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Pediatric obesity: A review

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Abstract

Pediatric obesity is becoming a challenging disorder in recent times and needs a proper approach in order to prevent future threats. The causes and consequences related to pediatric obesity need immediate attention, in order to prevent health-related complications. This review focuses on overview of pediatric obesity including risk factors, diagnosis, complications, and treatment. Due to the limitation in use and efficacy of each treatment method, preventive strategies including dietary modification, exercise and behavioral modification are recommended for the entire family and obese children.

Keywords: Child, obesity

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โรคอ้วนในเด็ก

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**ภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยศรีนครินทรวิโรฒ

บทคัดย่อ

ในปัจจุบันโรคอ้วนในเด็กเป็นปัญหาที่ท้าทายและต้องการการดูแลรักษาที่เหมาะสมเพื่อป้องกันผลแทรกซ้อนที่อาจเกิดขึ้นในภายหลัง จึงควรให้ความสนใจทั้งสาเหตุและผลกระทบที่เกี่ยวข้องกับโรคอ้วนในเด็กเพื่อป้องกันภาวะแทรกซ้อนที่เกี่ยวข้องกับสุขภาพ บททบทวนวรรณกรรมนี้มุ่งเน้นทบทวนภาวะโรคอ้วนในเด็กในด้านต่างๆ เช่น ปัจจัยเสี่ยง การวินิจฉัย ภาวะแทรกซ้อนของโรคอ้วน และการรักษา เนื่องจากปัจจุบันวิธีการและผลการรักษาโรคอ้วนมีจำกัด จึงควรให้ความสำคัญแก่การป้องกันการเกิดโรคอ้วน เช่น ปรับรับประทานอาหารที่เหมาะสม การออกกำลังกาย และการปรับพฤติกรรม ซึ่งควรให้คำแนะนำทั้งแก่ครอบครัวและแก่เด็ก

Definition

Obesity is defined[1] as excessive accumulation of fat in the body with a body mass index (BMI) equal to or greater than 30 kg/m^2 in adult. However, Asian population is susceptible for obesity-related health problems at the low cutoff levels of ≥ 25 kg/m^2.[2] By the International Obesity Task Force (IOTF) criteria, childhood overweight and obesity are defined as BMI by gender passing through BMI 25 and 30 kg/m^2 at age 18, respectively[3]. American Academy of Pediatrics also defined childhood overweight and obesity as the BMI passing through the 85th and 95th percentile, respectively[4].

Prevalence of childhood obesity

Childhood obesity has reached epidemic levels worldwide. WHO estimated that approximately 1.6 billion and 400 million adults were overweight and obese, respectively. Moreover, at least 20 million children under the age of 5 years were overweight[5]. In USA, the prevalence of obesity had increased from 5% in 1963 to 17% in 2003[6]. In Asia, prevalence of childhood overweight was varied from 1-25%[5] . However, it had some limitation in interpretation of this wide variety due to differing age range and diagnostic criteria. In Thailand, the prevalence of childhood obesity had been rapidly increased from 12.2% in 1991 to 15.6% in 1993[7]. In general, prevalence of obesity was varied among the different area such as the greater in urban areas and developed countries[8]. Sakamoto et at [9] reported that obesity rates among Kindergarten children in Thailand were 22.7% in urban areas and 7.4% in rural areas. Our recent study revealed that 22% of school children in Ongkharak, a rural district of Thailand were obese or overweight children[10].

Classification of obesity

BMI is the most popular methods for the assessment of obesity in adult due to it is well correlate with metabolic syndrome[11]. Classification of obesity by BMI is depicted in Table 1[2]. In childhood obesity, weight for height over than 120% had been used for the diagnosis in some literatures[12, 13]. Recently, BMI criteria has been employed for the diagnosis childhood obesity[3, 4]. Other classification method is by it's cause as followed.

a. Simple obesity is the most common type of obesity. It characterizes by less energy expenditure with no abnormality in the body system. It can be divided in-to 2 types – constitutional or infancy type obesity which is a hereditary disorder and acquired or adult type or diet-induced obesity which causes from over eating.

b. Secondary obesity is caused as a consequence of some existing primary diseases such as Cushing's syndrome, hypothalamic obesity, insulin-secreting tumor, etc[14].

