

REVIEW ARTICLE

METABOLIC SYNDROME IN CHILDREN: DEFINITION, RISK FACTORS, PREVENTION AND MANAGEMENT-A BRIEF OVERVIEW

Prateek Kumar Panda

Department of Pediatrics, Kalinga Institute of Medical Sciences, Bhubaneswar, Orissa, India.

ABSTRACT

Metabolic syndrome in children is an emerging health problem, especially in developed countries and the prevalence is also increasing in developing countries. It is a constellation of obesity with increased waist-hip ratio, dyslipidemia, insulin resistance, hypertension and non-alcoholic fatty liver disease (NAFLD). Separate definitions exist for defining metabolic syndrome in children and adults. Faulty dietary habit, sedentary lifestyle and increased television screen time are predominant risk factors for its development, which are all modifiable. However, hereditary and perinatal factors also play a significant role. Dietary modification, regular physical exercise, oral hypoglycemic agents, dyslipidemia management and in rare cases bariatric surgery may be required for management of metabolic syndrome in children. Early recognition and prompt treatment are crucial for optimum outcome.

Introduction

Food is the most abused anxiety drug while exercise is the most under-utilized antidepressant.¹ Metabolic syndrome is a syndrome which is characterized by dyslipidemia, insulin resistance and risk of coronary artery disease. Previously it was called Insulin resistance syndrome or Syndrome X.²

Definition and various components of metabolic syndrome in children

Definition and diagnostic criteria

The National Cholesterol Education Program's Adult Treatment Panel III report (ATP III) identified the metabolic syndrome as a combination of six components, which increases the risk of cardiovascular syndrome.³ These six essential components are abdominal obesity, dyslipidemia, hypertension, insulin resistance and glucose intolerance, proinflammatory and prothrombotic state.³ When 3 of 5 of the listed characteristics are present, a diagnosis of metabolic syndrome is usually made. However, in children there is no consensus regarding the diagnosis of metabolic syndrome, although three criteria proposed by International Diabetes Federation (IDF) including Cook et al, de Ferrari et al and Weiss et al are commonly used.³⁻⁷ Comparison of components of these three diagnostic criteria have been demonstrated in table 1.

Although it is evident that each component of the syndrome must be identified as early as possible in order to prevent cardiovascular disease, the question is how to do this in children and which cut-offs should

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Table 1. Comparison of three diagnostic criteria for metabolic syndrome given by Cook et al, de Ferrari et al and Weiss et al

	Cook et al ³	de Ferrari et al ⁴	Weiss et al ⁵
Adiposity: AC or BMI	AC $\geq 90^{\text{th}}$ centile	AC $> 75^{\text{th}}$ centile	BMI z score ≥ 2.0
Fasting glycemia or at OGTT (mg/dL)	Fasting glycemia ≥ 110	Fasting glycemia ≥ 110	Glycemia at OGTT of 140-200
Blood pressure	$\geq 90^{\text{th}}$ centile	$> 90^{\text{th}}$ centile	$> 95^{\text{th}}$ centile
HDL Cholesterol (mg/dL)	≤ 40	< 50 (girls), < 5 (boys)	$< 5^{\text{th}}$ centile
Triglycerides (mg/dL)	≥ 110	≥ 110	$> 95^{\text{th}}$ centile

Note: BMI – Body Mass Index, OGTT – Oral glucose tolerance test, HDL – High density lipoprotein, AC – abdominal circumference.

be adopted for diagnosing metabolic syndrome. The criteria proposed by Cook et al and de Ferrari et al relied-on waist circumference, while Weiss et al relied-on BMI $> 95^{\text{th}}$ percentile.³⁻⁵ All three criteria use age specific cut off nomograms and fixed values for various components of metabolic syndrome.³⁻⁵ IDF definition for metabolic syndrome has been described in table 2.⁷ Definitions of obesity, diabetes and various scientific terms related to metabolic syndrome in children have been demonstrated in table 3.

CONTACT Prateek Kumar Panda

Email: drprateekpanda@gmail.com

Address for Correspondence: Prateek Kumar Panda, Assistant Professor, Department of Pediatrics, Kalinga Institute of Medical Sciences, Bhubaneswar, Orissa, India.

