Childhood Obesity

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Abbreviations:

BMI
: Body mass index

LDL
: low-density lipoprotein

PYY
: peptide YY3–36

Obesity has become a pandemic, with more than a billion people affected worldwide [1] . Over the past 30 yr, the frequency of overweight children, defined as a body mass index (BMI) greater than the 85th percentile for age and sex, has tripled [2] . More than 30% of children in the United States are overweight or obese (BMI > 95th percentile) [3] . Data from the International **Obesity** Task Force indicate that 22 million of the world's children under 5 yr of age are overweight or obese [4] . **Obesity** has replaced malnutrition as the major nutritional problem in some parts of Africa, with overweight/obesity being as much as four times more common than malnutrition [5] .

More than two thirds of children 10 yr and older who are obese will become obese adults [6] [7] . **Obesity** in young adults decreases **life expectancy** by 5–20 yr [8] . Pediatric obesity-related hospital costs have increased 3-fold during the past 20 yr, reaching $127 million per year, and continue to rise [9] [10] . The increased frequency and severity of childhood

obesity is accompanied by the expected medical complications. One in four overweight children in the 6- to 12-yr age group has impaired glucose tolerance, and 60% of these children have at least one risk factor for heart disease [11] . Childhood **obesity** threatens to thwart the reduction in cardiovascular mortality achieved over the past decades through control of hypertension, hyperlipidemia, and smoking.

Nature or Nurture?

The increased incidence of childhood **obesity** cannot be blamed on either environment or genetics alone. Changes in the environment (*i.e.* nutrition and lifestyle) are primarily responsible for the current epidemic in the United States because it is not possible for the gene pool to change in less than a generation.

The past few decades have brought marked lifestyle changes throughout the world, which have resulted in a decrease in physical activity and an increase in caloric intake. Children use automobiles and other automated means of transportation, including elevators and escalators, rather than walking or climbing stairs to get from place to place. The amount of time that children spend playing outside has diminished over the past few decades, and physical education programs in the schools have been reduced or eliminated [12] . The majority of families now have both parents or the single parent working, resulting in the need to find nonparental supervision after school. Fear of children playing outside without adult supervision has led many parents to admonish their children to stay inside after school. Children are thus spending more time watching television and playing on the computer than exercising [13] . Television watching has been directly linked to **obesity** in childhood, with a rate of **obesity** that is 8.3 times greater in children who watch over 5 h of television per day compared with those who watch 2 h or less of television per day [14] . Many parents rely on schools to provide their children with appropriate exercise, but only 25% of students participate in daily physical education classes [15] . Only 22% of American children meet basic activity level recommendations, and 25% of American children are classified as completely sedentary [16] .

Changes in diet have also contributed to pediatric **obesity**. Portion sizes in food outlets have more than doubled over the past two decades [17] . In addition to a baseline increase in portion sizes, most fast food restaurants offer up to 20% larger portion sizes for minimal additional cost, adding hundreds of extra calories. Fast food is marketed to children using toys, music, and social icons. Studies have found that children's food preferences are influenced by just 30-sec exposures to television commercials [18] . One third of American children age 4–19 yr eats fast food daily; it is estimated that this increases their weight by 6 lb/yr [19] . Additionally, many schools now offer fast food concessions as an alternative to school lunch. Even children who receive free school lunches will spend their money to buy preferred high-fat food. The schools receive financial incentives to allow vending machines, thus providing increased availability of soda, juice, snack cakes, and chips.

The genetic component of **obesity** has been demonstrated by twin and adoption studies. Twin analysis indicates a heritability of fat mass of 40–70% [20] . Adopted children have BMIs that correlate to those of their biological parents but not to the fat mass of their adoptive parents [21] . These findings indicate that, although environment plays a crucial role in the development of childhood **obesity**, genetic background is also important.