Table 1 Classification of obesity in adult according to BMI for European and Asian population[2]

Classification	BMI (kg/m^2)	
	European	**Asian**
Underweijht	< 18.5	< 18.5
Normal weight	18.5-24.9	18.5-22.9
Overweight	25.0-29.9	23.0-24.9
Class I Obesity	30.0-34.9	25.0-29.9
Class II Obesity	35.0-39.9	≥ 30.0
Class III Obesity	≥ 40.0	

Causes

Up to the present the cause of obesity development is not fully understood. However, environmental factors, living-lifestyle and genetic factors are believed to play a major roles of the increasing in prevalence of obesity. Excessive caloric intake such as high fat-containing food, sugar-added soft drinks and high portion size of diet is one of the contributing factors for childhood obesity. Decrease in physical activity had been proposed to be one cause of obesity. Excessive television viewing and playing computer game were also associated with obesity prevalence[15]. Currently, The American Academy of Pediatrics recommended the appropriate TV viewing time in children should not more than 2 hours/day[16]. It has been observed that pediatric obesity is associated with overweight mothers and single-parent family, but is not associated with poor maternal or family characteristics such as maternal depression, negative life events, poor general family functioning or ineffective parenting style[17]. Other factors including endocrinal disturbances, hereditary factors and medication such as antipsychotics, antidepressants, steroids may relate to obesity[15]. Several endocrine diseases have been linked with obesity such as hypothyroidism, polycystic ovarian syndrome, Cushing's syndrome, central hypothyroidism and hypothalamic disorders[18]. Genetic syndromes which had been reported to be a cause of obesity are Prader-Willi syndrome, Alstrom syndrome, Bardet-Biedl syndrome, Werner syndrome and Cohen syndrome[19-21]. Apart from these, genetic mutation causing obesity are Melanocortin-3-receptor gene (MCR-3) mutation, lipoprotein lipase (LPL-S447X), cholesterol ester transfer protein (CETP-Taq1B) apolipoprotein (APO) E

(epsilon2, epsilon3, epsilon4), APOA5, APOA4 and APOC3, plasminogen activator inhibitor-1 gene 4G/5G polymorphism[22].

Methods for body composition measurement

Various techniques that used for body composition measurement can be broadly categorized into direct and indirect measurements[23].

Direct measurements include density based methods such as hydrodensitometry and air displacement plethysmography, scanning methods such as computerized tomography (CT), magnetic resonance imaging (MRI) and absorptiometry and bioelectrical impedance methods. Hydrodensitometry methods perform by weighing the subject while submerged in a large tank. This method is based on Archimedes principle that an object which has density more than water will sink in water. Air displacement plethysmography method is based on the measuring the air volume which is displaced by a subject in a closed chamber. Computerized tomography (CT) and magnetic resonance imaging (MRI) are measured by using the x-rays images and magnetism, radio waves, and a computer to produce images of body structures, respectively. Absorptiometry is based on the principle that low energy x-ray beam absorption differs from tissue to tissue (fat, cardiac muscles, bones etc.) in the body. Bioelectrical impedance method includes the use of conductors placed mostly on ankles and wrists with a passage of low and safe current. The resistance for the conduction is a measure of fat present in the subject.

Indirect measurements include anthropometric methods such as BMI, waist circumference, waist-hip ratio and skin-fold measurements. Waist circumference is measured with a plastic tape with a sprung handle reflects total and abdominal fat levels. Large waist-hip ratio indicates more amount of abdominal fat. Subcutaneous fat indicates total fat, hence the skin-fold measurements, use this concept. Calipers are used to measure the fat, mostly triceps skin folds are preferred sites for measurement.

Complications

Obesity has been reported to associate with various morbidity and mortality. Cardiovascular and other obesity related disease risks are directly correlated with the increasing BMI exceeds the normal values. These obesity-related diseases include of hypercholesterolemia, hypertension, hypertriglyceridema, atherosclerosis, ischemic heart disease, insulin resistance, type 2 diabetes mellitus, glucose intolerance, non-alcoholic fatty liver disease (NAFLD), malignancies, obstructive sleep apnea disorder, asthma, orthopedic disorders and psychological problems[24].

Cardiovascular Complications

Cardiovascular complications in childhood obesity include hypertension, dyslipidemia and insulin resistance[24]. Ambulatory blood pressure monitoring is recommended to measure in all case of obese. Low levels of high-density lipoprotein, high levels of low-density lipoprotein and high levels of triglycerides were reported to associate with an increase in waist circumference, BMI and total body fat in obese children[24].

