REVIEW

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Current Treatments for Patients with Genetic Obesity

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Abstract

Obesity derives from impaired central control of body weight, implying interaction between environment and an individual genetic predisposition. Genetic obesities, including monogenic and syndromic obesities, are rare and complex neuro-endocrine pathologies where the genetic contribution is predominant. Severe and early-onset obesity with eating disorders associated with frequent comorbidities make these diseases challenging. Their current estimated prevalence of 5-10% in severely obese children is probably underestimated due to the limited access to genetic diagnosis. A central alteration of hypothalamic regulation of weight implies that the leptin-melanocortin pathway is responsible for the symptoms. The management of genetic obesity has so far been only based, above all, on lifestyle intervention, especially regarding nutrition and physical activity. New therapeutic options have emerged in the last years for these patients, raising great hope to manage their complex situation and improve quality of life. Implementation of genetic diagnosis in clinical practice is thus of paramount importance to allow individualized care. This review describes the current clinical management of genetic obesity and the evidence on which it is based. Some insights will also be provided into new therapies under evaluation.

Keywords: Genetic obesity, syndromic obesity, personalized medicine, setmelanotide

Introduction

Obesity is a multifactorial and complex disease defined as an excess of body fat resulting from an inadequate energy balance over the long term. It is driven by the interaction between genetic predisposition and environmental factors and can manifest in early childhood with a lifelong burden (1).

Obesity is a major public health issue in our modern society, and its incidence has been increasing significantly among children in recent decades. According to the World Health Organization (WHO) in 2020, 12% of children aged 7-9 years in the 33 participating countries of the European Region can be considered obese (2). Worldwide, WHO has estimated the number of overweight or obese children under the age of 5 to be 39 million (3).

Obesity derives from impaired central control of body weight with a high genetic heritability (up to 80%) in populations developing severe and early obesity, before the age of six years (4,5). Within this genetic susceptibility, frequent polygenic variants with small effects may be distinguished from rare pathogenic variants with large effects causing monogenic and syndromic obesities. Regarding the latter, most of these genes are part of the leptin-melanocortin pathway, which is crucial in central nervous system regulation of body weight. Patients affected by these genetics anomalies show major eating disorder, such as impaired satiety and disruptive food-seeking behavior, from the first years of life resulting in severe early-onset obesity. Some of these patients may also suffer from childhood from neuropsychological and psychiatric disorders, endocrine comorbidities, and complications deriving from obesity.

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Thus, the clinical considerations in these obesities are often complex and challenging. The treatment of genetic obesity has so far been based on environmental control, starting as early as possible, to avoid obesity progression and to help the acquisition of appropriate eating and exercise behavior. The recent development of new therapeutic options for the management of these genetic obesities has made early diagnosis crucial to avoid massive weight gain in childhood and its negative effects on the health of affected children.

In this review, we will briefly describe the principal clinical pictures observed in patients with genetic obesity and then we will outline the distinct aspects of its current management, with a special focus on innovative therapeutics targeting hyperphagia.

Clinical Features of Genetic and Syndromic Obesities

Monogenic and syndromic obesities are part of the same spectrum of hypothalamic pathologies affecting the satiety signal. Both show early-onset obesity, defined for children by body mass index (BMI) higher than the International Obesity Task Force curve corresponding to BMI 30 kg/m^2 in adulthood before six years of age. A very early adiposity rebound before three years of age, or the lack of rebound, is regularly observed. This is related to eating behavior disorders which can be observed from the first months of life. Parents often describe a lack of satiety, intolerance of food restriction, and conflicts about limiting food intake. Later on, patients may have obsessions with food that interfere with other activities, and foraging strategies that may include stealing and night-time feeding (6). An important phenotypic variability is evident between patients with similar genetic disorders. It is partly explained by its interaction with environmental factors such as family and social conditions, ethnicity, and gender. Most common syndromic and monogenic obesities with associated genetic alteration and specific clinical features besides severe early-onset obesity are summarized in Table 1. They are mainly

Table 1. Most prevalent syndromic and monogenic obesities including the specific clinical features, and genetic alterations

