Current Cardiovascular Risk Reports (2019) 13:39
https://doi.org/10.1007/s12170-019-0632-y

OBESITY AND DIET (G. RAO, SECTION EDITOR)

Pediatric Obesity: Endocrinologic and Genetic Etiologies and Management

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Abstract

Purpose of Review The prevalence of pediatric obesity has increased significantly over the past couple of generations. While monogenic obesity, syndromic obesity, and endocrinopathies associated with obesity have been increasingly recognized, they do not account for the increase in prevalence. We describe these rare conditions and the dysregulation of neuropathways in obesity and review successes and failures in treatments in both syndromic and nonsyndromic obesity.

Recent Findings The best-described form of syndromic obesity is Prader–Willi Syndrome (PWS). While recent pharmacotherapies (specifically beloranib) demonstrated improvements in weight in PWS, the unfortunate adverse effect of deep vein thrombosis and pulmonary embolism necessitated the halting of its further development. Additional treatments are in development which target the signaling of ghrelin and other hypothalamic targets known to be dysregulated in PWS. For nonsyndromic obesity, lifestyle modifications remain the mainstay of treatment. However, recent large-scale interventions have had disappointing results. Bariatric surgery in children holds some promise, though complications and reoperations are common. Pharmacotherapies have been developed that treat rare monogenic forms of obesity, including MC4R agonists, which hold promise for these uncommon explanations for early childhood weight gain. There is evidence that methylation patterns in key genes in the neuroregulation of appetite are altered in individuals with obesity. Interestingly, this altered methylation is evident in sperm, which may have an impact on the heritability of gene expression across generations.

Summary Pediatric obesity is complex and multifactorial. Efforts in rare monogenic and syndromic obesity may give rise to potential treatment opportunities in circumstances where lifestyle interventions are unsuccessful.

Keywords Pediatrics · Obesity · Monogenic · Syndromic · Interventions · Therapeutics

Introduction

The purpose of the review is to describe rare genetic syndromes and endocrinologic conditions associated with obesity in children. We also describe pathophysiologic mechanisms distorting energy balance in such conditions, a better understanding of which may lead to effective treatments.

Neuroregulation of Appetite and Genetic/Epigenetic Implications

The regulation of energy balance is complex and under the influence of multiple competing signals from the gut, pancreas, and adipose tissues. Figure 1 depicts these afferent inputs and their influence on hypothalamic signaling of appetite downstream. In examining these aforementioned pathways,

This article is part of the Topical Collection on *Obesity and Diet*

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Published online: 27 November 2019

