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Review

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Severe Obesity in Children and Adolescents: Metabolic Effects, Assessment, and Treatment

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Childhood obesity has been increasing steadily in recent decades, and severe childhood obesity has emerged as a major public health problem both nationally and internationally. A current concern is that lockdown due to the coronavirus disease 2019 (COVID-19) pandemic could exacerbate the spread of childhood obesity and increase the gap in obesity risk. Recent research results indicate the aggravation of obesity after school closures. The consequences of severe childhood obesity are more devastating than those of mild to moderate obesity. Children with severe obesity are at greater risk than others for hypertension, type 2 diabetes, metabolic syndrome, non-alcoholic fatty liver disease, atherosclerosis, and adult obesity. Accurately assessing and diagnosing a child with severe obesity is the key to implementing successful therapy. A detailed and accurate patient history and physical examination are important to discriminate monogenic obesity and metabolic syndrome diagnoses from severe obesity without an underlying cause. Psychosocial factors, including eating behaviors, should be assessed to facilitate better weight management outcomes. Treatment options for severe pediatric obesity include lifestyle modification therapy, pharmacotherapy, and metabolic and bariatric surgery. However, lifestyle modification should be the priority. Although progress has been made, safe and effective treatment for severe pediatric obesity is still challenging. More efforts and innovations are needed to find a solution for the huge medical and emotional burden that these children and their families carry. Public health organizations also need to make efforts to encourage and normalize healthy eating habits and exercise to prevent severe obesity in childhood.

Key words: Pediatric obesity, Obesity morbid, Obesity management, Healthy lifestyle

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INTRODUCTION

The prevalence of pediatric obesity has increased dramatically during the past forty years in Korea and worldwide.[1,2] Although recent data suggest that the increase in pediatric obesity has slowed and its overall prevalence has begun to stabilize, severe pediatric obesity continues to increase consistently.[3,4] The overall prevalence of severe pediatric obesity in Korea increased from 1.2%–1.8% in 2001 to 2.1%–2.4% in 2013–2014.[4] The coronavirus disease 2019 (COVID-19) pandemic is causing long-term school closures, which could be exacerbating the spread of childhood obesity and increasing the gap in obesity risk.[5,6] Indeed, according to recent reports, reduced physical activity due to school closures during the COVID-19 pandemic is aggravating obesity and glucose intolerance in children and adolescents with obesity.[6-8] Low socioeconomic status (SES) significantly affects pediatric obesity. Many studies have reported that SES is associated with a risk of obesity in both adults and children because it can influence lifestyle factors such as food choices and physical activities.[9,10] A consistent association between low SES and obesity has been reported in Korean studies.[11,12]

Pediatric obesity is associated with numerous comorbidities, such as type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia, non-alcoholic fatty liver disease (NAFLD), obstructive sleep apnea, polycystic ovary syndrome (PCOS), and psychiatric problems in

childhood.[13-16] Children with severe obesity have more adverse cardiometabolic risks than children who are overweight or have mild to moderate obesity. Early signs of vascular dysfunction and subclinical atherosclerosis have also been reported in children with severe obesity.[17-19] When adiposity was tracked from childhood into adulthood, the degree of retained adiposity was stronger in cases of severe childhood obesity.[20,21] Therefore, preventing and treating severe pediatric obesity is important to prevent and attenuate the risk of preclinical atherosclerosis.[21]

In this article, we focus on ways to assess pediatric patients with severe obesity and outline the main therapeutic approaches used to treat severe childhood obesity: lifestyle modification therapy, pharmacotherapy, and metabolic and bariatric surgery (MBS).

