Complications of Obesity in Childhood

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Childhood obesity is a serious health problem. Associated dyslipidemia, atherosclerosis, hypertension, and type 2 diabetes decrease quality of life and life span. Excessive carbohydrate and fat consumption and lack of exercise are important keys to the development of these complications, especially during adolescence.

U.S. EPIDEMIOLOGY OF CHILDHOOD OBESITY

Children with body mass indices (BMI) higher than the 85th percentile for age and gender are classified as overweight, whereas those with BMIs higher than the 95th percentile are designated as obese. The 1999-2002 National Health and Nutrition Examination Survey (NHANES) indicates that 16% of children and adolescents ages 6 to 19 are overweight. This represents a 45% increase over the findings of the NHANES III report in which 11% of children were overweight (1988-1994). Body mass indices (BMI) in excess of 28 kg/m² are associated with a three- to fourfold increase in risk of hypertension, dyslipidemia, and diabetes, and a twofold increase in incident death rates. The latest data for adolescents are of notable concern because overweight adolescents are at increased risk to become overweight adults with adiposity-related morbilities. However, modest weight reductions of 5% to 10% significantly decrease the risk of complications of obesity.

PATHOGENESIS

The dramatic rise in obesity reflects increased availability and consumption of food with high carbohydrate and fat contents in the environment, and decrease in physical activities. Genetic predispositions to obesity favor selec-
tion of metabolically advantaged (energy thrifty) traits, resulting in an enhanced ability to store excess calories in tissues as fat sparing and to spare protein breakdown for gluconeogenesis, favoring survival in times of hunger.

**The Thrifty 'Catch-up Fat' Phenotype**

In humans, risk of obesity is particularly apparent when a small for gestational age (SGA) newborn undergoes rapid postnatal weight gain, which progresses through to childhood obesity. Curiously, large for gestational age (LGA) children and children born prematurely are both at risk of obesity.\(^5,6\) The same U-shaped relation between birth weight, BMI, and fat mass was demonstrated recently in adolescents.\(^7\) Gestational diabetes perse increases significantly the subsequent risk of obesity and type 2 diabetes.\(^8\) Children of mothers with type 1 diabetes are predisposed to the development of type 2 diabetes as adults as compared to children born to fathers with type 1 diabetes but to mothers who were non-diabetic.\(^9\) The fetal metabolic and hormonal responses to intrauterine environment and to rapid postnatal growth may be key to the early pathogenesis of adulthood disease.

**Insulin, Leptin, Ghrelin, and Satiety**

The insulin/leptin-arcuate nucleus (ARC) of the hypothalamus axis regulates energy homeostasis through appetite control and energy expenditure. Both hormones rise in direct proportion to adipose mass. They cross the blood-brain barrier and have receptors in the ARC. Leptin acts on expression of proopiomelanocortin (POMC) and release of a-melanocyte-stimulating hormone (a-MSH). POMC is the source of several biologically active substances. POMC can be cleaved enzymatically into a-MSH.

A-MSH, in turn, interacts with melanocortin 3 and 4 receptors (MC3/4R) to reduce food intake and increase energy expenditure through activating the nervous system. The catabolic cocaine and amphetamine regulated transcript (CART) and corticotrophin-releasing hormone (CRH) are upregulated by leptin. Leptin downregulates anabolic neuropeptide Y (NPY), agouti-related peptide (AGRP), orexins, and melanin-concentrating hormone (MCH) in the hypothalamus. The central melanocortin system is a mediator of the catabolic effects of insulin in the brain.

Gastric secretion of ghrelin is increased by fasting and increases pituitary GH release. Ghrelin stimulates NPY-AGRP to antagonize a-MSH-CART. The lack of anorexic pressure on MC4Rs results in increased feeding behavior and energy efficiency to store energy as fat. In the fed state, insulin and leptin levels are increased, which increase the synthesis and processing of hypothalamic
POMC to its component peptides, which act at the MC4R to decrease appetite. Insulin and leptin directly inhibit NPY-AGRP, further limiting feeding and providing for unantagonized MC4R occupancy. Therefore, ghrelin, insulin, and leptin represent hormonal links between peripheral energy metabolism and central feeding behavior and tie together the gut, pancreas, adipocyte, hypothalamus, and pituitary to form a growth and energy regulatory system.