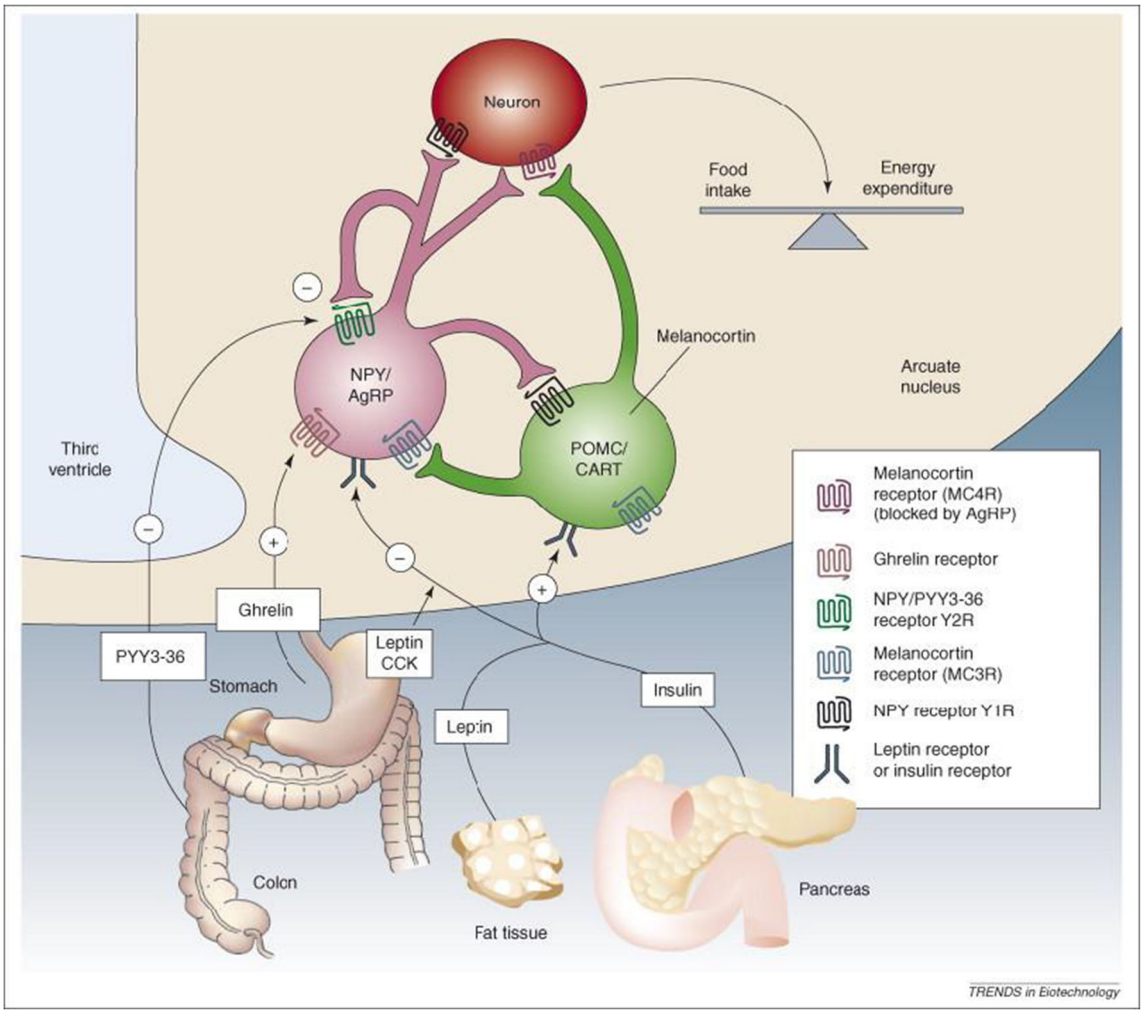

Fig. 1 The regulation of appetite and energy balance. Neuroregulation of energy balance is mediated through several different influences within the body on several key neurons within the arcuate and paraventricular nuclei within the hypothalamus. Hormonal signaling from several different organs gives rise to behaviors responsible for energy balance and appetite: Two key mediators of acute appetite regulation include ghrelin and peptide YY (PYY3-36). In a fasting state, one of the primary mediators of appetite is ghrelin, secreted by P/D sub 1 cells in the oxyntic glands of the stomach. Ghrelin is released into systemic circulation and within the central nervous system will stimulate neuropeptide Y (NPY) and agouti-related protein (AgRP) neurons in the arcuate nucleus. These neurons in turn have impacts on second and third order neurons that have downstream targets responsible for endocrine, behavioral, and autonomic responses in the body that drive appetite and caloric preservation. Conversely, peptide YY (PYY) is an anorexic hormone of intestinal origin that appears to be upregulated with feeding and acts antagonistically on NPY- and AgRP-secreting neurons. Additionally, PYY has agonistic effects on receptors of pro-opiomelanocortin (POMC) neurons, resulting in downstream release of melanocyte stimulating hormone and its binding to the melanocortin receptor type 4 (MC4R), which results in satiety. Chronic effects of appetite regulation include adipokines such as leptin and hormones such as insulin and cholecystokinin (CCK). Leptin is thought to be secreted by adipocytes in a manner proportionate to weight gain. Its signaling within the central nervous system is primarily through the inhibition of NPY/AgRP neurons, though it also stimulates POMC neurons similarly to PYY. The end effects include downregulation of appetite and upregulation of metabolic rate.

it follows that disruptions in the signaling effects of these neurons may induce a predilection towards rapid weight gain. Indeed, single mutations among these mediators of energy regulation result in a phenotype of early onset weight gain starting as early as the first year of life. These single mutations that have been identified to date are categorized as monogenic obesity and are critical to identify, as several forms may be able to be treated with newer pharmacologic agents presently in development.

Known Causes of Monogenic Obesity

MC4R mutations are among the most common causes of monogenic obesity, with an incidence of close to 6% of early onset obesity [1]. Both autosomal dominant and recessive mutations have been described [2]. Hyperphagia and early onset food-seeking behavior are commonly described. Inability of alpha-MSH to bind at the altered MC4R site results in ineffective satiety signaling and predisposition to

obesity. Agouti-related peptide (AgRP), meanwhile, continues to have inverse agonist activity at the receptor, resulting in ongoing hunger and feeding behaviors. It appears that at least some forms of heterozygous MC4R mutations may be able to be treated with a new MC4R agonist known as setmelanotide, which more avidly binds the receptor and can result in satiety signaling. In homozygous MC4R deletions or in mutations that impact the trafficking of the receptor to the membrane, setmelanotide will have little impact on appetite control [3].

