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Review Article

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Novel Insights into the Pathogenesis and Management of the Metabolic Syndrome

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ABSTRACT

The metabolic syndrome, by definition, is not a disease but is a clustering of individual metabolic risk factors including abdominal obesity, hyperglycemia, hypertriglyceridemia, hypertension, and low high-density lipoprotein cholesterol levels. These risk factors could dramatically increase the prevalence of type 2 diabetes and cardiovascular disease. The reported prevalence of the metabolic syndrome varies, greatly depending on the definition used, gender, age, socioeconomic status, and the ethnic background of study cohorts. Clinical and epidemiological studies have clearly demonstrated that the metabolic syndrome starts with central obesity. Because the prevalence of obesity has doubly increased worldwide over the past 30 years, the prevalence of the metabolic syndrome has markedly boosted in parallel. Therefore, obesity has been recognized as the leading cause for the metabolic syndrome since it is strongly associated with all metabolic risk factors. High prevalence of the metabolic syndrome is not unique to the USA and Europe and it is also increasing in most Asian countries. Insulin resistance has elucidated most, if not all, of the pathophysiology of the metabolic syndrome because it contributes to hyperglycemia. Furthermore, a major contributor to the development of insulin resistance is an overabundance of circulating fatty acids. Plasma fatty acids are derived mainly from the triglycerides stored in adipose tissues, which are released through the action of the cyclic AMP-dependent enzyme, hormone sensitive lipase. This review summarizes the latest concepts in the definition, pathogenesis, pathophysiology, and diagnosis of the metabolic syndrome, as well as its preventive measures and therapeutic strategies in children and adolescents.

Keywords: Obesity; Diabetes; Insulin resistance; Dyslipidemia; Hyperglycemia

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INTRODUCTION

The metabolic syndrome is defined as a clustering of metabolic abnormalities that include central obesity, insulin resistance, hypertriglyceridemia, hypercholesterolemia, hypertension, and reduced high-density lipoprotein (HDL)-cholesterol concentrations [1-4]. It is also associated with other comorbidities including the proinflammatory state, prothrombotic state, nonalcoholic fatty liver disease (NAFLD), cholesterol gallstone disease, and reproductive disorders [5-16]. The metabolic syndrome has been considered to be one of the most risk factors for the epidemic of type 2 diabetes and cardiovascular disease in the 21 century [17-22]. Furthermore, it could be mainly caused by inactive lifestyle, overconsumption of food, and the resulting abdominal obesity. However, it has been recognized that the metabolic syndrome is not a disease but is a common complex entity that emerges as a worldwide epidemic and major public health concern with a prevalence rate of approximately 25% in American adults [23-26]. Moreover, the prevalence of the metabolic syndrome is increasing not only in the USA and Europe, but also in Asian countries such as China, India, and South Korea [27-41]. Most studies have found that the metabolic syndrome is associated with an approximate doubling of cardiovascular disease risk and a 5-fold increased risk for type 2 diabetes. Although it is unclear whether there is a unifying pathogenic mechanism that could decipher the pathophysiology of the metabolic syndrome, it is highly likely that abdominal obesity and insulin resistance could play a central role in promoting the development of the metabolic syndrome [42-44]. Therefore, lifestyle modification and weight loss should be considered to be the first step for preventing or treating the metabolic syndrome [45-47]. In addition, other cardiac risk factors should be actively managed in individuals with the metabolic syndrome [48].

Although there are many different definitions of the metabolic syndrome, almost all the metabolic abnormalities include central obesity, hypercholesterolemia, reduced HDL-cholesterol levels, hypertension, and elevated plasma triglycerides, with insulin resistance as the potential uniting pathogenic factor [49]. The importance of the metabolic syndrome is not just related to its high prevalence rate worldwide but also because it could help predict the development of type 2 diabetes and cardiovascular disease [50-52]. Both NAFLD and cholesterol gallstone disease are now recognized to be the two major hepatic components of the metabolic syndrome, a kind of "fellow travelers" [6,53-55]. Moreover, high triglyceride and cholesterol concentrations in the liver together with other risk components, particularly insulin resistance, elevated plasma fatty acid concentrations, and diabetes, are the major risk factors for the development of nonalcoholic steatohepatitis (NASH), the most severe form of NAFLD [56-59]. However, the importance of the metabolic syndrome lies not in a specific definition but rather in its causative role and association with the worldwide epidemics of diabetes, cardiovascular disease, NAFLD, and NASH. According to the Guidelines of the National Cholesterol Education Program (NCEP) expert panel on the detection, evaluation and treatment of high blood cholesterol in adults (adult treatment panel III) (ATPIII), the main goal of identifying patients with the metabolic syndrome is to find individuals at high risk of cardiovascular disease that extends beyond low-density lipoprotein (LDL)-cholesterol levels and is highly obesity-related morbidity and mortality [60].

Similar to adults, overweight and obesity in children and adolescents have become major public health issues as their prevalent rates have substantially increased not only in the USA and European countries, but also in Asian countries during the past three decades [61-68]. Based on the definition of the metabolic syndrome for adults, some modified

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definitions of this syndrome for children and adolescents have been proposed over the past 13 years; however, no unified definition has been proposed to assess risk or outcomes of the metabolic syndrome specially in pubertal subjects [69]. Obviously, a simple easy-to-use clinical definition is strongly needed to identify the metabolic syndrome in young people globally. Because obesity is associated with increased risk of cardiovascular disease and type 2 diabetes, which may persist from childhood and adolescence into young adulthood [70-72], it is important to make early identification of children and adolescents who are at high risk of developing the metabolic syndrome. Therefore, it would be possible to give early preventive measures, including lifestyle modification, to these young people to halt the development of the metabolic abnormalities. In this review, we summarize recent advances in the definition, pathogenesis, pathophysiology, and diagnosis of the metabolic syndrome, as well as its prevention and treatment interventions in children and adolescents.

DEFINITION AND CLINICAL DIAGNOSIS

Although the term, the metabolic syndrome, has become widely used since the 1990s, it is recently that the concept of "clustering" metabolic disorders and cardiovascular disease risk factors is intensively discussed in the literature [73-77]. In 1923, Kylin [78] first reported a relationship between hypertension, hyperglycemia, and gout in adult patients. In 1978, Phillips [79] found the coexistence of impaired glucose metabolism with hyperinsulinemia, hyperlipidemia, and hypertension, thus increasing the risk of developing cardiovascular disease. In 1980, Albrink [80] reported a relationship between obesity, hypertriglyceridemia, and hypertension. In 1988, Reaven [81] described a clustering of the metabolic abnormalities with insulin resistance as the central pathophysiological feature and used the term, the syndrome X, to depict the potential relationship between insulin resistance, hypertension, type 2 diabetes, and cardiovascular disease. In addition, the syndrome X and other terms, such as the deadly quartet and the insulin resistance syndrome, have been largely used in the literature to describe the clustering of cardiovascular and metabolic risk factors for several decades [82-85]. However, the metabolic syndrome is most widely used for describing the metabolically associated disorders including obesity, insulin resistance, type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease, NAFLD, NASH, and cholesterol gallstone disease [1,5,6,11,86-89].

