero*, and obesity were the major factors in the development of childhood hypertension, apart from being the risk factors for diabetes [86]. Insulin resistance and hypertension have been correlated independent of body weight [87].

Prevalence of hypertension in urban Asian Indian children have been shown to be 4.5% in those with normal BMI, 15.3% in overweight children, and 43% in obese children [88]. Even in rural areas, a 6.8% prevalence of sustained hypertension was reported in overweight children compared with 61.7% in obese children [88].

Other conditions associated with the metabolic syndrome in children

Polycystic ovarian syndrome is now known to be strongly associated with insulin resistance and the metabolic syndrome. A higher prevalence of PCOS was reported in South Asian women than in White Caucasians in a recent study [89]. South Asians present and seek treatment of PCOS at a younger age than do White Caucasians and have more severe symptoms, higher fasting insulin concentrations, and lower insulin sensitivity than do White Caucasians [89]. Furthermore, hirsutism, acne, acanthosis nigricans, and secondary infertility have been found to be significantly more prevalent in South Asians [89].

NAFLD, sometimes resulting in non-alcoholic steatohepatitis (NASH) and occasionally cryptogenic cirrhosis [90], has been shown to be the new and important hepatic correlate of insulin resistance and the metabolic syndrome. NAFLD probably is the most common form of liver disease in children. It is likely that it will continue to increase with increasing obesity and the metabolic syndrome in childhood [91]. Often NASH may be the first clinical indication of insulin resistance [92]. In a study conducted in children and adults with muscle-liver-brain-eye nanism, NAFLD was present in all adolescents and adults, and 46% of prepubertal children and 70% of adults fulfilled the NCEP criteria for the metabolic syndrome [93]. Early development of fatty liver in non-obese prepubertal children suggests that accumulation of fat in the liver may be the crucial step in the development of insulin resistance in these subjects [93].

The prevalence of fatty liver has been reported to be about 2.6% of urban children in Japan [94]. The metabolic syndrome was reported to be strongly associated with elevated serum aminotransferase concentrations in Korean adolescents, and this association was graded across the number of metabolic components [95]. Despite these studies, the relation of NAFLD to the metabolic syndrome in children needs more investigations [96]. Whether the presence of

NAFLD and elevated serum aminotransferase levels in children would predict onset of diabetes in adults also needs to be researched.

According to some studies, hyperuricemia is a component of the metabolic syndrome [97]. In obese children and adolescents, uric acid was significantly correlated to levels of lipids, BMI, and systolic blood pressure [98]. More interestingly, uric acid was shown to be a reliable indicator for the “pre-metabolic syndrome” in these obese youths [98]. However, despite these data, it is presently believed to be a “weak” associate of insulin resistance and the metabolic syndrome.

The link between subclinical inflammation and the metabolic syndrome has been shown in White Caucasians but has not yet been fully established in other ethnic groups. However, in Asian Indian adolescents, high levels of C-reactive protein were seen in 13% of non-obese and 22% of overweight subjects [99]. Further, a high prevalence of elevated C-reactive protein levels in adolescents and young adult Asian Indians in north India correlated with generalized and abdominal adiposity [99]. Interestingly, further studies by our group showed that predictors of fasting hyperinsulinemia and subclinical inflammation in young individuals have clearly different anthropometric correlates [100]. Several recent investigations from our group have shown that the link between C-reactive protein and insulin resistance is far from clear in Asian Indians [99,101,102]. Whether elevated CRP levels in children predict future cardiovascular risk remains to be investigated.

Role of genetics and environment

Significant heritability and pleiotropy seen for the components of the metabolic syndrome indicate a strong genetic contribution [103]. Twin and family studies have shown a familial aggregation [104], and children with at least one parent affected are more insulin resistant and obese than are children with two unaffected parents [104]. Further, many studies have provided strong evidence for a genetic contribution to obesity [105,106]. However, changing gene pools are unlikely to explain the doubling or even tripling prevalence of obesity over a short period of 20 y and suggests other etiologic factors. The association of low birth weight with blood pressure, total cholesterol and LDL-C levels, fibrinogen levels, and sympathetic activation within dizygotic twin pairs, and not in monozygotic twins, point towards genetic influences. In contrast, association of low birth weight with insulin resistance, low HDL-C levels, and shorter height within dizygotic and monozygotic twin pairs suggests contributory factors independent of genetic factors [107]. An adverse perinatal milieu leading to intrauterine growth retardation and its association with diabetes in later life has been documented [108]. However, because insulin is an *in utero* growth factor, genetically mediated insulin resistance is also hypothesized to be a factor associated with

low birth weight in the offspring [109]. Moreover, even though adiposity is a prominent correlate of insulin resistance in South Asians [110], ethnic differences in insulin concentrations may not be accompanied by a concomitant difference in adiposity [55]. All these observations clearly indicate that non-genetic or environmental factors are important.