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Table 2. International Diabetes Federation (IDF) definition of metabolic syndrome in children⁷

Age group (years)	Obesity(Waist Circumference)	Triglycerides	HDL-C	Blood pressure	Glucose(mmol/l) or known T2DM
6 to <10 years	≥90 th percentile	Metabolic syndrome cannot be diagnosed, but further measurements should be made if there is a family history of metabolic syndrome, T2DM, dyslipidemia, cardiovascular disease, hypertension and/or obesity			
10 to <16 years	≥90 th percentile or adult cut-off if lower	≥150 mg/dl	<40 mg/dl	Systolic ≥130 mm Hg or diastolic ≥85 mm Hg	≥100 mg/dl (If >100 OGTT recommended)
>16 years	Use existing IDF criteria for adults Central obesity + any 2 of following: Central obesity: Waist circumference ≥94 cm for European men and ≥80 cm for European women (with ethnicity specific values for other groups- Indian men 90 cm and women 80 cm) 1. TG >150 mg/dl 2. HDL-C <40 mg/dl in males and <50 mg/dl in females 3. BP: systolic BP >130 or diastolic >85 mg/dl or previous treatment of diagnosed hypertension 4. Impaired fasting glucose >100 mg/dl or previously diagnosed T2DM				

Note: T2DM – Type 2 Diabetes Mellitus, HDL-C – High density lipoprotein cholesterol, OGTT – Oral glucose tolerance test, TG – triglycerides, BP – blood pressure

Table 3. Definition of various terms related to metabolic syndrome in children^{8,9}

Condition	Definition (IAP)	Definition (WHO)
Overweight	<5 years: WHO definition 5-19 years: Adult equivalent [>71 st centile (boys), >75 th centile (girls)]	<5 years: weight for height >+2SD 5-19 years: >+1SD
Obese	<5 years: WHO definition 5-19 years: Adult equivalent [>90 st centile(boys), >95 th centile (girls)]	<5 years: weight for height >+3 SD 5-19 years: >+2 SD
Hypertension	BP of >90 th percentile to <95 th percentile or >120/80 = Prehypertension BP >95 th percentile to <99 th percentile + 5 mm Hg = stage 1 HTN BP >99 th percentile + 5 mm Hg = stage 2 HTN	-
Diabetes mellitus	HbA1c >6.5% OR Fasting plasma glucose of >126 mg/dL OR Two-hour plasma glucose of >200 mg/dL OR If symptomatic, a random plasma glucose of >200 mg/dL	-
Dyslipidemia	TG >130 mg/dL LDL >130 mg/dL Total Cholesterol >200 mg/dL HDL <40 mg/dL Non-HDL Cholesterol >145 mg/dL	-
NAFLD	ALT >25 U/L (boys) and >22 U/L (girls) Steatosis on USG/ MRI	-

Note: IAP – Indian Academy of Pediatrics, WHO – World Health Organization, HTN – hypertension, HbA1c – hemoglobin A1c, TG – triglycerides, LDL – low-density lipoproteins, HDL – high-density lipoproteins, ALT – alanine aminotransferase, USG – ultrasonography

Waist circumference and Waist Hip ratio

Waist circumference is an independent predictor of insulin resistance, hypertension and dyslipidemia.⁵ Extrapolating single definition of adults to children may be problematic. Insulin sensitivity and secretion varies with fat distribution, age, development and puberty. The 90th centile of waist circumference is used as cutoff with

higher risk of cardiovascular effects. In Indian adult males 90 cm and in adult females 80 cm are considered as 90th percentile for waist circumference.⁶

Waist Hip ratio (WHR) is a more refined measure of abdominal fat accumulation and more relevant in adolescents.⁶ The cutoff of WHR for females is > 0.85 and males >0.95. Cutoff values of more than 70th

percentile for screening of metabolic syndrome risk are often used and provided in several articles.⁶ Waist circumference is a measure of upper-body obesity due to high release of non-esterified fatty acid from adipose tissue. Ectopic lipid accumulation usually occurs in muscle and liver due to insulin resistance and dyslipidemia.¹⁰

Relevance of various components of metabolic syndrome

Abdominal obesity is a type of obesity which presents clinically as increased waist circumference.¹⁰ Dyslipidemia usually seen in metabolic syndrome are raised triglycerides and low concentrations of high-density lipoprotein (HDL) cholesterol. A more detailed analysis many times also reveals, elevated apolipoprotein B, small low-density lipoproteins (LDL) particles, increased remnant lipoproteins and small HDL particles.¹¹ Hypertension, obesity and insulin resistance are intricately related to each other. Hypertension in metabolic syndrome is usually multifactorial in origin.¹¹ Prothrombotic and proinflammatory states are metabolically interconnected in these children.¹¹ The proinflammatory state in children with metabolic syndrome can be recognized clinically by variable elevations of C-reactive protein (CRP), is commonly present in persons with metabolic syndrome.¹¹ Excess adipose tissue in obese children releases inflammatory cytokines leading to proinflammatory state.¹¹ Similarly, the prothrombotic state is characterized by increased plasma plasminogen activator inhibitor (PAI)-1 and fibrinogen. Fibrinogen is also an acute-phase reactant like CRP and increases in response to a high-cytokine state.¹¹