Notably, many different definitions have been proposed to describe the metabolic syndrome in adults. In general, the metabolic syndrome is defined as a cluster of risk factors for cardiovascular disease and type 2 diabetes, including visceral obesity, dyslipidemia, impaired glucose tolerance, and hypertension. In 1998, the World Health Organization (WHO) was the first to propose a definition and diagnostic criteria [90], in which insulin resistance is considered to be the major pathogenic factor underlying the metabolic syndrome. However, the WHO definition has been criticized because of these weaknesses: (i) it is difficult to use the clamp technique to analyze insulin resistance and apply it to large-scale epidemiological surveys; (ii) it is not a precise method to use the ratio of waist to hip to measure abdominal obesity; and (iii) it is unclear about the relationship between insulin resistance and microalbuminuria [90].

Subsequently, the European Group for the Study of Insulin Resistance (EGIR) used fasting plasma glucose and insulin levels instead of the insulin clamp technique to define insulin sensitivity and proposed a new criterion for non-diabetic patients based on these parameters

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[91,92]. In addition, the EGIR definition used the waist circumference, but not the ratio of waist to hip, to measure abdominal obesity. This significantly promoted wide-ranging epidemiological surveys.

In 2001, the NCEP:ATPIII proposed a new criterion to define the metabolic syndrome in adults, which worked as part of the educational program for the prevention of cardiovascular disease [93]. The NCEP:ATPIII definition did not list insulin resistance as a component. In contrast, it made all five components equally important, which greatly facilitates the diagnosis of the metabolic syndrome in clinical practice. Using the NCEP:ATPIII guidelines, the diagnosis of the metabolic syndrome requires the presence of at least three of the five components [93]. In general, the NCEP:ATPIII and the WHO criteria identify the same prevalence of the metabolic syndrome in adult patients, but the NCEP:ATPIII definition may be superior in identifying patients at increased risk of cardiovascular disease and for predicting type 2 diabetes. Nevertheless, these existing criteria for diagnosing the metabolic syndrome are less accurate in predicting clinical endpoints compared to other established models such as the Framingham risk score of cardiovascular disease. In addition, the American Association of Clinical Endocrinologists proposed a new criterion with a focus on insulin resistance and an exclusion of patients with type 2 diabetes.

Because of the use of different criteria for defining the metabolic syndrome in adults, the prevalence rates collected from epidemiological surveys vary greatly from country to country, as well as from region to region even in the same country. Thus, it is quite difficult to compare the reported prevalence rates of the metabolic syndrome around the world, as well as the data between studies due to these different diagnostic criteria. In 2005, the International Diabetes Federation (IDF) proposed a unifying definition that emphasizes the importance of central obesity and has it as a necessary condition to diagnose the metabolic syndrome [94,95]. In other words, the diagnosis of the metabolic syndrome requires central obesity plus two additional components. It should point out that the IDF criteria do not emphasize insulin resistance, but instead focus on fasting plasma glucose levels. In addition, a new set of criteria with ethnic/racial specific cutoffs were defined. For example, the guideline for measuring waist circumference was proposed and the ranges of waist circumference were specified for different ethnic/racial groups. In 2007, harmonizing the definition of the metabolic syndrome was proposed by comparison of the criteria of the NCEP:ATPIII and the IDF criteria in American and European populations [96]. In 2009, this harmonized definition for the metabolic syndrome was revised, which reached an agreement: (i) there should not be an obligatory component, but waist measurement would continue to be a useful preliminary screening tool; (ii) three abnormal findings out of 5 would qualify a person for the metabolic syndrome; (iii) a single set of cut points would be used for all components except waist circumference, for which further work is required; and (iv) in the interim, national or regional cut points for waist circumference can be used [97]. Nevertheless, clinical practice and epidemiological investigations strongly demand a simple easy-to-use unifying definition of the metabolic syndrome.

For children and adolescents, the IDF Task Force on the Epidemiology and Prevention of Diabetes set a practical clinical criterion for the diagnosis of the metabolic syndrome in 2007 [98,99]. Based on a modification of previous adult standards, the IDF has promoted a new criterion for the diagnosis of the metabolic syndrome mainly for children and adolescents between the ages of 10 and 16 years [98,99], as shown in **Table 1**. The definition of the metabolic syndrome in this age group is central obesity (≥90th percentile) plus the presence

Table 1. The IDF definition of the at-risk group and the metabolic syndrome in children and adolescents (2007)

Age group (yr)	Obesity (WC)	Triglycerides	HDL-C	Blood pressure	Plasma glucose
6–<10*	≥90th percentile				
10–<16	≥90th percentile or adult cut-off if lower	≥1.7 mmoL/L (≥150 mg/dL)	<1.03 mmoL/L (<40 mg/dL)	Systolic BP ≥130 or Diastolic BP ≥85 mmHg	FPG ≥5.6 mmoL/L (100 mg/dL)‡ or known T2DM
16+ (adult criteria)	WC ≥94 cm for Europid males and ≥80 cm for Europid females, with ethnic-specific values for other groups†)	≥1.7 mmoL/L (≥150 mg/dL) or specific treatment for high triglycerides	<1.03 mmoL/L (<40 mg/dL) in males and <1.29 mmoL/L (<50 mg/dL) in females, or specific treatment for low HDL	Systolic BP ≥130 or diastolic BP ≥85 mmHg or treatment of previously diagnosed hypertension	FPG ≥5.6 mmoL/L (100 mg/dL)‡ or known T2DM

IDF: International Diabetes Federation, WC: waist circumference, HDL-C: high-density lipoprotein cholesterol, BP: blood pressure, FPG: fasting plasma glucose; T2DM: type 2 diabetes mellitus.
*The metabolic syndrome cannot be diagnosed, but further measurements should be made if there is a family history of the metabolic syndrome, type 2 diabetes, dyslipidemia, cardiovascular disease, hypertension, and/or obesity.
†For those of South and South-East Asian, Japanese, and ethnic South and Central American origin, the cutoffs should be ≥90 cm for men, and ≥80 cm for women. The IDF Consensus Group recognize that there are ethnic, gender and age differences, but research is still needed on outcomes to establish risk.
‡For clinical purposes, but not for diagnosing the metabolic syndrome, if fasting plasma glucose is 5.6–6.9 mmoL/L (100–125 mg/dL) and it is not known to have diabetes, an oral glucose tolerance test should be performed.
Diagnosing the metabolic syndrome requires the presence of central obesity plus any two of the other four factors. Modified and reproduced with permission from reference [98].

of two or more other components (**Fig. 1**), including hypertriglyceridemia (≥1.7 mmoL/L; ≥150 mg/dL), high blood glucose (≥5.6 mmoL/L; ≥100 mg/dL), high blood pressure (≥130 mmHg systolic or ≥85 mmHg diastolic), or low HDL-cholesterol levels (≤1.03 mmoL/L; ≤40 mg/dL). To date, the available data, however, were not sufficient to make a recommendation for children aged <6 years. For children aged between 6 and 10 years, as the metabolic syndrome cannot be diagnosed, they should be strongly recommended weight loss, especially those with abdominal obesity. For adolescents aged 16 years or older, the adult criteria could be used.