Leptin and leptin receptor mutations are also well-documented in the literature to present with profound early onset obesity [4]. Leptin, secreted by adipocytes, binds to the leptin receptor located on both pro-opiomelanocortin (POMC) and neuropeptide Y (NPY) neurons in the arcuate nucleus. Leptin activity on NPY neurons results in inhibited release of AgRP, an orexigenic ligand. Simultaneously, leptin binds and activates POMC neurons to cause the release of alpha-MSH, signaling satiety at the level of MC4R expressing cells in the paraventricular nucleus. Mutations in either the leptin gene or the leptin receptor result in disruption of these signaling pathways, resulting in hyperphagia. Beyond the rapid onset obesity, individuals may also be at risk for systemic infections due to impaired T cell immunity, as well as hypogonadotropic hypogonadism [4]. Leptin receptor mutations tend to be somewhat more common, with a potential incidence of 2–3% of severe early onset obesity in certain populations. Recombinant leptin (metreleptin) is available for individuals who are found to be leptin deficient, though this treatment is less effective in leptin receptor mutations.

Individuals who are homozygous or compound heterozygous for loss-of-function mutations in PCSK1 exhibit a pleiotropic syndrome consisting of obesity, malabsorptive diarrhea, hypogonadotropic hypogonadism, altered thyroid and adrenal function, and impaired regulation of plasma glucose levels in association with elevated circulating proinsulin-to-insulin ratio. Recently, more common variants in the PCSK1 gene have been found to be associated with alterations in body mass index, increased circulating proinsulin levels, and defects in glucose homeostasis [5]. Since it is a germline genetic disorder expressed through out many endocrine cell types in the body, there is no specific targeted therapy for PCSK1 deficiency. There are no published clinical trials of antiobesity strategies or weight loss–promoting drugs in patients with PCSK1 deficiency. It has been postulated that the lack of alpha-MSH tone in the hypothalamus is a contributor to the obesity. Therefore, patients with PCSK1 deficiency might benefit from agents that act centrally to reduce appetite.

Pro-opiomelanocortin (POMC) deficiency, while exceptionally rare, results in deficiency not only in alpha-MSH production but also other products from the same pro-protein including adrenocorticotrophic hormone (ACTH), resulting in isolated central adrenal insufficiency. Additionally, lack of pigmentation results in some degree of pale skin and red hair, although this is not a universal trait. While uncommon, the rapid onset of weight gain in childhood is thought to be potentially treatable with setmelanotide an MC4R agonist, while the adrenal insufficiency is typically managed with replacement hydrocortisone at physiologic doses. In clinical trials, setmelanotide has been effective in POMC deficiency as well as some heterozygous forms of MC4R mutations [3, 6].

Epigenetic Influences on Obesity

While severe and important to recognize, monogenic obesity on the whole remains rare and certainly is not the explanation for the evolving obesity crisis over the last several decades. In light of the fact that the genome has not undergone dramatic changes in this timeframe, speculation has developed on the impact of histone modification and DNA methylation patterns on the expression of genes responsible for appetite regulation. This influence of the individual's environment on the subsequent expression patterns of certain genes is referred to as epigenetics. The concept of epigenetics has been well-studied in animal and human models. Mouse models have demonstrated that being born to an undernourished mother increases cardiometabolic risk upon exposure to a high-fat diet. Maternal obesity has been associated with altered locomotor activity in animals and rates of offspring obesity, with some evidence that this may be perpetuated over multiple generations.

Within humans, a study of 18 men who underwent ≥ 5% weight loss after an 8-week nutritional intervention found higher pre-intervention methylation levels of *POMC* and lower *NPY* methylation in the individuals who maintained weight loss [7]. Similar effects on altered methylation patterns have been documented in individuals participating in episodes of physical stress and exercise in timeframes as short as 20 min after a bout of physical activity [8, 9].

More recently, eloquent studies examining methylation patterns of specific genes responsible for appetite and energy balance are beginning to suggest potential heritability of genetic expression. A Danish study in 2016 compared the sperm of 13 normal weight subjects with 10 obese subjects, and a distinct epigenome was able to be characterized based on healthy vs. obese phenotypes [10]. Sperm collections of an additional cohort of obese males before and after undergoing bariatric weight loss surgery showed significant remodeling of DNA methylation, particularly of genes implicated in central control of appetite. Almost 300 genes were found to have altered expression, including key regulators of appetite control such as MC4R, NPY, and other genes downstream in the appetite pathways such as BDNF and cannabinoid receptor 1. In summary, weight loss surgery resulted in a transition from an obese methylome to a lean methylome in sperm. In animal models, it has previously been demonstrated that

alterations in sperm methylomes have multigenerational impacts on offspring [11].

The pathways of appetite regulation and the models of monogenic obesity help clarify the role of epigenetic influences on the expression of the key genes responsible for energy homeostasis. It is becoming increasingly apparent that while these changes are potentially malleable within individuals' lifetimes, they are also potentially capable of being transmitted across multiple generations, impacting health outcomes for future offspring.

Syndromic Obesity

Syndromic forms of obesity are rare forms that describe obese children or adults with dysmorphic features, intellectual disability, and organ–specific abnormalities, with or without signs of hypothalamic dysfunction [12]. Obesity syndromes are extremely heterogeneous with multiple genes within the same pathway producing identical phenotypes. Studies have demonstrated different molecular mechanisms underlying various syndromes. There are now over 25 syndromic forms of obesity for which a genetic basis has been partially or completely elucidated, thus providing insights into the pathogenesis of derangements of energy homeostasis [12, 13]. These syndromes may be inherited in either an autosomal or X-linked pattern.