Epidemiology and global burden of obesity and metabolic syndrome

Overweight/obesity in various countries of world varies and is more in developed western countries as compared to developing countries like India. In western countries prevalence in adolescents is around 20% for obesity and in India it is around 10-20%.¹² As per the recent data provided by Center for Disease Control and Prevention (CDC), USA, the prevalence of obesity is 18% and affects around 13 million children in USA. During first two decades of life, the prevalence increases with increase in age.¹³ Obesity prevalence is 13.9% among 2-5-year age group, 18.4% among 6-11 year age group and 20.6% among 12-19 year age group. In USA, obesity prevalence was more in Hispanic and non-Hispanic blacks as compared to the white population and also is more in children of parents with lower monthly income and less educational achievement.¹³ The prevalence of the metabolic syndrome in USA has been estimated to be around 4.5% and almost all of these children are obese or overweight.¹⁴ Thus, almost one in every four obese children have metabolic syndrome.¹⁴ In India, also the prevalence of obesity among children was estimated to be around 19.3%, as calculated by Ranjani et al from the pooled data of around 52 studies performed over 16 different states of India.¹⁵ The overall prevalence of metabolic syndrome in a study done at Srinagar was found to be 3.8% (males 3.9% and females 3.8%), with approximately equal sex distribution. Singh et al found that the prevalence of metabolic syndrome among 1083

adolescent children of 12-17 year old from North India (Chandigarh) was 4.2%, without any sex difference.¹⁶

Pathophysiology of Metabolic Syndrome

Three interconnected plausible pathogenetic mechanism behind development of metabolic syndrome are obesity with excess adipose tissue; insulin resistance; and other independent factors including bioactive molecules of hepatic, vascular, and immunologic origin that mediate specific components of the metabolic syndrome.¹⁷ Proinflammatory state and hormonal changes are other contributors.¹⁷

Insulin resistance remains the underlying pathogenetic mechanism for various clinical features of metabolic syndrome.¹⁷ In obese children, adipose tissue is more insulin resistant as compared to normal population. In absence of insulin action, lipolysis leads to release of non-esterified fatty acid into blood, raising their level.¹⁸ It subsequently causes abnormal lipid accumulation in muscle and liver. This is one of the postulated mechanisms for non-alcoholic fatty liver disease (NAFLD) seen in these children.¹⁸ Moreover, in obese children there is increased production of inflammatory cytokines and plasminogen activator inhibitor by adipose tissue and at the same time production of the potentially protective adipokine, adiponectin, is reduced.¹⁸

Ectopic lipid accumulation in muscle and liver on the other hand also predisposes to insulin resistance and dyslipidemia.¹⁹ Upper body fat including abdominal subcutaneous fat and visceral fat correlates more strongly with insulin resistance and the metabolic syndrome than lower body obesity. They are also more prone to release of non-esterified fatty acids into blood.¹⁹

At the same time, insulin has some effect on sodium reabsorption and sympathetic nervous system, which is maintained even in children with insulin resistance.¹⁹ Along with this increase in angiotensin, renin, and leptin secretion all lead to hypertension in children with metabolic syndrome.¹⁹ Lastly, insulin resistance also causes abnormalities in nitric oxide (NO) bioavailability and reduced PI3K/AKT signaling in the vascular wall. These two bioactive pathways have a crucial role in mobilization of endothelial progenitor cells from bone marrow. Reduction in nitric oxide causes more vasoconstriction.²⁰ As such insulin resistance also promotes apoptosis of endothelial cells through various intermediate pathways.²⁰

Risk factors

Maternal/hereditary factors

Duration of breastfeeding is inversely proportional to obesity in later life.²¹ Childhood metabolic syndrome is also attributed to relation with gestational diabetes mellitus (GDM) and large birth weight (Barker's hypothesis) (1990).²¹ Thrifty phenotype hypothesis and fetal origins of adult disease are other hypothesis describes the antenatal and perinatal factors describing the impact of birth weight & features of insulin resistance syndrome in infants.²²

There must be other hereditary factors also responsible for development of metabolic syndrome.²² Risk of obesity is more than double if one parent is obese.