In 2014, a new criterion for defining the metabolic syndrome in prepubertal children was proposed by the identification and prevention of dietary- and lifestyle-induced health effects in children and infants (IDEFICS) study [100], which addressed the limitations of previous definitions in children and the need for early diagnosis in young people. Using reference values from the study of 18,745 children in eight European countries, the IDEFICS study set up the age-specific and sex-specific (and height-specific in the case of blood pressure) percentiles to identify cutoffs for the components of the metabolic syndrome in children at the age of 2-11 years [100]. However, the proposed cutoffs were based on a statistical

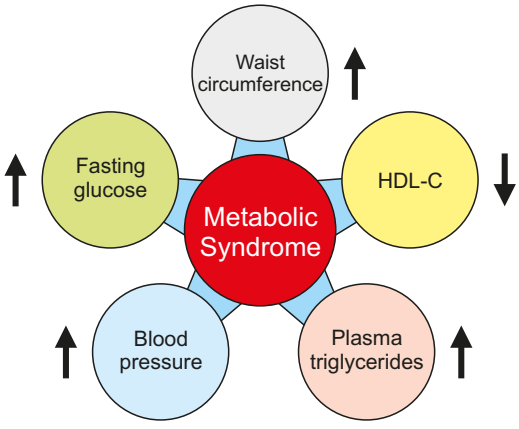

Fig. 1. Criteria for clinical diagnosis of the metabolic syndrome in childhood and adolescence. The definition of the metabolic syndrome in this age group is central obesity plus the presence of two or more than two components. HDL-C: high-density lipoprotein cholesterol.

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definition and these did not allow to quantify the risk of subsequent diseases such as type 2 diabetes and cardiovascular disease.

Obviously, the diagnostic standards for adults cannot be simply used in children and adolescents, particularly in toddlers and even younger children, because of significant changes in body size and continuous growth and development with age. Furthermore, puberty has a drastic effect on fat redistribution in the body, leading to an enhanced insulin sensitivity in the liver, adipose tissues, and muscle, as well as an increased insulin secretion by the pancreatic β cells. In other words, compared to that in adults, insulin sensitivity is lower by 25 to 50% during childhood and returns to normal after pubertal development. Growth and developmental changes with age are also associated with physiological adjustments in blood pressure, plasma lipid levels, and energy metabolism, as well as glucose and lipid metabolism in the liver and adipose tissues. All these factors make it difficult to develop a precise definition for the diagnosis of the metabolic syndrome in young people with different ages, different ethnic/racial groups, and genders. In particular, because of the lack of reference values for some of the components of metabolic syndrome in children and adolescents, a consensus definition is not proposed easily. Notably, over the past 30 years, there is a significant increase in the prevalent rate of obesity-related complications in children and adolescents [101-108]. This high prevalence underscores the urgent need to develop a new definition for the diagnosis of the metabolic syndrome in young people. In addition, further research is imperative to identify biomarkers of the metabolic syndrome in early childhood. Long-term studies are also needed in children and adolescents with obesity, with a particular focus on intervention strategies. This will allow early diagnosis and timely action, including lifestyle modification and pharmaceutical intervention, to halt the development of metabolic abnormalities, thereby preventing long-term metabolic and cardiovascular consequences in children and adolescents [109-111].Obviously, the diagnostic standards for adults cannot be simply used in children and adolescents, particularly in toddlers and even younger children, because of significant changes in body size and continuous growth and development with age. Furthermore, puberty has a drastic effect on fat redistribution in the body, leading to an enhanced insulin sensitivity in the liver, adipose tissues, and muscle, as well as an increased insulin secretion by the pancreatic β cells. In other words, compared to that in adults, insulin sensitivity is lower by 25 to 50% during childhood and returns to normal after pubertal development. Growth and developmental changes with age are also associated with physiological adjustments in blood pressure, plasma lipid levels, and energy metabolism, as well as glucose and lipid metabolism in the liver and adipose tissues. All these factors make it difficult to develop a precise definition for the diagnosis of the metabolic syndrome in young people with different ages, different ethnic/racial groups, and genders. In particular, because of the lack of reference values for some of the components of metabolic syndrome in children and adolescents, a consensus definition is not proposed easily. Notably, over the past 30 years, there is a significant increase in the prevalent rate of obesity-related complications in children and adolescents [101-108]. This high prevalence underscores the urgent need to develop a new definition for the diagnosis of the metabolic syndrome in young people. In addition, further research is imperative to identify biomarkers of the metabolic syndrome in early childhood. Long-term studies are also needed in children and adolescents with obesity, with a particular focus on intervention strategies. This will allow early diagnosis and timely action, including lifestyle modification and pharmaceutical intervention, to halt the development of metabolic abnormalities, thereby preventing long-term metabolic and cardiovascular consequences in children and adolescents [109-111].

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EPIDEMIOLOGY AND PREVALENCE

The prevalence rates of the metabolic syndrome have markedly increased not only in adults, but also in children and adolescents throughout the world over the past 30 years [112-115]. However, there is a striking difference in the prevalence rates of the metabolic syndrome in the USA and other countries, greatly depending on which definition is used to categorize individuals and determine inclusion and exclusion (**Table 2**) [62,63,65,98,438-441], as well as to analyze the composition of the population, e.g., gender, age, race, and ethnicity [116-118]. Additionally, lifestyle habits and socioeconomic status have a marked impact on the prevalence rates of the metabolic syndrome across gender, age, and race/ethnicity cohorts, as found by some epidemiological studies [112,119,120].

