Published in final edited form as:

Pediatr Clin North Am. 2011 October ; 58(5): 1217–xi. doi:10.1016/j.pcl.2011.07.004.

Pediatric Obesity: Etiology and Treatment[^]

Melissa K. Crocker, MBA, MD and Jack A. Yanovski, MD, PhD^{*}

In the United States, the prevalence of pediatric overweight, defined by the Centers for Disease Control as a body mass index (BMI) ≥ 95 th percentile for age and sex, has more than tripled during the past 4 decades.^{1–3} Of children and adolescents, 16.3% are now obese, and an additional 15.6% are classified as overweight (BMI in the 85th–95th percentile).³ Of all children, 11.3% have a BMI that exceeds the 97th percentile for age and sex,³ a degree of excess weight that some believe may be a reasonable cut-point for pediatric obesity.⁴ Some racial and ethnic minority populations, especially African American, Hispanic, and American Indian groups, are at particular risk for the development of overweight and obesity.³ The increase in obesity prevalence among children is particularly alarming because obesity-related diseases rarely seen in children in the past, including obesity-associated sleep apnea,⁵ non-alcoholic fatty liver disease⁶ with resultant cirrhosis,⁷ and type 2 diabetes,^{8,9} are increasingly diagnosed in pediatric patients. The earlier onset of chronic health conditions such as type 2 diabetes in childhood has been shown to lead to an earlier onset of related medical complications such as end-stage renal disease.¹⁰ Pediatric obesity has been shown to have a tremendous impact on later health,¹¹ even independent of adult weight.¹² In the absence of effective strategies to prevent and treat childhood obesity, millions of children will enter adulthood with the physical and psychologic consequences of excess adiposity. The current childhood obesity epidemic in the United States also has the potential to reverse the improvements in life expectancy that have been seen during the twentieth century¹³ and to result in more functional disability and decreased quality of life for those who survive to old age.¹⁴ This article reviews factors that contribute to excessive weight gain in children and outlines current knowledge regarding approaches for treating pediatric obesity.

ETIOLOGY

Obesity is a genetic disease, because all available data suggest that 60% to 80% of the observed variance in human body weight can be accounted for by inherited factors.¹⁵ Obesity is also just as clearly an environmentally caused disorder; our genetic endowments have changed minimally during the last 40 years, yet the prevalence of abnormally high BMI in US children has tripled, an observation that can only be explained by changes in external factors affecting children's energy economy (Fig. 1). Some theorists hypothesize that in the past it was evolutionarily advantageous for proto-humans to have to the capacity to consume energy in excess of the quantity now needed to maintain normal body composition. One version of this theory proposes that overeating enough to store calories in adipose tissue would augment the human's ability to survive periods of relative starvation. Another version makes the assumption that normal daily human energy expenditure was frequently significantly greater than commonly found today, such that most humans had body weight below that considered ideal in terms of reproductive fitness. All versions of this hypothesis lead to an expectation that natural selection would favor polymorphisms in perhaps many genes that would predispose children and adults to overeat whenever excessive energy was available. More than 300 genetic loci that are potentially involved in

[^]Portions of this article were previously published in the *Endocrinology and Metabolism Clinics of North America*, 38:3.

^{*}Corresponding author: jy15i@nih.gov.

human body weight regulation have been identified through analyses in humans, rodents, and *Caenorhabditis elegans*.^{16, 17} Some exceedingly rare gene variants affect gene function and behavior to such an extent that obesity results even without a particularly “obesogenic” environment (Fig. 2), but the vast majority of genetic factors are presumed to affect body weight enough to cause obesity only when specific environmental conditions pertain. Factors known to influence body weight are described in the following sections.

Classical Endocrine Disorders Associated with Weight Gain

Children with identifiable endocrinopathies are believed to comprise only a small minority of children referred for the evaluation of overweight, ranging from 2% to 3%¹⁸; however, because treatment of these conditions generally resolves obesity, they are frequently considered.

Hypothyroidism

Hypothyroidism is associated with modest weight gain and may cause a BMI increase in children of approximately 1 to 2 BMI units (ie, only a few kilograms).¹⁹ Hypothyroidism leads to increased permeability of capillary walls,²⁰ which creates extravascular leakage and retention of water²¹ causing excess weight gain; consequently, most of the weight gained in patients who have hypothyroidism appears to be fluid rather than triglyceride. Resting energy expenditure may also decrease, potentially biasing energy balance toward storage of ingested calories.²² Because children with hypothyroidism usually have diminished linear growth, their BMI may be high even though weight does not exceed the 95th percentile.²³ Any overweight child with a diminution of linear growth should be evaluated for the possibility of hypothyroidism with measurement of both serum thyroid-stimulating hormone and free T4 concentrations. Few data are available regarding the weight response in children treated for hypothyroidism, but the accelerated linear growth during treatment of these children appears to lead to a reduction in BMI.²⁴

Growth hormone deficiency

In obese children who have no true endocrinopathy, the 24-hour secretion of growth hormone (GH), the GH peak during the night,²⁵ and the GH response to various pharmacologic stimuli are invariably diminished.^{26–29} Interpretation of the results of provocative testing in obese children may be difficult. Growth velocity is either normal or supranormal, and the concentration of insulin-like growth factor 1 (IGF-1) is generally normal or only modestly decreased in obesity,^{30,31} whereas both growth velocity and IGF-1 are diminished in true GH deficiency. Diminished linear growth that is accompanied by continued increase in body weight should lead to consideration of GH deficiency.

In addition to its ability to stimulate protein synthesis and increase fat-free mass, GH also stimulates adipocyte lipolysis.³² GH deficiency leads to increased fat mass, especially in a central distribution, along with decreased lean mass. Adults with GH deficiency are more likely to develop metabolic syndrome.³³ In GH-deficient children, improvements in body composition can be detected as early as 6 weeks after the initiation of GH therapy.³⁴

Cushing syndrome

Cushing syndrome in adults causes central obesity, although the weight gain may be more generalized in children. The excess glucocorticoid production leads to increased gluconeogenesis, insulin resistance, inhibition of lipolysis,³⁵ and stimulation of lipogenesis.³⁶ The prevalence of Cushing syndrome in children is low; only one child in every million is diagnosed with endogenous hypercortisolism. Obesity due to hypercortisolism is associated with markedly diminished height velocity.^{37,38}

Insulinoma

Insulinomas are even rarer in children, with an incidence rate of 4 cases per 5 million population per year; fewer than 10% occur before 20 years of age. Elevated insulin production leads to increased food intake to counter lower blood sugars and leads to obesity.^{39,40}

Structural Disorders of the Hypothalamus Associated with Weight Gain

Hypothalamic obesity may arise after injury to, or congenital malformation of, the hypothalamus. The ventromedial hypothalamic nucleus, arcuate nucleus, paraventricular nucleus, dorsomedial nucleus, and the lateral hypothalamic area are all involved in control of appetite and energy expenditure. These areas produce several neuropeptides involved in appetite regulation, including orexigenic peptides such as neuropeptide Y and anorexigenic peptides such as the melanocortins (see Fig. 2).⁴¹ Injury or malformation may also affect binding of peripheral intake-related signals, including cholecystokinin, glucagon-like peptide, ghrelin, insulin, and leptin. These peptides cross the blood-brain barrier and bind to their receptors in the hypothalamus to regulate appetite. Loss of function of the hypothalamic developmental factor Sim1 leads to obesity in mice. Chromosomal deletions inactivating one copy of Sim1 have also been found to be associated with obesity in humans,⁴² although point mutations in Sim1 associated with obesity are not common.⁴³ Many congenital disorders associated with hypothalamic neuroanatomical disruption are associated with obesity. Obesity occurs in approximately 50% of children treated surgically for craniopharyngioma.^{33,44,45}

Leptin Signaling Pathway Genes

One of the major advances in obesity science over the last 15 years has been elucidation of the leptin signaling pathway (see Fig. 2). Inactivating mutations affecting these genes may account for as much as 3% or 4% of severe, early-onset obesity.

Leptin

Leptin is produced by adipose tissues and binds to leptin receptors in the arcuate nucleus and elsewhere in the brain. Leptin concentrations rise with increasing fat mass; individuals with low fat mass, such as those with lipodystrophy syndromes and anorexia nervosa, have low circulating leptin concentrations.^{46–49} Fasting acutely lowers leptin, and absence of sufficient leptin is a potent signal that stimulates food seeking and consummatory behaviors and promotes reduced energy use. Restoration of normal leptin concentration leads to reductions in food intake^{50,51} and changes in activation of brain regions involved in appetitive control.⁵² Inactivating mutations affecting both alleles of the leptin gene result in excessive food intake and severe, early-onset obesity in the context of very low (<5 ng/mL) serum leptin concentrations.^{53,54} These features are successfully reversed with leptin therapy.⁵⁰ Heterozygous leptin deficiency may present with no findings other than somewhat lower leptin concentrations out of proportion to fat mass.⁵⁵ Individuals with inactivating mutations of both alleles of the leptin receptor gene may also have central hypothyroidism and excess cortisol along with delay in sexual development⁵⁶; heterozygotes appear to have a normal phenotype.⁵⁷ Leptin receptor mutations were first described in the context of markedly supraphysiologic serum leptin; however, more recent studies suggest substantial overlap in serum leptin among those with and without function-altering leptin receptor mutations.⁵⁸ Leptin concentrations have not been successfully used to identify patients bearing leptin receptor abnormalities.