Significant association between asthma and obesity has been noted, especially during puberty. One of the possible mechanisms is that obesity represents a proinflammatory state and that leptin levels influence Th1 cytokine responses. BMI correlated with the prevalence of asthma in both boys and girls. It was noted that girls who became obese between ages 6 to 11 were seven times more likely to develop new asthmatic symptoms at ages 11 to 13.

Leptin plays a role in the development of steatohepatitis. Leptin and liver injury correlate independently of age, BMI, and gender in children.10

The Natural History of Obesity

The natural history of obesity begins in childhood, from the interplay of genetic and environmental factors. The natural history includes SGA birth weight, excessive weight gains during childhood, premature pubarche, acanthosis nигricans, and striae, followed by hypertriglyceridemia, hepatic steatosis, premature atherosclerosis, hypertension, polycystic ovarian syndrome, diabetes type 2 and predisposition to cancer and Alzheimer’s disease.

The majority of people with obesity do not develop type 2 diabetes. The genetic background in which hyperinsulinism and insulin resistance develop strongly influences the possibility of adequacy of pancreatic cell compensation.11 Insulin resistance appears to be the best predictor of the development of diabetes in the children of patients with type 2 diabetes. Skeletal muscle of insulin-resistant offspring of patients with type 2 diabetes shows dysregulation of intramyocellular fatty acid metabolism, possibly because of an inherited defect in mitochondrial oxidative phosphorylation.12

Pancreatic beta-cell failure may represent independent genetic interactions and may be mediated by the HLA haplotype.13 Disposition index (Di) characterizes the relationship of insulin secretion to the degree of insulin resistance. Di calculated by (AIR x SI) describes the hyperbolic relationship between insulin secretion and insulin sensitivity. DI is sensitive to even latent beta-cell defects.14 The heritability of beta-cell function assessed by DI was 70% in 94 normal glucose-tolerant people.15 Linkage to DI on chromosome 11q was demonstrated in 284 African-American people from 21 pedigrees in the Insulin Resistance Atherosclerosis Study Family Study (IRASFS). Later, an additional 214 African-American people in 21 pedigrees from the IRASFS yielded independent evidence of linkage to DI. No evidence of linkage to the insulin sensitivity index SI was observed. These recent genetic analyses provide strong evidence of a DI locus on 11q in African-American pedigrees, with additional evidence of independent AIR loci in the same region.16

Although children with insulin resistance and obesity who can compensate with hyperinsulinemia may not develop diabetes, other complications still can occur, such as early atherosclerosis. Progression of obesity (especially central type), acanthosis nигricans, increased skin tags, hypertension, dyslipidemia, hypercoagulation (HC), polycystic ovary syndrome, fatty liver infiltration, focal segmental glomerulosclerosis, and increased susceptibility to cancers can result. Thus progression of obesity is not benign even when diabetes does not develop (see Figure 1, page 99).

COMPLICATIONS ASSOCIATED WITH OBESITY

Adipose Tissue, Visceral Fat

Waist circumference and waist-height ratio may be better predictors than overall obesity for the risk of cardiovascular disease and type 2 diabetes. Data from the three most recent NHANES, conducted between 1988 to 1994 and 1999 to 2004, revealed a great increase in the prevalence of abdominal obesity in children. Using the 90th percentile values of waist circumference for gender and age, the prevalence of abdominal obesity increased by 65.4% (from 10.5% to 17.4%) for boys and by 69.4% (from 10.5% to 17.8%) for girls. Waist circumference is as highly correlated with cardiovascular morbidities as are BMI or percentage of body fat.17 Visceral fat tissue, through its portal drainage, could be an important source for free fatty acids that increase hepatic lipogenesis and decrease glucose oxidation. Omental adipose tissue contains significantly more 11-beta hydroxysteroid dehydrogenase type-1
(11b-HSD-1) activity than subcutaneous adipose tissue promoting increased cortisol production from conversion from inactive cortisone. Local increase of glucocorticoid hormone action in visceral fat may contribute to the pathogenesis of key features of the metabolic syndrome.