A recent study reported chromosomal micro array results of 279 patients with syndromic obesity who were tested negative for PWS and found pathogenic copy number variants (CNVs) in 61 patients (22%) and, among them, 35 had overlapping/recurrent CNVs. The study reported genomic imbalance disorders known to cause syndromic obesity in 8.2% of cases, most commonly deletions of 1p36, 2q37 and 17p11.2 (5.4%), and also detected deletions at 1p21.3, 2p25.3, 6q16, 9q34, 16p11.2 distal and proximal, as well as an unbalanced translocation resulting in duplication of the GNB3 gene responsible for syndromic childhood obesity [14].

The clinical and genetic aspects of 5 classic but rare obesity-related syndromes (Prader–Willi, Bardet–Biedl, Alstrom, 16 p deletion, and WAGR) are described below. Additional syndromic forms of obesity are listed in Table 1.

Prader–Willi Syndrome (PWS)

PWS is the most common cause of syndromic obesity with a prevalence of 1 in 10,000–30,000 live births. It has distinct clinical features including neonatal hypotonia, initial poor feeding followed by hyperphagia with excess weight gain, hypogonadism, and intellectual disability (ID) with an average IQ of 65 [15]. Patients with PWS have characteristic facial features including almond-shaped eyes, thin upper lip, down-turned corners of the mouth, and/or a narrow face. In addition, behavioral problems such as temper tantrums, stubbornness, and skin picking, sleep abnormalities, small hands and feet, and short stature are frequently described [15, 16].

PWS is caused by the absence of expression of the paternal genes (small nuclear ring finger (SNURF), small nuclear ribonucleoprotein polypeptide N (SNRPN), makorin ring finger protein 3 (MKRN3), MAGE family member 2 (MAGEL2), and necdin MAGE family member (NDN)) on the imprinting region 15q11.2-q13 due to a paternal deletion (70–75%), maternal uniparental disomy (UPD; 20–25%), or an imprinting defect of the critical region (1–3%) [17].

Methylation-specific multiplex ligation–dependent probe amplification analysis (MS-MLPA) is the gold standard test for diagnosing PWS, though it is unable to detect genetic subtypes [16]. This test can also differentiate PWS from Angelman Syndrome (AnS), a condition genetically related to PWS [16].

Excessive hyperphagia and the constant hunger have been linked with altered brain structures, in addition to reduced oxytocin neurons in the hypothalamus. Recently, it has been documented that selective disruption of Snord116 expression in the Medio basal hypothalamus models the hyperphagia of PWS. Involvement of the amygdala and reduced coupling of the ventral striatum with limbic structures for basic internal homeostasis suggest several brain areas responsible for regulation of food intake in PWS [18].

Patients with PWS are known to have high ghrelin levels, both before the development of obesity and also after the onset of hyperphagia in older children and adults. Ghrelin's orexigenic action is the potential cause of increased appetite and weight gain in PWS [18]. The underlying mechanism for this dysregulation is unknown.

There is no specific therapy to treat the primary cause of PWS. Therefore, management includes symptomatic treatment of hypothalamic dysfunction and prevention of obesity and its comorbidities. A strictly controlled diet and food security, both physical and psychological, are critical in the management of PWS [19] to prevent excess weight gain. Since the propensity to sneak and hoard food starts as early as age 2, behavioral therapy and dietary control by limiting the access to food is essential. Growth hormone therapy has demonstrated positive effects on weight gain by decreasing fat mass and increasing lean body mass. Furthermore, GH therapy has shown to help with linear growth [20] and improvement in respiratory function [16]. While we use behavioral measures to address food-seeking behavior, Liraglutide therapy has been tried to reduce the high ghrelin levels in PWS, which is the main driver of appetite at the hypothalamic level. Liraglutide has shown to decrease plasma ghrelin levels and BMI, but the long-term effects are not known [21]. Long-acting octreotide treatment has been tried which also lead to decrease in ghrelin levels but did not affect weight, appetite, and compulsive behavior towards food [22].

