Review Article

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Metabolic Syndrome in Children and Adolescents

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Metabolic syndrome (MetS) is a cluster of metabolic abnormalities that include hypertension, altered glucose metabolism, dyslipidemia, and abdominal obesity and is strongly associated with an increased risk for diabetes and cardiovascular disease onset in obese adults and children. A progressively greater number of children and adolescents are being affected by this syndrome due to the constant increase in the prevalence of obesity. Like obesity, childhood MetS highly tracks to adulthood. The pathogenesis of MetS includes the interaction between obesity, insulin resistance, and inflammation. Early diagnosis and intervention are important in order to conduct lifestyle modification. In this article, we review the definition and pathophysiology of MetS, the importance of screening, and prevention and treatment options for MetS in childhood.

Introduction

Metabolic syndrome (MetS) is characterized by a cluster of cardiovascular risk factors (hypertension, altered glucose metabolism, dyslipidemia, and abdominal obesity) that occur in obese adults and children [1]. MetS risk is rising in children and adolescents as childhood obesity continues to rise [2,3]. In order to better manage MetS in childhood, we must understand its pathophysiology, risk factors, and management methods.

MetS affects >30% of the adult population >30 years of age in South Korea [4]. According to the Korea National Health and Nutrition Examination Survey, its prevalence has been increasing gradually in young adults since 1998 [5]. Controversy exists regarding the various definitions of the syndrome and its ability to predict future adverse cardiometabolic events in a manner surpassing other well-described risk factors. Despite this, there can be little controversy regarding the current national and worldwide epidemic of obesity, and the links between risk factors in youth and subsequent adult cardiovascular disease (CVD) [6]. Also, the rise in the prevalence of pediatric obesity is one of the most alarming public health issues facing the world, including Korea, today [7].

MetS is associated with many clinical conditions besides CVD and type 2 diabetes (T2DM), including chronic low-grade inflammation, oxidative stress, hyperuricemia, hypertension, dyslipidemia, hyperandrogenism and polycystic ovarian syndrome (PCOS), hepatic steatosis and non-alcoholic fatty liver disease (NAFLD), impaired glucose tolerance, obstructive sleep apnea, hypogonadism, vascular dementia and Alzheimer' disease, and certain forms of cancer [8,9].

Despite the risks and associated conditions, several factors contribute to the controversy

surrounding pediatric MetS. First of all, it is difficult to define MetS in pediatric populations. MetS in adults is predictive of CVD and T2DM; however, several definitions of MetS have been proposed for children and adolescents, and there is no clear consensus on which one should be applied [10,11]. Moreover, regardless of the definition used, there is no uniform way to treat MetS other than weight management.

Our purpose in this review article is to provide an overview of MetS in the pediatric population, focusing on its definition, pathophysiology, screening, prevention, and treatment.

Definition of Metabolic Syndrome in Childhood

MetS among adults has been defined clinically by at least five health organizations, including the World Health Organization (WHO); the U.S. National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III; the American Association of Clinical Endocrinologists/American College of Endocrinology; the International Diabetes Federation (IDF); and the American Heart Association (AHA) in conjunction with the National Heart, Lung, and Blood Institute (NHLBI) of the U.S. National Institutes of Health. In 2001, the NCEP developed the first risk criteria definition for atherosclerosis and cardiovascular disease based on the "any three of five" risk criteria. NCEP ATP III defines five risks: (I) hyperglycemia, (II) hypertriglyceridemia, (III) low high-density lipoprotein cholesterol (HDL-C) level, (IV) hypertension, and (V) an increase in waist circumference. In 2005, the AHA/NHLBI modified this definition of MetS by reducing glucose cut points, and the IDF introduced its "worldwide" definition of MetS, placing greater emphasis on abdominal obesity by making it a necessary criterion for MetS diagnosis. Although the AHA/NHLBI and IDF definitions have many similarities, there are important differences between them with respect to cut points of the various component risks. However, most commonly used definitions agree that the following components are relevant: central obesity, impaired glucose tolerance, dyslipidemia, and hypertension.