	Affected gene	Specific clinical features
Syndromic obesity		
Prader Willi syndrome	Abnormal parental genomic imprinting of paternal 15q11-q13 region.	Neonatal hypotonia, suckling disorders in the first months, hyperphagia and food impulsivity around 4 years, moderate intellectual disability, social interaction and behavioral disorders, endocrine abnormalities (growth hormone deficiency, hypogonadism), dysmorphia, scoliosis.
16p11.2 microdeletion syndrome	Autosomal dominant transmission, small region of chromosome 16.	Developmental delay, intellectual disability.
Fragile X syndrome	X-linked dominant transmission, CGG trinucleotide expansion of *FMR1* promotor leading to a lack of transcription.	Intellectual deficiency and dysmorphic features of varying degree, more severe and frequent in males. 40% of obesity with some PWS-like phenotypes.
Bardet-Biedl syndrome	Autosomal recessive transmission, 22 genes known.	Retinal dystrophy, polydactyly, renal abnormalities, hypogonadism, hepatic fibrosis, learning disabilities.
Alström syndrome	Autosomal recessive transmission, *ALMS1* gene.	Retinal dystrophy, dysmorphic features, short stature, central deafness, endocrine abnormalities (central or peripheral hypogonadism and hypothyroidism, polycystic ovary syndrome) dilated cardiomyopathy, liver and renal fibrosis and no intellectual disability.
Pseudohypoparathyroidism	Autosomal dominant transmission, *GNAS* gene.	Dysmorphia, shot bones, short stature, subcutaneous ossifications, variable developmental delay, hypocalcemia, hypothyroidism, pubertal delay, epilepsy.
MYT1L	Autosomal dominant transmission, *MYT1L* gene.	Developmental and language delay, intellectual disability, behavioral disorders and dysmorphic features.
Monogenic obesity		
LEP	*LEP, LEPR, POMC, PCSK1, MC4R* genes: Autosomal recessive transmission: severe, early-onset obesity and eating disorders with related signs (see beside). Milder phenotype in heterozygous patients without related signs and more metabolic obesity complications.	Endocrine abnormalities (gonadotropic and thyrotropic insufficiency).
LEPR		Endocrine abnormalities (gonadotropic, somatotropic and thyrotropic insufficiency).
POMC		Endocrine abnormalities (corticotropic, gonadotropic, somatotropic and mild thyrotropic insufficiency), red hair.
PCSK1		Severe neonatal diarrhea, endocrine abnormalities (corticotropic, gonadotropic, somatotropic and thyrotropic insufficiency), hypoglycemia.
MC4R		Increased height growth in childhood.

ALMS1: Alström syndrome associated protein 1, FMR1: fragile x messenger ribonucleoprotein 1, LEP: leptin, LEPR: leptin receptor, POMC: proopiomelanocortin, PCSK1: prohormone subtilisin/kexin 1 convertase, MC4R: melanocortin receptor type 4, MYT1L: myelin transcription factor 1 like

related to dysfunction of the leptin-melanocortin pathway, a main contributor to the satiety signal and energy expenditure regulated in the hypothalamic arcuate and paramedian nuclei (Figure 1). This pathway involves the hormone leptin, synthesized by the leptin gene (*LEP*) in adipocytes, that activates its receptor (*LEPR*) inducing, in anorexigenic neurons, prohormone subtilisin/kexin 1 convertase (*PCSK1*) activity which converts proopiomelanocortin (*POMC*) to alpha-melanocyte stimulating hormone (α-MSH). The latter is the natural ligand of the melanocortin receptor type 4 (*MC4R*) which induces a satiety signal by its activation (7). Other genes are also implicated in the regulation of this pathway including *MRAP2* encoding for the melanocortin receptor accessory protein 2 (8,9), *ADCY3* encoding for adenylate cyclase 3 which transmits the MC4R activation signal intracellularly (10). Several genes involved in development of the hypothalamus or MC4R regulation have been reported to influence this signaling, including semaphorin 3A-G (*SEMA3A-G),* plexinA1–4 (*PLXNA1–4*), neuropilin1–2 (*NRP1–2*) (11), kinase suppressor of ras 2 (*KSR2*) (12), and the steroid-receptor co-activator 1 (*SRC-1*) (13). Genetic alterations in these genes lead to the phenotype described in both monogenic obesity and also in syndromic obesity.

Monogenic obesity (ORPHANET 98267) is due to a pathogenic variant on a gene involved in the leptin-melanocortin pathway (14-16). Most variants in the genes described above (*LEP, LEPR, POMC, PCSK1, MC4R* mainly) lead to severe and early obesity with eating disorders when the mutation is homozygous or compound heterozygous, with inconstant association to various endocrine disorders. Cohort studies have shown that heterozygous variant bearers in the same genes display milder phenotypes with a frequency of 10-12% of heterozygous variants in severe early-onset obesity cohorts, especially among children (17,18). Of these, *MC4R* variants are known to be frequent with an incidence of 0.3% in the general population from a cohort of screened newborns in the UK (19), and more than 5% in children with severe obesity (20). Besides these five genes, the other