**Fatty Liver or Hepatic Steatosis**

Fatty liver affects 22.5% to 52.8% of obese children; 10% to 25% of obese adolescents have elevated alanine aminotransferase (ALT) levels. Serum levels of ALT and aspartate aminotransferase (AST), alkaline phosphatase (ALKP), and g-glutamyltranspeptidase (GGT) are elevated and proposed as surrogate markers of hepatic fat accumulation. The ratio of AST to ALT is usually less than 1, but this ratio increases as fibrosis advances. Leptin plays a significant role in liver injury and correlates independently with liver injury in children independent of age, BMI, and gender. Leptin, free leptin index, and insulin resistance can lead to liver fibrosis in children with non-alcoholic fatty liver disease. Two distinct clinical and histological patterns of steatohepatitis have been identified in obeise, insulin-resistant pubertal boys of Hispanic ethnicity and in non-Hispanic white children. The natural history of pediatric steatohepatitis has yet to be defined, but most biopsies in this age group demonstrate some degree of fibrosis. In addition, cirrhosis can be observed in children as young as age 10.

**Hypertension**

Systolic and diastolic blood pressure among overweight children were reported to be significantly higher compared to non-overweight children. Prevalence of elevated systolic blood pressure increased sharply beyond BMI values of 20 kg/m² in boys and 21.5 kg/m² in girls, whereas such cutoffs for body fat were above 25% in both sexes. Hyperinsulinemia can increase blood pressure by several mechanisms: via its effect to increase renal sodium absorption, via increased activity of the sympathetic nervous system, and via free fatty acid-induced sensitivity to adrenergic stimuli and antagonized nitrergic vasorelaxation.

**Obesity and Insulin Resistance as Initiators of Atherosclerosis**

Atherosclerosis begins early in life; however, children are not universally screened for the presence of modifiable cardiovascular disease risk factors. The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study confirmed the origin of atherosclerosis in childhood, showed that progression toward clinically significant lesions may occur in young adulthood, and demonstrated that the progression of atherosclerosis is strongly influenced by coronary heart disease (CHD) risk factors. The Muscatine study provided the first data that linked childhood coronary risk factors to atherosclerosis in asymptomatic adults. The most predictive childhood risk factor was increased BMI. Coronary artery calcifications were also associated with increased blood pressure and decreased high-density lipoprotein cholesterol levels measured during childhood. Fatty streaks can be found in the aortas of children older than 3 years old and in the coronary arteries by adolescence. The Bogalusa Heart Study confirmed that the same risk factors that are important for adults, such as elevated BMI, systolic blood pressure, serum triglycerides, and low-density lipoproteins, are associated with a greater extent of atherosclerosis in the aorta and coronary arteries in children. Increased thickness of the carotid wall and endothelial dysfunction represent an early stage of atherosclerosis. They are validated surrogate markers for atherosclerosis in teenagers and young adults and are sensitive to the intake of cholesterol, serum level of cholesterol and triglycerides, BMI, smoking, hypertension, and fasting glucose. Endothelial dysfunction is similar in children with obesity or with type 1 diabetes mellitus.
Hyperandrogenism and Reproductive Abnormalities

Obesity can present in adolescent girls with hirsutism, menstrual irregularity, persistent acne, scalp hair loss, hyperhidrosis, infertility, or precocious adrenarche in childhood. Hyperinsulinemia potentiates ovarian hyperandrogenism by 1) enhancing pituitary luteinizing hormone secretion and ovarian 17-hydroxylase and 17,20-lyase activity, and 2) suppressing blood sex hormone binding globulin (SHBG) capacity and corticosteroid binding globulin (CBG) level capacity. CBG, or transcortin, is an alpha-globulin that binds and transports unconjugated and biologically active cortisol in plasma. SHBG is a glycoprotein that binds to sex hormones. SHBGs in the circulation are often low, resulting in increased free androgens with their increased bioavailability. This is often seen with testosterone, which can be raised or normal in girls with hirsutism in whom increased free testosterone levels are common. Obesity and insulin resistance contribute to early onset and rapid progression of puberty in SGA girls. Early mifepristone treatment of SGA girls with precocious puberty resulted in less adipose body composition after two years as well as slower onset of puberty, whereas height gain was maintained.28

