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Pediatric Obesity: Etiology and Treatment

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Synopsis

This paper reviews factors that contribute to excessive weight gain in children and outlines current knowledge regarding approaches for treating pediatric obesity. Virtually all of the known genetic causes of obesity primarily increase energy intake. Genes regulating the leptin signaling pathway are particularly important for human energy homeostasis. Obesity is a chronic disorder that requires long-term strategies for management. The foundation for all treatments for pediatric obesity remains restriction of energy intake with lifestyle modification. There are few long-term studies of pharmacotherapeutic interventions for pediatric obesity. Bariatric surgical approaches are the most efficacious obesity treatments but, because of their potential risks, are reserved for those with the most significant complications of obesity.

Keywords

Overweight; differential diagnosis; pharmacotherapy; bariatric surgery; adiposity; leptin

1. Introduction

In the United States the prevalence of pediatric overweight, defined by the CDC as BMI $\geq$ 95th percentile for age and sex, has more than tripled during the past four decades.^{1–3} 16.3% of children and adolescents are now overweight, and an additional 15.6% are classified as at-risk for overweight (BMI 85–95th percentile).³ 11.3% of all children have 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 disease (NAFLD)⁶ with resultant cirrhosis,⁷ and type 2 diabetes^{8,9} are increasingly diagnosed in pediatric patients.

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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 psychological consequences of excess adiposity. The current U.S. childhood obesity epidemic also has the potential to reverse the improvements in life-expectancy that have been seen during the 20th century in the U.S.¹³ and to result in more functional disability and decreased quality of life in those who survive to old age.¹⁴

In this chapter, we review factors that contribute to excessive weight gain in children and outline current knowledge regarding approaches for treating pediatric obesity.

2. Etiology

Obesity is a genetic disease, because all available data suggest that 60–80% 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 (Figure 1).

Some theorists hypothesize that in the past it was evolutionarily advantageous for proto-humans to have 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 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 human body weight regulation have been identified through analyses in humans, rodents, and *C 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 (Figure 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 include:

a. Classical endocrine disorders associated with weight gain

Children with identifiable endocrinopathies are believed to comprise only a small minority of children referred for evaluation of overweight, on the order of 2–3%.¹⁸ However, since 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 (i.e., only a few kg).¹⁹ Hypothyroidism leads to increased permeability of capillary walls,²⁰ which creates extravascular leakage and retention of water,²¹ causing excess weight gain; consequently, most of the weight gained in those with hypothyroidism appears to be fluid rather than triglyceride. Resting energy expenditure may also decrease, potentially biasing energy balance towards storage of ingested calories.²² Because children with hypothyroidism usually have diminished linear growth, 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 TSH 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 (GH) deficiency—In obese children who have no true endocrinopathy, the 24-hour secretion of GH, the GH peak during the night,²⁵ and GH response to various pharmacological stimuli are invariably diminished.^{26–29} Thus, interpretation of the results of provocative testing in obese children may be difficult. Growth velocity is either normal or supranormal and the IGF-1 concentration is generally normal or only modestly decreased in obesity,^{30,31} while 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 thus 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 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 lipolysis³⁵ and stimulation of lipogenesis.³⁶ The prevalence of Cushing syndrome in children is quite 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 more rare in children, with an incidence rate of 4 per 5,000,000 per year in the whole population; fewer than 10% occur prior to 20 years of age. Elevated insulin production leads to increased food intake to counter lower blood sugars and therefore leads to obesity.^{39,40}

b. 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 (VMH), arcuate nucleus (ARC), paraventricular nucleus (PVN), dorsomedial nucleus (DMH), and the lateral hypothalamic area (LHA) are all involved in control of appetite and energy expenditure. These areas produce several neuropeptides involved in appetite regulation, including orexigenic peptides like neuropeptide Y and anorexigenic peptides like the melanocortins (Figure 2).⁴¹ Injury or malformation may also affect binding of peripheral intake-related signals, including cholecystokinin (CCK), glucagon-like peptide (GLP-1), 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 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}

c. Leptin signaling pathway genes (Figure 2)

One of the major advances in obesity science over the last 15 years has been the elucidation of the leptin signaling pathway. 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 utilization. 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 development;⁵⁶ 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 thus not been successfully used to identify those bearing leptin receptor abnormalities.