The thrifty genotype hypothesis was advanced over 40 yr ago to explain the modern emergence of **obesity** and type 2 diabetes [22] . This hypothesis postulates that humans survived by the genetic selection of those whose metabolic storage capabilities permitted survival during periods of famine by taking advantage of episodic periods of plenty in a feast and famine existence. Continuous feasting with an abundance of calorie-rich foods results in fat deposition without

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the concomitant period of fasting to maintain a normal body weight. Historically, only the prosperous met this condition, but modern food production and marketing have led to low-cost abundance, with **obesity** now disproportionately affecting those at the less prosperous end of the economic scale.

The environmental counterpart to the thrifty genotype hypothesis, the thrifty phenotype concept, has more recently been proposed to explain epidemiological evidence that metabolic programming can occur as a result of *in utero* environmental exposures [23] . Small-for-gestational age babies have an increased incidence of adverse health outcomes later in life associated with insulin resistance, including type 2 diabetes, **obesity**, and cardiovascular disease. The thrifty phenotype hypothesis of **obesity** postulates that poor nutrition in fetal life is detrimental to the development and function of β-cells and insulin-sensitive tissues, resulting in emergence of insulin resistance or the metabolic syndrome later in life [24] .

Maternal malnutrition, intrauterine exposure to elevated insulin levels, and early introduction of high-carbohydrate formula all result in a hyperinsulinemic state in infant mice, which persists through adulthood [25] . Molecular adaptations are observed in the islet cells, liver, and adipose tissue of these rats. When the hyperinsulinemia occurs during a period of brain development, disorganization is seen in the ventromedial hypothalamic nuclei of these rats, leading to alterations in body weight, blood pressure, and glucose metabolism [25] . Data from these rat models suggest that nutritional alterations early in life, such as overfeeding of formula and early introduction of high-carbohydrate foods, may contribute to metabolic programming, leading to **obesity**, diabetes, and early cardiovascular disease in humans.

The results of these rodent studies are consistent with observations that breastfeeding in humans may be protective against childhood **obesity**. Possible mechanisms for this protective effect include metabolic programming or early learned self-regulation of food intake [26] . Infants who were bottle fed before 3 months of age consistently had higher

BMIs and skinfold thickness during early childhood than those infants who were breastfed longer than 3 months [27] . Nonetheless, all of the studies examining the protectiveness of breastfeeding have concluded that environmental and genetic factors, such as maternal weight and socioeconomic status, also play a role in the development of **obesity** in childhood [28] .

Neuroendocrine Control of Obesity

The intricacies of the neuroendocrine control of weight, specifically the signaling pathways between the adipose tissue and the brain, are being investigated (Fig. 1). Complex interactions exist between the systems that control intake and satiety and those that control relative fat mass. Some instances of severe, early-onset, morbid **obesity** may result from defects in genes encoding adipose-derived hormones such as leptin, neuropeptides such as proopiomelanocortin, cocaine- and amphetamine-regulated transcript (CART), and melanocortin-4, or the receptors for these ligands (Table 1) [29] . Although most of these monogenetic causes of **obesity** are rare, one study showed that as many as 4% of children who become obese before the age of 10 yr have a melanocortin-4 receptor defect [30] . As evaluations for genetic etiologies of **obesity** become more available, the screening for these known causes of **obesity** may become routine.

Metabolic Consequences of Obesity

As the incidence of childhood **obesity** has increased, so has the identification of the consequences of **obesity** in children, including obstructive sleep apnea, orthopedic problems, hyperandrogenism, type 2 diabetes, and cardiovascular disease. Children who develop these conditions track them into adulthood, thus increasing both their medical burden on society and their risk for early morbidity and mortality [31] .