Table 1 Syndromes associated with obesity

Syndrome	Inheritance	Prevalence	Genetics	Characteristics
Alstrom	AR	1–9 in 1 000 000	Homozygous or compound heterozygous mutations in ALMS1, centrosome and basal body associated protein (ALMS1)	Blindness, hearing impairment, childhood obesity, insulin resistance, T2DM
Bardet–Biedl	AR	1 in 13 500 (Israel and Arab counties) 1 in 160 000 (Switzerland	Homozygous or compound heterozygous mutations in > 20 Bardet–Biedl associated genes	Obesity, polydactyly, retinal defects, renal defects, hypogonadism
16 p 11.2 deletion	AD	NA)	Microdeletion chromosome 16p11.2 (220 kb, 593 kb, or 1.7 Mb deletion)	Autism, severe early onset obesity, intellectual disability, congenital anomalies
WAGRO	AD	1 in 1,000,000	De novo heterozygous deletion on chromosome 11p13 in which haploinsufficiency of Wilms tumor 1 (WT1) and paired box 6 (PAX6)	Wilms tumor, aniridia, genitourinary anomalies, mental retardation, and obesity
Carpenter	AR	< 1 in 1,000,000	Homozygous mutations in RAB23, member Ras oncogene family (RAB23)	Acrocephaly, obesity. syndactyly of hands and feet, congenital heart defects, growth retardation, hypogenitalism
Cohen	AR	N.A.	Homozygous or compound heterozygous mutations in VPS13B	Developmental delay, facial dysmorphism, microcephaly, retinal dystrophy, truncal obesity, joint laxity, and intermittent neutropenia
Albright osteodystrophy	AD	N.A.	Heterozygous mutations in GNAS complex locus (GNAS) - Maternally: pseudohypoparathyroidism type IA - Paternally: pseudopseudohypoparathyroidism	Obesity, short stature, round face, skeletal defects, multi-hormone resistance in pseudo hypoparathyroidism type IA
Borjeson-Forssman-Lehmann	X-linked dominant/-recessive	< 1 in 1,000,000	Heterozygous mutations in PHD finger protein 6 (PHF6)	Severe intellectual disability, epilepsy, obesity microcephaly, short stature, hypogonadism, gynecomastia
Smith-Magenis	AD	1 in 15,000	17p11.2 interstitial deletion or, less frequently, heterozygous mutations in retinoic acid induced 1 (RAI1)	Intellectual disability, delayed speech and language, sleep disturbances, behavioral problems and obesity
Fragile X	X-linked dominant	1 in 2500–4000 males and 1 in 7000–8000 females	Mutation in fragile X mental retardation 1 (FMR1), trinucleotide (CGG)n repeat expansion > 200	Obesity, long face, large ears, prominent jaw, macro-orchidism, autism. Moderate to severe intellectual disability.
Kleefstra	AD	< 1/1,000,000	Heterozygous deletion at chromosome 9q34.3 or heterozygous intragenic euchromatic histone lysine methyltransferase 1 (EHMT1)	Mental retardation, obesity, hypotonia, brachycephaly, characteristic facial features, cardiac anomalies
Rubinstein-Taybi	AD	1 in 100,000–125,000	CREBBP and EP300 (deletions or mutations)	Short stature, obesity, dysmorphic facies, visual difficulties, eating problems

Beloranib, a previously studied drug in PWS-related obesity, is a methionine aminopeptidase 2 inhibitor that has shown positive effects in PWS patients. Its mechanism of action includes reduced fat biosynthesis, increased fat oxidation, increased lipolysis, and may also have additional effects within the hypothalamus. While studies demonstrated significant improvements in weight and hyperphagia in PWS patients, there were unfortunate adverse effects of thromboembolism, resulting in two fatal cases of pulmonary emboli [23]. While individuals with PWS may also be predisposed to thrombosis at baseline, these adverse events necessitated the postponement of further use of beloranib.

Diazoxide has also been investigated in the treatment of PWS. Its primary effect on K_{ATP} channel opening in the brain is thought to reduce the activation of NPY and AgRP, which in turn could reduce hyperphagia. It is associated with

hypertrichosis, fluid retention, and reduced endogenous insulin secretion, which may predispose to elevated blood sugars. It is currently under investigation in a phase III clinical trial [18].

Use of intranasal oxytocin (and its analog carbetocin) to treat hyperphagia is under investigation and has garnered attention despite contradictory results of different clinical trials. Thus far, one study involving younger children (< 11 years) showed improvement in food-seeking behavior [24]. Studies have highlighted the importance of daily physical activity by showing a significant reduction in total, resting, sleep, and activity energy expenditure in PWS patients compared with age-, sex- and BMI-matched subjects using whole-room indirect calorimeters. This was attributed to reduced activity and lower energy utilization due to reduced lean body mass which primarily consists of muscle [25]. On a significant note, restrictive bariatric surgery is not recommended in PWS as it is associated with high complication rates and even mortality [26]. Serotonin reuptake inhibitors are recommended to address behavioral issues. In patients with hypogonadism, hormonal replacement therapy is used to induce puberty; however, there have been documented adverse effects of testosterone replacement on behavior [27].

Additional therapies that alter the balance of acylated vs. unacylated ghrelin have also been investigated with some initial evidence of short-term efficacy [18]. Further studies are ongoing for these potential treatments.