Other findings such as left ventricular hypertrophy, high levels of C-reactive protein, homocysteine and lipoproteins were also reported from obese children. These obese-related health problems are the same types that found in adulthood[24].

Hypertension

Obese children had 3-fold higher risk of primary hypertension than non-obese children[22]. The leading causes of hypertension were increased activity of sympathetic nervous system and renin-angiotensin system, reduced activity of parasympathetic system and insulin resistance. Decrease of sodium intake and weight reduction should be encouraged in all cases for the control of hypertension[25]. Moreover, the endothelial and smooth muscle dysfunctions and arterial stiffness were considered as the first marker of atherosclerosis in obese children[26].

Non-Alcoholic Fatty Liver Disease (NAFLD)

Non-alcoholic fatty liver disease (NAFLD) is a common complication found in obesity[25]. NAFLD is a spectrum of disease activity including fatty accumulation in liver (steatosis), inflammation of hepatocyte (steatohepatitis) and fibrosis. In simple steatosis, liver function tests are generally normal, whereas in steatohepatitis, there are mild elevations in serum liver enzyme activities (alanine amino-transferase and aspartate aminotransferase). The pathogenic mechanism is related to insulin resistance and metabolic syndrome. Hyperinsulinemia will increase lipolysis and fatty acid synthesis in hepatocytes. This leads to hypertriglyceridemia and increases in fatty acid uptake by liver cells. Excessive accumulation of triglycerides in liver will induce cytochrome P450 2E1 activity that will lead to free radical generation, lipid peroxidation and cell necrosis. Moreover, excessive free fatty acid can cause of liver cell injury by an immune response process through various cytokines and oxidant stress[27].

Insulin Resistance

Insulin resistance is one of the complications associated with pediatric obesity leading to hyperinsulinemia, decrease in glucose metabolism, hypertension, hepatic steatosis, endothelial dysfunction, early atherosclerosis, abnormal pubertal development, disordered

fibrinolysis, development of polycystic ovary syndrome (PCOS) and asthma[28]. The effect of various mediators produced during insulin resistance and their effect are depicted in Table 2. Various tests used for assessment of insulin resistance in obesity are fasting levels of insulin and glucose, oral glucose tolerance test (OGTT), hyperinsulinemic euglycemic clamp, frequently sampled intravenous glucose tolerance test (FSIVGTT) and insulin tolerance test[28]. Treatment strategy for obesity associated with insulin resistance includes change in the life style, food habits, decrease in body weight and exercise. Drugs used are metformin, sibutramine (limited use due to increase in heart rate and blood pressure) and orlistat (associated with gastrointestinal disturbances and multiple vitamin deficiency)[28].

Table 2 Various markers and levels associated during insulin resistance in obesity

Markers produced during insulin resistance	**Levels during insulin resistance**
Adiponectin	Cytokine having antiatherogenetic, low levels
Tumor necrosis factpr-α	Inflammatory mediatior, increased levels
Interleukin (IL-6)	Cytokine stimulates synthesis of hepatic C-reactive protein, Increased levels
Resistin	Impair insulin resistance, Increased levels
Retinol binding protein (RBG-4)	Impair insulin resistance
Leptin	Increased levels
Plasminogen activator inhibitor-1 and Fibrinogen	Enhance coagulability, Increased levels
Intramyocellular lipid (IML)	Increased levels
Free fatty acids and Alanine aminotransferases (ALT)	Causes hepatic steatosis, Increased levels

Thyroid dysfunction

It has been found that increase in thyroid stimulating hormone (TSH) is associated with BMI, levels of leptin, neuropeptide Y and α-melanocyte stimulating hormone (MSH). Increased levels of TSH cause hyperthyrotropinemia ultimately leading to increase in the levels of thyroid hormones, T_3 and T_4. Adiposity, leptin secretion, various neuropeptides and TSH levels are associated with thyroid dysfunction. Leptin administration has been found to decrease deiodinase activity in pituitary gland, modifying feedback of thyroid hormone T3 on TSH in animal models. Elevated TSH is associated with lipid levels, blood pressure and insulin resistance[29].