Pro-opiomelanocortin

In some leptin-responsive hypothalamic neurons, leptin stimulates the production of pro-opiomelanocortin (POMC), which is the precursor for corticotropin (ACTH), alpha, beta, and gamma melanocyte-stimulating hormone (MSH), beta-lipoprotein, and beta-endorphin. Alpha-MSH binds to the melanocortin receptors MC3R and MC4R in the arcuate nucleus to regulate appetite and energy expenditure. A handful of patients have been described who have inactivating mutations of POMC that prevent its cleavage into alpha-MSH or ACTH. Such patients have hyperphagia (presumed secondary to absent signaling at MC3R and MC4R), red hair (lack of peripheral alpha-MSH to bind at melanocortin 1 receptors), and adrenal insufficiency (insufficient ACTH to bind at adrenal melanocortin 2 receptors).^{59–64}

Pro-opiomelanocortin processing

Mutations in prohormone convertase 1 (PC1), an enzyme that cleaves POMC, have also been found in a few pediatric patients. PC1 is involved in the processing of numerous hormones. PC1 deficiency presents not only with obesity and ACTH deficiency but also with postprandial hypoglycemia (insufficient cleavage of pro-insulin), hypogonadotropic hypogonadism, and small bowel malabsorption.^{65–67}

Melanocortin receptors

Alpha-MSH exerts its effects on weight regulation by binding to MC3R and MC4R.⁶⁸ MC3R appears to act by affecting feeding efficiency,^{69–71} whereas MC4R seems mostly involved in appetite regulation in mouse models. In humans, heterozygous and homozygous MC4R mutations cause obesity, hyperphagia, hyperinsulinism, and increased linear growth during childhood.⁷² MC4R inactivating mutations are the most common known cause of severe, early-onset obesity; in some series, as many as 3% of patients may have heterozygous or homozygous inactivating MC4R mutations.⁷³ Recent data suggest that MC4R is important not only for body weight but also for blood pressure regulation via effects on the sympathetic nervous system.⁷⁴ Some data also support a role for polymorphisms in the MC3R for regulation of body weight, particularly in African American children.⁷⁵

Brain-derived neurotrophic factor

Brain-derived neurotrophic factor (BDNF) is believed to function downstream from MC4R in the leptin signaling pathway. In mice, haploinsufficiency for BDNF or its receptor TrkB leads to obesity. Haploinsufficiency for BDNF has been suggested to be the cause of pediatric-onset obesity in patients with WAGR syndrome (Wilms' tumor, aniridia, genitourinary malformations, and mental retardation), which results from heterozygous contiguous 11p gene deletions.⁷⁶ In one recent case series, 100% of patients with WAGR syndrome whose deletions included BDNF were obese by age 10 years; serum BDNF concentrations in such patients were found to be reduced by 50% when compared with serum BDNF in patients with WAGR syndrome retaining two copies of the BDNF gene. A heterozygous inactivating mutation in the gene coding for the BDNF receptor TrkB has also been found in a single patient with obesity, seizures, and developmental delay.⁷⁷

Albright's hereditary osteodystrophy

Albright's hereditary osteodystrophy describes a phenotype of short stature and obesity found in pseudohypoparathyroidism 1a (PHP1a) and in pseudopseudohypoparathyroidism (PPHP), both of which are the result of inactivating defects in the Gs alpha protein complex. PHP1a is the result of maternally derived mutations, whereas PPHP is caused by paternally derived gene abnormalities. PHP1a is also associated with endocrinopathies resulting from insufficient signal transduction through the Gs alpha subunit in tissues where expression of Gs alpha is affected by paternal imprinting. PPHP does not have such associated endocrine

disorders but presents with the Albright's hereditary osteodystrophy phenotype, although the obesity is less severe.⁷⁸ The etiology of the obesity in PHP1a may be related, in part, to diminished signaling via the Gs alpha subunit in the many Gs alpha-coupled receptors found in the leptin pathway.⁷⁹

Common Allelic Variation in Genes that May Affect Energy Balance

Single nucleotide polymorphisms (SNPs) of many genes and chromosomal regions have been found to be associated with body weight or body composition.^{80–82} The mechanisms explaining how such SNPs might change energy balance are often not fully understood. Even in studies including thousands of genotyped people, such SNPs can be linked to body weight only when they are relatively common in the population.

Fat mass and obesity associated gene locus

Recent genome-wide association studies have found that common SNPs in the fat mass and obesity associated (FTO) gene locus are consistently associated with higher BMI and adiposity in children and adults.^{83–87} Rodent studies indicate that FTO mRNA is highly expressed in brain areas important for regulation of energy- and reward-driven consumption.⁸⁸ Food deprivation alters FTO expression in the hypothalamus in rats and mice.^{88–90} When compared with children with the more common FTO T allele at rs9939609, children with two copies of the A allele variant have greater BMI and fat mass. Some limited data also suggest such children may have greater food intake^{91,92} and reduced satiety⁹³ but show no differences in energy expenditure.⁹¹

Peroxisome proliferator-activated receptors

Peroxisome proliferator-activated receptors (PPAR- α) help regulate metabolism and storage of fat and are involved in differentiation of adipocytes from precursors. A rare gain-of-function mutation is associated with extreme obesity.⁹⁴ Heterozygous Pro12Ala substitution is associated with a differential response to dietary fats; a high saturated fat intake compared with polyunsaturated fats leads to higher fasting insulin levels in patients with this allelic variation.⁹⁵

Beta adrenergic receptor

Activation of the beta-2 adrenergic receptor stimulates lipolysis in adipocytes. Polymorphisms rs1042713 (Arg16) and rs1042714 (Glu27) have shown associations with obesity, although the data show some inconsistencies among studies. A recent meta-analysis described increased risk for obesity among Asians, Pacific Islanders, and American Indians with the Glu27 variation. No other populations reached statistical significance for obesity risk factors with either of these polymorphisms.⁹⁶

Perilipin

Perilipin proteins protect lipid droplets in adipocytes from unregulated lipolysis. Studies of the perilipin A gene have suggested that carriers of some perilipin SNPs may be more resistant to weight loss when compared with controls.⁹⁷

Syndromic Obesity

Multiple genetic syndromes involve obesity as part of their presentation, although patients with these syndromes usually come to medical attention for reasons other than obesity. Even when grouped together, these etiologies (Box 1) account for only a small percentage of overweight children. All of these syndromes involve multiple other medical problems or dysmorphic features. The root of obesity in these disorders is often poorly understood. Particularly notable for hyperphagia are the Prader-Willi, Bardet-Biedl, and Alström

syndromes. Patients with Prader-Willi syndrome display high circulating concentrations of ghrelin,⁹⁸ a factor that is primarily stomach-derived and is a peripheral orexigen, at least in short-term studies in humans.⁹⁹ The role of hyperghrelinemia in the obesity of Prader-Willi syndrome remains in dispute. The Bardet-Biedl and Alström syndromes appear to be associated with disruption of ciliary function. Cilia have been demonstrated to be necessary for body weight regulation in mice, in which inducible disruption of primary cilia by inactivating the ciliogenic genes *Tg737* and *Kif3a* specifically in POMC-expressing neurons leads to hyperphagia and obesity.¹⁰⁰ Some recent data also suggest that the proteins affected by several of the Bardet-Biedl syndromes may interact with the leptin receptor and alter its trafficking.¹⁰¹

Acquired Obesity

Medications associated with weight gain—Multiple medications may lead to weight gain. Iatrogenic obesity can result from administration of insulin or insulin secretagogues, glucocorticoids, psychotropic drugs including antipsychotics such as olanzapine and clozapine, mood stabilizers such as lithium, antidepressants including the tricyclics, anticonvulsants such as valproate and carbamazepine, antihypertensives including propranolol, nifedipine, and clonidine, antihistamines, and chemotherapeutic agents.¹⁰²

AD36: the “obesity virus”—An avian form of adenovirus has been found to cause increased adiposity in infected chickens, both from spontaneous infection and inoculation.¹⁰³ After the publication of that observation, the consequence of infection with human adenovirus strain AD36 on body weight was studied in rhesus monkeys, marmosets,¹⁰⁴ chickens, and mice.¹⁰⁵ All species showed increased adipose tissue but paradoxically decreased serum cholesterol in those infected with the virus. In vitro studies of human adiposederived stem/stromal cells infected with AD36 demonstrate increased accumulation of lipids and induction of pre-adipocytes to become lipid-accumulating adipocytes.¹⁰⁶ Prevalence studies suggest that humans with antibodies to AD36 (indicating past infection) also tend to have higher rates of obesity and lower serum cholesterol and triglycerides¹⁰⁷; twin pair studies have also demonstrated associations between seropositivity for AD36 and higher BMI and body fat.¹⁰⁸ Such evidence suggests this virus may potentially have a role in acquired obesity.

Environment and behavior—As outlined in Fig. 1, the sociocultural environment has a major role in determining who becomes obese. This observation is demonstrated by comparing human samples that share the same genetic background but are raised in different cultures. Arizona Pima Indians who live on a reservation have much higher rates of obesity and diabetes than their counterparts in an isolated Mexican village,¹⁰⁹ and Asian and Hispanic adolescents born in the United States have a higher prevalence of obesity than immigrant members of the same community.¹¹⁰ A full discussion of social and environmental factors is beyond the scope of this article but has been elegantly summarized elsewhere.^{111,112}

Epigenetics—The differential response of some people to environmental conditions may be the result of genetic variation alone, but there is increasing recognition that genetic expression related to disease risk may be modified by the environment during development. These so-called “epigenetic changes” include methylation and alterations to histone proteins that alter the likelihood that specific genes are transcribed. Epigenetic changes usually occur during prenatal development or the early postnatal period. Strong evidence suggests that maternal nutrition is a key factor leading to epigenetic changes. Maternal nutrition includes levels of vitamins consumed in pregnancy, such as folate, methionine, and vitamin B¹², which affect methylation.¹¹³ Undernutrition during prenatal development has been

suggested to lead to postnatal consumption of a fatty diet.¹¹⁴ The most convincingly shown factor is glycemic status during pregnancy. Hyperglycemia clearly affects infants' birth weight but, beyond its effects on body weight, may increase the risk for subsequent development of insulin resistance and obesity. Nutritional signals reaching the developing hypothalamus during pregnancy may influence the sensitivity of these neurons to respond to similar signals postnatally.¹¹³ Infant nutrition in the neonatal period may also potentially affect future risk for obesity and its complications. Although some studies have shown protection against obesity after extended breastfeeding, others have not confirmed these findings.¹¹³

Evaluation—Most genetic and hormonal causes of obesity are rare. The decision to test for these abnormalities should depend upon the presence of clinical features suggesting the possibility of a diagnosable disorder. Fig. 3 provides an algorithm for this evaluation.