An adverse intrauterine environment has been shown to be a contributory factor to insulin resistance and the metabolic syndrome in children and adults [111]. Low birth weight babies have been reported to be less insulin sensitive than a normal-weight group [108]. Asian Indian babies born small had increased plasma total and LDL-C concentrations, higher systolic blood pressure, and adiposity at 8 y of age [112]. Investigators from other parts of the world have also found insulin resistance to be independently related to small size at birth and manifesting at a young age [113]. Many studies have also indicated that the metabolic syndrome may originate *in utero*, suggesting a fetal origin [114–116], even though the exact roles of nutritional and genetic factors have not been clearly elucidated. Recently, velocity of weight gain during childhood and “catch-up” obesity in low-birth-weight babies have been suggested to be important for adult-onset insulin resistance and associated cardiovascular risk factors [62]. Whether low birth weight, childhood “catch-up” obesity, and increased velocity of weight gain in childhood are independent factors or additive in causation of insulin resistance and the metabolic syndrome has not been investigated.

Apart from undernutrition, overnutrition during critical periods has shown adverse metabolic effects. *In utero* exposure to maternal diabetes had an epigenetic impact of transmitting the metabolic abnormalities of impaired glucose tolerance in adult offspring in experimental studies [117]. Large-for-gestational-age offspring of diabetic mothers and those born to obese mothers are at an almost twice the significant risk of developing the metabolic syndrome in childhood [67]. Excessive insulin secretion *in utero* has been observed to lead to obesity and impaired glucose tolerance in adolescence [118]. Higher blood pressure in adolescent offspring is also an abnormality associated with fetal overnutrition [119].

Homozygosity of a particular insulin gene (VNTR class III allele) has been observed to predispose to increased weight gain and fat mass, suggesting it as an important factor in the gene-environment interaction eventually leading to obesity and insulin resistance [120]. Genetic and environmental variances of insulin resistance measured by the Homeostatic Model of Assessment in monozygotic and dizygotic twins have been shown to correlate with BMI. Hence, gene-environment interactions influence insulin sensitivity in children and adolescents even though environment may play a more important role [121].

Rural-to-urban transition

A graded increase in insulin resistance, T2DM, and other cardiovascular risk factors has been seen when rural people move to urban areas in developing countries. Further, the prevalence of T2DM in urban Indians is fast approaching the figures seen in affluent migrant Indians [122]. An adverse coronary risk profile has been reported in rural-to-urban migrant populations living in urban slums in Delhi [123]. Adverse lipid levels have been reported in urbanized tribes [124]. Studies in children have also found similar trends, with South Asian children showing increasingly high CHD risk with urbanization [125]. It appears that migration itself is a risk factor for development of metabolic syndrome and T2DM [42]. Further impact of migration on first and second generation children of migrants remains to be investigated.

Ethnic differences in the metabolic syndrome

South Asians appear to be highly susceptible to the metabolic syndrome, which needs further discussion. Some of the ethnic differences in specific attributes related to the metabolic syndrome have been highlighted in previous sections.

Although the mean ponderal index was found to be lower in South Asian children than in White Caucasian children in the United Kingdom, mean fasting and post-glucose load insulin concentrations were higher [55]. Further, mean heart rate and serum triacylglycerol and fibrinogen concentrations were higher among South Asian children than among White Caucasian children [55]. The relation between adiposity and insulin concentrations (in particular fasting insulin) was much stronger among 8- to 11-y-old South Asian children than among White Caucasian children [55]. Similar differences were seen when data of older children and adolescents were compared. Whincup et al. [126] reported that, compared with European Caucasians, South Asian children 13–16 y of age had higher mean fasting levels of insulin and fasting blood glucose and a higher prevalence of impaired fasting glucose [126]. Although South Asian children tended to have slightly higher indices of adiposity than Europeans, the differences in glucose and insulin levels persisted after adjustment for adiposity and pubertal status [126]. In contrast, Ehtisham et al. [127] reported that South Asian adolescents were less insulin sensitive than White European adolescents, but this difference was no longer tenable after adjusting for body fat, indicating that the differences in body composition of South Asians have a critical role to play in the pathogenesis of insulin resistance. The relative risk of T2DM was 13.7 in South Asians compared with British White Caucasian children [128]. In particular, these affected children were usually overweight or obese and had a family history of T2DM.