The WHO and the NCEP:ATPIII definitions for adults are basically similar in the diagnostic criteria on obesity, hypertension, and dyslipidemia [90,93]. However, type 2 diabetes, insulin resistance, and/or impaired glucose tolerance are a prerequisite for the WHO definition, making the criterion relatively more restrictive [90]. The exclusion of patients with type 2 diabetes from the EGIR definition also makes its definition less inclusive [91,92]. In contrast, the IDF definition has central obesity as its prerequisite and this may make it relatively less restrictive comparted to the NCEP:ATPIII definition [94,95]. Prevalence became more inclusive after the original NCEP:ATPIII criteria were revised to include the cutoff for impaired fasting glucose, i.e., ≤100 mg/dL vs. 110 mg/dL, as recommended by the 2003 criteria of the American Diabetes Association [121]. Because the vast majority of diabetic patients meet the minimum criteria for the diagnosis of the metabolic syndrome, inclusion or exclusion of patients with type 2 diabetes has a marked impact on the prevalence rates while using the WHO or the NCEP:ATPIII definitions for epidemiological studies. In general, higher prevalence may be estimated using the IDF definition compared to the NCEP:ATPIII definition, as well as using the revised NCEP:ATPIII definition compared to the original one. Moreover, there is a difference in the age-adjusted prevalence rates among the various

Table 2. Different definitions of the metabolic syndrome in children and adolescents [62,63,65,98,438-441]

Cook (2003)	Cruz (2004)	Weiss (2004)	de Ferranti (2004)	Ford (2005)	Viner (2005)	IDF (2007)	IDEFICS (2012)
Fasting glucose ≥110 mg/dL	Impaired glucose tolerance (ADA criterion)	Impaired glucose tolerance (ADA criterion)	Fasting glucose ≥6.1 mmoL/L (≥110 mg/dL)	Fasting glucose ≥110 mg/dL (additional analysis with ≥100 mg/dL)	Hyperinsulinemia ≥104.2 pmoL/L (15 mU/L) or impaired fasting glucose ≥6.11 mmoL/L (110 mg/dL)	Impaired fasting glucose ≥5.55 mmoL/L (100 mg/dL)	HOMA-insulin resistance ≥90th percentile or fasting glucose ≥90th percentile
WC ≥90th percentile (age and sex specific, NHANES III)	WC ≥90th percentile (age, sex and race specific, NHANES III)	BMI–Z score ≥2.0 (age and sex specific)	WC >75th percentile	WC ≥90th percentile (sex specific, NHANES III)	BMI ≥95th percentile	WC ≥90th percentile	WC ≥90th percentile
Triglycerides ≥110 mg/dL (age specific, NCEP)	Triglycerides ≥90th percentile (age and sex specific, NHANES III)	Triglycerides >95th percentile (age, sex and race specific, NGHS)	Triglycerides ≥1.1 mmoL/L (≥100 mg/dL)	Triglycerides ≥110 mg/dL (age specific, NCEP)	Triglycerides ≥1.69 mmoL/L (150 mg/dL)	Triglycerides ≥1.69 mmoL/L (150 mg/dL)	Triglycerides ≥90th percentile
HDL-C ≤40 mg/dL (all ages/sexes, NCEP)	HDL-C ≤10th percentile (age and sex specific, NHANES III)	HDL-C <5th percentile (age, sex and race specific, NGHS)	HDL-C <1.3 mmoL/L (<50 mg/dL)	HDL-C ≤40 mg/dL (all ages/sexes, NCEP)	HDL-C <0.91 mmoL/L (35 mg/dL) or high total cholesterol ≥95th percentile	HDL-C <1.03 mmoL/L (40 mg/dL)	HDL-C ≤10th percentile
Blood pressure ≥90th percentile (age, sex and height specific, NHBPEP)	Blood pressure >90th percentile (age, sex and height specific, NHBPEP)	Blood pressure >95th percentile (age, sex and height specific, NHBPEP)	Blood pressure >90th percentile	Blood pressure ≥90th percentile (age, sex and height specific, NHBPEP)	SBP ≥95th percentile	SBP ≥17.3 kPa (130 mmHg) or DBP ≥11.3 kPa (85 mm Hg)	SBP ≥90th percentile or DBP ≥90th percentile

IDF: International Diabetes Federation, IDEFICS: identification and prevention of dietary- and lifestyle-induced health effects in children and infants, WC: waist circumference, NHANES: National Health and Nutrition Examination Survey, NCEP: National Cholesterol Education Program, HDL-C: high-density lipoprotein cholesterol, NHBPEP: National High Blood Pressure Education Program, ADA: American Diabetes Association, BMI: body mass index, NGHS: National Growth and Health Study, SBP: systolic blood pressure, DBP: diastolic blood pressure, HOMA: homeostatic model assessment.

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Table 3. The IDEFICS definition of the metabolic syndrome in children aged 2–11 years (2014)

· Obesity: ≥90th percentile as assessed by waist circumference
· Triglycerides: ≥90th percentile
· HDL cholesterol: ≤10th percentile
· Blood pressure: systolic ≥90th percentile or diastolic ≥90th percentile
· Glucose: insulin ≥90th percentile or fasting glucose ≥90th percentile, according to homeostasis model assessment

Each category counts as one risk criterion.
IDEFICS: identification and prevention of dietary- and lifestyle-induced health effects in children and infants, HDL: high-density lipoprotein.
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definitions of metabolic syndrome [122-124]. It is worth noting that definition-related differences in prevalence are not consistent among countries, whereas these differences may be attributed, in part, to the race-specific waist circumference guidelines.

Although one definition with cutoffs specific for gender and ethnic origin could be appropriate for at-risk adults, using such definition for children and adolescents is problematic because lipid concentrations in the liver, adipose tissues, and plasma, as well as anthropometric variables, blood pressure, and insulin sensitivity change dramatically with age and pubertal development [124]. Furthermore, for children aged 10 years or older, the diagnosis of the metabolic syndrome is often made by abdominal obesity plus the presence of two or more other clinical features, i.e., hyperglycemia, hypertriglyceridemia, hypertension, or low plasma HDL-cholesterol levels (**Table 3**) [100]. Despite this, a major problem with the diagnosis of the metabolic syndrome in children and adolescents is that no established criteria for this young population are available to date. The uniqueness of pubertal growth patterns, effects of hormonal changes of puberty on insulin sensitivity and lipid profile, redistribution of adipose tissues in the body, and the impact of ethnic background on components of the metabolic syndrome make such criteria difficult to establish for children and adolescents [34,64,125-152].

As shown by epidemiological investigations, the presence of the metabolic syndrome in children and adolescents could be an important predictor of future risk for type 2 diabetes and cardiovascular disease in adulthood [63,64,153,154]. The results from the Bogalusa Heart Study suggested that cardiovascular risk factors present in childhood could be predictive of coronary artery disease in adulthood [155-162]. This study pointed out that plasma LDL-cholesterol concentrations and BMI determined in childhood could be used to predict carotid intima-media thickness in young adults. In addition, visceral obesity is the major determinant of insulin resistance in children and adolescents [163-170], which increases the risk not only for the metabolic syndrome in young people, but also for the development of cardiovascular disease and type 2 diabetes in adulthood [124].