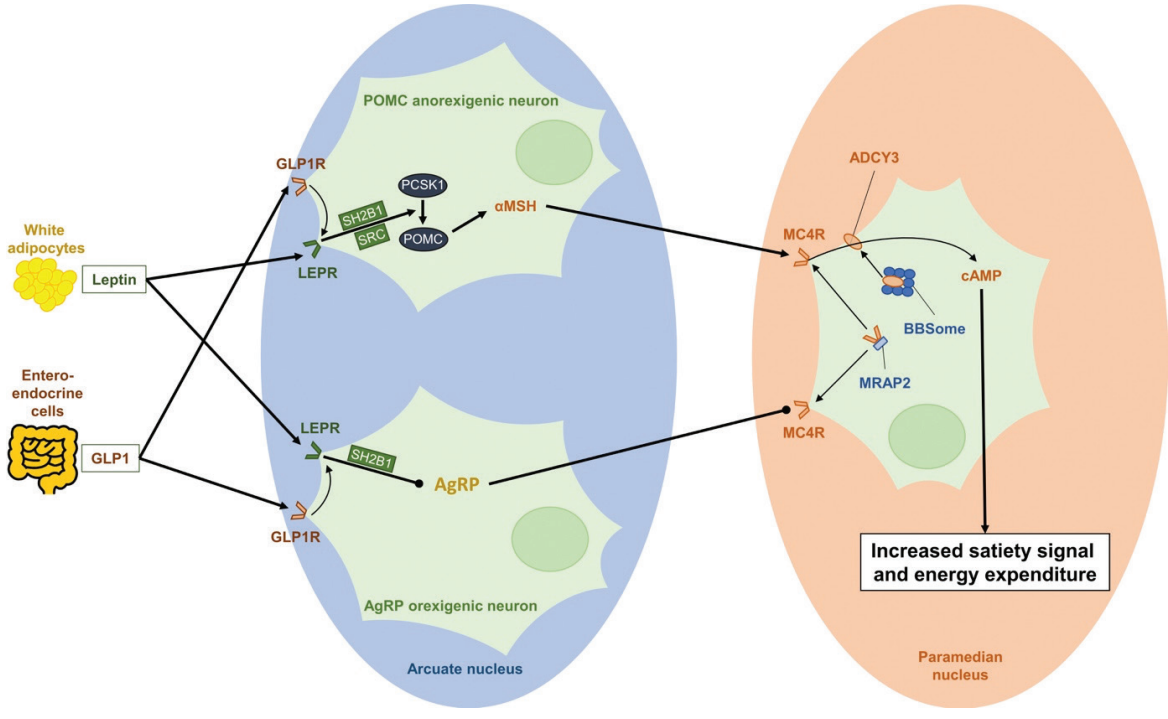

Figure 1. Schematic representation of the leptin-melanocortin pathway in the hypothalamic nuclei.

Peak-ended arrows represent stimulation, circle-ended arrows represent inhibition.

SH2B1 and SRC are activated secondary to leptin liaison on its receptor and potentialize its effect on POMC and PCSK1 in anorexigenic neurons, and SH2B1 potentialize LEPR inhibition effect on Agouti-related protein in orexigenic neuron. GLP1-R activation facilitates LEPR activation in both neuron populations. BBSome is an octameric complex composed of BBS1, BBS2, BBS4, BBS5, BBS7, BBS8 and BBS9 proteins which mediates transmembrane proteins localization in the primary cilium, including ADCY3. MRAP2 addresses MC4R to the cellular membrane.

α-MSH: melanocyte stimulating hormone type α, BBSome: Bardet-Biedl syndrome associated protein complex, BDNF: brain-derived neurotrophic factor, GLP1: glucagon-like peptide 1, GLP1-R: GPL1 receptor, LEPR: leptin receptor, MC4R: melanocortin receptor type 4, MRAP2: melanocortin receptor accessory protein 2, NTRK2: neurotrophic receptor tyrosine kinase 2, PCSK1: prohormone convertase subtilisin-kexin 1, POMC: pro-opiomelanocortin, SH2B1: SRC homology 2 B adapter protein 1, SRC1: steroid receptor coactivator 1

genes cited above have been reported to cause obesity in human in cases series or in rodent models but the frequency of mutations in cohorts of patients with early and severe obesity remains currently unknown.

Syndromic obesities (ORPHANET 240371) are characterized by association with malformations, dysmorphic features and/or neurodevelopmental disorders (psychomotor development delay, intellectual disability, autism spectrum disorders). Around 80 syndromes have been identified to date, some without elucidated genetic cause (21). The leptin melanocortin pathway is involved in several of them.