Type 2 diabetes

The increase in incidence of type 2 diabetes in children parallels the increase in the prevalence and severity of pediatric **obesity** [32] . In North America, African-Americans, Mexican-Americans, and Native-Americans are disproportionately affected [33] . African-Americans are from 1.4–2.2 times more likely to have type 2 diabetes than white persons, whereas the prevalence of type 2 diabetes in Native-Americans is 2.8 times the overall rate in North America. In one center, up to 75% of the cases of type 2 diabetes were African-American children, and this experience has been replicated in other centers [34] . Whereas in 1990 only 4% of newly diagnosed childhood diabetes was type 2, by 2001 the proportion was 45% in adolescents in areas with a large population of African-American, Mexican-American, or Native-American children [35] . The higher incidence of type 2 diabetes in these ethnic groups is partially due to their high rates of **obesity**; studies of African-American children and Pima Indians have suggested a genetic basis for this

finding [36] . African-American children do not have the compensatory increase in insulin secretion that is noted in Caucasian children in response to the high levels of GH during puberty [37] . Additionally, insulin sensitivity is less and resting metabolic rate is lower in African-American children than in white children matched for age, sex, and BMI [37] [38] . Insulin resistance is greater in Pima Indian children who later developed diabetes than in matched Pima controls [39] . Additionally, certain minorities have much higher rates of diabetes-related complications and death [40] . For example, African-Americans are 2.6 times more likely than whites to develop end-stage renal disease and retinopathy with type 2 diabetes [41] .

Type 2 diabetes in youth is more common in girls than in boys, with one study showing that up to 80% of children who develop type 2 diabetes are female [42] . Girls carry 26% more sc fat than boys, which may contribute to relative insulin resistance in the female population. Girls are less insulin sensitive than boys as early as 5 yr of age [42] . Thus, sexlinked genes may contribute to insulin resistance with later development of type 2 diabetes and the metabolic syndrome in the current food-rich environment.

Approximately 17 million Americans have type 2 diabetes, and an additional 16 million Americans have insulin resistance, or prediabetes, associated with **obesity** [43] . The adipocyte

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Figure 1. Neuroendocrine control of body weight. *Dashed lines* indicate net inhibitory effect. *Solid lines* indicate net stimulatory effect. ARC, Arcuate nucleus; AGRP, agouti related protein; VMN, ventromedial nucleus; NPY, neuropeptides Y; POMC, proopiomelanocortin; MC4, melanocortin-4; CART, cocaine- and amphetamine-regulated transcript; PP, pancreatic polypeptide; PYY3–36, peptide YY3–36; CCK, cholecystokinin; GLP-1, glucagon-like peptide; LHA, lateral hypothalamic area; PVN, paraventricular nucleus; DMN, dorsomedial nucleus.

is the major contributor to the development of insulin resistance and the metabolic syndrome. The relationship between **obesity** and insulin resistance was originally explained by lipotoxicity [44] . The lipotoxicity theory states that accumulation of excess fat in the muscle cells and hepatocytes interferes with insulin signaling, leading to the development of hyperglycemia and glucose intolerance. It is now known, however, that adipose tissue secretes a number of bioactive molecules, termed adipokines [29] . The adipokines include proteins and cytokines that are associated with insulin metabolism (Fig. 2). TNFα and IL-6 are proinflammatory adipokines that play a direct role in insulin resistance by inhibiting insulin action [45] . These adipokines contribute to a hypercoagulable state by stimulating the release of acute-phase reactants and by promoting the release of vascular adhesion molecules. Other adipokines, however, including adiponectin and leptin, actually improve insulin sensitivity [45] . Whereas elevated leptin levels are associated with vascular dysfunction, adiponectin appears to be an endogenous antiinflammatory and antiatherogenic compound [46] .

