Predictors of Childhood Obesity and Pathogenesis of Comorbidities

Michael Freemark, MD

The epidemic of childhood obesity has put increasing numbers of young people at risk for serious complications and has placed increasing demands on their health care providers. Among the third of their patients who are now overweight or obese, caregivers must distinguish those with hormonal, genetic, and syndromic (endogenous) obesity from those with exogenous obesity and must use cost-effective laboratory-based tools for detection of obesity-related metabolic and reproductive comorbidities. They are expected to provide dietary and lifestyle counseling to children and their families during abbreviated clinic visits and may be asked to advise community and social groups, school boards, and local governmental councils on issues of nutritional policy.

To assist primary care providers in the evaluation and management of obese children, the next two articles in this issue outline a rational approach to the identification of endogenous obesity disorders and the detection of obesity comorbidities. Additional articles focus on the selection of pediatric candidates for bariatric surgery and the role of the health care provider as a community advocate.

FACTORS THAT PREDISPOSE TO THE DEVELOPMENT OF CHILDHOOD OBESITY

Obesity is a complex disorder with genetic and environmental determinants. Factors that predispose to common exogenous obesity are shown in Table 1.1-9 Some of these factors lie beyond individual control (eg, genetic predisposition, family history, ethnicity), but all can be moderated by the behavior of the child and his/her family and by intervention in the school, community, and social spheres.

PATHOGENESIS OF OBESITY COMORBIDITIES

Like the factors predisposing to the development of obesity, the pathogenesis of comorbidities in overweight and obese children is complex. At least five overlapping processes are involved.

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TABLE 1.
Factors That Predispose to Development of Exogenous Childhood Obesity

1. Genetic predisposition and family history of obesity
2. High-risk ethnicity and lower socioeconomic status
3. Intrauterine growth retardation with rapid postnatal catch-up weight gain
4. Excess maternal weight gain; large for gestational age
5. Intrauterine exposure to gestational diabetes
6. Formula (rather than breast) feeding
7. Dietary indiscretion: excess sugars, starches, and fried foods
8. Sedentary lifestyle

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About the Guest Editor

Michael Freemark, MD, is Robert C. and Veronica Atkins Professor of Pediatrics, Chief of the Division of Pediatric Endocrinology and Diabetes, and Vice Chair for Pediatric Research, Duke University Medical Center.

He received his medical degree from Duke University School of Medicine and completed a residency in pediatrics and a fellowship in Pediatric Endocrinology at Duke. He subsequently undertook research sabbaticals in molecular endocrinology at the Lineberger Cancer Center of the University of North Carolina and at the Faculté de Médecine (INSERM), Hopital Necker, in Paris.

He served as a leader of a Pediatric Endocrine Consensus Committee on pediatric obesity and co-authored the Endocrine Society’s guidelines for evaluation and management of obese children. He is the editor of a textbook on pediatric obesity (Childhood Obesity: Pathogenesis, Complications, and Treatment).

Address correspondence to Michael Freemark, MD via email: michael.freemark@duke.edu
The key determinants of insulin resistance are preferential storage of fat in visceral and abdominal regions and redistribution of fat from white adipose tissue to extra-adipose tissues such as the liver, skeletal muscle, heart, and pancreas (Figure 1). In obese, insulin-resistant patients, the redistribution of fat may reflect white adipose tissue dysfunction: there is decreased free fatty acid uptake, impaired adipogenesis, exaggerated lipolysis, decreased adiponectin and increased leptin expression, and inflammatory cytokine production.1

The accumulation of lipids in extra-adipose tissues is associated with resistance to insulin action and changes in tissue metabolism and function (Figure 2).1,10-16 There are increases in hepatic and renal gluconeogenesis (GNG) causing fasting hyperglycemia; reductions in skeletal muscle glucose uptake causing postprandial hyperglycemia; a paradoxical increase in glucagon secretion, which promotes hepatic GNG and lipolysis; and a reduction in serum osteocalcin, a marker of bone formation and an insulin sensitizer. Resistance to insulin in the brain exacerbates lipolysis and GNG and thereby increases free fatty acid and glucose levels, which may explain the fall in basal and stimulated levels of growth hormone in obese patients.

### Hyperinsulinemia

It should be noted that insulin resistance in obesity is tissue and function selective. Certain tissues become resistant to insulin action, whereas others remain insulin sensitive. Likewise, certain metabolic processes within a given organ may be resistant to insulin action, whereas other processes within the same organ retain sensitivity to insulin. Tissues and processes that remain insulin sensitive in the obese state are responsive to increases in insulin production.

The pancreas responds to insulin resistance with an exaggerated but dysregulated increase in insulin secretion, which protects against overt metabolic decompensation until beta cell failure ensues. In addition to promoting the development of acanthosis, hyperinsulinemia has important metabolic consequences (Figure 2). Although the

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**Figure 1.** White adipose tissue (WAT) dysfunction in obesity, type 2 diabetes (T2D), and polycystic ovary syndrome (PCOS).