DEFINITION OF OBESITY AND SEVERE OBESITY IN CHILDHOOD

Most adult obesity begins in childhood,[22,23] making pediatric obesity a concern and giving impetus to medical professionals to prevent and treat childhood obesity. Body mass index (BMI) is the acknowledged indicator of obesity in both children and adults.[24] Using normal BMI curves for age and sex in children, a BMI at or above the 85th percentile and below the 95th percentile is categorized as overweight, and a BMI at or above the 95th percentile is categorized as obesity. Obesity is further divided into three classes by using the 95th percentile for age and sex as the reference value and categorizing 100% to 120% of the 95th percentile as class I obesity, 120% to 140% as class II obesity, and more than 140% as class III obesity (Table 1).[3,25,26] Severe pediatric obesity is defined as class II and III obesity. Cardiometabolic risk increases with rising degrees of obesity, and class II and III obesity have a strong association with these risks.[25]

METABOLIC EFFECTS OF SEVERE PEDIATRIC OBESITY

In pediatric obesity, metabolic and cardiovascular complications are observed during childhood and are closely related to the development of insulin resistance, which is the most widely recognized biochemical change in obesity.[27] The comorbidities related to obesity from early childhood are glucose intolerance, dyslipidemia, and hypertension. The cluster of these medical conditions is called metabolic syndrome, or insulin resistance syndrome, and includes T2DM, hypertension, dyslipidemia, and coronary heart disease.[28]

Table 1. Pediatric definitions of overweight, obesity, and severe obesity[26]

Weight status category	Percentile range
Overweight	85th–<95th percentile
Obesity/class I	100%–120% of the 95th percentile
Severe obesity/class II	120%–140% of the 95th percentile
Severe obesity/class III	>140% of the 95th percentile

Insulin resistance is defined as a decreased tissue response to insulin-mediated cellular actions and is the inverse of insulin sensitivity. The insulin resistance seen in obesity does not affect all tissues equally because insulin affects the liver, adipose tissues, and muscle in different ways. Insulin in the liver diminishes hepatic glucose production and increases the transcription of genes required for fatty acid and triglyceride biosynthesis. Insulin-resistant subjects can have selective hepatic insulin resistance, which is impaired glucose homeostasis but normal insulin-mediated hepatic *de novo* lipogenesis.[29,30] The resulting increase in free fatty acid (FFA) flux within the liver impairs hepatic insulin action via fatty acyl-CoA intermediates within hepatocytes,[31] which increases hepatic glucose output, the synthesis of proinflammatory cytokines, and triglyceride secretion by the liver; lowers high-density lipoprotein cholesterol levels; and increases relatively cholesterol-depleted low-density lipoprotein particles.[32] Furthermore, the intrahepatic accumulation of FFA and lipids is itself detrimental to liver insulin sensitivity.[33] Intrahepatic insulin resistance results in greater first-pass insulin clearance in the liver, which lowers the amount of insulin reaching systemic circulation. The expanded adipose tissue mass that accompanies obesity leads to increased lipolysis and FFA turnover.

Insulin resistance accelerates the lipolytic process, leading to increased FFA release into the circulation. Moreover, visceral adipocytes are more sensitive to catecholamine-stimulated lipolysis than subcutaneous adipocytes, which further increases FFA release.[34] A greater FFA concentration following an oral glucose load worsens glucose tolerance.[35] Increased plasma FFA flux into skeletal muscle results in fatty acyl-CoA derivatives that alter the insulin signal transduction pathway and reduce insulin-mediated glucose trans-

port in skeletal muscle, further facilitating the development of hyperglycemia.[33] Intramyocellular lipid deposition is tightly associated with insulin resistance and has been detected in children with obesity who have altered glucose metabolism.[36,37]

The risk of the metabolic syndrome is higher in teenage boys with severe obesity than girls, as shown by a Korean population study, which found that the rates of metabolic syndrome in obese teenage boys were more than double those in girls, which is consistent with a prior study from the United States.[4,25]

ASSESSMENT OF SEVERE PEDIATRIC OBESITY

When an accurate diagnosis is made and complications are properly identified, severe pediatric obesity can be treated successfully. A thorough medical history from birth to the present should be taken, including birth weight, BMI of both parents, exposure to gestational diabetes, maternal obesity, prematurity, history of breastfeeding, neonatal complications, neurodevelopmental abnormalities, signs of dysmorphism, and medication use, especially glucocorticoids, antiepileptics, and antipsychotics. Orthopedic problems, headaches, and snoring must also be assessed. It is very important to identify the potential underlying contributors to metabolic dysregulation because obesity is a heterogeneous disease.[38] In a physical examination, linear growth gives clues that can be used to exclude organic causes of obesity; however, hyperinsulinemia and insulin resistance can cause accelerated growth through cross-reactivity between insulin and the insulin-like growth factor 1 receptor.[39] Acanthosis nigricans and waist circumference are important physical features because both clinical characteristics are correlated with insulin resistance and metabolic syndrome.