Children with at least one parent with the metabolic syndrome had significantly more obesity and insulin resistance than control.²³

Lifestyle factors

Lifestyle factors like lack of physical activity, fatty food consumption, preference for simple carbohydrates and fewer vegetables are more important factors than hereditary factors probably for development of metabolic syndrome in adolescents.²⁴ Eating junk food incessantly and increased screen time in front of television and computers are the emerging risk factors for metabolic syndrome in twenty first century.²⁴ Especially the children of parents with higher socioeconomic status are more reluctant to physical activity and preferring indoor games and unhealthy food habits.²⁵ Tobacco smoking which remains an important risk factor for metabolic syndrome in adults, although less prevalent in children, still its incidence is increasing in recent days in adolescents of India and other countries.²⁵

Screening

Screening criteria for various components of metabolic syndrome has been given in table 2 both according to Indian Academy of Pediatrics (IAP) guidelines and World Health Organization (WHO) guidelines.^{8,9} Recommendations for laboratory workup are described in table 4.²⁶

Table 4. Recommendations for screening various laboratory parameters for metabolic syndrome²⁶

BMI	Age 2-8 years	Age 9-18 years
>85 th -94 th centile with no risk factors (adult equivalent BMI 23-28)	No lab testing	Fasting lipid profile
>85 th -94 th centile with risk factors (elevated BP, dyslipidemia, family history, smoking)	Fasting lipid panel	Fasting lipid panel Fasting glucose AST, ALT
>95 th centile (adult equivalent more than 28)	Fasting lipid panel	Fasting lipid panel Fasting glucose AST, ALT

Note: BMI – Body mass index, BP – Blood pressure, AST – aspartate aminotransferase, ALT – alanine aminotransferase

Co-morbid conditions

In adults, metabolic syndrome is considered one of the most important risk factors for coronary vascular disease and type two diabetes mellitus (T2DM).²⁷ Although children are at less risk of developing cardiac complications, insulin resistance is almost universally seen in these children and in later life many of them develop cardiac complications also.²⁷ These children are also more susceptible to other diseases like polycystic ovary syndrome, cholesterol gallstones, NAFLD, asthma, sleep disturbances, and some malignancies.²⁷

Polycystic ovarian syndrome with irregular menstrual cycle and later on infertility is quite common in these children. Obstructive sleep apnea often accompanies obese children, especially those with BMI >30 kg/sqm.²⁸ Severe obstructive sleep apnea and hypoventilation during sleep may lead to cor-pulmonale and right-side heart failure.²⁸ In NAFLD, steatosis (excessive fat accumulation in the form of triglycerides) is found in >5% hepatocytes. It is the one of the leading causes of chronic liver disease in children.²⁸ Ultrasound abdomen and liver function testing are recommended in these children.²⁸

Prevention

Exclusive breast feeding for 6 months, cow's milk (12 months-2 years), low fat milk for overweight, minimizing frequent mid-meal snacks are part of healthy lifestyle and should be adapted for prevention of metabolic syndrome.²⁹ Never skipping breakfast, taking mainly home cooked food and adequate fruits and vegetable servings are also important.²⁹ Family based, multi component lifestyle weight management services for obese children, TV screen time to <2 hours/day, healthy school environment, health and nutrition literacy, reduction in intake of junk food and sweetened beverages, at least 60 min of daily moderate exercise and annual diet, activity and sedentary behavior assessment are other measures to prevent the development of metabolic syndrome.²⁹

Treatment

Goal of treatment in metabolic syndrome is to reduce obesity, reduce BMI and waist-hip ratio, manage the metabolic complications and insulin resistance and also management of hypertension if present.³⁰ For attaining these goals, dietary modification and physical activity are essential.³⁰ Pharmacological measures include oral hypoglycaemic agents like metformin, antihypertensive agents, HMG CoA reductase inhibitors like atorvastatin for dyslipidemia and injectable insulin if required.³⁰ Anti-obesity drugs like orlistat and fenfluramine are only rarely used.³¹ Similarly, bariatric surgery is also normally kept preserved for refractory cases of morbid obesity, with BMI>35-40, with a number of other associated complications like obstructive sleep apnea and cardiovascular compromise.³¹

Metformin and other oral hypoglycaemic drugs

In cases with documented hyperinsulinemia and insulin resistance, even if the glucose intolerance has not reached diabetic level, metformin may be tried to improve insulin sensitivity, reduce obesity, acanthosis nigricans and symptoms of polycystic ovarian syndrome if present.³¹ In cases with T2DM in adults, almost universally metformin is used, often in combination with various sulfonylurea drugs. Lactic acidosis is one of the important adverse effects of metformin.³¹ Glimepiride, glibenclamide and gliclazide are other oral hypoglycaemic agents sometimes used in adolescents with T2DM.³¹ However, prevalence of type 1 diabetes mellitus (T1DM) is many times higher in children as compared to T2DM, for which insulin injection is the main treatment option utilized to achieve glycemic control.³¹