Acanthosis Nigricans

Acanthosis nigricans (AN) is a skin lesion that is widely used as a clinical surrogate of laboratory-documented hyperinsulinemia. Common sites of involvement include the axillae, posterior region of the neck, antecubital fossae, and groins. Less commonly, it involves the other flexural areas, the umbilicus, the submammary region and, in extreme cases, the entire skin, including the palms and soles. The severity of acanthosis nigricans correlates well with the degree of hyperinsulinemia. In our experience, the appearance of acanthosis nigricans is an early lesion in childhood, especially in Hispanic children, developing even before fasting insulin level is elevated. In white patients, acanthosis often appears as light yellow, emphasizing that the lesion represents a thickening of the stratum corneum, which is pigmented in a racially dependent manner. Both insulin and IGF-1 receptors have been identified in cultured human keratinocytes. It has been shown that when the insulin level is high enough, it can activate both receptors.29 Additionally, TNF-a and INF-g cytokines that are often elevated in obesity can induce upregulation of peroxisome proliferators-activated receptors (PPAR-beta/delta), which act as ligand-activated transcription factors, and thereby induce keratinocyte proliferation.30

Pseudoacromegaly

Linear and acral growth can be accelerated and can present as pseudoacromegaly in obese children. Hyperinsulinemia promotes linear growth by activating skeletal IGF-1 receptors. Low levels of IGFBP-1 can promote IGF-1 action by allowing it to be freely and metabolically available. Increased aromatization of androgens to estrogens leads estrogen to affect longitudinal bone growth through action on endochondral bone formation. Direct action of leptin on bone growth also leads to pseudoacromegaly.

Psychological Complications of Obesity

Obese children are commonly teased and bullied. Obesity causes suffering and stigmatization, but obesity is not classified as a behavioral or psychiatric disorder. In adulthood, the psychosocial consequences include fewer years of education, lower family income, higher poverty rates, and lower marriage rates.31 Obese children with obstructive sleep apnea demonstrate significant problems with learning, memory, and cognition.32,33 Prevalence of depression, anxiety, and eating disorders is increased in obesity compared to those who are not obese.34 Among obese adolescents, 60% of girls and 35.3% of boys reported binge-eating episodes,34 while 30% to 50% had depression.35

Obesity and Sleep Apnea

Excess body fat leads to a decline in the expiratory reserve volume, vital capacity (VC), total lung capacity (TLC), and functional residual volume (FRV).36 Excess body mass, elevated plasma insulin, leptin deficiency and resistance, and altered sympathetic nervous system activity were noted in the development of sleep apnea. Studies performed in obese C57BL/6J-Leprdb mice, which lacked circulating leptin, demonstrated that leptin deficiency is associated with elevated PaCO2 and hypoventilation, and leptin replacement improved ventilation independent of weight, particularly during sleep. Leptin resistance that presented as hyperleptinemia was associated with hypercapnic respiratory failure in obesity similar to a leptin-deficient mice model.37

Other Complications Associated with Obesity

Orthopedic problems, such as hip pain, knee pain, or altered gait, are seen in obese children. About 50% to 70% of patients with slipped capital epiphyses are obese. Blount's disease involves bowing of the legs and tibial torsion from bearing excess weight, and up to 80% of patients with Blount's disease have it bilaterally and symmetrically. Incidence of gallstones is increased in obese children: in 14- to 20-year-old obese girls, gallstones are approximately 4.2 times more common than in their peers of normal weight.38
No data suggest that childhood obesity contributes directly to an increased risk of cancer in adulthood. However, a high-fat childhood diet may increase long-term cancer risks, because excess fat intake in adults correlates with an increased risk of breast, uterine, cervical, colon, prostate, and pancreatic cancer. Additional complications include focal segmental glomerulosclerosis, uric acid elevation, asthma, and pseudotumor cerebri.

CONCLUSION

The U.S. obesity epidemic continues unabated, with ever-increasing numbers of the nation’s obese children becoming irreversibly obese adults. Aggressive prevention and intervention in childhood in schools and communities are urgently needed.

REFERENCES