A laboratory evaluation should be conducted and assessed for obesity-related comorbidity markers, including aspartate aminotransferase, alanine aminotransferase, lipids, fasting glucose, and hemoglobin A1c. Luteinizing hormone, follicular-stimulating hormone, and testosterone levels should be examined to evaluate delayed puberty in boys and PCOS in girls.[40] An oral glucose tolerance test for T2DM could be necessary when familial risk factors are present.[40]

Biological factors

Genetics is the greatest contributor to obesity, and 30%–90% of genetic variation in BMI is heritable.[41] Simple obesity arises through the additive effects of multiple genes associated with obesity.[42] On the other hand, 5% to 10% of children with hyperphagia and obesity in early childhood have a monogenic condition that causes obesity; most of those cases arise from monogenic disorders of the leptin-melanocortin pathway.[43] Therefore, patients with severe obesity or obesity in early childhood who also have developmental delay, dysmorphic features, short stature, or intellectual disability require a genetic evaluation. The identification of monogenic obesity could help to identify pharmacological treatments, such as setmelanotide, a melanocortin-4 receptor agonist for proopiomelanocortin, or proprotein convertase subtilisin/kexin type 1 or leptin, a hormone related to satiety, for leptin receptor deficiency,[44] and direct further evaluations for other comorbidities, including organ-specific anomalies. Other biological factors, including endocrine disorders such as growth hormone deficiency, hypothyroidism, and Cushing syndrome, should also be evaluated.

Eating behaviors are an additional determining factor of obesity. In addition to the typical assessment of dietary components, such as the frequency of fast food or sugar-sweetened beverage consumption, a thorough and detailed history of eating behaviors can provide information about the etiology of obesity. For example, children who are described as always having food in their mouths, eating adult portion sizes, or eating snacks between meals might have impaired homeostatic appetite control.[45] On the other hand, non-homeostatic mechanisms that contribute to obesity are suggested in patients who emotionally overeat to deal with negative emotions or stressful situations (hedonic hunger).

A low level of physical activity and sedentary lifestyle is another biological contributor to severe pediatric obesity. Obese children might hesitate to exercise, in part, because of musculoskeletal pain, developmental delays in gross motor skills, poor cardiorespiratory fitness, or depression. Insufficient sleep quantity due to the use of an electronic device late at night or poor sleep quality caused by obstructive sleep apnea or central hypoventilation syndrome increase the level of ghrelin, a hunger hormone, and cortisol and decrease the response to leptin, a satiety hormone, making a body prone to obesity.[46,47]

Psychosocial factors

Obese children, especially those looking for obesity treatment, have a greater tendency than normal-weight children to have psychological problems such as depression, anxiety, attention deficit hyperactive disorder (ADHD), and eating disorders.[48] The incidence of depression is three times higher and anxiety is five times higher in adolescents with severe obesity than in those with moderate obesity.[49] The prevalence of binge eating is reported to be higher in children with severe obesity (17%) than mild to moderate obesity (10%).[50] Therefore, assessing those symptoms and offering proper treatment is important in clinical practice to facilitate better weight management outcomes. Simple screening tests for depression, anxiety, ADHD, and eating disorders can be completed through questionnaires. Referral to mental healthcare should be considered in patients with positive responses.

In addition to physical health, severe obesity has negative consequences on psychosocial well-being. In a multicenter observational study, 233 adolescents completed a questionnaire about physical comfort, body esteem, social life, and family relations. The results showed that a high BMI was a negative predictor for quality of life.[51] In a study of 361 youth looking for a weight loss program, the rate of weight-based victimization increased with body weight.[52] Identifying when children are experiencing victimization and providing the needed support or resources in school and at home is an essential part of any obesity management plan.