Among children and adolescents, MetS definitions differ even more than among adults. MetS was first studied among adolescents in a pediatric population; however, the prevalence varied by more than 2-fold in the same database. In 2007, the IDF assembled an international group of experts to develop a consensus definition. Specifically, the IDF recommended pediatric MetS should only be applied to children ≥10 years of age with three or more of following risk factors: high waist circumference, high blood pressure, IR, and dyslipidemia [10]. Among those 10–15 years of age, those in the >90th percentile for waist circumference or with a systolic blood pressure>130 mmHg or diastolic blood pressure>85 mmHg, triglycerides>150 mg/dL, or HDL-C<40 mg/dL would be defined as having MetS. For adolescents>15 years of age, the adult criteria should be used for diagnosis (Table 1).

In its scientific statement published two years later, the AHA stressed the importance of identifying pediatric cardiometabolic risks and noted that only some of them could be identified by the current MetS criteria. The AHA did not include a definition of MetS for pediatric populations and noted that adapting adult definitions to pediatric populations had limitations. To date, there is no clear consensus on whether MetS should be defined in pediatric populations and, if defined, which definition should be used. However, this definition also stated that children <10 years of age should not be diagnosed with MetS. This was explained by the absence of age-specific reference values for MetS components for this age group [10]. In 2014, Ahrens et al. proposed a quantitative MetS score using age- and gender-specific anthropometric and metabolic parameters in children 2–11 years of age [11]. To help physicians identify children at

Table 1. Pediatric definition of MetS (IDF definition)

Variables	IDF definition age<10 years	IDF definition ages 10–16 years
Defining criteria	Cannot be diagnosed in the age group	Central obesity with at least 2 out of 4 criteria
Central obesity		WC≥90th percentile or adult cutoff if lower
Hypertension		SBP≥130 mmHg or DBP ≥85 mmHg or treatment with anti-hypertensive medication
Hypertriglyceridemia		TG≥150 mg/dL
Low HDL		HDL<40 mg/dL
Impaired glucose		FPG≥100 mg/dL or known T2DM

IDF, International Diabetes Federation; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; HDL, high-density lipoprotein; FPG, fasting plasma glucose; T2DM, type 2 diabetes mellitus.

risk, the scoring system recommends strict monitoring of children in the ≥90th percentile of body mass index (BMI), and for those in the ≥95th percentile, urgent intervention is recommended [11].

MetS' utility in pediatrics is contested beyond its definition. The presence of MetS predicts the presence of CVD and diabetes in adulthood. As compared to patients without MetS risk factors, Malik et al. found that a person with MetS and diabetes had an increased hazard ratio for coronary heart disease mortality by 1.75 times [12]. However, there has been some concern that the syndrome is ineffective in adolescents, given that there is some instability in the definition of the syndrome as adolescent's transition from adolescence to adulthood.

Most children defined as having MetS at childhood fail to meet diagnostic criteria three to six years later during follow-up. Even though the prevalence of MetS has increased at the population level, within-person variation in the presence or absence of MetS has been large in observational longitudinal studies. Many studies have shown that 50% of MetS-positive subjects become MetS-negative over time, either during short-term follow-up (~3 weeks) or long-term (9 years) [13]. There was no correlation between this instability and a change in weight [13]. As a result, MetS remains highly unstable throughout childhood. In a child, the criteria can be met at one point in time and not at another, and it is unclear whether this represents an improvement or a deterioration in health.

Given the absence of a consensus on the definition of MetS, the unstable nature of MetS, and the lack of clarity about the predictive value of MetS for future health in pediatric populations, pediatricians are rightly confused about MetS. Thus, rather than focusing on defining MetS in youth, the American Academy of Pediatrics (AAP) recommends that pediatricians focus on the concept of cardiovascular risk factor clustering and associated risk factor screening. This concept is especially important because the Bogalusa Heart Study demonstrated that increased clustering of atherosclerotic CVD risk factors was associated with increased severity of atherosclerotic lesions [14]. In addition, the AAP recommends pediatricians avoid using cut points based on MetS definitions. MetS identifies multiple components that cluster together and are associated with insulin resistance and adipose tissue pathology. Disparities in these thresholds are a major reason for discrepancy between definitions. In addition, there is a continuum of risk associated with many risk factors. A continuous variable may be more reliable in predicting the future risk of young adults from early adolescence [15]. Risk factor screening and the identification of youth with MetS risk factor abnormalities allow providers to allocate scarce resources to children who are at a higher cardiometabolic risk, specifically those

with multiple components. The screening and associated treatment of MetS is an important component of preventive pediatric care.