THERAPY

Indications

The Maternal and Child Health Bureau of the Department of Health and Human Services recommended in 1998 that children aged 7 years and older with a BMI greater than the 95th percentile for age should be offered obesity interventions.¹¹⁵ For adolescents, a cut-off BMI of 30 kg/m² should be used when the 95th percentile standard is above 30 kg/m².¹¹⁶ Some practitioners refer to these patients as obese, whereas others avoid the terminology in pediatrics given the associated stigma and instead describe these patients as “at risk for obesity” or “overweight.” “Overweight” is the word choice that children with a BMI _95th percentile greatly prefer.¹¹⁷ Consensus statements from the American Academy of Pediatrics as well as from the Endocrine Society recommend use of the term obesity to denote elevated adipose tissue.^{116,118} Some suggest a BMI above the 99th percentile should be called severe obesity.¹¹⁶ Regardless of the title, the prevalence of comorbidities rises as BMI increases, such that half of those persons with a BMI exceeding the 99th percentile meet criteria for the metabolic syndrome.¹¹⁹ Those with a BMI in the 85th to 95th percentiles, referred to as overweight in both sets of guidelines^{116,118} and by the Centers for Disease Control, should also be considered for dietary counseling if they have overfatness but should probably not be involved with medical or surgical treatments unless they already sustain medical complications secondary to obesity. The American Academy of Pediatrics expert panel has recommended assessing risk factors for these patients, including family history, trends in the patient's weight gain, their fitness level, and the distribution of adipose tissue versus lean mass to determine the need for intervention.¹¹⁶ Additionally, the American Academy of Pediatrics expert panel, noting that younger patients have the benefit of significant future vertical growth, has suggested such growth can compensate for weight already gained; therefore, the goal for young patients (particularly those aged <5 years) is weight maintenance to allow the height to attain the same percentile as the weight. Nevertheless, there are few data demonstrating that approaches aiming for weight maintenance, rather than weight reduction, are successful in reducing adiposity. For older children, weight loss is needed, because for most height gain alone will not correct the obesity; for these children, a goal of 0.5 to 1 kg loss per month is appropriate, although adolescents may tolerate 1 to 2 kg of weight loss per month.¹¹⁶ Interventions for obesity in pediatric patients range from basic diets and lifestyle interventions to more intensive very low energy diets, medications, and surgery. Each of these methods has varying levels of success, both short and long term, as well as side effects that must be considered. None of these interventions will be successful if the patient and family lack motivation and education. The participation and cooperation of the entire family is critical regardless of the mode of therapy employed.

Diets

Several dietary approaches are available, including low fat, low carbohydrate, low calorie, Mediterranean (based on diets of that region which are high in olive oil and nuts), and others. Despite many studies in adults comparing and contrasting these diets, few have been performed on adolescents and fewer still in younger children. A meta-analysis through February 2006 has examined trials using diet alone as a weight loss intervention in pediatrics. Six such articles were found using a comprehensive literature review, including studies that employed a reduced glycemic load diet, a protein-sparing modified diet, a low carbohydrate diet, a high protein diet, and a hypocaloric diet. Overall pooled benefit showed an effect size of only 0.22 points in the treatment arms.¹²⁰ Although dietary therapy in the context of behavioral management is recommended for all obese children because some children experience long-lasting weight reductions and do not require other therapy,¹²¹ diets by themselves are considered relatively ineffective for those with severe obesity. Very low energy diets are based on restricting energy intake to 600 to 800 kilocalories per day. In the past, these diets were frequently liquid based but may be food based and are usually designed to be “protein-sparing modified fasts” intended to maximize fat loss while minimizing loss of lean body mass. These diets are reviewed in detail elsewhere.¹²² To avoid nutritional deficiencies, such diets must contain 1.5 to 2.5 g of high quality protein per kilogram of ideal body weight. Typically, such diets limit carbohydrates to 20 to 40 g per day. A multivitamin should be included in the daily regimen given the lack of sources for many critical elements. A total of 1500 mL of free water is also recommended to avoid dehydration. These diets are rapid in their weight loss among teens (up to 11 kg in 10 weeks has been noted); most published data limit the length of the diet to 12 weeks. These diets are generally prescribed only in patients who need to lose substantial amounts of weight (ie, adolescents usually above the 99th percentile for body weight). Risks associated with the rapid weight loss include cholelithiasis, hyperuricemia, decreased serum proteins, orthostatic hypotension, halitosis, and diarrhea.¹²² Unfortunately, the short-term improvement in weight is often reversed in the long term when regular dietary habits are resumed.¹²³ Most clinicians refrain from using such diets in children unless rapid weight loss is needed for medical purposes.

Exercise

Most recommendations for weight loss rarely endorse exercise without additional dietary intervention. A few pediatric studies have analyzed weight loss from exercise alone. A meta-analysis examining 17 of these trials in pediatric patients demonstrated inconsistent results across studies. Studies that considered adiposity as the outcome found a moderate decrease in the treatment arm, but those using BMI as the outcome saw little or no effect. When the effect of a combination of exercise and diet was analyzed among 23 trials, there was a small-to-moderate effect of intervention. The largest change in weight was found in the trials that involved parents in the therapy. Although not statistically significant, there was a trend toward improved outcomes in younger children, primarily those aged 8 years or less.¹²⁰

Behavior Modification

Behavior modification as an approach to weight loss may include encouragement to reduce screen time and increase physical activity, psychologic training to motivate a change in eating behaviors or exercise, family counseling to support weight loss goals, and school-based changes to promote physical activity and healthy eating. Often, these interventions involve frequent meetings with a counselor individually or in group sessions. Studies employing these techniques have recently been reviewed elsewhere.¹²⁴ A Cochrane review¹²⁵ compared four studies of children aged less than 12 years and three studies of adolescents enrolled in behavioral intervention versus conventional treatment.

Among the children under 12 years, there was a 0.06 point change in BMI standard deviation score (SDS) in the parent-focused behavioral interventions. Among the older patients, a 0.14 point decrease in BMI SDS and a 3.04 point decrease in BMI were seen with behavioral therapy.¹²⁵ A meta-analysis of 14 studies using behavioral interventions compared with no intervention or standard weight loss counseling interventions found significant but small effect sizes ranging from 0.48 to 0.91.¹²⁶ Although short-term success has primarily been the endpoint of behavior modification, one group has shown long-term improvement in weight control over 10-year periods when the family was also involved in counseling and behavior changes.^{121,127,128} Some data support better maintenance of weight loss using continued behavioral management strategies.¹²⁹ Schools settings may serve as outlets for implementing behavior modification programs. One study of increased exercise during an after school program, which also served healthy snacks, showed a decrease in body fat throughout the school year but negative progress during the summer.¹³⁰ Another study provided education on nutrition and healthy behaviors during school along with physical activity sessions; results demonstrated decreases in obesity rates over several years, although only in females.¹³¹

Recommendations on Combined Treatment Approaches

The American Academy of Pediatrics recommends a four-step approach to obesity treatment, the first three of which are dietary and lifestyle interventions of escalating intensity.¹¹⁶ If there is insufficient progress after 3 to 6 months, the guidelines recommend advancing to each successive stage and, finally, to referral to obesity management experts for specialized interventions such as medication or surgery.¹¹⁶

Medications

Although several forms of medications to treat obesity are on the market, only one is approved for children aged less than 16 years. Success has been limited with these medications, which usually only show promise in combination with exercise and dietary interventions. The Endocrine Society has suggested limiting pharmacotherapy to patients with a BMI over the 95th percentile who have failed diet and lifestyle intervention, or in limited cases with a BMI over the 85th percentile and severe comorbidities.¹¹⁸ Others have suggested, given the limited efficacy of medications, that only pediatric-aged patients with a BMI over the 95th percentile who also have significant medical complications of their obesity should be exposed to the risks of obesity pharmacotherapy.¹³²

Anorexigenic agents

A major class of medications used in weight treatment is appetite suppressants. Currently available agents affect the neurotransmitters norepinephrine, dopamine, and serotonin in the brain to regulate appetite.¹³³ In 1997, the appetite suppressant sibutramine was approved by the US Food and Drug Administration (FDA) for longterm use in adults. Sibutramine was removed from use in 2010, when a greater incidence of cardiovascular events were found among adults who took the drug. Sibutramine inhibited reuptake of all three of these anorexigenic neurotransmitters. The increased levels of these hypothalamic neurotransmitters promote satiety and decrease hunger.¹³⁴ Side effects included hypertension, tachycardia, premature ventricular contractions, prolonged QTc, insomnia, dizziness, dry mouth, cholelithiasis, and constipation.^{122,134} Four randomized controlled trials examined the effect of sibutramine on weight in adolescents and on average found 7.7 kg of weight loss in the short term.¹³⁴ A meta-analysis of three of these trials showed a change in BMI by 2.4 units after 6 months of medication treatment.¹²⁰ The largest sibutramine trial enrolled 498 patients aged 12 to 16 years with a BMI 2 points above the 95th percentile for age and randomized them to sibutramine or placebo. After 12 months of therapy, 24% of the treatment group and 38% of the placebo group had left the study. Of

those remaining, the sibutramine group had a decrease in BMI by 2.9 units more than the control arm; however, they also had a statistically significant increase in tachycardia.¹³⁵ There were no published reports of sibutramine treatment for adolescent obesity that have lasted longer than 1 year.¹²² Another trial has examined the use of sibutramine in patients with syndromes or conditions that made behavioral interventions difficult. Of the 50 patients, 22 had hypothalamic obesity from central nervous system damage, Bardet-Biedl syndrome, MC4R mutations, or Prader-Willi syndrome. The other 28 patients had mental retardation, autism spectrum disorder, attention deficit hyperactivity disorder, or a myelomeningocele. During a cross-over period during which each group received sibutramine for 20 weeks and placebo for 20 weeks, the overall loss of BMI SDS was 0.7 units on sibutramine; however, the hypothalamic obesity group only lost 0.3 to 0.4 BMI SD units, whereas the remaining patients lost closer to 0.9 to 1 BMI SD units.¹³⁶

Other neurotransmitter regulators that are marketed for weight loss include phentermine, chlorphentermine, mazindol, and diethylpropion, all of which have shown shortterm weight loss of 2 to 5 kg in excess of placebo over 1 to 3 months in adults. There are no long-term follow-up data in pediatric samples for these medications. Ephedrine in combination with caffeine induced significant weight loss but was banned by the FDA after reported deaths from hypertensive crises and arrhythmias. Fenfluramine was also withdrawn after valvulopathies developed due to what appears to have been a serotonin excess syndrome.¹³⁷ Another appetite suppressant, rimonabant, which has never been FDA-approved in the United States and was recently withdrawn in Europe, works as an inhibitor of the central nervous system cannabinoid type 1 receptor, leading to decreased appetite; rimonabant probably also acts peripherally to increase thermogenesis.¹³⁸ No randomized controlled trials have been published in adolescents. In adults, side effects included anxiety, depression, insomnia, dizziness, nausea, and vomiting.