Pro-opiomelanocortin (POMC)—In some leptin-responsive hypothalamic neurons, leptin stimulates the production of POMC, which is the precursor for 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}

POMC 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, so 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} while 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% 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 (BDNF)—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, 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% compared to 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 (AHO)—AHO 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, while 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 does still present with the AHO phenotype, although the obesity is less severe.⁷⁸ The etiology of the obesity in PHP1a may in part be related to diminished signaling via the Gs alpha subunit in the many Gs alpha-coupled receptors found in the leptin pathway.⁷⁹

d. 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.

FTO—Recent Genome-Wide Association Studies have found that common SNPs in the *FTO* (fat mass and obesity associated) gene locus are consistently associated with higher body mass index and adiposity in both 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 both rats and mice.^{88–90} Compared to 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 intake⁹¹ and reduced satiety⁹³ but show no differences in energy expenditure.⁹¹

PPAR-γ—Peroxisome proliferator-activated receptors (PPAR) 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 to 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 (Gln27) 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 Gln27 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 to controls.⁹⁷

e. Syndromic obesity

Multiple genetic syndromes involve obesity as part of their presentation, although patients with these syndromes rarely come to medical attention because of obesity. Even when grouped together, these etiologies, displayed in Table 1, account for only a very small percentage of overweight children. All of these syndromes involve multiple other medical problems and/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 Alstrom 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 Alstrom syndromes appear to be associated with disruption of ciliary function. Cilia have been demonstrated to be necessary for body weight regulation in mice, where inducible disruption of primary cilia by inactivating the Alstrom syndrome gene 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

f. 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 like lithium, antidepressants including 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 adipose-derived 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 triglycerides;¹⁰⁷ 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 play a role in acquired obesity.

Environment and Behavior—As outlined in Figure 1, the sociocultural environment plays a major role in determining who becomes obese. This observation is demonstrated by comparing human samples that share 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 chapter, 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 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

g. 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. Figure 3 provides an algorithm for this evaluation.

3. Therapy

a. Indications

The Maternal and Child Health Bureau of the Department of Health and Human Services recommended in 1998 that children age 7 and above with BMI greater than the 95th percentile for age should be offered obesity interventions.¹¹⁵ For adolescents, a cutoff BMI of 30 kg/m² should be utilized when the 95th percentile standard is above 30.¹¹⁶ Some practitioners refer to these patients as obese while others avoid the terminology in pediatrics given the associated stigma and instead describe these patients as “at risk for obesity” or “overweight,” which is the word choice that children with BMI $\geq 95^{\text{th}}$ 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 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 with 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 set of guidelines,^{116,118} but called “at risk for overweight” 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 suffer from 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, fitness level, and distribution of adipose tissue versus lean mass to determine need for intervention.¹¹⁶ Additionally, the AAP expert panel, noting that younger patients have the benefit of significant future vertical growth, have suggested such growth can compensate for weight already gained; thus the goal for young patients (particularly those under 5 years of age) is weight maintenance to allow the height to attain the same percentile as the weight. However, 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, since for most height gain alone will not correct the obesity; for these children a goal of 0.5–1 kg loss per month is appropriate, although adolescents may tolerate 1–2 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 has varying levels of success, both short and long term, as well as side effects that must be considered. None of these 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.

b. 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 weight loss intervention in pediatrics. Six such papers were found using a comprehensive literature review, including studies that employed reduced-glycemic-load diet, protein-sparing modified diet, low carbohydrate diet, high protein diet, and 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 (VLEDs) 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 grams of high quality protein per kilogram of body weight. Typically such diets limit carbohydrates to 20 to 40 grams per day. A multivitamin should be included in the daily regimen given the lack of sources for many critical elements. 1500 cc of free water is also recommended to avoid dehydration. These diets are rapid in their weight loss among teens (up to 11 kilograms 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 (i.e., 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.