Pathogenesis of Metabolic Syndrome

Despite the lack of clarity about MetS pathogenesis, recent research suggests that obesity, insulin resistance, and inflammation play a key role in the development of MetS.

1. Insulin resistance

Insulin resistance is the opposite of insulin sensitivity and is defined as a decreased response to insulin-mediated cellular actions. The phrase "insulin resistance," as generally applied, refers to whole-body reduced glucose uptake in response to physiologic insulin levels and its consequent effects on glucose and insulin metabolism. However, it is now clear that not all insulin-responsive tissues are equally sensitive to insulin. Generalized insulin resistance would result in global metabolic dysfunction, such as leprechaunism or Rabson–Mendenhall syndrome. Thus, the insulin resistance in obesity inevitably affects different tissues quantitatively.

1) Hepatic insulin resistance

In addition to being a primary target of insulin action, the liver plays a critical role in substrate metabolism. After insulin is released from β-cells following a glucose loading, it travels directly to the liver via the portal vein, where it binds to insulin receptors and elicits two key actions at the level of gene transcription. First, insulin stimulates the phosphorylation of FoxO1, preventing it from entering cell nuclei and decreasing the expression of genes required for gluconeogenesis, which are principally phosphoenolpyruvate carboxykinase and glucose 6-phosphatase [16]. This process leads to decreased hepatic glucose production. A second effect of insulin is that it activates the transcription factor sterol regulatory element–binding protein (SREBP)-1c. This increases the transcription of genes required for fatty acid and TG biosynthesis, particularly adenosine triphosphate citrate lyase, acetyl-coenzyme A carboxylase, and fatty acid synthase, which together promote the process of de novo lipogenesis (DNL). TGs synthesized by DNL are then packaged with apoliprotein B into very-low-density lipoproteins (VLDLs), which are then exported to the periphery to be stored. The use of VLDLs is then enabled by the reciprocal activation of lipoprotein lipase on the surface of endothelial cells within the adipose tissue or the muscle tissue [17]. For reasons that remain unclear, in insulin-resistant individuals, hepatic insulin resistance is usually selective or dissociated; that is, they have impaired insulin-mediated glucose homeostasis (mediated by the FoxO1 pathway) but enhanced insulin-mediated hepatic DNL (mediated by the SREBP-1c pathway) [18]. The increase in free fatty acid (FFA) flux within the liver, either by DNL or FFA delivery via the portal vein, impairs hepatic insulin action, which, in turn, leads to increases in hepatic glucose output, the synthesis of pro-inflammatory cytokines; excess TG; low HDL-C secretion by the liver; and an elevated number of relatively cholesterol-depleted, small, dense LDL particles. As a result of these intrahepatic accumulations of FFA and lipids, liver insulin sensitivity is also negatively affected [19].

2) Adipose tissue insulin resistance

The expanded adipose tissue mass attributable to obesity often increases lipolysis and FFA turnover. Normally, insulin inhibits adipose tissue lipolysis; however, in the insulin-resistant state, the process is accelerated, increasing the release of FFA into the circulation. Furthermore,

visceral adipocytes are more sensitive to catecholamine-stimulated lipolysis than subcutaneous adipocytes, which increases the FFA flux [20]. Adipose tissue also receives macrophage infiltration, which leads to the hypertrophy of adipocytes and the release of cytokines [21]. These circulating cytokines also affect insulin action in liver and muscle tissues.

3) Muscle insulin resistance

The increased plasma FFA levels from insulin-resistant livers disrupt the glucose-fatty acid or Randle cycle, facilitating hyperglycemia by impairing insulin-mediated glucose transport to skeletal muscle [22]. The ectopic deposition in skeletal muscle of fat as intramyocellular lipid may also play a direct role in the pathogenesis of insulin resistance and MetS via lipid metabolite-induced activation of protein PKCε with subsequent impairment of insulin signaling [23]. In childhood, ethnicity and puberty are the two most important biological factors influencing insulin resistance.