Bardet–Biedl Syndrome (BBS)

BBS is an autosomal recessive disorder belonging to the family of ciliopathies with a prevalence of 1 in 13, 500 (Israel and Arab counties) to 1 in 160, 000 (Switzerland) individuals [28]. Apart from obesity, patients with BBS are primarily characterized by cone-rod dystrophy, post-axial polydactyly, cognitive impairment, hypogenitalism, and renal abnormalities. Secondary features include speech deficits, olfaction disorders (anosmia or hyposmia), psychiatric problems, T2DM, and ataxia/impaired coordination [28, 29].

Although BBS can be diagnosed clinically, a substantial clinical overlap exists with other ciliopathies like Alstrom's syndrome. There are 23 genes identified to be associated with BBS [BBS1—BBS20, Nephrocystin 1 (NPHP1), Fibrillin 3 (FBN3), and Centrosomal Protein 19 (CEP19)] among which mutations in BBS1 and BBS10 account for 23.2% and 20% of BBS cases in the populations of Europe and North America [29]. Disease-causing mutations in other BBS genes have a prevalence below 10% and even in most cases ≤ 5% [30]. Interestingly, to date, there has not been a genotype-phenotype correlation identified [31].

Apart from preventative measures to control weight gain and comorbidities of obesity, hormone replacement therapy has been approved to induce and maintain adequate secondary sexual characteristics [28]. Given the association of renal disease, studies have looked at the effect of diet on the progression of renal function and have reported a positive effect by slowing down the progression of renal failure [32].

Alstrom Syndrome (AS)

AS is an autosomal recessive with a prevalence of 1 to 9 cases per 100,000 individuals [33]. Patients with AS share some features with BBS such as obesity, cone-rod dystrophy, renal anomalies, male hypogonadism/female hyperandrogenism, and adult short stature. Additionally, AS is characterized by progressive sensorineural hearing impairment, T2DM, and dilated or restrictive cardiomyopathy [34]. AS is caused by homozygous or compound heterozygous mutations in Alstrom syndrome protein 1 (ALMS1) on chromosome 2p13 [35]. Studies have postulated that ALMS1 could play a role in β-cell function and/or peripheral insulin signaling pathways because AS patients are more likely to develop T2DM in contrast to BBS patients [36, 37]. Growth hormone appears to be beneficial for body composition and liver fat content [38] and in cases with T2DM, better glycemic control is noted with a combined therapy using a high-dose metformin and rosiglitazone [39].

16 p Deletion Syndrome

Prevalence is unknown. The primary features in 16p Deletion Syndrome include autism spectrum disorders (ASD) [40], schizophrenia, and neuropsychiatric disorders. Additional features include severe early onset obesity [41], DD, ID, hypotonia, epilepsy, behavioral problems, and speech problems. To date, no particular candidate gene located within the 593 kb region has been identified to explain the obesity phenotype [42]. Treatment options are based on the clinical presentation.

WAGR Syndrome

It is an autosomal dominant disorder with an estimated prevalence of 1 in 1,000,000. Its main features include the following: Wilms tumor, aniridia, genitourinary malformations (hypospadias, cryptorchidism), and ID. Obesity or severe hyperphagia has also been described in a subgroup of these patients, in which case the condition is often called WAGRO [43].

WAGR results from a de novo heterozygous deletion on chromosome 11p13 involving haploinsufficiency of WT1, PAX6, and brain-derived neurotrophic factor (BDNF). It is suggested that BDNF is a key player in the obesity phenotype seen in WAGR patients and even in overall energy homeostasis in humans [44].

There is more data available on the genetics of these syndromes in the recent years; however, treatment is still tailored to patients' symptoms. An early and accurate diagnosis is

critical since early recognition can help the health care team to deliver appropriate genetic counseling and anticipatory guidance. This approach will also help the parents to better understand the condition and allow them to participate in appropriate screening, follow-up, and early intervention programs.

Endocrinopathies

Classic endocrinopathies such as hypothyroidism and Cushing disease are commonly associated with obesity and should be assessed for in the evaluation of pediatric obesity. These conditions, in contrast to other causes of obesity, are characteristically associated with linear growth deceleration. A detailed clinical history and examination will identify children who warrant additional work-up and screening for these disorders.

In addition to growth failure, children often exhibit additional findings including fatigue, constipation, dry skin/hair, cold intolerance, and mood changes including apathy, decreased motivation, and/or depression. They may be noted to have enlarged thyroid and delayed relaxation phase on reflex examination. Obesity in hypothyroidism is primarily caused by relative increase in BMI related to growth failure, while weight gain continues within normal range for age. In addition, clinical hypothyroidism is associated with increased fluid retention and decreased energy expenditure which are additional contributing factors [45]. When obesity is accompanied by growth deceleration, screening labs including TSH and free T4 should be obtained to evaluate for possible hypothyroidism. Recent guidelines from the Endocrine Society now recommend against routine screening for endocrinologic etiologies of obesity in children unless there is concurrent short stature or height deceleration [46].