HMG CoA reductase inhibitors

In children often these drugs like atorvastatin and

rosuvastatin are used when serum levels of total cholesterol and LDL cholesterol are more than 95th percentile for age and sex.³² Its usefulness to improve level of HDL in blood is often proposed, especially if serum level of HDL is less than 5th centile for age and sex. Upper cut offs between 170-200 mg/dl for total cholesterol and 110-130 mg/dl for LDL cholesterol are often used in children.³²

General principles of dietary modification

Individualized diet plan, well balanced healthy meals, instituting small, gradual and permanent changes, involving the family, starting early intervention, avoiding "accelerated crossing" of centiles, avoiding force feeding are all essential steps of dietary modification.³³ Dietary management also consists of timely, regular meals, and avoiding constant "grazing" during the day, increased protein intake, increased fibre intake (8-10 g/day), reducing cholesterol intake to <200 mg/day, reducing saturated fatty acid to <7%, decreased consumption of high-fructose corn syrup, decreased consumption of high-fat, high-sodium, or processed foods. (HFSS).³³

Goals of dietary therapy

The initial goal is reduction of body weight by 10% from baseline. Weight loss should be about 1 to 2 pounds per week for a period of 6 months.³³ A diet that is individually planned to help create a deficit of 500 to 1,000 kcal/day should be an integral part of any program aimed at achieving a weight loss of 1 to 2 pounds per week.³³

Physical activity

Currently adolescent children are more sedentary than ever with the widespread availability of mobiles, computer and video games.³⁴ A recent clinical study found about 61.5% of children did not participate in organized physical activity outside school hours, on any days of the week. Particular community of children who are at risk of having low physical activity include preadolescent and adolescent girls, those residing in apartments or public housing, children living in neighbourhoods, where outdoor physical activity is restricted by climate or inappropriate, excessive safety concerns by parents, restricting participation in outdoor games.³⁴

Physical activity is a universal requirement for comprehensive weight loss therapy and weight control program.³⁴ It reduces abdominal fat, increases cardiorespiratory reserve, and helps in long term sustenance of weight loss.³⁴ Physical activity improves insulin resistance, as well as hepatomegaly and derangement of liver transaminases in children with NAFLD.³⁴ Resistance exercise like weightlifting after aerobic exercise is helpful in reducing hypertension. Also, regular physical activity is beneficial psychologically in these children, as it helps in increasing self-esteem and self-concept and reducing anxiety and depression.³⁴

For controlling obesity, aerobic exercise is more optimal as compared to resistance exercise. Moderate to vigorous exercise for at least 60 minutes daily is the minimum recommended duration.³⁴ Ideally it should comprise of at least 30 minutes aerobic exercise and 15 minutes muscle strengthening resistive exercise,

apart from 15 minutes of daily work-related exercise. Instalments of high intensity short duration instalments of exercises are more favoured than long duration low intensity exercise.³⁴

Behaviour therapy

Behaviour therapy is a useful adjunct when incorporated into treatment for weight loss and weight maintenance.³⁵ Target for behavioral therapy in obese individuals is maladapted eating and exercise patterns.³⁶ These maladaptive behaviors can be modified with specific behavioral interventions based on principles of classical and operant conditionings. Behavioral therapy is used to train obese individuals to learn new behaviors that either reduce calorie intake or increase physical activity.³⁷ Common components of behavioral therapy for these children include self-monitoring, stimulus control, slower eating, clear goal setting, cognitive restructuring, adopting positive outlooks, assertiveness training including learning to say no and stress reduction.³⁸

Pre-requisites for bariatric surgery

Bariatric surgery are only rarely preferred especially for pathological obesity and the prerequisites are child with BMI>40 or >35 with significant comorbidities, child has attained Tanner 4/5 pubertal development and bone age of >13 years (girls) and 15 years (boys), failure of all other modalities of treatment, strong family support and strong will to adhere to treatment both before and after surgery.³⁹

Conclusion

Metabolic syndrome is an escalating problem in children of developed countries, now getting increasing recognition worldwide as a health problem. It is usually underdiagnosed, and diagnosis missed in early stages. Early recognition and prompt treatment are crucial for optimum outcome. Dietary therapy and increasing physical activity are cornerstones of management.

Compliance with Ethical Standards

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