The metabolic syndrome includes type 2 diabetes, hypertension, dyslipidemia, and a prothrombotic, inflammatory vascular environment (Table 2) [47] . **Obesity** plays a central role in the development of the metabolic syndrome, which increases the risk for development of cardiovascular disease. Those individuals who have the components of the metabolic syndrome in youth continue with them into adulthood [48] . The lipid profile associated with the metabolic syndrome puts individuals at increased risk for cardiovascular disease. The characteristic lipid profile includes hypertriglyceridemia,

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TABLE 1 -- Known monogenetic causes of **obesity**

	Leptin deficiency	**Leptin receptor mutation**	**Melanocortin-4 receptor mutation**	**Proopiomelanocortin**	**Pseudohypoparathyroidism**
Phenotype	EMO, hyperphagia, decreased T-cell function and number	EMO, hyperphagia, aggressive food-seeking behavior	EMO, tall stature, increased lean muscle mass; phenotype improves with time (adults report less intense hunger and have decreased insulin resistance)	EMO, hyperphagia, red hair	EMO, hyperphagia, can have tall stature
Endocrine abnormalities	Hypogonadotropic hypogonadism, hyperinsulinemia, hypothyroidism	Central hypothyroidism, low GH and IGF-I, absence of puberty	Hyperinsulinemia	Hypocortisolism, hypoglycemia	Primary hypothyroidism

EMO, Early-onset morbid **obesity**.

reduced high-density lipoprotein cholesterol, and elevated levels of small, dense low-density lipoprotein (LDL) particles. The most recent epidemiologic data show that 4% of all adolescents and 30% of overweight adolescents in the United States have the metabolic syndrome [49] . The fact that the metabolic syndrome is being identified in children suggests that the development of cardiovascular disease will also occur earlier.

Cardiovascular consequences of obesity

Childhood risk factors predict later development of cardiovascular disease. The Muscatine Study demonstrated that cardiovascular risk in adults is related to childhood

LDL cholesterol levels and childhood BMI in females [50] . The Cardiovascular Risk in Young Finns Study also showed that childhood LDL cholesterol and BMI correlated with adult cardiovascular disease [51] . The increased cardiovascular risk in adulthood was irrespective of adult risk factor status, indicating that permanent damage to the arterial wall may occur during childhood. Postmortem studies in children showed that 50% of children age 2–15 yr had fatty streaks in their coronary arteries, and 8% of these children had raised fibrous plaques in their coronary arteries [52] . The Pathobiological Determinants of Atherosclerosis in Youth study found that 12% of adolescents age 15–19 yr had raised lesions or advanced lesions of atherosclerosis in their right coronary arteries [53] . In both of these postmortem studies, the extent and severity of lesions correlated with BMI and lipoprotein levels.

Endothelial dysfunction is one of the earliest signs of increased risk for cardiovascular disease and has been shown to be predictive of cardiovascular events [54] . Endothelial dysfunction develops in the milieu of cardiovascular risk factors such as **obesity**, hypertension, dyslipidemia, insulin resistance, and type 2 diabetes [55] . In obese children, endothelial dysfunction is related to the severity of **obesity**, as well as to the degree of insulin resistance [56] .

Dysfunctional endothelium produces increased levels of cytokines and cellular adhesion molecules. The cytokines and cellular adhesion molecules mediate the recruitment of macrophages and leukocytes, which then accumulate in the intima of the vessel wall, initiating the formation of atherosclerotic plaques [57] . Activation of the endothelium results in a proinflammatory, procoagulant, proadhesive surface and reduced nitric oxide availability, thereby decreasing nitric oxide-dependent processes, such as inhibition of platelet aggregation and coagulation and activation of fibrinolysis [58] . Unopposed atherogenic factors promote atherogenesis and thrombosis (Fig. 3).

With the exception of adiponectin, all of the adipokines appear to contribute to endothelial dysfunction [59] [60] . Adiponectin is underexpressed in individuals with **obesity** or type 2 diabetes [61] . Adiponectin decreases endothelial inflammation, inhibits vascular smooth muscle proliferation, and suppresses transformation of macrophages to foam cells [60] . Adiponectin concentration is inversely related to other markers of inflammation, and low levels of adiponectin are associated with increased cardiovascular risk [62] .

Figure 2. Effects of adipokines on insulin metabolism. *Dashed lines*, Increases in adipose tissue cause increased insulin resistance.