Table 4 [15] shows the recommended waist circumference thresholds for abdominal obesity in adults by different organizations. Although numerous variables have been used to define obese children, waist circumference is an important predictor that is independent of insulin resistance, plasma lipid levels, and blood pressure in young people [171-177], which is consistent with the situation in adults [178-182]. Even if children and adolescents are obese and have similar BMI, insulin sensitivity is lower in those with large amounts of visceral adipose tissues compared to those with small amounts [183-187]. For the new IDF criteria, it is critical to use waist circumference to define central obesity in children and adolescents [94,95]. Moreover, percentiles, but not absolute values, of waist circumference are used by

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Table 4. Recommended waist circumference thresholds for abdominal obesity in adults by different organizations (2009)

Population	Organization	Recommended waist circumference threshold for abdominal obesity	
		Men	Women
Europid	IDF	≥94 cm	≥80 cm
Caucasian	WHO	≥94 cm (increased risk) ≥102 cm (still higher risk)	≥80 cm (increased risk) ≥88 cm (still higher risk)
United States	AHA/NHLBI (ATP III)*	≥102 cm	≥88 cm
Canada	Health Canada	≥102 cm	≥88 cm
European	European Cardiovascular Societies	≥102 cm	≥88 cm
Asian (including Japanese)	IDF	≥90 cm	≥80 cm
Asian	WHO	≥90 cm	≥80 cm
Japanese	Japanese Obesity Society	≥85 cm	≥90 cm
China	Cooperative Task Force	≥85 cm	≥80 cm
Middle East, Mediterranean	IDF	≥94 cm	≥80 cm
Sub-Saharan African	IDF	≥94 cm	≥80 cm
Ethnic Central and South American	IDF	≥90 cm	≥80 cm

IDF: International Diabetes Federation, WHO: World Health Organization, NHLBI: National Heart, Lung, and Blood Institute, ATPIII: the adult treatment panel III.
*The guidelines of the American Heart Association and the National Heart, Lung, and Blood Institute for the metabolic syndrome recognize an increased risk for cardiovascular disease and diabetes at waist-circumference thresholds of ≥94 cm in men and ≥80 cm in women and identify these as optional cut points for individuals or populations with increased insulin resistance.
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the new IDF definition to compensate for variation in child development and ethnic origin [94,95]. Children and adolescents with a waist circumference higher than the 90th percentile have multiple risk factors for cardiovascular disease compared to those with lower one. Many studies have used the 90th percentile as a cutoff for waist circumference in young people. As a result, the concept of using percentiles of waist circumference, which is specific to ethnic origin, is becoming increasingly acceptable for clinical studies [188-193]. In addition, the 90th percentile as a cutoff for waist circumference has been used as the essential standard for the diagnosis of the metabolic syndrome in children and adolescents [94,95,194].

The reported prevalence rates of the metabolic syndrome in young people vary greatly depending on the age and population studied and the definition used. Because it is more difficult to assess the prevalence rates of the metabolic syndrome in children and adolescents compared to adults, this has greatly prompted the development of new simple-to-use definitions. Many new definitions of the metabolic syndrome in young people builds on previous studies that used the modified adult criteria to investigate prevalence in children and adolescents [195-200]. A study using the modified NCEP:ATPIII criteria found that the prevalence of metabolic syndrome in adolescents is 12% [98]. The National Health and Nutrition Examination Survey III (NHANES) reported approximately 10% of children and adolescents aged 12–19 years suffer from the metabolic syndrome [62]. As estimated by population-weighted studies, it is highly likely that more than 2 million American youngsters suffer from the phenotypes of the metabolic syndrome [61-63]. The metabolic syndrome is most frequent in obese adolescents, with a prevalence of 32.1%, compared with only 7.1% in overweight adolescents [65,201]. Because of the increasing prevalence of overweight and obesity in children and adolescents, as well as the compelling relationship between obesity and the metabolic syndrome, it is well understood that the prevalence rates of the metabolic syndrome have augmented in American youngsters over the past 30 years.

In addition, there are racial/ethnic differences in the prevalence rates of the metabolic syndrome, as well as of individual components of the metabolic syndrome in children and adolescents. Using the 1986–1994 NHANES data as analyzed by the modified NCEP:ATPIII criteria, the overall prevalence rates of the metabolic syndrome in 2,430

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American adolescents are 4.2%, with 6.1% being boys and 2.1% being girls, respectively [62,71,202,203]. Among obese and overweight adolescents, the prevalence rates of the metabolic syndrome are 28.7% and 6.8%, respectively [62,71,202,203]. Similar to adults, the prevalence of individual components of the metabolic syndrome differed by race/ethnicity, e.g., the prevalence of hypertension is higher in African American adolescents compared to that in young non-Hispanic Caucasians or Mexican Americans. In contrast, the prevalence of hypertriglyceridemia and low plasma HDL-cholesterol concentrations is lower in the former than in the latter [204-213].

PATHOPHYSIOLOGY

Clinical and epidemiological studies have clearly demonstrated that obesity is often associated with many metabolic abnormalities including insulin resistance, impaired glucose tolerance, hypertension, hypercholesterolemia, and hypertriglyceridemia [214], as shown in **Fig. 2**. The cluster of these metabolic abnormalities is defined as the metabolic syndrome, a state associated with increased prevalence of several metabolic diseases such as type 2 diabetes and cardiovascular disease, and all-cause mortality not only during adulthood, but also in children and adolescents [215]. The prevalence rates of obesity in adolescents (≥95th percentile of BMI for age) have dramatically increased from 15 to 37% over the last 30 years [107,216-220]. There is a risk of 50 to 77% for obese adolescents to become obese adults [221-223]. If parents are obese, this risk can increase to 80% for obese adolescents [224]. In addition, obese children and adolescents are at high risk of developing obesity-related complications and have shown an increased risk of adult morbidity and mortality [225-227].

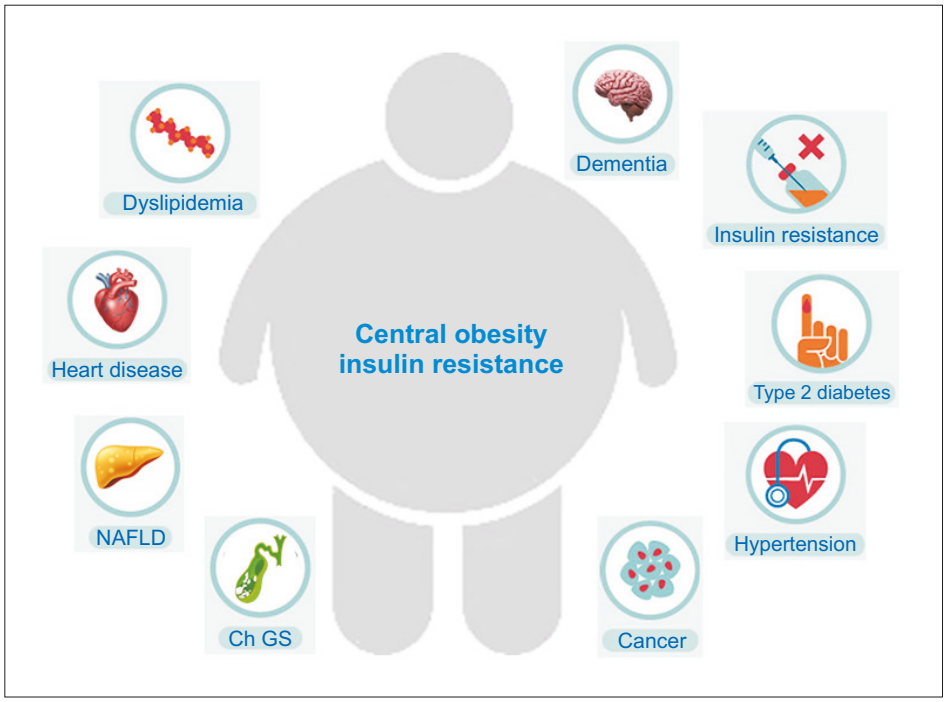

Fig. 2. Obesity and insulin resistance play a key role in the pathogenesis of the metabolic syndrome in childhood and adolescence.
Ch GS: cholesterol gallstones, NAFLD: nonalcoholic fatty liver disease.