Prevention and treatments

Primary prevention of obesity by the healthy dietary and activity habits are highly recommended for all children. Breast-feeding for a minimum of 6 months should be encouraged for all infants. In older children, a moderate to vigorous exercise for at least 60 minutes per day should be encouraged. Not only children, but also parents should be educated and through anticipatory guidance about healthy dietary and activity habits. Moreover, the policies to decrease the exposure of children and adolescents to the promotion of unhealthy food choices in the community such as media advertisements should be advocated. Treatments for childhood obesity range from basic diets and lifestyle interventions to more intensive methods such as very low energy diets, medications, and surgery. However, the success of each method is varied as well as side effects that must be considered. All of the treatment methods need the cooperation from patients, family and community. Life style modification including dietary, physical activity, and behavioral modification are general recommended. There are evidences that successful weight management, through lifestyle interventions, can reduce the incidence of type 2 diabetes millitus[30] and improving cardiovascular fitness[31], improving body composition and metabolic parameters[32, 33].

Dietary modifications

The concept is based on the fact that obesity is due to consumption of too much of energy with less expenditure. Approaches for control on diet include reduction of calorie intake, teaching good dietary habits and doing regular exercise. There are several dietary modifications for childhood obesity management including low fat, low carbohydrate and low calorie. However, there are few studies comparing the efficacy of each modification in children compared to the studies in adult population. MaGovern et al[34] did a meta-analysis study from studies that evaluate the efficacy of diet modification in pediatrics. From 6 available studies, they found

that the overall pooled benefit showed an effect size of only 0.22 points in the treatment arms. Although dietary modification is recommended for all obese children, diets as a sole treatment are considered relatively ineffective for those with severe obesity[35]. Very low energy diets (VLEDS) or protein-sparing modified fast diets (PSMF) are based on restricting energy intake to 600 to 800 kcal/day and 1.5 to 2.5 g of high biological protein/kg/day. Carbohydrates usually are limited at 20 to 40 g/day. Multivitamin, mineral and 1.5 liter/day of water should be supplied to avoid vitamin and mineral deficiency states and dehydration. This diet modification had been reported to have rapid weight loss (up to 11 kg in 10 weeks of study) and most of the studies limited the use of this diet for 12 weeks. VLEDS are generally limited to use only in severe obese patients who need intensive therapy because of the adverse effects of rapid weight loss and the weight gain after stop diets.

Exercise

Exercise as the sole methods of treatment may not achieve weight loss in obese children. A meta-analysis from 17 original studies showed the inconsistent results on weight loss by exercise alone across studies[34]. However, the combination between exercise and dietary intervention has shown the beneficial effects in weight loss especially the trials that utilized parents in the therapy[18, 34]. Sustention of moderate or vigorous exercise at least 60 minutes per day, even without weight loss, showed the evidences in reduction of cardiovascular risk factor in obese children[18]. Moreover, a reduction in time spent in sedentary activities, such as watching television, playing video games, or using computers should be encouraged. TV viewing time should be limited to < 2 hours per day[16].

Medications

Medication management in combination with dietary and lifestyle modification is recommended for obesity treatment in children after a failure of non-pharmacotherapy[4,18]. Moreover, overweight children presented with severe comorbidities persist despite intensive lifestyle modification, particularly in children with a strong family history of type 2 diabetes or premature cardiovascular disease are also be considered for treatment. Many medications which had been used for obesity treatment were withdrawn from the markets due to various adverse effects for examples; amphetamines (abuse potential ability, tachycardia, psychosis and pulmonary artery hypertension (PAH)), phenylpropanolamine (PAH, cardiac arrest, stroke, seizures), diethylpropion (insomnia, psychosis, PAH), fenfluramine (valvulopathy, PAH, depression), aminorex (PAH) and mazindol (nervousness, atrial fibrillation, syncope)[36].

Currently the only approved drugs by

US-FDA in market as anti-obesity drugs is orlistat (Roche Laboratories, GSK). Anti-obesity drugs are categorized into peripherally acting, centrally acting or combination. Orlistat, a peripherally acting medication, is a hydrogenated derivative of lipstatin produced by Streptomyces toxytricini. It inhibits pancreatic and gastric lipases, thereby reducing the hydrolysis of ingested fats into absorbable free fatty acids and monoglycerides by approximately 30%[37]. Adverse reactions of orlistat that had been reported include flatus, abdominal cramps, fecal incontinence, oily spotting, fat soluble vitamin malabsorption . Orlistat should be used with precaution while using with other drugs such as cyclosporine, warfarin, glipizide, glyburide, metformin and insulin. Patients suffering from any disease such as cholestasis, malabsorption syndrome, anorexia nervosa, bulimia, diabetes, kidney stones, pancreatitis, gallbladder disease and thyroid disease should be caution in use of this drug[38].