2. Lipid partitioning

The phrase "lipid partitioning" refers to the distribution of body fat in various organs and compartments. The majority of excess fat is stored in its conventional subcutaneous depot, yet other potential storage sites exist as well, such as the intraabdominal (visceral) fat compartment and insulin-responsive tissues like muscle and the liver. Although still under debate, a potential etiology of MetS involves a pattern of lipid partitioning (i.e., the specific depots in which excess fat is stored). This pattern of lipid storage determines the secretion profile of adipocytokines and its effect on circulating levels of inflammatory cytokines and FFA flux. Through their combined effects, these factors impact insulin-mediated pathways in target organs (such as muscle and the liver) and vascular system by influencing endothelial function.

3. Adipocytokines

1) Leptin

Adipocytes secrete several proteins that act as regulators of glucose and lipid metabolism. Because they share structural similarities with cytokines, these proteins are collectively termed adipocytokines. The level of circulating leptin serves as an adiposity sensor to prevent starvation and correlates with the degree of obesity in the body. Leptin probably has a permissive role in high-energy metabolic processes such as puberty, ovulation, and pregnancy, but its role in states of energy excess is less known. In obesity, the development of leptin resistance may lead to abnormal partitioning of surplus lipids within adipocytes [24].

2) Adiponectin

Adiponectin is distinctive in obesity because, in contrast to the other adipocytokines, its level is decreased in obese people. The adiponectin gene is found on chromosome 3q27, which has previously been associated with the emergence of T2DM and MetS. Numerous single-nucleotide polymorphisms in the adiponectin gene have been linked to the emergence of T2DM in people all over the world, indicating that adiponectin is crucial for the regulation of glucose and lipid metabolism [25]. Two adiponectin receptors, ADIPOR1 and ADIPOR2, have been identified. ADIPOR1 is expressed in numerous tissues, including muscle, while ADIPOR2 is mostly restricted expression in the liver. Both ADIPOR1 and ADIPOR2 are receptors for the globular head of adiponectin and operate as start-up molecules for signal transduction pathways that result in

elevated peroxisome proliferator–activated receptor (PPAR)-α and adenosine monophosphate kinase activity, which encourages the absorption of glucose and the oxidation of fatty acids. Additionally, it has been demonstrated that adiponectin has strong anti-atherogenic properties because it accumulates in the subendothelial region of damaged vascular walls and inhibits the development of adhesion molecules and the attraction of macrophages [26].

Studies in obese children and adolescents have revealed that adiponectin levels are inversely associated to the degree of obesity, insulin resistance, visceral adiposity, IHCL, and IMCL, while weight loss increases adiponectin concentrations.

3) Inflammatory cytokines

It is becoming increasingly clear that obesity contributes to chronic inflammation in a subclinical manner [27]. Thus, adipose tissue functions not only as an energy reservoir but also as an active secretory organ, releasing peptides into the circulation, such as inflammatory cytokines. As obesity progresses, the balance between these peptides is altered, and large adipocytes and macrophages embedded within them produce more inflammation-inducing cytokines (i.e., tumor necrosis factor–α and interleukin-6) and fewer anti-inflammatory peptides such as adiponectin. One hypothesis posits that, as adipocytes store energy, the perilipin borders of the fat vacuoles break down, leading to the adipocyte's dismiss. Cell death then recruits macrophages in the adipose tissue, especially the visceral compartment, which also secrete inflammatory cytokines in the process of clearing debris, initiating a pro-inflammatory cascade that anticipates and possibly drives the development of systemic insulin resistance, diabetes, and endothelial dysfunction [28]. Elevated levels of CRP also correlate with other components of MetS in obese children [29]. Thus, inflammation may be one of the links between obesity and insulin resistance, and it may also promote endothelial dysfunction and early atherogenesis.

Most of the aforementioned molecules have been associated with elements of MetS and its characteristic pattern of lipid partitioning. Specifically, low adiponectin levels have been associated with insulin resistance, low-grade inflammation, and increased intramuscular fat [30]. Moreover, component analyses of plasma leptin concentrations and the variables that are considered relevant to MetS revealed that plasma leptin concentrations were clustered with insulin resistance and hyperinsulinemia [31].