Cushing syndrome, also known as hypercortisolism, is exceedingly rare in pediatric population with an overall incidence of 2 to 5 cases per million people per year and only 10% of new cases occurring in children [47, 48]. The most common features at presentation are abnormal weight gain and suboptimal growth velocity occurring in 90% and 83% of cases [49]. Additional features such as hypertension, plethora, central obesity/adipose distribution, and thick, violaceous striae are often, but not always, present. Depending on the underlying cause of Cushing syndrome and pubertal status, children may also present with evidence of hyperandrogenism or hypogonadism. In children with suspected endogenous Cushing syndrome, screening with either 24-h urinary cortisol excretion or midnight salivary cortisol (2 separate samples) should be obtained followed by additional confirmatory testing if indicated [50].

Treatments/Challenges/Controversies in Pediatric Obesity

Traditionally, family-based behavioral interventions have formed the cornerstone of the treatment approach to obesity in children and adolescents. The central idea has been to target changes in eating habits, physical activity, and sedentary behaviors, with improvements in parenting techniques, using various tools, including goal setting, self-monitoring, providing contingent rewards, and problem solving [51]. Studies have shown that the effectiveness of behavioral interventions is dependent on dose and duration, social support available to participants, and delivery format and setting. A recent systematic review of intervention trials in youth reported that lifestyle-based interventions with a minimum of 26 contact hours between providers and families were likely to help reduce excess weight in children and adolescents, with higher intensity resulting in increased effectiveness [52]. Over the past 2 decades, multiple studies have shown efficacy of behavioral interventions in reducing weight and BMI in the short term, generally over 1–2 years, particularly when intense initial treatment is followed by specialized maintenance strategies [53]. It has also been reported that reduction of BMI *z*-score of 0.25 or greater significantly reduced cardiovascular risk factors (hypertension, hypertriglyceridemia, and low-HDL cholesterol) in overweight children, with a doubling of the effect with BMI *z*-score reduction of 0.50 or greater [54]. Increasingly, novel approaches are being incorporated into behavioral interventions, including motivational interviewing, mindfulness, executive functioning and acceptance, and commitment therapy. With technological advances, remote administration of interventions is also being tested. However, the most robust studies have been conducted in academic medical settings, and the concern is that outcomes may not be as significant when applied in community settings [55].

Managing obesity in specific populations of youth poses additional challenges, particularly among low-income minority populations, adolescents, and youth with severe degrees of obesity. The National Institutes of Health invested in 2 major groups of multi-center trials aimed at treatment or prevention of obesity in high-risk populations of low-income Hispanic and African-American children—the Childhood Obesity Prevention and Treatment Research Consortium (COPTR) and the Girls' Health Enrichment Multi-Site Studies (GEMS). Of the 4 studies under COPTR, 3 have been published over the past year, and all failed to alter the trajectory of weight gain among their participants, compared with controls [56]. The COPTR trial conducted in Cleveland Ohio randomized 360 primarily African-American urban youth at entry to sixth grade with BMI ≥ 85th percentile into 1 of 2 behaviorally distinct family interventions or an education-only control; neither of the interventions improved the BMI slope or health-related secondary outcomes over the 3-year period of the

study [57]. Similarly, disappointing results of randomized intensive obesity prevention interventions on BMI trajectories were reported in the COPTR studies conducted in predominantly Hispanic preschool children aged 2–5 years in Nashville, Tennessee [58], and Minneapolis, Minnesota [59]. These results temper our expectations for resource-intense lifestyle interventions outside the setting of academic medical institutions and challenge the notion that these approaches are scalable in the larger context of diverse communities.

With more severe obesity in youth, particularly in adolescents, and when associated with obesity-related comorbidities such as hypertension, type 2 diabetes mellitus, dyslipidemia, and sleep apnea, additional treatment modalities may be considered. Many pharmacologic options with differing mechanisms of action have been investigated and FDA approved for use in adults with obesity. These include the GI and pancreatic lipase inhibitor orlistat (Xenical, Alli); appetite suppressants such as lorcaserin (Belviq, Belviq XR), phentermine/topiramate (Qsymia), and naltrexone/bupropion (Contrave); and the GLP-1 analog liraglutide (Saxenda) [60]. When combined with lifestyle interventions, these medications lead to weight reduction of 5–10%, with multiple attendant cardiovascular and metabolic benefits. Many medications have been investigated in youth with severe obesity. These include metformin, liraglutide, phentermine, and topiramate [61]. These interventions resulted in BMI reductions of 2–5% and variable improvements in comorbidities. Adverse effects associated with these agents mainly include gastrointestinal symptoms, hypertension, and tachycardia. Octreotide, a somatostatin analog, has also been investigated in the short-term treatment of hypothalamic obesity in pediatric subjects. Effects on weight reduction were variable and small. However, biliary sludging, cholelithiasis, and other GI adverse effects were major limiting factors [62]. As with adult subjects, challenges with the use of medications for pediatric obesity include inadequate data, limited efficacy on weight reduction, cost, lack of coverage by insurance carriers, adverse effect profiles, and rebound weight gain upon discontinuation of the medications. At the current time, orlistat is the only medication approved by FDA for treatment of children 12–16 years of age; "short term" use of phentermine is FDA approved in youth above 16 years of age [63]. No weight loss medications are approved for use in children under 12 years of age.