TABLE 2 -- Definition of the metabolic syndrome

NCEP (ATP III) Must have 3 of 5 risk factors	WHO criteria
Abdominal **obesity**: waist circumference, >102 cm in men; >88 cm in women	Dysglycemia: type 2 diabetes or impaired fasting glucose or impaired glucose tolerance. +2 other criteria
Hypertriglyceridemia: >150 mg/dl (1.69 mmol/liter)	**Obesity**
Low HDL cholesterol: <40 mg/dl in men, <50 mg/dl in women	Dyslipidemia
High blood pressure: ≥130/85 mm Hg	Hypertension
High fasting glucose: ≥110 mg/dl (6.1 mmol/liter)	Microalbuminuria
NCEP, National Cholesterol Education Program; ATP, Adult Treatment Panel; WHO, World Health Organization; HDL, high-density lipoprotein.	

Treatment of Childhood Obesity

Prevention of **obesity** in children should be the first line of treatment. In 2003, the American Academy of Pediatrics (AAP) issued a policy statement on prevention of pediatric overweight and **obesity**. This statement recommended health supervision and advocacy to prevent **obesity** in children. The AAP states that pediatricians should become adept at recognizing children at risk for **obesity**, calculate and plot BMI at all visits, use change in BMI to identify excessive weight gain, and monitor for comorbidities associated with **obesity**. Additionally, the AAP states that pediatricians should encourage, support, and protect breastfeeding, promote healthy eating habits, promote physical activity, and recommend limitation of television viewing. The policy statement also encourages pediatricians to become advocates for the prevention of **obesity** by identifying and targeting influential people for education on **obesity** and by directing funding toward the prevention of **obesity** in children.

If **obesity** is not prevented, the cornerstone of treatment for childhood **obesity** is modification of dietary and exercise habits [63] . Decreasing portion sizes, decreasing high-calorie food and drinks, and decreasing snacks are the most common dietary recommendations for obese children. However, diet modification alone is not sufficient to achieve weight loss. When caloric intake decreases, metabolism slows, resulting in decreased calorie utilization and difficulty achieving weight loss. Therefore, exercise is vital for weight loss [64] . The Centers for Disease Control and Prevention recommends 30 min of moderate-intensity exercise 7 d/wk for every person in the United States [65] . For those individuals attempting to achieve weight loss, the Institute of Medicine recommends 60 min of moderate-intensity exercise 7 d/wk [64] . To achieve these recommendations, perceived barriers to exercise, such as lack of motivation, lack of time,

and lack of support, must be overcome [66] . The benefits of exercise include improved metabolic state with increased insulin sensitivity, cardiovascular fitness, and maintenance of weight loss [67] . Exercise for 30 min/d results in improvements in endothelial function and inflammatory markers [68] . Japanese researchers showed a halving of cardiovascular risk from just 1 h/wk of exercise [69] .

Fewer than 5% of people who attempt diet and exercise

Figure 3. Mechanisms of endothelial dysfunction and formation of atherosclerotic plaques.

modifications to lose weight actually lose a substantial amount of weight and maintain that weight loss [70] . Greater than 90% of people regain their weight within 1 yr. Psychological intervention is often necessary to help patients initiate and maintain behavior change.

Although lifestyle modification is the gold standard for achievement and maintenance of weight loss, dismal long-term success results in many obese individuals turning to fad diets, pharmacotherapy, or surgery to lose weight. These options have not been proven to be safe or successful in children, but many parents, children, and practitioners are so desperate to achieve weight loss that they are willing to try anything.

The two most popular diets are the low-calorie, low-fat diet (hypocaloric diet) and the low-carbohydrate diet [71] . The long-term safety and efficacy of these diets have not been evaluated in children, but studies have shown that the implementation of either of these diets in young children (ages 3–5 yr) results in an increase in **obesity** in the teenage years [72] . In adults, both types of diet result in weight loss, decreased blood pressure, and reduced insulin resistance [73] . The low-carbohydrate diet, however, resulted in greater improvements in high-density lipoprotein and triglyceride levels than the hypocaloric diet. Adults who are obese and insulin sensitive lose more weight on hypocaloric diets, whereas those who are obese and insulin resistant lose more weight on low-carbohydrate diets [74] .