Overall, it appears that South Asian children have higher insulin resistance and other related features of the metabolic

syndrome than do White Caucasian children, and much of the difference could be accounted by adverse features of obesity, including higher adiposity and adverse body fat patterning.

Pathology

That atherosclerosis starts in childhood and is accelerated in individuals with the metabolic syndrome has been substantiated using surrogate markers of atherosclerosis or pathologically [129]. The Bogalusa Heart Study showed that insulin resistance in childhood promotes the development of premature atherosclerosis and significantly increases cardiovascular risk early in life [130]. The association of hyperglycemia and high BMI with adverse arterial endothelial dysfunction and intima-media thickening was also demonstrated in the Chinese Atherosclerosis in the Aged and Young study [131] and the Atherosclerosis Risk in Young Adults study [132], respectively. Even though atherosclerotic cardiovascular disease and death are not frequently seen in the young, the pathologic processes and risk factors associated with its development have been shown to begin during childhood [133]. Autopsy findings of the Pathobiological Determinants of Atherosclerosis in Youth study showed atherosclerotic lesions to be associated positively with non-HDL-C concentration, hypertension, obesity, and blood glucose concentrations and inversely with HDL-C concentrations [134]. Obese adolescents and particularly those with impaired glucose tolerance had more extensive fatty streaks and raised lesions than did non-obese adolescents, with more severe lesions of the left anterior

descending coronary artery [135]. Youths 15–24 y old with hypertension were seen to have a thicker intima in the aorta and left anterior descending coronary artery compared with normotensive subjects [136]. Autopsy findings in 5- to 15-y-old children showed coronary fatty streaks in obese compared with lean children [137]. Autopsy studies of antemortem healthy boys 13–19 y of age also related coronary atherosclerotic lesions to thicker intimal lesions with an increase in the amount of visceral fat [138]. Overall, those children who are obese and show metabolic derangements have early evidence of atherosclerosis.

Clinical features and correlates

The pediatric features of the metabolic syndrome are listed in Table 3 according to different age groups. Please note that these features are based on the current medical literature; however, in some areas the information may be less than complete and less intensively researched.

Principles of prevention, evaluation, and management

1. The key to obesity prevention rests with identification of subjects with modifiable risk factors [139]. Hence, it is important to screen and diagnose these cases early. The main emphasis is on lifestyle changes, moderate physical activity, and appropriate dietary modifications, leading to weight reduction and maintenance of normal weight. There is evidence that prevention of the metabolic syndrome in childhood leads to less metabolic syndrome in adults [140].

Table 3
Correlates of insulin resistance and the metabolic syndrome during infancy, childhood, and adolescence

	Infancy	Childhood	Adolescence
Clinical features			
Family history of obesity or type 2 diabetes mellitus	+	++	++
Low birth weight/childhood “catch-up” obesity	±	+	+
Large-for-gestational age	–	±	+
Maternal diabetes	–	±	+
Obesity	±	+	++
Abdominal obesity	–	+	++
Excess subcutaneous fat	+	+	++
Excess truncal fat	±	+	+
Acanthosis nigricans	±	+	++
Hirsutism/hyperandrogenism	–	–	+
Congenital generalized lipodystrophy	+	++	++
Familial partial lipodystrophy	–	–	++
Non-alcoholic fatty liver disease	–	+	++
Laboratory features			
Hyperinsulinemia	+	+	++
Low insulin-like growth factor binding protein-1	±	±	±
High plasminogen activator inhibitor-1 /fibrinogen	±	+	+
Hypertriglyceridemia and low levels of high-density lipoprotein cholesterol	±	+	++

+, Variably present/associated with insulin resistance and the metabolic syndrome; ++, strongly present/associated with insulin resistance and the metabolic syndrome; –, no data available; ±, insufficient data.