TREATMENT

Lifestyle modification

Lifestyle modification therapy is essential for pediatric obesity treatment. Especially for children with severe obesity, it should be used as the first-line therapeutic option.[26] Numerous treatment programs apply strategies such as dietary modification, increasing physical activity, and behavioral changes such as self-monitoring, stimulus control, positive reinforcement, social support, and cognitive behavior therapy. An essential component in the treatment of pediatric obesity is parental involvement to offer support and model healthy behavior; the family-based program is the most successful weight management program. However, even though lifestyle modification is a relevant first-line treatment, the effects appear disappointing in children with severe obesity. The most effective programs are correlated with only a modest reduction (5%–20%) in BMI among children with severe obesity, and those effects are not durable over time.[26] The treatment efficacy was related to the child's age at the onset of obesity. Thus, early treatment might be one way to reduce treatment failure during adolescence.[53]

Basic dietary recommendations are mostly based on low-fat diets, though recently, low-carbohydrate diets have gained popularity.[54] A systematic review of 107 studies found that low-carbohydrate diets had weight loss outcomes proportionate to those of low-fat diets and did not have any particular adverse effects on serum lipids, fasting serum glucose and insulin levels, or blood pressure.[54] Among the various low-carbohydrate diets, the protein-sparing modified fast diet showed marked weight reduction, especially in children and adolescents with severe obesity. This diet is a calorie reduction, low-carbohydrate, and high-protein diet based on weight loss related to ketosis. Patients who participated in this intervention reached a mean weight reduction of 8 kg from baseline at 13 weeks; following a slight increase, the net weight reduction was 11% at 36 weeks.[55]

Meal replacement therapy is a form of low-calorie diet in which one or two full-calorie meals daily are replaced with low-calorie frozen meals, shakes, or bars. It has been used with short-term success in adolescents with severe obesity.[56] These kinds of meals provide convenient portion control; however, weight regain began at the finish of therapy when a normal diet was resumed. In addition, long-term compliance is poor, and using this therapy in children might be limited by poor acceptance among both parents and patients.

Physical activity is the second most important behavioral intervention. The American Academy of Pediatrics and European Society for Pediatric Endocrinology recommend physical activity regardless of weight status, encouraging daily moderate-to-vigorous physical activity and limiting screen time to 1 to 2 hours a day.[57,58] Most children, including children with severe obesity, do not achieve those recommendations. Exercise physiologists and physical therapists can help children by developing individual exercise plans, especially when movement is limited by gross motor delays or musculoskeletal pain.[59] However, although interest in the application of physical therapy to severe obesity is increasing, many program developments are needed to apply it within the current medical system.

Pharmacotherapy

The primary treatment option for pediatric obesity is lifestyle modification therapy. Pharmacotherapy is the next logical treatment for patients who fail to meet their weight loss goals with lifestyle modification therapy alone (Table 2). The indications for pharmacotherapy in pediatric obesity are patients aged 10 years or more and BMI ≥95th percentile with weight-related comorbidities or BMI ≥120% of the 95th percentile irrespective of comorbidities who have not responded appropriately to lifestyle modification.[58,60]

The only medication approved by the U.S. Food and Drug Administration (FDA) for long-term use to treat pediatric obesity is orlistat (≥12 years), a lipase inhibitor that prevents the absorption of fats from the human diet. However, its clinical use is fairly limited due to its modest efficacy (about a 2.61 kg reduction after 1 year of treatment) and adverse effects, which can be intolerable for many adolescents (flatulence, oily spotty stools, and diarrhea).[61,62] Phentermine, a norepinephrine reuptake inhibitor, is FDA approved for short-term treatment in children older than 16 years with lifestyle modifications. The efficacy of phentermine is also relatively modest, approximately 4% BMI reduction. Phentermine is a substituted amphetamine that can cause tachycardia, hypertension, restlessness, dizziness, and trouble sleeping.[63] Metformin, a biguanide primarily used for glycemic control, is FDA approved for children ≥10 years of age with T2DM, and it has been used off-label to achieve weight loss in children. Masarwa et al.[64] reported the efficacy of metformin in a systematic review of randomized controlled trials (RCTs) in children and adolescents. They demonstrated that metformin use offered modest benefits in BMI reduction in subjects with obesity. Among the 14 RCTs that reported BMI, metformin was modestly efficacious at decreasing it (range of mean changes, –2.70 to 1.30) compared with placebo (–1.12 to 1.90). Among the seven RCTs in which a BMI z-score was reported, metformin consistently resulted in a decrease in the BMI z-score (range of mean change, –0.37 to –0.03) compared with placebo (–0.22 to 0.15), with largest decrease in BMI z-score in children and adolescents with NAFLD. In a meta-analysis of 616 pediatric patients that compared the use of metformin and placebo for weight reduction (BMI baseline 36.0 kg/m^2 and metformin dose ranging from 1 to 2 g per day), metformin treatment reduced the BMI z-score (–0.10; 95% CI, –0.17 to –0.03) and BMI (–0.86; 95% CI, –1.44 to –0.29).[65] Some studies reported an improvement in fasting plasma glucose and insulin resistance without a decrease in lipid levels. However, metformin was associated with a doubling of gastrointestinal adverse effects compared with placebo.[64] Whether metformin is a reasonable adjunct therapy with lifestyle modification for treatment of childhood obesity remains an open question.