c. 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. Those 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 combination of exercise and diet were analyzed among 23 trials, there was a small to moderate effect of intervention. The largest change in weight was found in those trials that utilized parents in the therapy. Although not statistically significant, there was a trend toward improved outcomes in younger children, primarily eight years of age or less.¹²⁰

d. Behavior modification

Behavior modification as an approach to weight loss may include encouragement to reduce screen time and increase physical activity, psychological training to motivate 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 invoking such technique have been recently reviewed elsewhere.¹²⁴ A Cochrane Review¹²⁵ compared four studies of children under 12 years and three studies of adolescents enrolled in behavioral intervention versus conventional treatment. Of those under 12 years, there was a 0.06 point change in BMI SDS in the parent-focused behavioral interventions. Among the older patients, a 0.14 point decrease in BMI SDS and 3.04 point decrease in BMI was seen with behavioral therapy.¹²⁵ A meta-analysis of 14 studies using behavioral interventions compared to no intervention or standard weight loss counseling interventions found significant, but small effect sizes ranging 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 is 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 modifications programs. One study of increased exercise during an after school program, which also served healthy snacks, showed 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

e. 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 three to six months, these guidelines recommend advancing to each successive stage and finally to referral to obesity management experts for specialized interventions, such as medication or surgery.¹¹⁶

f. Medications

Although several forms of medications to treat obesity are on the market, only one is approved for children with age 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 those with 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 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 The only appetite suppressant currently FDA approved for long-term use in adults is sibutramine. Such approval allows its use in older adolescents, age 16 years and up. Sibutramine inhibits reuptake of all three of these anorexigenic neurotransmitters. The increased levels of these hypothalamic neurotransmitters promote satiety and decrease hunger.¹³⁴ Because of its mechanism of action, sibutramine cannot be taken in combination with MAOIs or SSRIs. Side effects include hypertension, tachycardia, premature ventricular contractions, prolonged QTc, insomnia, dizziness, dry mouth, cholelithiasis, and constipation.^{122,134} Four randomized control trials have examined the effect of sibutramine on weight in adolescents and on average found 7.7 kilograms of weight

loss in the short term.¹³⁴ A meta-analysis of three of these showed a change in BMI by 2.4 units after six months of medication treatment.¹²⁰ The largest sibutramine trial enrolled 498 patients age 12 to 16 with 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 are no published reports of sibutramine treatment for adolescent obesity that last 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 their 50 patients, 22 had hypothalamic obesity either from CNS damage, Bardet-Biedl syndrome, MC4R mutations, or Prader-Willi syndrome. The other 28 had mental retardation, autism spectrum disorder, attention deficit hyperactivity disorder, or a myelomeningocele. During a cross over period where 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 0.3–0.4 BMI SD units, while the remaining patients lost closer to 0.9–1 BMI SD units.¹³⁶

Other neurotransmitter regulators that are marketed for weight loss include phentermine, chlorphentermine, mazindol, and diethylpropion, all of which have shown short-term weight loss of 2 to 5 kg in excess of placebo over one to three months in adults; there are no long term follow up data in pediatric samples for these medications. Ephedrine in combination with caffeine did induce 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 U.S., works as an inhibitor of the CNS 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 1/3 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 compared to the control group. Diminished fat absorption also limits the absorption of the fat soluble vitamins (A, D, E, and K). Thus, 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 BMI, but increased rates of abdominal pain and discomfort as well as oily stools compared to placebo.¹²⁰ The largest adolescent orlistat study¹³⁹ enrolled 539 patients ages 12 to 16 who were randomized to placebo or orlistat. After one 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 did experience improvement in glucose and insulin levels while taking orlistat, no similar effects have been observed in the pediatric studies so far conducted.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 10 years and older. Three randomized control trials have evaluated metformin as an obesity medication in adolescents, and an average loss of 3.15 kilograms was noted by one author,¹³⁴ although another meta-analysis described the pooled results as “a small nonsignificant change in obesity outcome at 6 months”.¹²⁰ Additionally, a randomized control trial of 39 patients (of whom 30 completed the study) age 10 to 17 taking atypical antipsychotics showed a decrease of 0.13 kg and 0.43 BMI points in the metformin arm compared to a weight gain of 4.01 kg and BMI gain of 1.12 points in the placebo arm after 16 weeks of intervention.¹⁴⁰ Improvements in steatohepatitis have also been noted.¹²² All studies thus far are short term, so 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 so a multivitamin is recommended.¹²² Finally 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 analog binds receptors on the beta cells of the pancreas and inhibits insulin release. A randomized controlled trial comparing octreotide to placebo demonstrated reduced weight gain among those treated with octreotide given subcutaneously three times per day. Over six months the placebo group experienced an average weight gain of 9.2 kg and BMI changed by 2.2 points, whereas the treatment group gained 1.6 kg and decreased their BMI by 0.2.¹⁴¹ Because of its mode of action, octreotide use is also 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.¹⁴² Among those rare individuals with true leptin deficiency, however, leptin is quite effective at reducing BMI and fat mass over the long term.^{50,143}