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Although the exact etiology of the metabolic syndrome is not fully understood, insulin resistance is considered as a key factor for the development of the metabolic syndrome and is largely involved in the pathogenesis of individual metabolic components of the syndrome [49-51]. As found by the insulin-modified, frequently-sampled intravenous glucose tolerance assay, insulin sensitivity is significantly lower in patients with two or more than two components of the metabolic syndrome compared to those with none of these components [228-230]. It is well known that insulin plays a critical role in the regulation of glucose, lipid, and energy metabolism in many organs and tissues such as the liver, adipose tissue, muscle, heart, and gastrointestinal track [231]. Therefore, early identification of children and adolescents who are at risk of developing the metabolic syndrome, type 2 diabetes, and cardiovascular disease in later life is extremely important [232-235]. Conditions in utero and in early childhood could predispose a child to metabolic disorders such as obesity, insulin resistance, hypertension, hypercholesterolemia, hypertriglyceridemia, type 2 diabetes, NAFLD, NASH, cardiovascular disease, and the metabolic syndrome [236-240]. Furthermore, urbanization, overconsumption of nutrients, unhealthy diet, and sedentary lifestyle have been found to be major contributors to such disorders [241-243]. Epidemiological investigations have clearly shown that obesity is associated with increased risk of type 2 diabetes and cardiovascular disease [244-246], which may persist from childhood and adolescence into young adulthood [247-250].

PREVENTION AND TREATMENT

Because obesity is associated with increased risk of type 2 diabetes and cardiovascular disease, this may continue into childhood and adolescence until adulthood. Therefore, lifestyle changes are the main options for the prevention of the metabolic syndrome in childhood and adolescence with a special focus on keeping weight within normal range [251,252]. Lifestyle modification includes eating healthy diet and appropriate amounts of total calories, increasing physical activity, and maintaining the right weight. In general, the therapeutic interventions are divided into (i) lifestyle modification, (ii) pharmaceutical therapy, and (iii) bariatric surgery [253-255].

Lifestyle modification

1. Diet

It is well known that Western diet contains high total calories, cholesterol, saturated fatty acids, refined carbohydrates, proteins, and salt, as well as low fibers, and it is highly associated with the metabolic abnormalities [256-258]. Moreover, overconsumption of fast foods in combination with inactive physical activity is strongly associated with the high prevalence of overweight, obesity, dyslipidemia, hypertension, type 2 diabetes, and cardiovascular disease in children and adolescents over the past 30 years [259]. Clearly, eating healthy diet has a significant impact on all the components of the metabolic syndrome [260]. Although each case should be treated individually, it is important to recommend a healthy diet with low total calories, cholesterol, saturated fat, and sodium, as well as high unsaturated fat, complex carbohydrates, and fiber [261]. This should be the first step in halting the development of metabolic abnormalities in children and adolescents [262-264].

It is well established that weight loss has a great benefit for the treatment of all the components of the metabolic syndrome, including excessive adiposity, dyslipidemia, hypertension, insulin resistance, and hyperglycemia [265-268]. The intensive lifestyle

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intervention with a special focus on a significant decrease in daily caloric intake could lead to weight loss [269]. It is worthwhile noting that even if the magnitude of weight loss is not drastic, some metabolic abnormalities could be improved. As shown by the Finnish Diabetes Prevention Study [270], lifestyle intervention with modest weight loss could significantly reduce the prevalence of the metabolic syndrome compared with the control group. A modest weight loss often improves blood pressure regulation and decreases the risk of developing hypertension [271-273]. In addition, weight loss may increase plasma HDL-cholesterol concentrations, as well as reduce plasma triglyceride and fasting blood glucose levels, and hemoglobin A1c values [274-276]. A 7-day negative energy balance without measurable weight loss has found that reducing daily caloric intake may improve insulin sensitivity [277-279].

It has been recognized that high dietary cholesterol is a risk factor for cardiovascular disease, dyslipidemia, NAFLD, NASH, and cholesterol gallstone disease, with all of these being the major components of the metabolic syndrome [280-282]. Therefore, it is important to recommend a low cholesterol diet to children and adolescents. The NCEP:ATPIII guidelines and the recommendations from the American Heart Association and the American College of Cardiology have proposed a lower (<100 mg/dL) target for plasma LDL-cholesterol levels for individuals at high risk for adverse cardiovascular events [283-286]. Therefore, the low cholesterol diet could reduce not only total cholesterol concentrations in the plasma, liver, and bile, but also plasma LDL-cholesterol concentrations [287].

Dietary carbohydrates are often divided into two types: simple and complex. It is recommended that complex carbohydrates should make up most of daily carb intake [288-290]. In contrast, simple carbohydrates, especially refined carbohydrates such as added sugars, should be limited [291-293]. Common sources of added sugars include soft and fruit drinks, as well as candies, cakes, cookies, dairy desserts, pies, and purified sugars [294-296]. Although chemical structures are identical between added sugars and naturally occurring simple sugars, e.g., sugars found in fruit, added sugars contain less or no vitamins and minerals. Thus, large amounts of added sugar intake could lead to a lack of nutrients found in foods. In addition, added sugars quickly raise blood glucose levels and increase the risk of insulin resistance. Based on these observations, a concept was proposed that carbohydrates are classified as “good” or “bad” for disease risk, as indicated by the glycemic index [297-299]. For example, low glycemic index foods may improve components, i.e., hyperlipidemia and hyperglycemia, of the metabolic syndrome, whereas high glycemic index foods may increase the risk of insulin resistance and the metabolic syndrome [299-302]. Moreover, the Nurses' Health Study showed that a lower glycemic load is associated with a decreased risk of developing cardiovascular disease [303].