Screening

Clinicians should recognize children who are obese and overweight and at risk for T2DM and CVD. It is important to screen these children for behavioral and medical risks, including persistent obesity, as well as its associated co-morbidities [32]. A significant risk factor for childhood obesity that needs to be considered during the screening evaluation is the presence of obese parents [32]. The history and physical examination are the first steps in the comorbidity screening process. Clinicians should request information about the signs and symptoms for associated comorbidities that may be present, such as PCOS, liver disease, and obstructive sleep apnea, which can be confirmed as a comorbidity with polysomnography [32]. Serum alanine aminotransferase and aspartate aminotransferase levels are respectably effective screening tests for fatty liver disease. When values are double the upper limit of normal, a pediatric hepatologist should be consulted [32]. Bi-annual liver disease screening is recommended starting at the age of 10 years for children with obesity or those who are overweight with other risk factors [33]. Screening for T2DM is recommended in overweight (≥

85th percentile) or obese (≥95th percentile) children and adolescents with ≥1 of the following risk factors: (I) Family history of T2DM in first- or second-degree relatives; (II) at risk race or ethnicity (Native American, African American, Latino, Asian American, and Pacific Islander); (III) signs of insulin resistance or associated conditions, such as acanthosis nigricans, hypertension, dyslipidemia, PCOS, or a history of being born small for gestational age; and (IV) maternal history of diabetes or gestational diabetes during the child's gestation [34]. The ADA recommends starting screening at the age of 10 years or at the onset of puberty, whichever arrives earlier, and be repeated every three years [34]. Generally, fasting plasma glucose, 2-hour plasma glucose measured during the 75-gram oral glucose tolerance test, and the glycated hemoglobin test are equally appropriate for diagnostic screening [34]. Starting at age 3 years, blood pressure should be obtained annually at all regular health check-ups, and results should be compared to reference ranges from tables issued by the NHLBI [35]. Finally, children should be routinely screened for dyslipidemia with universal lipid screening between 9–11 years of age with a non-fasting, non-HDL lipid profile. Screening children 2–8 years of age with fasting lipid profiles is recommended for obese children since obesity is considered a moderate- to high-risk factor [35]. The NHLBI recommends repeating lipid profiling in overweight adolescents at 12–16 years of age. The level of abnormality, the presence of additional known risk factors, and the presence of high-risk diseases should determine whether to pursue dietary or medicinal intervention [35].

Prevention and Treatment of Metabolic Syndrome

1. Prevention

Pediatric obesity prevention involves promoting healthy diet and increasing physical activity as the primary prevention strategies in order to avoid MetS in children. Lifestyle modifications to achieve a healthy diet include increasing consumption of vegetables and fruits; increasing fiber intake while reducing dietary fat; and avoiding carbonated beverages, refined carbohydrates, high-fructose corn syrup, high sodium, and processed foods [36]. Fruit juice should be replaced with whole fruits for additional nutritional value. Physical activity is also recommended 3–5 days per week with ≥20 min of vigorous short bursts to improve metabolic measures in children and adolescents, which may prevent obesity [36]. A meta-analysis conducted by Kamath et al. found that lifestyle modification had a positive effect on reducing sedentary behavior in long-term trials and reduced unhealthy dietary habits. In comparison to adolescents, those adjustments were more successful with children [37]. Adopting healthy sleep habits, limiting non-academic screen time, involving the entire family and community in prevention efforts, and using school-based programs and community engagement for the prevention of pediatric obesity are additional lifestyle changes that can lower the risk of developing obesity [36].

2. Treatment

In general, childhood MetS is treated through weight reduction by lifestyle modifications, including dietary intervention, increased physical activity, and the management of various disease-specific factors. Pharmacological treatments and bariatric surgery are other alternatives for managing obesity.

1) Lifestyle modifications and behavioral treatment

For the first step to change, clinicians should assess patients and families. In this way, family and patient interventions will be more easily incorporated. When compared to programs

focused solely on the child, those that involved the entire family in lifestyle change were found to have favorable outcomes for lowering BMI [37]. Comprehensive weight reduction programs, including nutritional, physical activity, education, and behavioral therapy, have been linked to improvements in a number of metabolic parameters, including blood pressure and lipid profile indices in obese children and adolescents [38]. Obese children and adolescents should be screened for mental health, including eating disorders, depression, and other mood disorders. Support and referral to available behavioral health resources for those disorders are essential.