Gastrointestinal lipase inhibition

Blocking the absorption of fat from the gastrointestinal tract provides another medical approach to weight loss. Orlistat, an inhibitor of gastrointestinal lipases, prevents the breakdown of triglycerides into absorbable fatty acids and monoglycerols. When orlistat 120 mg capsules are taken three times a day with meals, approximately one third of dietary triglycerides are excreted intact rather than absorbed. Side effects of this medication include oily stools, flatulence, and uncontrolled leakage of oil from the rectum. In addition, gallbladder disease has been seen in greater frequency in trials of orlistat when compared with a control group. Diminished fat absorption also limits absorption of the fat-soluble vitamins A, D, E, and K; therefore, a multivitamin should be part of the diet regimen, with consumption of the vitamin more than 2 hours apart from administration of orlistat. Additionally, because orlistat must be consumed at each meal, pediatric patients will require therapy during school hours, which adds logistical complications to the regimen.¹¹⁸ An analysis of three randomized control trials in adolescents found a net loss of 0.7 units in the BMI but with increased rates of abdominal pain and discomfort as well as oily stools when compared with placebo.¹²⁰ The largest adolescent orlistat study¹³⁹ enrolled 539 patients aged 12 to 16 years who were randomized to placebo or orlistat. After 1 year of therapy, approximately 35% of participants had dropped out. The BMI in the orlistat group fell by 0.55 and rose by 0.31 kg/m² in the placebo group, leading to a small but significant difference in BMI. Although adult patients have experienced improvement in glucose and insulin levels while taking orlistat, no similar effects have been observed in the pediatric studies conducted to date.¹³⁴

Therapies altering insulin secretion or insulin resistance

Another medical approach to weight control involves metformin, which inhibits hepatic gluconeogenesis, diminishes insulin resistance and hyperinsulinemia, and may decrease lipogenesis in adipose tissues.¹³⁴ Currently, metformin is approved for treatment of type 2 diabetes mellitus in patients aged 10 years and older. Several randomized controlled trials have evaluated metformin as an obesity medication in adolescents, including one trial lasting 48 weeks¹⁴⁰ and one in children 6–12y.¹⁴¹ An average loss of 3.15 kg was noted by one investigator,¹³⁴ although another metaanalysis described the pooled results as “a small nonsignificant change in obesity outcome at 6 months.”¹²⁰ Additionally, a randomized controlled trial of 39 patients (of whom 30 completed the study) aged 10 to 17 years taking atypical antipsychotics showed a decrease of 0.13 kg and 0.43 BMI points in the metformin arm compared with a weight gain of 4.01 kg and BMI gain of 1.12 points in the placebo arm after 16 weeks of intervention.¹⁴² Improvements in steatohepatitis have also been noted.¹²² All studies thus far are 1 year or shorter; therefore, the degree of long-term improvement in body weight or its complications is unknown. Patients treated with metformin report abdominal discomfort, which improves when the medication is taken with food. There is also a risk of vitamin B¹² deficiency; therefore, a multivitamin is recommended.¹²² There is a risk of lactic acidosis, which has been observed in adults but not seen in pediatric patients thus far.¹³⁴ Metformin is contraindicated in heart, kidney, and liver disease; however, because the clearance is renal, patients with liver function tests less than three times the upper limit of normal are considered appropriate to take the medication.

Octreotide has been investigated as a treatment for hypothalamic obesity. This somatostatin analogue binds receptors on the beta cells of the pancreas and inhibits insulin release. A randomized controlled trial comparing octreotide with placebo demonstrated reduced weight gain among those treated with octreotide given subcutaneously three times per day. Over 6 months, the placebo group experienced an average weight gain of 9.2 kg and a BMI change by 2.2 points, whereas the treatment group gained 1.6 kg and decreased their BMI by 0.2.¹⁴³ Because of its mode of action, octreotide use is associated with significant risks for cholelithiasis and abnormalities of glucose homeostasis.

Leptin

Leptin poses another possibility for obesity treatment. Thus far, clinical trials in obese subjects without leptin deficiency have shown only small effects on weight loss. Leptin must be delivered as frequent subcutaneous injections given its short half-life, and patients in these studies experienced painful injection site reactions, especially in the larger dosages needed to alter body weight.¹⁴⁴ Among those rare individuals with true leptin deficiency, leptin is effective at reducing BMI and fat mass over the long term.^{50,145}

Bariatric Surgery

Bariatric surgery is by far the most definitive and longest lasting form of weight loss treatment. In adults, surgical intervention leads to significant weight loss and improvement or resolution of multiple other problems, including type 2 diabetes, hypertension, and obstructive sleep apnea. Similar effects have been noted in smaller studies of adolescents following bariatric surgery.¹⁴⁶ Surgical interventions are not without significant drawbacks. As with any surgery, immediate complications can include mild wound infections, more serious pneumonias and abscesses, and life-threatening pulmonary emboli and sepsis. Bowel obstructions and perforations are also described. The decision to perform bariatric surgery should not be taken lightly.

Adult patients are considered candidates for bariatric surgery if they have a BMI of 40 or higher, or a BMI of 35 or higher along with comorbid conditions directly as a result of their

weight. For pediatric patients, most practitioners of bariatric surgery recommend a stricter guideline of a BMI greater than 50, or a BMI greater than 40 with comorbidities present along with insufficient weight loss from at least a 6-month trial of a nonsurgical weight loss program.^{118,147–149} Given that nutritional insufficiencies after surgery could impact growth and development, guidelines recommend that adolescents have achieved Tanner IV staging in their pubertal development and a bone age that demonstrates 95% of their final height has been reached.¹⁴⁷ Extensive pre- and postoperative counseling and evaluation are required from a multidisciplinary team,¹⁵⁰ particularly to evaluate the family's capacity to support the patient and the patient's ability to maintain a healthy lifestyle postoperatively.

Three forms of bariatric surgery have been most commonly used in adolescent patients. The first, the Roux-en-Y gastric bypass, involves marked reduction of stomach size along with bypass of the proximal small bowel. This configuration restricts total food intake and creates a situation of malabsorption. Studies have also demonstrated decreased production of ghrelin¹⁵¹ as well as increases in peptide YY and glucagon-like peptide 1.^{152–154} Bariatric case series in adolescents show large degrees of weight loss, with many patients maintaining a lower weight several years after the surgery. Steatohepatitis also improves significantly.¹²² A recent retrospective review¹⁴⁶ of Roux-en-Y procedures performed at five centers over a course of 2 years found that 11 adolescent patients (age <21 years) with type 2 diabetes lost an average of 34.4% of their body weight 1 year after the surgery. BMI changed by an average of 17 points. Weight loss ranged from 33 to 99 kg. All of the patients remained at least somewhat overweight; however, all but one had remission of their diabetes.¹⁴⁶

The two other forms of bariatric surgery in adolescents involve decreasing the size of the stomach to impact satiety and food intake but do not produce malabsorption because no bypass is involved. One of these methods, vertical banded gastroplasty, involves stapling the stomach into a smaller pouch. One report of adolescents followed up 5 years postoperatively found an average of 55% of excess weight was lost, and only one of the 14 patients did not have a significant decrease of BMI.¹²² The other approach is laparoscopic adjustable gastric banding (LAGB). Although not currently approved for adolescents by the FDA,¹¹⁸ LAGB has been performed on several pediatric patients. In this procedure, a saline-filled band that is attached to an externally accessible port is placed around the exterior of the stomach. Using the port, the degree of outflow restriction from the small proximal pouch created by the procedure can be modified according to the amount of saline placed in the band. Problems have arisen when the band has slipped or leaked, and gastric perforation has occurred during initial surgery. There have also been reports of anemia despite placing patients on vitamin supplementation. Several studies that have observed patients during the first 4 years after LAGB have shown an average BMI change of 8 to 14.5 points and a loss of 40% to 70% of excess weight. Based on adult data, LAGB is expected to be somewhat less efficacious than malabsorptive procedures but potentially safer. Currently, more long-term data are available for the Roux-en-Y gastric bypass procedure.¹⁴⁸

One review of surgeries registered in the Health Care Cost and Use Nationwide Inpatient Sample from 1996 to 2003 found 566 cases of either gastric bypass or gastroplasty involving adolescents (aged 10–19 years) with a diagnosis of obesity.¹⁵⁵ The overall complication rate of any kind was 4.2%, and 84.4% of these complications were respiratory in nature. In the same surgeries in adults, the complication rate was 6.6%. No in-hospital deaths were observed among adolescents.¹⁵⁵ The context in which these encouraging results have been obtained must be understood before surgical procedures are promulgated more widely for adolescent obesity. In general, the adolescents selected for surgery in the past have had significant obesity-related health problems that were considered likely to lead to an early death and supportive families expected to be able to care for them successfully after the operation; therefore, the cost-benefit ratio for adolescent bariatric surgery may have been

maximized. Given the high frequency with which adolescents choose to undertreat their chronic diseases,¹⁵⁶ there is great concern that the risks from procedures that induce nutritional deficiencies might outweigh the benefits of weight reduction. In one study of adolescents treated with Roux-en-Y gastric bypass, only 14% were regularly taking nutritional supplements as prescribed.¹⁵⁷ Neurologic complications of bariatric procedures, believed largely to be due to vitamin B₁₂, folate, and thiamine deficiencies, are common, reported in 5% to 16% of patients,^{158,159} and not always reversible, even after prompt nutritional repletion.¹⁶⁰ Bariatric surgery should continue to be offered only to adolescents who have life-threatening complications of their obesity.