g. 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.¹⁴⁴ Surgical interventions, though, 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. Thus the decision to perform bariatric surgery should not be taken lightly

In adults, 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. In pediatrics, most practitioners of bariatric surgery recommend a stricter guideline of BMI greater than 50 or greater than 40 with comorbidities present along with insufficient weight loss from at least a 6-month trial of a nonsurgical weight loss program.^{118,145–147} 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.¹⁴⁵ Extensive pre and post-operative counseling and evaluation are required from a multidisciplinary team,¹⁴⁸ particularly to evaluate the family's capacity to support the patient and the patient's ability to maintain a healthy lifestyle post-operatively.

Three forms of bariatric surgery are available to adolescent patients. The first, termed the roux en Y, involves marked reduction of stomach size along with bypass of the proximal small bowel. This configuration both restricts total food intake and creates a situation of malabsorption. Studies have also demonstrated decreased production of ghrelin¹⁴⁹ as well as increases in peptide YY and glucagon-like peptide 1.^{150–152} Bariatric case series in adolescents do 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 review¹⁴⁴ of roux en Y procedures performed at five centers over a course of two years found 11 adolescent patients (age less than 21 years) with type 2 diabetes lost an average of 34.4% of their body weight one year after the surgery. BMI changed by an average of 17 points. Weight loss ranged from 33 to 99 kilograms. All patients remained at least somewhat overweight; however, all but one had remission of their diabetes.¹⁴⁴

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, termed vertical banded gastroplasty, involves the stapling of the stomach into a smaller pouch. One report of adolescents followed 5 years post-operatively 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 approved for adolescents by the FDA,¹⁵³ LAGB has been performed on a number of 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 followed patients during the first four years after LAGB showed an average BMI change of 8 to 14.5 points and a loss of 40–70% of excess weight. Based on adult data, LAGB is expected to be somewhat less efficacious than malabsorptive procedures, but potentially safer. At present, more long term data are available for the Roux en Y gastric bypass procedure.¹⁴⁶

One review of surgeries registered in the Healthcare Cost and Utilization Nationwide Inpatient Sample from 1996 to 2003 found 566 cases of either gastric bypass or gastroplasty involving adolescent (age 10–19) with diagnosis of obesity.¹⁵⁴ 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.¹⁵⁴ 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 both 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. Thus, the cost-benefit ratio for adolescent bariatric surgery may have been maximized. Given the high frequency with which adolescents choose to under-treat their chronic diseases,¹⁵⁵ 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 RYGB, only 14% were regularly taking nutritional supplements as prescribed.¹⁵⁶ Neurologic complications of bariatric procedures, believed largely to be due to vitamin B₁₂, folate, and thiamine

deficiencies, are common, reported in 5–16% of patients,^{157,158} and not always reversible, even after prompt nutritional repletion.¹⁵⁹ Bariatric surgery should continue to be offered only to adolescents who have life-threatening complications of their obesity.

4. Summary/Conclusion

Treating obesity in children and adolescents is critical to prevent adult obesity-related complications, both to decrease health care costs and to 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 both prevention and intervention programs in schools have generally been modest. Genetic predisposition to obesity is also a large element of the picture but is still incompletely understood. Research in the future needs to address how best to understand these predispositions and, it is hoped, should help dictate which weight loss approaches will be successful in individual patients.

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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 work up of an obese child. Physical exam, growth patterns, and the child's age should narrow the scope of the differential 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