For most people, a carbohydrate intake of 45 to 65% of total daily calories is appropriate, as recommended by the US Department of Agriculture. In general, a diet high in complex, unrefined carbohydrates with an emphasis on fiber (25 g per day) and low in added sugars (<25% of caloric intake) is recommended for individuals with or at risk for the metabolic syndrome [304-307]. Clinical studies found that high daily carbohydrate intake is associated with increased plasma total cholesterol, LDL-cholesterol, and triglyceride concentrations, and reduced HDL-cholesterol levels [292,293,308-310]. In contrast, low carbohydrate diets may improve glucose metabolism in subjects with insulin resistance and/or type 2 diabetes [170,311,312]. It is unclear whether low daily carbohydrate intake may influence lipid metabolism and reduce the risk of hypercholesterolemia and hypertriglyceridemia. Another explanation is that low daily carbohydrate intake may enhance insulin sensitivity,

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thus improving cholesterol and triglyceride metabolism in the liver and plasma [30,313-315]. Although lower carbohydrate diets may be helpful in weight loss in the short term, the effects on long-term weight loss have been mixed and further studies are needed.

Most studies suggested that high fat intake, i.e., 20 to 40% of caloric intake, may increase the risk of overweight and obesity, thereby leading to insulin resistance. In addition, high fat intake may increase the prevalence of NAFLD, NASH, hypertension, type 2 diabetes, and cardiovascular disease [57,316-318]. However, because some conflicting results have been reported, it is unclear whether increased fat intake per se may have an impact on insulin sensitivity or may impair glucose metabolism [319]. Although the average fat intake in the USA has been reduced from 36.9 to 32.8% in men and from 36.1 to 32.8% in women over the past 50 years, there has been a marked increase in overweight, obesity, and the metabolic syndrome during the same time period [106,107,320]. This suggested that it may be the type of fats consumed, rather than the total amount of intake, producing a greater effect on the components of the metabolic syndrome [321,322].

The fatty acids in fat are often divided into two types: saturated and unsaturated fatty acids, with the latter being subclassified to monounsaturated and polyunsaturated fatty acids [57]. In general, saturated, but not unsaturated, fatty acids are associated with impaired glucose tolerance and obesity, as well as increased risk of developing NAFLD, NASH, hypertension, type 2 diabetes, and cardiovascular disease [323-325]. It is highly likely that a diet with high unsaturated fatty acids and low saturated fatty acids may improve insulin sensitivity and plasma lipid and lipoprotein metabolism [326]. The Nurses' Health Study has found that a 5% increase in saturated fat intake is associated with a 17% increment in risk of coronary heart disease [327]. In contrast, increased monounsaturated and polyunsaturated fat intake may be associated with a reduced risk of coronary heart disease [328].

Low sodium intake has a good benefit for blood pressure regulation because clinical and epidemiological studies have revealed a clear positive relationship between sodium intake and blood pressure [329]. It is well known that excessive sodium intake can cause hypertension not only in adults, but also in children and adolescents [260]. As shown by the Dietary Approaches to Stop Hypertension Study [330-332], lower sodium intake reduces blood pressure in people with mild or moderate hypertension, as well as sodium restriction may be associated with decreased risk of cardiovascular disease and congestive heart failure. Therefore, it is strongly recommended that sodium restriction or low sodium diet should be given to children and adolescents, especially to obese young people. This is a key step for the prevention and the treatment of hypertension, a major component of the metabolic syndrome [333].

Because of a lack of sufficient clinical and epidemiological data, it is unclear whether protein intake has an association with the development of the metabolic syndrome [334]. A daily protein intake of 10 to 35% of total calories has been recommended for the general population [335]. Nevertheless, appropriate daily protein intake is good for people, regardless of whether they have normal weight or are obese, except for patients with nephropathy [336].

2. Physical activity

Epidemiological surveys have found that a sedentary lifestyle in combination with unhealthy eating habits likely increases the risk of insulin resistance, type 2 diabetes, cardiovascular

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disease, NAFLD, and NASH [337]. Thus, increasing excise to reduce and/or maintain weight is another important approach for preventing or treating the metabolic syndrome [338-340]. Many epidemiological reports have shown that low physical activity is associated with increased prevalence of the metabolic syndrome, whereas high physical activity is likely to protect against the development of the metabolic syndrome [341]. Indeed, higher cardiorespiratory fitness and extensive physical activity have been shown to improve glucose metabolism and insulin sensitivity and reduce cardiovascular disease mortality, as well as the risk of type 2 diabetes, NAFLD, and NASH [342-345]. It is likely that increasing physical activity could reduce the risk of cardiovascular disease and the prevalence of type 2 diabetes, NAFLD, and NASH through weight loss [346-348]. Furthermore, cardiorespiratory fitness and intensive physical activity prevent the development of the metabolic syndrome likely through their effects on each of the individual components [343,349,350]. Clinical studies have revealed that combining with healthy dietary intake, high-intensity exercise, i.e., aerobic exercise, is very effective at enhancing insulin sensitivity and reducing weight, particularly abdominal adiposity, as well as potentially improving hypertension, hyperglycemia, and dyslipidemia [351-354].

As shown by a systematic review of the literature, aerobic exercise may reduce visceral adiposity in a dose-dependent manner [355-357]. However, it is unclear whether exercise could reduce visceral adipose tissue in the absence of weight loss [358]. To achieve continued benefit of exercise on insulin action, the American Heart Association and the American College of Sports Medicine have recommended exercise at least 30 minutes/day most days of the week [359]. Aerobic exercise may produce a persistent effect on glucose tolerance and insulin action beyond the immediate post-exercise effects and possibly through weight loss [360-362]. More importantly, while maintaining weight, regular aerobic exercise is still critical to reducing abdominal fat tissue and preventing weight regain in individuals who have successfully lost weight [362-364].

Pharmaceutical therapy

Because there are no published papers reporting double-blind, randomized controlled trials on the management of the metabolic syndrome, no guidelines or specific recommendations are currently available for treating the metabolic syndrome [365-371]. In addition, because the cellular and molecular mechanisms underlying the pathogenesis of the metabolic syndrome are not completely understood, the therapeutic options have not yet been developed [10]. The currently available therapeutic strategies focus mainly on treating the individual components of the metabolic syndrome, with the overall goals of reducing the risk of cardiovascular disease and type 2 diabetes or preventing them [86,372-376] Moreover, some therapeutic options may have a marked impact on two or more than two components of the metabolic syndrome [377-379]. Nevertheless, many therapeutic efforts on the treatment of the visceral obesity and insulin resistance associated with the metabolic syndrome may provide the most overall success in achieving these goals [380-387].