Sibutramine is a centrally acting anti-obesity agent which inhibits the reuptake of norepinephrine, 5-hydroxytryptamine and dopamine, resulting in loss of weight due to increased thermogenesis and satiety, and reduced hunger[38]. It had been approved to use in children and adults older than 16 years old. However, currently, it was withdrawn from US and Europe due to cardiovascular concern[39, 40]. The side effects are including of hypertension, tachycardia, premature ventricular contractions, prolonged QTc, insomnia, dizziness, dry mouth, cholelithiasis, and constipation.

Although metformin is not approved by FDA as pharmacotherapeutic agent for obesity, it is one of the most common used at present. It reduces hepatic glucose production and plasma insulin, inhibits lipogenesis, increases peripheral insulin sensitivity, and may reduce appetite by increasing levels of glucagon-like peptide. However, the exact mechanism on weight reduction is unresolved[18]. Growth hormone is currently approved for treatment of children with Prader-Willi syndrome. It showed beneficial effects on body composition (decrease in body fat mass and increase in lean body mass)[41].

Rimonabant is a cannabinoid, CB1 receptor antagonist, which acts peripherally as well as centrally. It acts centrally by increasing satiety and also acts peripherally by increasing thermogenesis, inhibiting ghrelin, decreasing hepatic lipogenesis, adipocyte differentiation, gut motility and nutrient absorption[42]. The reported side effects were anxiety, depression, insomnia, dizziness, nausea, and vomiting. Up to present, there is no clinical trial of rimonabant in children and it is not yet approved to use in obese children.

Octreotide, a somatostatin analog, acts by binding to receptors on the beta cells of the pancreas and inhibits insulin release. The RCT in children with hypothalamic obesity revealed that octreotide had successful effected in weight reduction comparing to placebo[43]. This finding also found in adults study[44]. The reported side effects include cholelithiasis and abnormalities of glucose homeostasis.

Leptin therapy has been studied in children with congenital leptin deficiency[45]. It can reduce weight, BMI and fat mass of the patients. However, there are some limitations in the use of leptin as it has short half life, painful at the site of injection and needs frequent administration[46].

Topiramate is a novel anticonvulsant which the exact mechanism of action is unknown. However, the mechanisms which may contribute to it property include a blockage voltage-dependent sodium channels, enhances the activity of the $GABA_A$ receptor, and antagonizes a glutamate receptor other than the N-methyl-D-aspartate receptor. There were some studies that showed it efficacy in for weight loss in adults with obesity, however, there is no clinical trial reported from children. The exact mechanism for weight loss is not known, however, it may induce insulin sensitivity in liver and muscle and directly in adipocytes[47]. Up to present, it is not approved for treatment of obesity in children.

Surgical treatment: In childhood obesity, Experts[18] recommended that bariatric surgery is considered for the treatment option only when:

1. Children are in the final or near final pubertal development (Tanner 4 or 5) and have final or near-final adult height.
2. BMI > 50 kg/m^2 or BMI above 40 kg/m^2 with significant, severe comorbidities
3. Persistent severe obesity and co-morbidity with resistant to conventional treatment
4. Normal for psychological evaluation
5. Capable of long-term follow-up
6. Ability to adhere to the principles of healthy dietary and activity habits

Bariatric procedures for weight loss can be grouped in three main categories: malabsorptive, restrictive, and combination procedures. Malabsorptive procedures aim to decrease the surface area for absorption (gastric bypass surgery). These procedures include the jejunoileal bypass, the biliopancreatic diversion and endoluminal sleeve. Restrictive procedures aim to reduce oral intake by limiting gastric volume leading to early satiety. These procedures include vertical banded gastroplasty, adjustable gastric band, sleeve gastrectomy and intragastric balloon (gastric balloon). Combination procedures which apply both techniques simultaneously include

gastric bypass surgery, sleeve gastrectomy with duodenal switch and implantable gastric stimulation. The details of each techniques had been extensively reviewed elsewhere[48, 49].

Conclusion

Obesity is a public health problem worldwide. The etiology is multifactorial involving environmental factors, living-lifestyle and genetic factors. Obesity has been reported to associate with various morbidity and mortality. From the literature, it is obviously that the present therapies are not satisfactory and drug development is in progress for the obesity. Surgical treatment is reserved for some severe obese patients especially in young adults with severe co-morbidity and resistant to conventional treatment. Thus, there is a need for preventive approach rather than medication for treatment of pediatric obesity in the present scenario.

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