2. Children who are obese and have excess abdominal fat and those with acanthosis nigricans (with or without obesity) should have a complete clinical and metabolic profiling.
3. Body fat distribution and lipodystrophy should be looked for in early and/or severe insulin resistance, dyslipidemia, and diabetes.
4. The investigation profiling should include fasting blood glucose, glycosylated hemoglobin concentration, and a lipid profile. Those with abnormal levels of these screening tests should have additional evaluation, including an oral glucose tolerance test [141], estimation of serum aminotransferases, and abdominal ultrasound for detection of NAFLD. In girls, an appropriate hormonal profile and other investigations for PCOS should be done. Estimation of fasting serum insulin levels is usually not necessary except as a supportive investigation in suspected cases of PCOS.
5. The presence of even one cardiovascular risk factor in an overweight subject should prompt screening for additional clinical abnormalities, with an aim of finding treatable disorders [141].
6. Secondary causes of obesity should be ruled out with appropriate additional tests.
7. In case of an obese child with metabolic abnormalities, siblings should be investigated in a similar manner.
8. Assessment of dietary intake, in particular referring to total calories gained by intake of saturated fat, carbohydrate, and fiber, and identification of other factors affecting energy balance should be done [142]. Daily calorie expenditures should be assessed and time spent in front of television and computer should be monitored and reduced if in excess [143].
9. Interviewing parents to assess and corroborate the diet, physical activity, and psychological patterns concerning lifestyle factors is required.
10. Evaluation by a child psychologist is required for behavioral assessment and counseling and should precede weight-control measures [144].
11. The management of the metabolic syndrome in children requires multifactorial intervention (Fig. 2). Therapeutic lifestyle change is an essential first step. Apart from lifestyle changes, hypertension and diabetes, if uncontrolled, have to be managed using standard management protocols as detailed below. The various interventional steps taken to treat and manage the metabolic syndrome in children are summarized in the following sections.

Behavior modification

It is essential to find any maladaptive behavior related to the eating habits of children and rewards should be designed to modify and improve such behaviors. Importantly, coun-

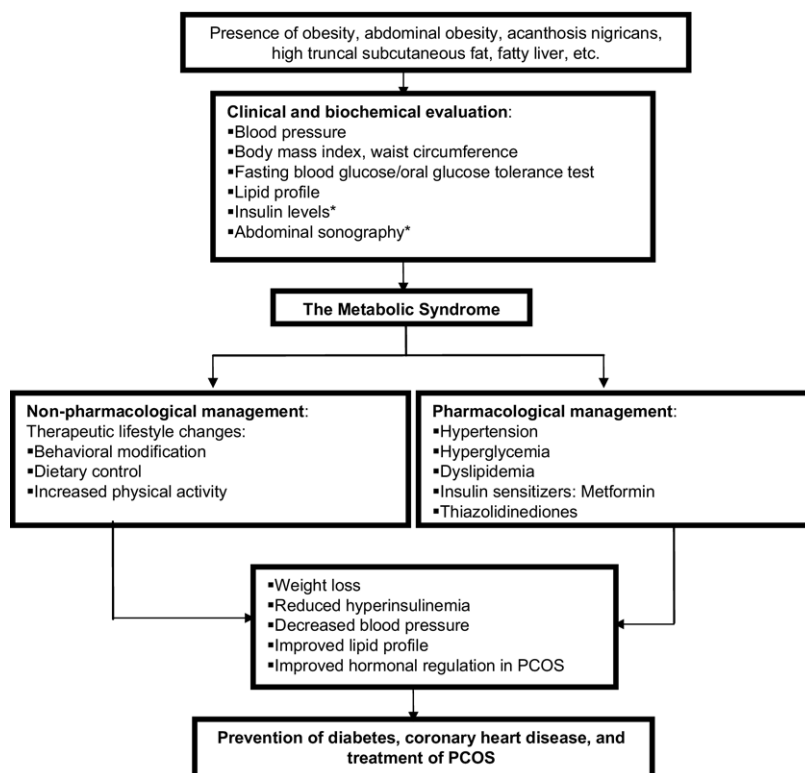


Fig. 2. Multifactorial management of the metabolic syndrome in children. PCOS, polycystic ovarian syndrome. *, if required.

selling in a stable group setting has been found to have a better therapeutic effect. It is essential that corrective measures continue even after the achievement of a healthy lifestyle. Importantly, other therapeutic modifications are liable to fail without proper behavioral modification.

Dietary modifications

Because modifying obesity in childhood has been shown to reduce hyperinsulinemia, lower blood pressure, and improve lipid abnormalities [145], dietary modifications to achieve weight loss are important. Most adolescents favor a high-carbohydrate and saturated fat diet with sweetened beverages. Such a dietary pattern is currently seen in developing countries in nutritional transition, including India [69].

Dietary strategies should include an emphasis on regular structured meals and increased fiber and protein intakes. Restriction of sweetened beverages, high saturated and *trans* fat-containing packaged foods should be emphasized. Snacking between meals should be avoided. The calorie intake should be reduced below the calorie expenditure levels. Diets rich in fruits, vegetables, and low-fat dairy products and avoidance of salted and processed food products are most appropriate for children and adolescents with labile or mild hypertension [146].