Bariatric surgery

For adults, if a body mass index (BMI) is ≥40 or a BMI is 35 in patients with significant obesity-related comorbidities, bariatric surgery can be considered as a weight loss procedure [388-392]. Because of a lack of clear evidence concerning surgical treatment for children and adolescents, bariatric surgery is not recommended by the NIH Consensus Panel as an acceptable alternative that can achieve sustained weight loss in young patients [393-396]. However, when lifestyle modification and standard pharmaceutical therapy are not effective in reducing body weight and BMI, bariatric surgery may be considered for children and

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Table 5. Indications and contraindications for bariatric surgery in children and adolescents

Indications:
· Failure of at least 6 months of organized, medically supervised weight loss attempts
· Ages 13 to 18 for girls, and 14 to 18 for boys
· BMI ≥40 with presence of severe obesity-related comorbidity
· BMI ≥50 with less severe obesity-related comorbidities
Contraindications:
· Substance abuse problem within the preceding year
· Psychiatric diagnosis that would impair ability to adhere to postoperative dietary or medication regimen (e.g., psychosis)
· Medically correctable cause of obesity
· Inability or unwillingness of patient or parent to fully comprehend the surgical procedure and its medical consequences
· Inability or refusal to participate in lifelong medical surveillance

BMI: body mass index.
Modified and reproduced with permission from reference [404].

adolescents [397-400]. In general, the surgical interventions include Roux-en-Y gastric bypass (RYGBP), adjustable gastric band, sleeve gastrectomy, and biliopancreatic diversions for obese children and adolescents [401-408]. The limited experience with bariatric surgery in young patients suggests that RYGBP surgery and adjustable gastric banding can effectively treat the comorbidities of adolescent obesity. The surgery can be open and/or laparoscopic procedures [409]. However, because children and adolescents are still developing, both physically and mentally, they and/or their parents may show less willingness to give consent to surgery [410]. Moreover, bariatric surgery may dramatically change their lives after operation. Therefore, careful consideration must be given to whether or not surgery is performed on obese children and adolescents [411-414]. **Table 5** [404] lists indications and contraindications for bariatric surgery in children and adolescents.

As shown in the data from the US National Inpatient Sample, 2,744 adolescents have received bariatric surgeries in the USA from 1996 to 2003 [415]. Because many children and adolescents with clinically severe obesity are interested in a bariatric surgical option to attain a healthier weight, it is estimated that more and more bariatric operations have been done since this time [415]. Similar to adults, bariatric surgery leads to very good short-term weight outcomes in children and adolescents [415]. Among different surgical methods, RYGB produces the greatest weight loss, as shown by the most reliable clinical evidence [416-419]. Because no other evidence-based medical interventions lead to a similar magnitude of weight loss, bariatric surgery could be considered a treatment option especially for children and adolescents who have obesity-related complications and comorbidities [420-423].

Although there are compelling reasons to offer bariatric procedures to some children and adolescents in whom prior weight management attempts have not been successful [424-429], there are also disagreements and dissenting voices because of the limited experience with bariatric surgery in young patients. Furthermore, children and adolescents can lose weight more effectively with lifestyle modification compared to adults, but they have not always made their best attempts at nonsurgical weight loss [430-432]. More aggressive steps should be taken to improve young people's lifestyles to achieve sustained weight loss. In addition, children and adolescents are still growing with age, which could be adversely affected by nutritional consequences of a bariatric operation [433-435]. Although many seriously obese adolescents are interested in bariatric procedures to achieve weight loss, they are not psychologically prepared for bariatric surgery [436]. Therefore, it is necessary to propose more strict bariatric surgery standards for young people compared to adults

[404]. In addition, to more carefully evaluate the harms and benefits of bariatric surgery for children and adolescents, it is imperative to perform long-term, prospectively designed clinical studies, with clear inclusion and exclusion criteria and reporting of beneficial effects, side effects, complications, and comorbidity resolution, as well as measures of health-related quality of life after operation [437].

CONCLUSIONS AND FUTURE DIRECTIONS

Clearly, the metabolic syndrome, by definition, is not a disease but is a clustering of individual metabolic risk factors that could dramatically increase the prevalence of type 2 diabetes and cardiovascular disease. Although many definitions of the metabolic syndrome in children and adolescents have been proposed, no unified definition exists to assess risk or outcomes in pubertal subjects to date. Because dysfunctional glucose, lipid, and energy metabolism across several organs and tissues occurs under insulin resistant conditions, together creating the observed interplay of several concurrent metabolic abnormalities, early identification of children and adolescents at risk of developing the metabolic syndrome is extremely important. A clinically accessible diagnostic tool is needed to identify the metabolic syndrome in young people globally. This will greatly prompt the development of a new simple definition that is easy to apply for clinical practice and epidemiological surveys.

For future research, it is imperative to decipher the relationship between body fat and its distribution in the body in children and adolescents and investigate whether early growth patterns predict future adiposity and other features of the metabolic syndrome. More importantly, it is urgent to perform long-term cohort studies on children and adolescents of different ethnic origin into adulthood by investigating the natural history and effectiveness of interventions, especially those related to lifestyle. As indicated in **Fig. 3**, early detection followed by treatment, particularly lifestyle intervention, is vital to halt the progression of the metabolic syndrome in children and adolescents. Such an action should reduce morbidity and mortality in adulthood and help minimize the global burden of cardiovascular disease and type 2 diabetes.

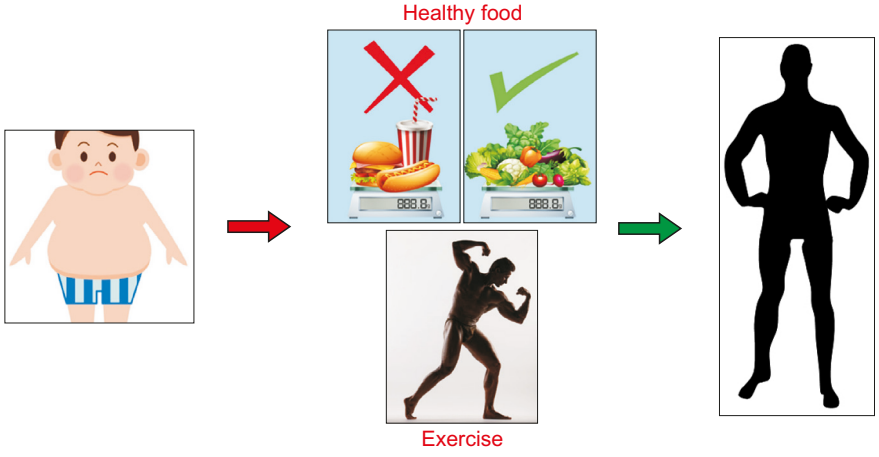

Fig. 3. Because obesity is associated with increased risk of type 2 diabetes and cardiovascular disease, this may continue into childhood and adolescence until adulthood. Therefore, lifestyle modifications, including eating healthy diet and appropriate amounts of total calories, increasing physical activity, and maintaining the right weight, are the main options for the prevention of the metabolic syndrome by halting the development of metabolic abnormalities in childhood and adolescence.

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Lifestyle interventions and other non-pharmacological treatments are often considered to be the first option but, such interventions have variable outcomes. Eating healthy diet and appropriate amounts of total calories, increasing physical activity, and maintaining the right weight could substantially improve insulin resistance, blood pressure, and plasma lipid and lipoprotein metabolism. Pharmacological treatment appears to have modest effectiveness. However, when combined with lifestyle interventions, it is associated with more adverse effects than lifestyle interventions alone. Several surgical procedures are available for children and adolescents; however, long-term effects of bariatric surgery from high quality studies are strongly needed.

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