Table 2. Summary of medications for weight loss in the pediatric population

Drug name	Mechanism of action	FDA indication	Off-label drug use	Consideration
Orlistat[61,62]	Pancreatic and gastric lipase inhibitor	Obesity, ≥12 years of age	Not indicated	Flatulence, oily spotty stools, diarrhea, vitamin/mineral deficiency
Phentermine[63]	Sympathomimetic amine	Obesity, >16 years of age for "short term" use	<16 Years of age or long term; beneficial in obesity with low-energy states, sleep apnea, hunger, decreased satiety	Increases heart rate, blood pressure, dry mouth, insomnia, constipation, anxiety, and irritability
Metformin[65]	Activation of protein kinase pathway	≥10 years of age, T2DM	PCOS, insulin resistance, prediabetes, metabolic syndrome, antipsychotic medication-induced weight gain, stress eating/emotional eating	Bloating, diarrhea, flatulence; contraindicated with risk of lactic acidosis
Exenatide[66-68]	GLP-1 agonist	T2DM in adults	<18 Years of age for obesity (polygenic with the presence of diabetes, hypothalamic, syndromic)	Bloating, nausea/vomiting, abdominal pain, elevation of pancreatic amylase and lipase; contraindicated with history or family history of medullary thyroid carcinoma, MEN type 2, ESRD
Liraglutide[69]	GLP-1 agonist	3.0-mg liraglutide approved for obesity in adolescents (12–17 years) with a reduced-calorie diet and increased physical activity	Not indicated	GI abdominal pain, nausea, vomiting, diarrhea, potential hypoglycemia; contraindicated with history or family history of medullary thyroid carcinoma, MEN type 2, ESRD

FDA, Food and Drug Administration; T2DM, type 2 diabetes mellitus; PCOS, polycystic ovary syndrome; GLP-1, glucagon-like peptide-1; MEN, multiple endocrine neoplasia; ESRD, end-stage renal disease; GI, gastrointestinal.

Exenatide and liraglutide are glucagon-like peptide-1 (GLP-1) receptor agonists. Exenatide has FDA approval to treat T2DM in adults, and a liraglutide 3.0 mg injection is FDA approved to treat obesity in adults. In December 2020, 3.0 mg liraglutide injection achieved FDA approval to treat obesity in adolescents (12 to 17 years) whose body weight is more than 60 kg and initial BMI is ≥ 30 kg/m^2, in combination with a reduced-calorie diet and increased physical activity. GLP-1 receptor agonist-associated weight reduction appears to be related to decreased gastric emptying and increased satiety and appetite suppression. In two RCTs of adolescents and children with severe obesity, 3 months of exenatide treatment elicited a significant reduction in BMI and body weight.[66,67] A 6-month double-blind RCT of weekly exenatide in adolescents with severe obesity reported a significant reduction in BMI and improvement in glucose tolerance and cholesterol compared with placebo.[68] Recently, an RCT of adolescent obesity with a 56-week liraglutide treatment period reported that 3.0 mg liraglutide plus lifestyle modifications resulted in a significant reduction in BMI z-scores.[69] GLP-1 receptor agonist therapy also has potential for weight reduction and weight stabilization in patients with syndromic and hypothalamic obesity with hyperphagia.[70,71]