Bariatric surgery is well established as a treatment option for adults with obesity, and it results in immediate and sustained weight reduction, as well as significant improvement in obesity-related comorbidities such as hypertension, diabetes mellitus, dyslipidemia, and sleep apnea. This modality of treatment, however, remains investigational in adolescents, due to the drastic changes induced in the nutritional status of subjects undergoing these procedures and is only pursued when the subjects are close to cessation of height growth. The Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) consortium was set up with support from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and enrolled 242 adolescents (19 years of age or younger) at 5 clinical centers from 2006 through 2012. Participants underwent Roux-en-Y gastric bypass ($n = 161$), vertical sleeve gastrectomy ($n = 67$), or adjustable gastric banding ($n = 14$). A recent publication reported on 5-year outcomes of gastric bypass among Teen-LABS participants compared with adult participants of LABS study [64]. Adolescent subjects achieved similar weight loss compared with adults (− 26% vs − 29%), but were more likely to have remission of type 2 diabetes (86% vs 53%), and of hypertension (68% vs 41%). Death rates were similar in the 5-year period—3 adolescents (1.9%) vs 7 adults (1.8%), but the rate of abdominal reoperations was significantly higher in adolescents than among adults (19 vs 10 reoperations per 500 person-years). These early results are very encouraging, but long-term follow-up is crucial to evaluate if and when weight rebounds and comorbidities recur. Vertical sleeve gastrectomy has less efficacy than gastric bypass. Adjustable gastric banding has fallen out of favor due to poor long-term efficacy and is rarely used now in adults or adolescents.

What does the future hold for managing obesity in youth? The prevention and treatment of obesity in children and adolescents is challenging for many reasons. In addition to the biology and behavior of youth and their family members, the specifics of the built environment of the community and social determinants of health may pose barriers to desired lifestyle change. Translating pilot studies from academic medical centers to the messy "real world" is resource intensive and reduces effectiveness. However, technical advancements in wearable devices and smart phone apps may aid youth and their families in behavioral monitoring towards more effective ways of weight control [65]. Combining currently available medications with different mechanisms of action may offer better efficacy, such as phentermine/topiramate (which is already FDA approved in adults) or SGLT2 inhibitors with GLP-1 agonists [66]. Other medications that hold promise in the treatment of pediatric obesity include lisdexamfetamine, a dopamine agonist that is FDA approved for the treatment of ADHD, and setmelanotide, a melanocortin-4 receptor agonist [63]. An additional area of research is the use of devices as alternatives to bariatric surgery to enhance satiety and decrease food intake. These include intermittent abdominal vagal blockade, intragastric balloon, and aspiration therapy with percutaneous gastrostomy [61]. These devices are FDA approved for use in adults, and as they are used more widely, the data generated will inform us of the appropriateness of their pursuit in the realm of pediatric obesity.

Ultimately, obesity in adults and youth represents a conglomeration of varied societal factors, priorities that have morphed over time, and entrenched business interests, in addition to biological and behavioral factors of individuals.

Changing the upward trend in the weights and BMI of youth and adults will require the willingness to change by multiple stakeholders, large-scale societal interventions using health policy tools, and the political will to enact change.

Conclusion

While current management techniques are presently unsuccessful in lowering national rates of obesity, our increased understanding of the neurocircuitry of energy balance and epigenetic impacts on the expression of mediators of appetite hold promise for future opportunities in weight management. Upcoming medical and surgical therapies hold potential in addressing difficult cases of obesity, though they are not without potential risks and consequences. While these therapies may hold promise on an individual level, broader impacts on children's health nationally will require the addressing of much more complicated issues that will require alterations in public policy and address the socioeconomic associations with obesity. Only through these necessary changes in health policy will we begin to see more significant impacts on obesity rates in future generations.

Compliance with Ethical Standards

Conflict of Interest Shashikala Gowda and Tasa Seibert declare that they have no conflict of interest.

Ryan Farrell has been principal investigator and/or coinvestigator for three different industry-sponsored pharmaceutical trials for Prader–Willi Syndrome (GLWL, Soleno, and Levo Therapeutics).

Naveen Uli has been principal investigator and/or coinvestigator for three different industry-sponsored pharmaceutical trials for Prader–Willi Syndrome (GLWL, Soleno, and Levo Therapeutics). He also was a coinvestigator for the Childhood Obesity Prevention and Treatment Research Consortium (COPTR).

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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