SUMMARY

Treating obesity in children and adolescents is critical to prevent adult obesity-related complications, decrease health care costs, and provide patients with higher qualities of life. Despite the rapidly rising rates of obesity in the United States, few successful approaches have emerged. Clearly, given the large impact of environmental factors, behavioral changes are critical to include in any weight loss program. School systems may seem to be optimal targets for reaching large numbers of children and providing health education; however, results of prevention and intervention programs in schools have generally been modest. The genetic predisposition to obesity is also a large element of the picture but is incompletely understood. Research in the future needs to address these predispositions in the hope of dictating which weight loss approaches will be successful in individual patients.

Acknowledgments

This research was supported by the Intramural Research Program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development. Dr Yanovski is a Commissioned Officer in the United States Public Health Service, Department of Health and Human Services. Unit on Growth and Obesity, Program in Developmental Endocrinology and Genetics, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services, 9000 Rockville Pike, Hatfield Clinical Research Center, Room 1-3330, MSC 1103, Bethesda, MD, 20892-1103, USA

References

1. Ogden CL, Flegal KM, Carroll MD, et al. Prevalence and trends in overweight among US children and adolescents, 1999–2000. *JAMA*. 2002; 288(14):1728–32. [PubMed: 12365956]
2. Ogden CL, Carroll MD, Curtin LR, et al. Prevalence of overweight and obesity in the United States, 1999–2004. *JAMA*. 2006; 295(13):1549–55. [PubMed: 16595758]
3. Ogden CL, Carroll MD, Flegal KM. High body mass index for age among US children and adolescents, 2003–2006. *JAMA*. 2008; 299(20):2401–5. [PubMed: 18505949]
4. l'Allemand D, Wiegand S, Reinehr T, et al. Cardiovascular risk in 26,008 European overweight children as established by a multicenter database. *Obesity (Silver Spring)*. 2008; 16(7):1672–9. [PubMed: 18451769]
5. Muzumdar H, Rao M. Pulmonary dysfunction and sleep apnea in morbid obesity. *Pediatr Endocrinol Rev*. 2006; 3(Suppl 4):579–83. [PubMed: 17237747]
6. Ogden CL, Yanovski SZ, Carroll MD, et al. The epidemiology of obesity. *Gastroenterology*. 2007; 132(6):2087–102. [PubMed: 17498505]
7. Molleston JP, White F, Teckman J, et al. Obese children with steatohepatitis can develop cirrhosis in childhood. *Am J Gastroenterol*. 2002; 97(9):2460–2. [PubMed: 12358273]
8. Dabelea D, Bell RA, D'Agostino RB Jr, et al. Incidence of diabetes in youth in the United States. *JAMA*. 2007; 297(24):2716–24. [PubMed: 17595272]
9. Liese AD, D'Agostino RB Jr, Hamman RF, et al. The burden of diabetes mellitus among US youth: prevalence estimates from the SEARCH for Diabetes in Youth Study. *Pediatrics*. 2006; 118(4):1510–8. [PubMed: 17015542]

10. Pavkov ME, Bennett PH, Knowler WC, et al. Effect of youth-onset type 2 diabetes mellitus on incidence of end-stage renal disease and mortality in young and middle-aged Pima Indians. *JAMA*. 2006; 296(4):421–6. [PubMed: 16868300]
11. Baker JL, Olsen LW, Sorensen TI. Childhood body-mass index and the risk of coronary heart disease in adulthood. *N Engl J Med*. 2007; 357(23):2329–37. [PubMed: 18057335]
12. Must A, Jacques PF, Dallal GE, et al. Long-term morbidity and mortality of overweight adolescents: a follow-up of the Harvard Growth Study of 1922 to 1935. *N Engl J Med*. 1992; 327(19):1350–5. [PubMed: 1406836]
13. Olshansky SJ, Passaro DJ, Hershow RC, et al. A potential decline in life expectancy in the United States in the 21st century. *N Engl J Med*. 2005; 352(11):1138–45. [PubMed: 15784668]
14. Alley DE, Chang VW. The changing relationship of obesity and disability, 1988–2004. *JAMA*. 2007; 298(17):2020–7. [PubMed: 17986695]
15. Wardle J, Carnell S, Haworth CMA, et al. Evidence for a strong genetic influence on childhood adiposity despite the force of the obesogenic environment. *Am J Clin Nutr*. 2008; 87:398–404. [PubMed: 18258631]
16. Ashrafi K, Chang FY, Watts JL, et al. Genome-wide RNAi analysis of *Caenorhabditis elegans* fat regulatory genes. *Nature*. 2003; 421(6920):268–72. [PubMed: 12529643]
17. Rankinen T, Zuberi A, Chagnon YC, et al. The human obesity gene map: the 2005 update. *Obesity* (Silver Spring). 2006; 14(4):529–644. [PubMed: 16741264]
18. Crino A, Greggio NA, Beccaria L, et al. Diagnosis and differential diagnosis of obesity in childhood. *Minerva Pediatr*. 2003; 55(5):461–70. [PubMed: 14608269]
19. Ning, C.; Yanovski, JA. Endocrine disorders associated with pediatric obesity. In: Goran, M.; Sothorn, M., editors. *Handbook of pediatric obesity*. Boca Raton (FL): CRC Press; 2006. p. 135–55.
20. Wheatley T, Edwards OM. Mild hypothyroidism and oedema: evidence for increased capillary permeability to protein. *Clin Endocrinol (Oxf)*. 1983; 18(6):627–35. [PubMed: 6684003]
21. Villabona C, Sahun M, Roca M, et al. Blood volumes and renal function in overt and subclinical primary hypothyroidism. *Am J Med Sci*. 1999; 318(4):277–80. [PubMed: 10522555]
22. AL-Adsani H, Hoffer LJ, Silva JE. Resting energy expenditure is sensitive to small dose changes in patients on chronic thyroid hormone replacement. *J Clin Endocrinol Metab*. 1997; 82(4):1118–25. [PubMed: 9100583]
23. Abbassi V, Rigtink E, Cancellieri RP. Clinical recognition of juvenile hypothyroidism in the early stage. *Clin Pediatr (Phila)*. 1980; 19(12):782–6. [PubMed: 6893685]
24. Teng L, Bui H, Bachrach L, et al. Catch-up growth in severe juvenile hypothyroidism: treatment with a GnRH analog. *J Pediatr Endocrinol Metab*. 2004; 17(3):345–54. [PubMed: 15112911]
25. Meistas MT, Foster GV, Margolis S, et al. Integrated concentrations of growth hormone, insulin, C-peptide and prolactin in human obesity. *Metabolism*. 1982; 31(12):1224–8. [PubMed: 6755165]
26. Bell JP, Donald RA, Espiner EA. Pituitary response to insulin-induced hypoglycemia in obese subjects before and after fasting. *J Clin Endocrinol Metab*. 1970; 31(5):546. [PubMed: 4319340]
27. Copinschi G, Wegienka LC, Hane S, et al. Effect of arginine on serum levels of insulin and growth hormone in obese subjects. *Metabolism*. 1967; 16(6):485–91. [PubMed: 6027286]
28. Mims RB, Stein RB, Bethune JE. The effect of a single dose of L-dopa on pituitary hormones in acromegaly, obesity, and in normal subjects. *J Clin Endocrinol Metab*. 1973; 37(1):34–9. [PubMed: 4715294]
29. Topper E, Gil-Ad I, Bauman B, et al. Plasma growth hormone response to oral clonidine as compared to insulin hypoglycemia in obese children and adolescents. *Horm Metab Res*. 1984; 16(Suppl 1):127–30. [PubMed: 6398251]
30. Attia N, Tamborlane WV, Heptulla R, et al. The metabolic syndrome and insulinlike growth factor I regulation in adolescent obesity. *J Clin Endocrinol Metab*. 1998; 83(5):1467–71. [PubMed: 9589640]
31. Kamoda T, Saitoh H, Inudoh M, et al. The serum levels of proinsulin and their relationship with IGFBP-1 in obese children. *Diabetes Obes Metab*. 2006; 8(2):192–6. [PubMed: 16448523]