(1) Dietary intervention

Basic dietary recommendations are mostly based on low-fat diets and, recently, low-carbohydrate diets are gaining popularity [39]. Recent Endocrine Society guidelines recommended avoiding beverages sweetened with sugar, elimination of fructose-rich corn syrup, and decreased consumption of processed foods high in salt and saturated dietary fat in children over 2 years of age and adolescents. Furthermore, consumption of dietary fibers, vegetables, and whole fruits other than fruit juice or carbonated drinks is encouraged. Additionally advocated for nutritional intervention are education about portion control, improved product labeling, and the consumption of frequent meals to prevent snacking [36]. In addition, because eating fast and the risk of developing T2DM are highly associated, slow eating should be taught as an important eating habit [40]. According to a systematic review of 107 trials, low-carbohydrate diets had weight reduction outcomes proportional to those of low-fat diets and had no particularly negative impact on blood pressure, insulin, fasting serum glucose, or cholesterol levels [39].

(2) Physical activity

The second-most important behavioral intervention is physical activity. The AAP and the European Society for Pediatric Endocrinology advise engaging in physical activity regardless of weight status, aiming for at least 30 minutes of daily moderate to vigorous activity, and keeping non-academic screen time to no more than one to two hours per day [36,41]. It is recognized that inactivity can decrease insulin sensitivity in skeletal muscle, which can be reversed by increasing physical activity. Physical activity is also helpful in improving the lipid profile by lowering LDL and triglyceride concentrations and increasing the HDL concentration [42]. Regular physical activity increases cardiorespiratory fitness by reducing blood pressure, arterial stiffness, and abdominal fat [43]. Most children, including children with obesity, do not achieve these recommendations. Exercise physiologists and physical therapists can help these children by developing individual exercise plans, especially when movement is limited by gross motor delay or musculoskeletal pain [44].

2) Pharmacological therapies

As previously stated, lifestyle modification therapy is the primary form of treatment for MetS. When patients are unable to achieve their weight loss objectives with lifestyle modification therapy alone, pharmacotherapy is the next logical treatment option to consider (Table 2) [45-49]. The indication for pharmacotherapy to treat pediatric obesity includes an age of ≥10 years and a BMI in the ≥95th percentile with weight-related co-morbidities or a BMI that is ≥120% of the 95th percentile, regardless of comorbidities, without an appropriate response to lifestyle modification [36]. Intense lifestyle modification programs should be considered along with pharmacotherapy [32].

Options for pharmacotherapy to treat pediatric obesity are limited. Orlistat, a lipase inhibitor

Table 2. Medications for weight loss in the pediatric population

Drug name	Mechanism of action	FDA indication	Off-label drug use	Side effects
Orlistat [45]	Pancreatic and gastric lipase inhibitor	Obesity≥12 years of age	Not indicated	Flatulence, oily spotty stools, diarrhea, vitamin/mineral deficiency
Exenatide [46]	GLP-1 agonist	T2DM in adults	<18 years of age for obesity (polygenic with the presence of diabetes, hypothalamic, syndromic)	Bloating, diarrhea, flatulence
Liraglutide [47,48]	GLP-1 agonist	3.0 mg of liraglutide approved for obesity in adolescents (12–17 years) with a reduced-calorie diet and increased physical activity	Not indicated	Bloating, nausea/vomiting, abdominal pain, the elevation of pancreatic amylase and lipase
Metformin [49]	Activation of protein kinase pathway	≥10 years of age, T2DM	PCOS, insulin resistance, prediabetes, metabolic syndrome, anti-psychotic medication–induced weight gain, stress eating/emotional eating	Bloating, diarrhea, flatulence, contraindicated with risk of lactic acidosis

T2DM, type 2 diabetes mellitus.

that blocks the absorption of fats from the human diet, is the only medicine recognized by the American Food and Drug Administration (FDA) for long-term use in the treatment of pediatric obesity (≥12 years of age). However, due to its modest efficacy (2.61-kg weight loss after one year of treatment), its therapeutic application is somewhat limited, and many adolescents may find its side effects unpleasant (flatulence; oily, spotty stools; and diarrhea) [45].