Metabolic and bariatric surgery

surgical treatment for obesity in children and adolescents has not yet been approved as a common treatment recommendation. Little research has examined the effects of surgical treatment on growth and development in children and adolescents. Thus, it is only considered after growth and puberty are complete. Also, surgical treatment in growing children and adolescents should be limited to strict standards. Before considering surgical treatment, an evaluation of less invasive treatments, such as multidisciplinary treatment and pharmacotherapy, should be conducted. Furthermore, adolescents and their families should have psychological stability and competence, appropriate follow-up care, and a demonstrated ability to comply with healthy dietary and activity routines. It is also very important that patients have a reliable caretaker who can provide physical and psychosocial support throughout the entire process. MBS in adolescents has been shown to be an effective treatment for severe obesity, and significant resolution for obesity-associated comorbidities has been reported.[72]

Current guidelines issued by the American Society for Metabolic and Bariatric Surgery's Pediatric Committee suggest that MBS can be considered for children ≥ 10 years with a BMI ≥ 120% of the 95th percentile with a weight-related comorbidity, such as T2DM, hypertension, NAFLD, or obstructive sleep apnea, or a BMI ≥ 140% of the 95th percentile regardless of comorbidities.[72] In accordance with the guidelines, adolescents with prior weight loss attempts, low Tanner stage, and immature bone growth should not be denied surgical treatment.[72] However, there is a lack of data to show how a child's pubertal status, as measured by Tanner staging, linear growth, or height, is affected by MBS. Therefore, further studies should be conducted on the effects of MBS on pubertal growth in children.

The two primary procedures for MBS that have been evaluated in pediatric patients are Roux-en-Y gastric bypass (RYGB) and vertical sleeve gastrectomy (VSG). In prospective studies among adolescents with severe obesity, medium-term weight reduction (1–3 years) ranged from 30% to 40% of BMI, and long-term results (5–8 years) showed a sustainable BMI reduction of about 30%.[73-76] In addition, studies of MBS in rare pediatric cases with genetic defects as the primary cause of severe obesity (Prader-Willi syndrome and melanocortin 4 receptor mutation) have shown promising BMI reduction and resolution of comorbidities.[77,78]

MBS has the potential to cause both macro- and micronutrient deficiency, and lifelong supplementation of protein, iron, calcium, and vitamins is required to prevent deficiencies. Because RYGB uses both restrictive and malabsorptive mechanisms for weight reduction, deficiencies are more likely to occur than in VSG.[72] Another complication of MBS is gastro-esophageal reflux, which occurs more frequently with laparoscopic VSG than RYGB; 12%–30% of patients require long-term use of proton pump inhibitors.[79] All of these surgical procedures put patients at risk for leakage at the anastomosis site, hernia, stricture, and wound infection; however, those complications occur less frequently in pediatric patients than in adult patients.[79]

CONCLUSION

The number of children and adolescents with severe obesity in Korea has increased substantially; because its short- and long-term

health consequences are unavoidable, severe pediatric obesity should be treated comprehensively. Furthermore, because accumulating evidence suggests that severe obesity in childhood is usually associated with adverse metabolic profiles, early screening for obesity-related comorbidities such as diabetes or hypertension should be recommended. By using early-life weight-gain trajectory data to differentiate young children who are at risk of developing severe obesity, clinicians could intervene early to reduce metabolic risk in adulthood. Family-based interventions in early life could be effective solutions to prevent severe pediatric obesity. The treatment options for children who have severe obesity include lifestyle modification therapy, pharmacological therapy, and bariatric surgery, but innovative therapies with progressively more intensive methods need to be developed and evaluated to improve outcomes for children afflicted with this disease.

To make meaningful progress, health professionals who treat pediatric obesity need to be aware of the causes and biological significance of severe obesity, and further research evaluating intensive treatment approaches is urgently needed. Also, those health professionals and public health officials must incorporate their area of expertise into public health programs and policies for childhood obesity to foster a community-based approach and develop and maintain obesity prevention programs for children and adolescents.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Study concept and design: all authors; drafting of the manuscript: YLC; critical revision of the manuscript: all authors; study supervision: YJR.

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