32. Dietz J, Schwartz J. Growth hormone alters lipolysis and hormone-sensitive lipase activity in 3T3-F442A adipocytes. *Metabolism*. 1991; 40(8):800–6. [PubMed: 1861630]
33. Srinivasan S, Ogle GD, Garnett SP, et al. Features of the metabolic syndrome after childhood craniopharyngioma. *J Clin Endocrinol Metab*. 2004; 89(1):81–6. [PubMed: 14715831]
34. Hoos MB, Westerterp KR, Gerver WJ. Short-term effects of growth hormone on body composition as a predictor of growth. *J Clin Endocrinol Metab*. 2003; 88(6):2569–72. [PubMed: 12788856]
35. Ottosson M, Lonnroth P, Bjorntorp P, et al. Effects of cortisol and growth hormone on lipolysis in human adipose tissue. *J Clin Endocrinol Metab*. 2000; 85(2):799–803. [PubMed: 10690893]
36. Berdanier CD. Role of glucocorticoids in the regulation of lipogenesis. *FASEB J*. 1989; 3(10):2179–83. [PubMed: 2666232]
37. Greening JE, Storr HL, McKenzie SA, et al. Linear growth and body mass index in pediatric patients with Cushing's disease or simple obesity. *J Endocrinol Invest*. 2006; 29(10):885–7. [PubMed: 17185896]
38. Magiakou MA, Mastorakos G, Oldfield EH, et al. Cushing's syndrome in children and adolescents: presentation, diagnosis, and therapy. *N Engl J Med*. 1994; 331(10):629–36. [PubMed: 8052272]
39. Bonfig W, Kann P, Rothmund M, et al. Recurrent hypoglycemic seizures and obesity: delayed diagnosis of an insulinoma in a 15-year-old boy. Final diagnostic localization with endosonography. *J Pediatr Endocrinol Metab*. 2007; 20(9):1035–8. [PubMed: 18038712]
40. Dizon AM, Kowalyk S, Hoogwerf BJ. Neuroglycopenic and other symptoms in patients with insulinomas. *Am J Med*. 1999; 106(3):307–10. [PubMed: 10190379]
41. Woods SC, D'Alessio DA. Central control of body weight and appetite. *J Clin Endocrinol Metab*. 2008; 93(11 Suppl 1):S37–50. [PubMed: 18987269]
42. Holder JL Jr, Butte NF, Zinn AR. Profound obesity associated with a balanced translocation that disrupts the SIM1 gene. *Hum Mol Genet*. 2000; 9(1):101–8. [PubMed: 10587584]
43. Hung CC, Luan J, Sims M, et al. Studies of the SIM1 gene in relation to human obesity and obesity-related traits. *Int J Obes (Lond)*. 2007; 31(3):429–34. [PubMed: 16924270]
44. Hoffman HJ, De Silva M, Humphreys RP, et al. Aggressive surgical management of craniopharyngiomas in children. *J Neurosurg*. 1992; 76(1):47–52. [PubMed: 1727168]
45. Muller HL, Bueb K, Bartels U, et al. Obesity after childhood craniopharyngioma: German multicenter study on preoperative risk factors and quality of life. *Klin Padiatr*. 2001; 213(4):244–9. [PubMed: 11528558]
46. Considine RV, Sinha MK, Heiman ML, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *N Engl J Med*. 1996; 334(5):292–5. [PubMed: 8532024]
47. Havel PJ, Kasim-Karakas S, Mueller W, et al. Relationship of plasma leptin to plasma insulin and adiposity in normal weight and overweight women: effects of dietary fat content and sustained weight loss. *J Clin Endocrinol Metab*. 1996; 81(12):4406–13. [PubMed: 8954050]
48. Maffei M, Halaas J, Ravussin E, et al. Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. *Nat Med*. 1995; 1(11):1155–61. [PubMed: 7584987]
49. Oral EA, Simha V, Ruiz E, et al. Leptin-replacement therapy for lipodystrophy. *N Engl J Med*. 2002; 346(8):570–8. [PubMed: 11856796]
50. Farooqi IS, Matarese G, Lord GM, et al. Beneficial effects of leptin on obesity, T cell hyporesponsiveness, and neuroendocrine/metabolic dysfunction of human congenital leptin deficiency. *J Clin Invest*. 2002; 110(8):1093–103. [PubMed: 12393845]
51. McDuffie JR, Riggs PA, Calis KA, et al. Effects of exogenous leptin on satiety and satiation in patients with lipodystrophy and leptin insufficiency. *J Clin Endocrinol Metab*. 2004; 89(9):4258–63. [PubMed: 15356018]
52. Farooqi IS, Bullmore E, Keogh J, et al. Leptin regulates striatal regions and human eating behavior. *Science*. 2007; 317(5843):1355. [PubMed: 17690262]
53. Montague CT, Farooqi IS, Whitehead JP, et al. Congenital leptin deficiency is associated with severe early-onset obesity in humans. *Nature*. 1997; 387(6636):903–8. [PubMed: 9202122]
54. Strobel A, Issat T, Camoin L, et al. A leptin missense mutation associated with hypogonadism and morbid obesity. *Nat Genet*. 1998; 18(3):213–5. [PubMed: 9500540]

55. Farooqi IS, Keogh JM, Kamath S, et al. Partial leptin deficiency and human adiposity. *Nature*. 2001; 414(6859):34–5. [PubMed: 11689931]
56. Tanofsky-Kraff M, Yanovski SZ, Wilfley DE, et al. Eating-disordered behaviors, body fat, and psychopathology in overweight and normal-weight children. *J Consult Clin Psychol*. 2004; 72(1): 53–61. [PubMed: 14756614]
57. Lahlou N, Issad T, Lebouc Y, et al. Mutations in the human leptin and leptin receptor genes as models of serum leptin receptor regulation. *Diabetes*. 2002; 51(6):1980–5. [PubMed: 12031989]
58. Farooqi IS, Wangenstein T, Collins S, et al. Clinical and molecular genetic spectrum of congenital deficiency of the leptin receptor. *N Engl J Med*. 2007; 356(3):237–47. [PubMed: 17229951]
59. Krude H, Biebermann H, Luck W, et al. Severe early-onset obesity, adrenal insufficiency and red hair pigmentation caused by POMC mutations in humans. *Nat Genet*. 1998; 19(2):155–7. [PubMed: 9620771]
60. Krude H, Biebermann H, Schnabel D, et al. Obesity due to proopiomelanocortin deficiency: three new cases and treatment trials with thyroid hormone and ACTH4–10. *J Clin Endocrinol Metab*. 2003; 88(10):4633–40. [PubMed: 14557433]
61. Challis BG, Pritchard LE, Creemers JW, et al. A missense mutation disrupting a dibasic prohormone processing site in pro-opiomelanocortin (POMC) increases susceptibility to early-onset obesity through a novel molecular mechanism. *Hum Mol Genet*. 2002; 11(17):1997–2004. [PubMed: 12165561]
62. Creemers JW, Lee YS, Oliver RL, et al. Mutations in the amino-terminal region of proopiomelanocortin (POMC) in patients with early-onset obesity impair POMC sorting to the regulated secretory pathway. *J Clin Endocrinol Metab*. 2008; 93(11):4494–9. [PubMed: 18697863]
63. Farooqi IS, Drop S, Clements A, et al. Heterozygosity for a POMC-null mutation and increased obesity risk in humans. *Diabetes*. 2006; 55(9):2549–53. [PubMed: 16936203]
64. Lee YS, Challis BG, Thompson DA, et al. A POMC variant implicates betamelanocyte-stimulating hormone in the control of human energy balance. *Cell Metab*. 2006; 3(2):135–40. [PubMed: 16459314]
65. Jackson RS, Creemers JW, Ohagi S, et al. Obesity and impaired prohormone processing associated with mutations in the human prohormone convertase 1 gene. *Nat Genet*. 1997; 16(3):303–6. [PubMed: 9207799]
66. Jackson RS, Creemers JW, Farooqi IS, et al. Small-intestinal dysfunction accompanies the complex endocrinopathy of human proprotein convertase 1 deficiency. *J Clin Invest*. 2003; 112(10):1550–60. [PubMed: 14617756]
67. Farooqi IS, Volders K, Stanhope R, et al. Hyperphagia and early-onset obesity due to a novel homozygous missense mutation in prohormone convertase 1/3. *J Clin Endocrinol Metab*. 2007; 92(9):3369–73. [PubMed: 17595246]
68. Cone RD. Anatomy and regulation of the central melanocortin system. *Nat Neurosci*. 2005; 8(5): 571–8. [PubMed: 15856065]
69. Butler AA, Cone RD. Knockout studies defining different roles for melanocortin receptors in energy homeostasis. *Ann N Y Acad Sci*. 2003; 994:240–5. [PubMed: 12851322]
70. Chen AS, Marsh DJ, Trumbauer ME, et al. Inactivation of the mouse melanocortin-3 receptor results in increased fat mass and reduced lean body mass. *Nat Genet*. 2000; 26(1):97–102. [PubMed: 10973258]
71. Butler AA. The melanocortin system and energy balance. *Peptides*. 2006; 27(2):281–90. [PubMed: 16434123]
72. Farooqi IS, Keogh JM, Yeo GS, et al. Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene. *N Engl J Med*. 2003; 348(12):1085–95. [PubMed: 12646665]
73. Farooqi IS, Yeo GS, Keogh JM, et al. Dominant and recessive inheritance of morbid obesity associated with melanocortin 4 receptor deficiency [see comments]. *J Clin Invest*. 2000; 106(2): 271–9. [PubMed: 10903343]
74. Greenfield JR, Miller JW, Keogh JM, et al. Modulation of blood pressure by central melanocortinergetic pathways. *N Engl J Med*. 2009; 360(1):44–52. [PubMed: 19092146]