Glucagon-like peptide-1 receptor (GLP-1) agonists include exenatide and liraglutide. Exenatide has FDA approval for adult T2DM, and a liraglutide 3.0-mg injection has FDA approval for adult obesity. Recently, a liraglutide 3.0-mg injection received FDA approval for the treatment of obesity in adolescents (aged 12–17 years) with a body weight>60 kg and an initial BMI≥30 kg/m^2 combined with a reduced-calorie diet and increased physical activity. GLP-1 agonist–associated weight reduction appears to be related to decreased gastric emptying and increased satiety and appetite suppression. Recently, a randomized controlled trial of adolescent obesity with a 56-week liraglutide treatment period reported that the use of a liraglutide 3.0-mg injection combined with lifestyle modification led to significant reduction in BMI z-score [46]. In patients with syndromic and hypothalamic obesity with hyperphagia, GLP-1 agonist therapy has the potential for weight reduction and weight stabilization [47,48].

Metformin, a biguanide primarily used for glycemic control, has been used off-label to achieve weight loss in children. Meformin is FDA-approved for children≥10 years of age for T2DM. Currently, in a systematic review of randomized controlled trials on children and adolescents, Masarwa et al. [49] assessed the effectiveness of metformin. Researchers discovered that metformin reduced BMI z-score modestly in obese subjects and had the greatest effect on children and adolescents with NAFLD. Several studies reported improvements in fasting plasma glucose and insulin resistance, but not in lipid levels. As compared to a placebo, metformin was associated with double the number of gastrointestinal adverse effects [49]. By this finding, the question of whether metformin is an appropriate adjuvant therapy to lifestyle change for the treatment of pediatric obesity is raised.

3) Surgical therapies

As a standard course of treatment, surgical intervention for childhood and adolescent obesity is still not approved. In children and adolescents, research on the effects of surgery on growth and development is limited. Thus, it should only be considered when growth and puberty are complete. Also, surgical treatment for children and adolescents in growing process should be limited to strict standards. Before considering surgical treatment, evaluation for previous treatment, such as multidisciplinary treatment and pharmacotherapy, should be conducted. Furthermore, adolescents and their families should have psychological stability and competence, availability for appropriate follow-up care, and a demonstrated ability to comply with healthy dietary and activity routines. It is also very important that the patient has a reliable caretaker who can provide physical and psychosocial support through the entire process. Recently, metabolic and bariatric surgery (MBS) has been shown to be an effective treatment for severe obesity in adolescences, and studies have reported significant improvements in co-morbidities associated with obesity [50]. According to the most recent recommendations issued by the American Society for Metabolic and Bariatric Surgical Pediatric Committee, MBS could be considered for children ≥10 years of age with a BMI that is ≥120% of the 95th percentile who also have a weight-related co-morbidity, such as T2DM, hypertension, NAFLD, and/or obstructive sleep apnea, or those with a BMI that is ≥140% of the 95th percentile regardless of co-morbidities [50]. According to the recommendations, treatment should be provided to adolescents who have previously attempted to reduce weight, have a low Tanner stage, and have immature bone growth [50]. Lack of evidence, however, suggests that MBS may have a negative impact on a child's pubertal status as determined by Tanner staging, linear development, or height. The impact of MBS on children's pubertal development should therefore be the subject of additional research. MBS has the potential to result in both macro- and micronutrient deficit, therefore lifetime supplemental protein, iron, calcium, and vitamins are necessary to prevent deficiencies [50]. Gastroesophageal reflux, which has been recorded in >12%–30% of patients requiring long-term usage of proton pump inhibitors, is another side effect of MBS [51]. Patients undergoing any of these surgical procedures are at risk of anastomosis site leaking, hernia, stricture, and wound infection; however, children are less likely than adults to experience these consequences [51].

Conclusion

It is known that early diagnosis and successful treatment of MetS are key to reducing the risk of cardiometabolic disease. Although sometimes the diagnosis is delayed because MetS is overlooked by families, early identification and management are crucial and help to attenuate the disease progression. Screening children and adolescents for overweightness and obesity by considering up-to-date reference values, age- and sex-related percentiles, and comorbidities using good clinical judgment is highly recommended. According to the 2017 Korean National Growth Charts (KNGC2017), BMI for age≥85th percentile and <95th percentile is defined as overweight and BMI for age≥95th percentile is defined as indicative of obesity [52]. To provide specialized care, it is crucial to assemble a knowledgeable multidisciplinary team, which has to be composed of a pediatrician, mental health professional, nutritionist, nurses, and other referral specialists for complications [35]. The health system must, however, confront with the question of how to support such a multidisciplinary team financially.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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