**Figure 2.** Roles of insulin resistance and hyperinsulinism in the pathogenesis of obesity-related comorbidities. BP = blood pressure; GH = growth hormone; Glut-4 = glucose transporter 4; GNG = gluconeogenesis; HDL = high-density lipoprotein; SHBG = sex hormone binding globulin; VLDL-TG = very-low-density lipoprotein-triglyceride.
liver is resistant to insulin suppression of hepatic glucose production, the hyperinsulinemia of insulin resistance stimulates hepatic lipogenesis. This promotes liver triglyceride storage (fatty liver), very-low-density lipoprotein production, systemic hypertriglyceridemia, and secondary reductions in high-density lipoprotein.\textsuperscript{12,13,16} Severe hypertriglyceridemia can cause eruptive xanthomas and pancreatitis. Insulin downregulation of hepatic insulin-like growth factor–binding protein-1 expression may increase free insulin-like growth factor-1 levels,\textsuperscript{1} which in theory may underlie the heightened risks of certain malignancies in obese and diabetic patients. Insulin suppression of hepatic sex hormone binding globulin, in combination with upregulation of ovarian thecal androgen production, increases free androgen levels, which may manifest as precocious adrenarche and, in teenagers, polycystic ovary syndrome.\textsuperscript{1} Hyperinsulinemia downregulates secretion of the orexigenic hormone ghrelin,\textsuperscript{1} which may limit further weight gain; however, insulin excess increases renal sodium and water retention, vascular endothelin-1 production, and sympathetic nervous system activity, leading to vasoconstriction and hypertension.\textsuperscript{1,17} Thus, the imposition of hyperinsulinemia on a background of insulin resistance largely explains the clinical phenotype of the metabolic syndrome.\textsuperscript{16-22}

**Chronic Inflammation**

Obesity is accompanied by selective tissue accumulation of macrophages; increases in proinflammatory cytokines such as leptin, interleukin-6, and tumor necrosis factor alpha; and a reduction in the anti-inflammatory cytokine adiponectin. Chronic inflammation may impair cellular function and cause cellular damage; a major example is fatty liver disease, which can progress to steatohepatitis, cirrhosis, and rarely (in children) hepatic failure.\textsuperscript{16}

**Cellular Proliferation**

In the setting of chronic inflammation, an excess of nutrients and enhanced nutrient/insulin/insulin-like growth factor-1 signaling may contribute to the development of malignancies.\textsuperscript{10,23-25} The incidence of a number of cancers (eg, hepatic, pancreatic, colonic, endometrial, breast) is increased in obese adults.

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**Adolescent obesity is associated with thickening of the carotid intimal medial surface, an imperfect marker of future cardiovascular risk.**

The risks are exacerbated by smoking and concurrent type 2 diabetes. Whether childhood obesity predisposes to malignancy is unclear; limited evidence suggests that increases in childhood and adolescent body mass index may be linked to the future development of breast and pancreatic cancer.\textsuperscript{10,25}

**Mass Effects of Excess Fat Deposition**

Accumulation of fat in the liver and heart may contribute to hepatomegaly and cardiomegaly.\textsuperscript{15} Accumulation of fat in the neck, palate, and tonsillar/adenoïd regions predisposes to obstructive sleep apnea, which manifests as excessive snoring, restless sleep, and daytime fatigue. The development of pseudotumor cerebri in obese (particularly female) patients may be related to heightened abdominal venous and intrathoracic pressure.\textsuperscript{18} Excess weight gain for any reason places severe stress on the bones and joints and can cause orthopedic problems, including Blount’s disease.

**PERSISTENCE OF CHILDHOOD OBESITY INTO ADULTHOOD AND RISKS FOR CARDIOVASCULAR AND RENAL DISEASE**

Major causes of death in obese adults include myocardial infarction, stroke, and chronic renal failure. These can be ascribed, at least in part, to obesity-related dyslipidemia, hypertension, and type 2 diabetes. Obese children who remain obese as adults are also at risk for cardiovascular and renal disease.\textsuperscript{1,10,15,17,19-22} Whether childhood obesity predisposes to long-term vascular and renal complications is currently unresolved; however, the Pathobiological Determinants of Atherosclerosis in Youth and Bogalusa Heart studies showed that obesity acts in synergy with hypertension, hyperlipidemia, and glucose intolerance to accelerate the development of atherosclerotic streaks and plaques in the coronary and carotid arteries in adolescents and young adults. Likewise, the Muscatine and Young Finns studies found that adolescent obesity is associated with thickening of the carotid intimal medial surface, an imperfect marker of future cardiovascular risk.\textsuperscript{1,10,19-22}

**DIETARY MACRONUTRIENTS AND THE DEVELOPMENT OF OBESITY AND ITS COMPLICATIONS**

Longitudinal prospective studies suggest that low-fiber diets that are high in energy density, fat, and sugar-sweetened beverages are associated with adiposity in childhood and adolescence.\textsuperscript{23,27} High fructose intake may in some cases be associated with insulin resistance, fatty liver, mild hypertriglyceridemia, and reduced levels of high-density lipoprotein.\textsuperscript{28} The deleterious effects of sugar beverages may be more evident in teenage girls.
than boys. Nevertheless, it seems prudent to recommend reductions in sugary drinks and fried foods in all overweight and obese children and to limit intake of packaged snacks, processed meats, and high-density white starches.

CONCLUDING REMARKS

With increasing awareness in the medical profession and the public, a concerted effort is now underway to reduce the prevalence of childhood obesity and to prevent its complications. The author hopes that this mini-compendium will prove useful to primary care providers faced with the challenges of coping with and managing the obesity crisis.

REFERENCES


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