75. Feng N, Young SF, Aguilera G, et al. Co-occurrence of two partially inactivating polymorphisms of MC3R is associated with pediatric-onset obesity. *Diabetes*. 2005; 54(9):2663–7. [PubMed: 16123355]
76. Han JC, Liu QR, Jones M, et al. Brain-derived neurotrophic factor and obesity in the WAGR syndrome. *N Engl J Med*. 2008; 359(9):918–27. [PubMed: 18753648]
77. Yeo GS, Connie Hung CC, Rochford J, et al. A de novo mutation affecting human TrkB associated with severe obesity and developmental delay. *Nat Neurosci*. 2004; 7(11):1187–9. [PubMed: 15494731]
78. Long DN, McGuire S, Levine MA, et al. Body mass index differences in pseudohypoparathyroidism type 1a versus pseudopseudohypoparathyroidism may implicate paternal imprinting of G alpha(s) in the development of human obesity. *J Clin Endocrinol Metab*. 2007; 92(3):1073–9. [PubMed: 17164301]
79. Xie T, Chen M, Gavrilova O, et al. Severe obesity and insulin resistance due to deletion of the maternal Gs alpha allele is reversed by paternal deletion of the Gs alpha imprint control region. *Endocrinology*. 2008; 149(5):2443–50. [PubMed: 18202131]
80. Meyre D, Delplanque J, Chevre JC, et al. Genome-wide association study for early-onset and morbid adult obesity identifies three new risk loci in European populations. *Nat Genet*. 2009; 41(2):157–9. [PubMed: 19151714]
81. Thorleifsson G, Walters GB, Gudbjartsson DF, et al. Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity. *Nat Genet*. 2009; 41(1):18–24. [PubMed: 19079260]
82. Willer CJ, Speliotes EK, Loos RJ, et al. Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. *Nat Genet*. 2009; 41(1):25–34. [PubMed: 19079261]
83. Frayling TM, Timpson NJ, Weedon MN, et al. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science*. 2007; 316(5826):889–94. [PubMed: 17434869]
84. Dina C, Meyre D, Gallina S, et al. Variation in FTO contributes to childhood obesity and severe adult obesity. *Nat Genet*. 2007; 39(6):724–6. [PubMed: 17496892]
85. Hinney A, Nguyen TT, Scherag A, et al. Genome wide association (GWA) study for early onset extreme obesity supports the role of fat mass and obesity associated gene (FTO) variants. *PLoS One*. 2007; 2(12):e1361. [PubMed: 18159244]
86. Hunt SC, Stone S, Xin Y, et al. Association of the FTO gene with BMI. *Obesity (Silver Spring)*. 2008; 16(4):902–4. [PubMed: 18239580]
87. Scuteri A, Sanna S, Chen WM, et al. Genome-wide association scan shows genetic variants in the FTO gene are associated with obesity-related traits. *PLoS Genet*. 2007; 3(7):e115. [PubMed: 17658951]
88. Fredriksson R, Hagglund M, Olszewski PK, et al. The obesity gene, FTO, is of ancient origin, up-regulated during food deprivation and expressed in neurons of feeding-related nuclei of the brain. *Endocrinology*. 2008; 149(5):2062–71. [PubMed: 18218688]
89. Stratigopoulos G, Padilla SL, LeDuc CA, et al. Regulation of Fto/Ftm gene expression in mice and humans. *Am J Physiol Regul Integr Comp Physiol*. 2008; 294(4):R1185–96. [PubMed: 18256137]
90. Gerken T, Girard CA, Tung YC, et al. The obesity-associated FTO gene encodes a 2-oxoglutarate-dependent nucleic acid demethylase. *Science*. 2007; 318(5855):1469–72. [PubMed: 17991826]
91. Cecil JE, Tavendale R, Watt P, et al. An obesity-associated FTO gene variant and increased energy intake in children. *N Engl J Med*. 2008; 359(24):2558–66. [PubMed: 19073975]
92. Wardle J, Llewellyn C, Sanderson S, et al. The FTO gene and measured food intake in children. *Int J Obes (Lond)*. 2008; 33(1):42–5. [PubMed: 18838977]
93. Wardle J, Carnell S, Haworth CM, et al. Obesity associated genetic variation in FTO is associated with diminished satiety. *J Clin Endocrinol Metab*. 2008; 93(9):3640–3. [PubMed: 18583465]
94. Celi FS, Shuldiner AR. The role of peroxisome proliferator-activated receptor gamma in diabetes and obesity. *Curr Diab Rep*. 2002; 2(2):179–85. [PubMed: 12643137]
95. Luan J, Browne PO, Harding AH, et al. Evidence for gene-nutrient interaction at the PPARgamma locus. *Diabetes*. 2001; 50(3):686–9. [PubMed: 11246892]

96. Jalba MS, Rhoads GG, Demissie K. Association of codon 16 and codon 27 beta 2-adrenergic receptor gene polymorphisms with obesity: a meta-analysis. *Obesity (Silver Spring)*. 2008; 16(9): 2096–106. [PubMed: 19186333]
97. Corella D, Qi L, Sorli JV, et al. Obese subjects carrying the 11482G>A polymorphism at the perilipin locus are resistant to weight loss after dietary energy restriction. *J Clin Endocrinol Metab*. 2005; 90(9):5121–6. [PubMed: 15985482]
98. Cummings DE, Clement K, Purnell JQ, et al. Elevated plasma ghrelin levels in Prader Willi syndrome. *Nat Med*. 2002; 8(7):643–4. [PubMed: 12091883]
99. Wren AM, Seal LJ, Cohen MA, et al. Ghrelin enhances appetite and increases food intake in humans. *J Clin Endocrinol Metab*. 2001; 86(12):5992. [PubMed: 11739476]
100. Davenport JR, Watts AJ, Roper VC, et al. Disruption of intraflagellar transport in adult mice leads to obesity and slow-onset cystic kidney disease. *Curr Biol*. 2007; 17(18):1586–94. [PubMed: 17825558]
101. Seo S, Guo DF, Bugge K, et al. Requirement of Bardet-Biedl syndrome proteins for leptin receptor signaling. *Hum Mol Genet*. 2009; 18(7):1323–31. [PubMed: 19150989]
102. Aronne LJ, Segal KR. Weight gain in the treatment of mood disorders. *J Clin Psychiatry*. 2003; 64(Suppl 8):22–9. [PubMed: 12892538]
103. Dhurandhar NV, Kulkarni P, Ajinkya SM, et al. Effect of adenovirus infection on adiposity in chicken. *Vet Microbiol*. 1992; 31(2,3):101–7. [PubMed: 1320784]
104. Dhurandhar NV, Whigham LD, Abbott DH, et al. Human adenovirus Ad-36 promotes weight gain in male rhesus and marmoset monkeys. *J Nutr*. 2002; 132(10):3155–60. [PubMed: 12368411]
105. Dhurandhar NV, Israel BA, Kolesar JM, et al. Increased adiposity in animals due to a human virus. *Int J Obes Relat Metab Disord*. 2000; 24(8):989–96. [PubMed: 10951537]
106. Pasarica M, Mashtalir N, McAllister EJ, et al. Adipogenic human adenovirus Ad-36 induces commitment, differentiation, and lipid accumulation in human adipose-derived stem cells. *Stem Cells*. 2008; 26(4):969–78. [PubMed: 18203674]
107. Dhurandhar NV, Kulkarni PR, Ajinkya SM, et al. Association of adenovirus infection with human obesity. *Obes Res*. 1997; 5(5):464–9. [PubMed: 9385623]
108. Atkinson RL, Dhurandhar NV, Allison DB, et al. Human adenovirus-36 is associated with increased body weight and paradoxical reduction of serum lipids. *Int J Obes (Lond)*. 2005; 29(3): 281–6. [PubMed: 15611785]
109. Ravussin E, Valencia ME, Esparza J, et al. Effects of a traditional lifestyle on obesity in Pima Indians. *Diabetes Care*. 1994; 17(9):1067–74. [PubMed: 7988310]
110. Popkin BM, Udry JR. Adolescent obesity increases significantly in second and third generation US immigrants: the National Longitudinal Study of Adolescent Health. *J Nutr*. 1998; 128(4): 701–6. [PubMed: 9521631]
111. Hawkins SS, Cole TJ, Law C. An ecological systems approach to examining risk factors for early childhood overweight: findings from the UK Millennium Cohort Study. *J Epidemiol Community Health*. 2009; 63(2):147–55. [PubMed: 18801795]
112. Lang T, Rayner G. Overcoming policy cacophony on obesity: an ecological public health framework for policymakers. *Obes Rev*. 2007; 8(Suppl 1):165–81. [PubMed: 17316322]
113. Waterland RA. Does nutrition during infancy and early childhood contribute to later obesity via metabolic imprinting of epigenetic gene regulatory mechanisms? *Nestle Nutr Workshop Ser Pediatr Program*. 2005; 56:157–74.
114. Wu Q, Suzuki M. Parental obesity and overweight affect the body-fat accumulation in the offspring: the possible effect of a high-fat diet through epigenetic inheritance. *Obesity Reviews*. 2006; 7:201–8. [PubMed: 16629875]
115. Barlow SE, Dietz WH. Obesity evaluation and treatment: Expert Committee recommendations. The Maternal and Child Health Bureau, Health Resources and Services Administration and the Department of Health and Human Services. *Pediatrics*. 1998; 102(3):E29. [PubMed: 9724677]
116. Barlow SE. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. *Pediatrics*. 2007; 120(Suppl 4):S164–92. [PubMed: 18055651]