Physical activity

Regular exercise should be promoted to increase energy expenditure to achieve weight loss and increase cardiovascular fitness. Exercise training decreases blood pressure in overweight/obese individuals with high normal blood pressure and hypertension [147]. Moderate exercise also improves the dyslipidemia by raising HDL-C and lowering serum triacylglycerol concentrations [148]. However, institution of physical activity should be gradual. Individualized counseling for participation in regular physical activity and games (walking, bicycling, swimming, soccer, etc.) and other preventive education should be imparted through effective family- and school-based health programs [142].

Pharmacologic therapy

1. Even though non-pharmacologic interventions such as weight reduction and increased physical activity improves glucose tolerance and decreases the progression to diabetes [149], pharmacologic agents are used in patients with uncontrolled hyperglycemia. Metformin, an antihyperglycemic agent, has been found to be efficacious in children with the metabolic syndrome and hyperglycemia [141]. Metformin therapy in obese children has been associated with beneficial effects on the body composition and fasting insulin levels [150]. Sometimes insulin therapy is necessary to control hyperglycemia.

2. According to current guidelines, pharmacologic treatment of dyslipidemia in childhood is not recommended unless the patient is older than 10 y and the LDL-C concentration is above 190 mg/dL (or >160 mg/dl with two additional risk factors) [151]. 5-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors are used to regulate lipids in children only if necessary, as against the current recommendation of their liberal use across all ranges of lipid profile in adults [152].
3. Secondary causes of hypertension should be searched for in children before starting therapy. In case the blood pressure is not controlled through therapeutic lifestyle changes, treatment with antihypertensive medication(s) may be started to achieve a target blood pressure level. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are the favored drugs in such situations.
4. Orlistat is an inhibitor of gastrointestinal lipases and results in weight loss due to fat malabsorption. It has been found to be an effective pharmacologic option in achieving weight loss in obese and overweight individuals with other risk factors such as hypertension, dyslipidemia, or hyperglycemia. Even though the weight loss produced is modest, it leads to sufficient improvement in obesity-related comorbidities [153]. Orlistat decreases leptin and increases adiponectin independent of decrease in body fat and waist circumference and may help in prevention of the metabolic syndrome in obese people [154]. Some studies have shown that orlistat is efficacious and safe in adolescents and children for inducing weight loss [155,156]. However, fat-soluble vitamins should be supplemented in children because orlistat causes malabsorption of these vitamins. Moreover, long-term safety of orlistat in children is not known.

Community intervention programs

Several programs have been initiated to combat obesity and the metabolic syndrome in children and have shown promising results. Project SPARK is a school intervention health-related physical education program, conducted in California, that showed lowering of adiposity in children [157]. Planet Health was another successful school-based health behavior intervention program focusing on lifestyle factors such as decreasing television viewing, decreasing consumption of high-fat foods, increasing fruit and vegetable intakes, and increasing physical activity [158]. Another community- and school-based intervention program called PATHWAYS was conducted in American Indian children on similar lines and also focused on family involvement. This program improved several aspects of obesity-related knowledge, attitudes, and practices and produced significant positive

changes in fat intake and in food- and health-related knowledge and behaviors [159,160].

On similar grounds, in India, we have initiated comprehensive intervention programs aiming at childhood obesity, the metabolic syndrome, nutrition, and physical activity, namely CHETNA (Children Health Education Through Nutrition and Health Awareness program; Hindi for “The Awareness”) and MARG (Medical Education for Children/Adolescents for Realistic Prevention of Obesity and Diabetes and for Healthy Ageing; Hindi for “The Path”) [161]. The objectives of the programs are to make children aware of obesity and diabetes and educate them regarding the beneficial effects of a healthy diet and increased physical activity. These comprehensive programs were initiated on a large scale for the first time in South Asia with the aim of covering 500 000 children in 15 cities in north India. Further, the MARG program aims to impart education regarding diet and physical activity not only to children but also to teachers and parents. Children are given nutritional and physical activity education through lectures and leaflets and involvement in debates, skits, and drama related to health topics. Parents and children also take part in making healthy recipes. The effect of these programs remains to be evaluated.

Conclusion

The metabolic syndrome in children assumes significant importance in view of the current epidemic of childhood obesity. A standard definition of the metabolic syndrome is needed to assess the exact prevalence and early diagnosis, with major preventive and therapeutic implications; however, ethnic variations should be taken in account. South Asian children are highly predisposed to develop insulin resistance, the metabolic syndrome and its components compared with White Caucasian children and need more aggressive prevention and management. The emphasis should be on therapeutic lifestyle changes incorporating moderate physical activity and dietary modifications. The prevention and management of the metabolic syndrome should be instituted early in childhood to prevent early-onset T2DM and CHD. For developing countries undergoing economic and nutritional transitions, large-scale community awareness and intervention programs are urgently necessary.

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