Pharmacologic therapy for **obesity** is an option that is limited to those individuals with serious comorbidities due to **obesity** who have failed lifestyle modification despite intensive effort by the healthcare team. None of the medications currently available for treatment of **obesity** are approved for children. The two most popular available medications are orlistat, an intestinal lipase inhibitor, and sibutramine, a central appetite regulator [75] . Both of these medications result in a 5–10% initial loss of weight in adult patients, with a concomitant decrease in insulin resistance and other cardiovascular risk factors [76] . However, weight is regained upon discontinuation of these medications [77] .

Long-term studies have not been done to evaluate the effects of these medications on mortality and cardiovascular morbidity. Trials using orlistat in the pediatric population are underway.

Other potential pharmacologic therapies for **obesity** include topiramate, peptide YY3–36 (PYY), and metformin. Topiramate is an anticonvulsant that induces weight loss. Although the effects of topiramate on weight loss are promising, the side effects, which include depression and difficulty with memory and concentration, make this medication unlikely to be acceptable for children [78] . PYY is a gut-derived peptide that modulates appetite circuits in the hypothalamus. PYY levels are low in obese individuals, and the administration of this hormone reduces food intake [79] . Pharmacologic manipulation of other gut-derived hormones and peptides related to hunger and satiety is being studied. Metformin (Glucophage; Bristol-Myers Squibb Company, Princeton, NJ) use is associated with weight loss in adults with polycystic ovarian syndrome and type 2 diabetes [80] . This medication is currently being evaluated for efficacy of weight loss in children who are overweight and have features of the metabolic syndrome.

Surgery is the last alternative for patients who have severe obesity-related health problems and have failed lifestyle modification and medication. Gastric bypass, the original surgical procedure for weight loss, resulted in a high rate of complications including nutrient malabsorption and even death [81] . Newer techniques that appear to be safer include gastric banding and vagal nerve stimulators [82] . However, the safety and efficacy of these procedures has not been evaluated over the long term.

Conclusion

The prevalence of **obesity** in childhood continues to increase throughout the world. Currently, **obesity** is the second-leading cause of preventable death, after cigarette smoking. If our children continue to gain weight at the current rates, **obesity** will soon become the leading cause of death in the United States. Although treatment strategies using pharmacologic agents and surgery are being investigated, earlier intervention and prevention strategies are more cost-effective.

Physicians should begin intervention and counseling on appropriate diet and exercise choices and portion sizes during infancy and continue counseling and close monitoring of BMI throughout childhood. Breastfeeding for the first 4–6 months of life should be promoted. Children need to be encouraged to eat nutritious foods and exercise regularly. A recent study done in a school setting, without parental involvement, showed that education of children about nutrition and the adverse effects of sweetened soft drinks on body weight resulted in improved food choices both at home and at school, with subsequent weight loss [83] . This study suggests that public health campaigns targeted at

children may be an effective means of approaching this problem and, if initiated, may herald the beginning of the end of the epidemic of **obesity**.

Since the recognition that the adipose tissue is an endocrine organ, more and more children with **obesity** are being referred to pediatric endocrinologists. With the increasing amount of pediatric **obesity** in the world, this influx of patients could conceivably overwhelm a practice. However, it is appropriate for an endocrinologist to care for children with the comorbidities of **obesity**, such as metabolic syndrome, type 2 diabetes, polycystic ovarian syndrome, and dyslipidemia. The best treatment strategy seems to be a multidisciplinary approach to the problem, involving an endocrinologist along with other subspecialists (such as cardiology, nephrology, and pulmonary), a nutritionist, a psychologist, and an exercise physiologist. Additionally, frequent follow-up of patients with **obesity** is absolutely necessary for success.

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