117. Cohen ML, Tanofsky-Kraff M, Young-Hyman D, et al. Weight and its relationship to adolescent perceptions of their providers (WRAP): a qualitative and quantitative assessment of teen weight-related preferences and concerns. *J Adolesc Health*. 2005; 37(2):163–578. [PubMed: 16026727]
118. August GP, Caprio S, Fennoy I, et al. Prevention and treatment of pediatric obesity: an Endocrine Society clinical practice guideline based on expert opinion. *J Clin Endocrinol Metab*. 2008; 93(12):4576–99. [PubMed: 18782869]
119. Weiss R, Dziura J, Burgert TS, et al. Obesity and the metabolic syndrome in children and adolescents. *N Engl J Med*. 2004; 350(23):2362–74. [PubMed: 15175438]
120. McGovern L, Johnson JN, Paulo R, et al. Clinical review: treatment of pediatric obesity: a systematic review and meta-analysis of randomized trials. *J Clin Endocrinol Metab*. 2008; 93(12):4600–5. [PubMed: 18782881]
121. Epstein LH, Valoski A, Wing RR, et al. Ten-year follow-up of behavioral, family based treatment for obese children. *JAMA*. 1990; 264(19):2519–23. [PubMed: 2232019]
122. Han, JC.; Yanovski, JA. Intensive therapies for the treatment of pediatric obesity. In: Jelalian, E.; Steele, RC., editors. *Handbook of child and adolescent obesity*. New York: Springer; 2008. p. 241–60.
123. Figueroa-Colon R, von Almen TK, Franklin FA, et al. Comparison of two hypocaloric diets in obese children. *Am J Dis Child*. 1993; 147(2):160–6. [PubMed: 8427238]
124. Epstein LH, Myers MD, Raynor HA, et al. Treatment of pediatric obesity. *Pediatrics*. 1998; 101(3 Pt 2):554–70. [PubMed: 12224662]
125. Oude Luttikhuis H, Baur L, Jansen H, et al. Interventions for treating obesity in children. *Cochrane Database Syst Rev*. 2009; (1):1–189.
126. Wilfley DE, Tibbs TL, Van Buren DJ, et al. Lifestyle interventions in the treatment of childhood overweight: a meta-analytic review of randomized controlled trials. *Health Psychol*. 2007; 26(5): 521–32. [PubMed: 17845100]
127. Epstein LH. Family-based behavioural intervention for obese children. *Int J Obes Relat Metab Disord*. 1996; 20(1):S14–21. [PubMed: 8646260]
128. Epstein LH, Valoski A, Wing RR, et al. Ten-year outcomes of behavioral familybased treatment for childhood obesity. *Health Psychol*. 1994; 13(5):373–83. [PubMed: 7805631]
129. Wilfley DE, Stein RI, Saelens BE, et al. Efficacy of maintenance treatment approaches for childhood overweight: a randomized controlled trial. *JAMA*. 2007; 298(14):1661–73. [PubMed: 17925518]
130. Gutin B, Yin Z, Johnson M, et al. Preliminary findings of the effect of a 3-year after-school physical activity intervention on fitness and body fat: the Medical College of Georgia Fit kid Project. *Int J Pediatr Obes*. 2008; 3 (Suppl 1):3–9. [PubMed: 18278626]
131. Gortmaker SL, Peterson K, Wiecha J, et al. Reducing obesity via a school-based interdisciplinary intervention among youth: planet health. *Arch Pediatr Adolesc Med*. 1999; 153(4):409–18. [PubMed: 10201726]
132. Yanovski JA. Intensive therapies for pediatric obesity. *Pediatr Clin North Am*. 2001; 48(4):1041–53. [PubMed: 11494637]
133. Samanin R, Garattini S. Neurochemical mechanism of action of anorectic drugs. *Pharmacol Toxicol*. 1993; 73(2):63–9. [PubMed: 7902561]
134. Freemark M. Pharmacotherapy of childhood obesity: an evidence-based, conceptual approach. *Diabetes Care*. 2007; 30(2):395–402. [PubMed: 17259519]
135. Berkowitz RI, Fujioka K, Daniels SR, et al. Effects of sibutramine treatment in obese adolescents: a randomized trial. *Ann Intern Med*. 2006; 145(2):81–90. [PubMed: 16847290]
136. Danielsson P, Janson A, Norgren S, et al. Impact of sibutramine therapy in children with hypothalamic obesity or obesity with aggravating syndromes. *J Clin Endocrinol Metab*. 2007; 92(11):4101–6. [PubMed: 17726084]
137. Connolly HM, Crary JL, McGoon MD, et al. Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med*. 1997; 337(9):581–8. [PubMed: 9271479]
138. Akbas F, Gasteyger C, Sjodin A, et al. A critical review of the cannabinoid receptor as a drug target for obesity management. *Obes Rev*. 2009; 10(1):58–67. [PubMed: 18721231]

139. Chanoine JP, Hampl S, Jensen C, et al. Effect of orlistat on weight and body composition in obese adolescents: a randomized controlled trial. *JAMA*. 2005; 293(23):2873–83. [PubMed: 15956632]
140. Wilson DM, Abrams SH, Aye T, et al. Metformin extended release treatment of adolescent obesity: a 48-week randomized, double-blind, placebo-controlled trial with 48-week follow-up. *Arch Pediatr Adolesc Med*. 2010; 164:116–23. [PubMed: 20124139]
141. Yanovski JA, Krakoff J, Salaita CG, et al. Effects of metformin on body weight and body composition in obese insulin-resistant children: a randomized clinical trial. *Diabetes*. 2011; 60(2):477–85. [PubMed: 21228310]
142. Klein DJ, Cottingham EM, Sorter M, et al. A randomized, double-blind, placebo-controlled trial of metformin treatment of weight gain associated with initiation of atypical antipsychotic therapy in children and adolescents. *Am J Psychiatry*. 2006; 163(12):2072–9. [PubMed: 17151157]
143. Lustig RH, Hinds PS, Ringwald-Smith K, et al. Octreotide therapy of pediatric hypothalamic obesity: a double-blind, placebo-controlled trial. *J Clin Endocrinol Metab*. 2003; 88(6):2586–92. [PubMed: 12788859]
144. Heymsfield SB, Greenberg AS, Fujioka K, et al. Recombinant leptin for weight loss in obese and lean adults: a randomized, controlled, dose-escalation trial [see comments]. *JAMA*. 1999; 282(16):1568–75. [PubMed: 10546697]
145. Farooqi IS, Jebb SA, Langmack G, et al. Effects of recombinant leptin therapy in a child with congenital leptin deficiency. *N Engl J Med*. 1999; 341(12):879–84. [PubMed: 10486419]
146. Inge TH, Miyano G, Bean J, et al. Reversal of type 2 diabetes mellitus and improvements in cardiovascular risk factors after surgical weight loss in adolescents. *Pediatrics*. 2009; 123(1): 214–22. [PubMed: 19117885]
147. Inge TH, Krebs NF, Garcia VF, et al. Bariatric surgery for severely overweight adolescents: concerns and recommendations. *Pediatrics*. 2004; 114(1):217–23. [PubMed: 15231931]
148. Apovian CM, Baker C, Ludwig DS, et al. Best practice guidelines in pediatric/adolescent weight loss surgery. *Obes Res*. 2005; 13(2):274–82. [PubMed: 15800284]
149. Xanthakos SA, Inge TH. Extreme pediatric obesity: weighing the health dangers. *J Pediatr*. 2007; 150(1):3–5. [PubMed: 17188602]
150. Inge TH, Garcia V, Daniels S, et al. A multidisciplinary approach to the adolescent bariatric surgical patient. *J Pediatr Surg*. 2004; 39(3):442–7. [PubMed: 15017567]
151. Cummings DE, Weigle DS, Frayo RS, et al. Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. *N Engl J Med*. 2002; 346(21):1623–30. [PubMed: 12023994]
152. Korner J, Bessler M, Cirilo LJ, et al. Effects of Roux-en-Y gastric bypass surgery on fasting and postprandial concentrations of plasma ghrelin, peptide YY, and insulin. *J Clin Endocrinol Metab*. 2005; 90(1):359–65. [PubMed: 15483088]
153. Morinigo R, Moize V, Musri M, et al. Glucagon-like peptide-1, peptide YY, hunger, and satiety after gastric bypass surgery in morbidly obese subjects. *J Clin Endocrinol Metab*. 2006; 91(5): 1735–40. [PubMed: 16478824]
154. Reinehr T, Roth CL, Scherthaner GH, et al. Peptide YY and glucagon-like peptide-1 in morbidly obese patients before and after surgically induced weight loss. *Obes Surg*. 2007; 17(12):1571–7. [PubMed: 18046613]
155. Tsai WS, Inge TH, Burd RS. Bariatric surgery in adolescents: recent national trends in use and in-hospital outcome. *Arch Pediatr Adolesc Med*. 2007; 161(3):217–21. [PubMed: 17339501]
156. Rianthavorn P, Ettenger RB. Medication non-adherence in the adolescent renal transplant recipient: a clinician's viewpoint. *Pediatr Transplant*. 2005; 9(3):398–407. [PubMed: 15910399]
157. Sugerman HJ, Sugerman EL, DeMaria EJ, et al. Bariatric surgery for severely obese adolescents. *J Gastrointest Surg*. 2003; 7(1):102–7. [PubMed: 12559191]
158. Berger JR. The neurological complications of bariatric surgery. *Arch Neurol*. 2004; 61(8):1185–9. [PubMed: 15313834]
159. Thaisethawatkul P, Collazo-Clavell ML, Sarr MG, et al. A controlled study of peripheral neuropathy after bariatric surgery. *Neurology*. 2004; 63(8):1462–70. [PubMed: 15505166]
160. Xanthakos SA, Daniels SR, Inge TH. Bariatric surgery in adolescents: an update. *Adolesc Med Clin*. 2006; 17(3):589–612. [PubMed: 17030281]

Figure 1.

A Social-Ecological Model of Influences on Pediatric Obesity and its Treatment. Levels of environmental influence begin with the family environment and extend to larger spheres of influence, including peers as well as neighborhoods, schools, community, and national factors. Some of the influences within each of these spheres are also given. For examples, neighborhood environment may influence children's activity if there are no sidewalks or if safe areas for play are not available. Figure courtesy of Denise E Wilfley, PhD, St. Louis, MO; adapted with permission.

Figure 2.

A simplified model of the leptin signaling pathway. Central insulin can bind to the same neurons as leptin and is an anorexigenic signal. The ligands leptin, POMC, CART, and BDNF, the receptors for leptin, melanocortins, and BDNF, and the enzyme PC1 have been found to have function-altering mutations associated with obesity in children. Mutations in the ligands and receptors for NPY, AGRP, CPE, and MCH have been found to cause excessive weight gain when mutated in rodents, but have not been as convincingly shown to be associated with human obesity. OB-Rb, the signal-transducing form of the leptin receptor; NPY, neuropeptide Y; AGRP, agouti-related protein; POMC, pro-opiomelanocortin; CART, cocaine-amphetamine related transcript; PC 1, prohormone convertase 1; CPE, carboxypeptidase E; MSH, melanocyte stimulating hormone; NPYR, neuropeptide Y receptor; MC3R, melanocortin 3 receptor; MC4R, melanocortin 4 receptor; TRH, thyrotropin-releasing hormone; MCH, melanin concentrating hormone, GABA, gamma amino butyric acid; BDNF, brain-derived neurotrophic factor.

Figure 3. An algorithm for the evaluation of an obese child. Physical exam, growth patterns, and the child's age should narrow the scope of the differential diagnosis and dictate appropriate testing.

Table 1**Genetic Syndromes Associated with Obesity**

Achondroplasia
Alström Syndrome
Bannayan-Riley-Ruvalcaba Syndrome
Bardet Biedl Syndromes
Beckwith-Wiedemann Syndrome
Borjeson-Forssman-Lehmann Syndrome
Carpenter syndrome
CDG 1a
Cohen Syndrome
Fragile X
Mehmo Syndrome
Meningomyelocele
Prader Willi Syndrome
Pseudo-hypoparathyroidism 1a
Simpson-Golabi-Behmel Syndrome
Smith-Magenis Syndrome
Sotos Syndrome
Turner Syndrome
Ulnar-Mammary Schinzel Syndrome
Weaver Syndrome
Wilson-Turner Syndrome