The Prader-Willi syndrome (PWS) is the most extensively studied form of syndromic obesity with an incidence of about 1/15000 births. It is often diagnosed in the neonatal period in the presence of severe hypotonia with feeding difficulties and dysmorphic traits. The evolution in childhood is marked by the appearance of challenging hyperphagia with an intense impulsivity which lead to early morbid obesity. The combination of obesity with interaction and behavioral disorders makes these symptoms even more problematic for care management (22). This syndrome also has a major impact on the quality of life and is also associated with an important mortality at all ages, with an average life expectancy of 30 years (23,24). The impact of severe obesity is most frequently involved in the cause of death, showing the great importance of its control in this specific population. PCSK1 deficiency and alterations of the orexigenic Agouti-related protein hypothalamic neurons have been described in PWS (25) as the inactivation of *MAGEL2* with decreased density of MSH neurons in rodents (26).

Bardet-Biedl syndrome (BBS), with a prevalence of about 1/125000 births, is also associated with severe early-onset obesity and with retinal dystrophy, polydactyly, renal abnormalities, dysmorphism, and learning disabilities. It is caused by a genetic alteration in the function of the primary cilium, with more than 20 involved genes identified to date. Current evidence suggests that the impairment of the primary cilium induces a hypothalamic dysfunction in the leptin-melanocortin pathway and partly explains the obesity phenotype with severe hyperphagia (27,28,29).

TO HEREThe 16p11.2 microdeletion syndrome has been more recently described and is the most frequent syndromic obesity known to date, with an estimated incidence of 1/2000 births. It is characterized by an altered satiety responsiveness leading to early-onset obesity, with developmental delay, neurodevelopmental disorders and is even more prevalent in patients with autism spectrum disorder. This syndrome is sometimes associated with non-specific malformations or dysmorphism (30,31). The mechanism related to obesity may be the deletion of *SH2B1* contained in this chromosomal region, which is involved in regulation of the melanocortin pathway. The specific deletion of *SH2B1* leads to hyperphagia and early obesity (32).

Another recently described genetic disorder is due to myelin transcription factor 1-like (*MYT1L*) variants. MYT1L is involved in development of the hypothalamus and its heterozygous variants are associated with syndromes showing severe obesity with abnormal feeding behavior, intellectual disability, neurobehavioral disorders and dysmorphic features (33).

All together, these descriptions illustrate the blurred distinction between syndromic and non-syndromic monogenic obesity and the overlap of phenotypes, also with similarity to those of hypothalamic obesity.

Lifestyle Modification Therapies in Genetic Obesities

In common obesity, the cornerstone of clinical management is to provide appropriate nutritional, behavioral and exercise intervention with the help of trained health professionals. The intervention of dieticians, psychologists and teachers of adapted physical activity is recommended for every patients suffering from genetic or syndromic obesity or at-risk of severe obesity later in life, in cases with early diagnosis (6,14). The instruction of caregivers is essential to enable environmental control. These measures should be implemented as early as possible in childhood, as they limit the development and aggravation of obesity and eating behavior disorders and maintained throughout life with increased vigilance during the transition from childhood to adulthood.

Concerning diet, the overall measures focus on avoiding uncontrolled food intake. Restricting food access, establishing a reassuring eating routine, and ritualization of food intake help to limit the impulsivity that leads to hyperphagia and disruptive food-seeking behavior. If dietary autonomy is seldom possible in genetic obesity with eating disorders, this strategy still improves the quality of life of patients and facilitates their social integration by easing their relationship with food. In monogenic obesities, absence of satiety is extremely severe, life-long and responsible for stigma and suffering for the patients (34). On the other hand, the early restriction of food intake through environment control has been shown to benefit PWS patients by slowing the progression of obesity (35).

It is also crucial to begin adapted physical activity. In patients with PWS, a decrease in baseline physical activity is noticed

compared to patients with non-syndromic obesity (36). Two recent systematic reviews about exercise in PWS showed improvement of physical capacities (maximum oxygen uptake, muscle strength, walking distance) but no weight or fat loss without associated dietary intervention (37,38). Children with pathogenic *MC4R* variants who received nutritional, physical, psychological, and family intervention for one year were able to lose as much weight as matched obese children without *MC4R* variation, approximately 0.4 BMI-standard deviation score (SDS) (39). Unfortunately, they were unable to maintain weight loss, unlike their mutation-free counterparts. Multicomponent lifestyle interventions thus have a positive effect on the health outcome of these patients but need to be intensive and sustained to remain effective over time.

Holistic and comprehensive approaches are essential to improve patients' clinical conditions and need expertise in specialized centers. Psychological follow-up is beneficial, both to manage the frequent neuropsychiatric comorbidities and the major psychosocial repercussions of these obesities and the resulting stigma. Neuropsychological evaluation may identify cognitive dysfunction or other specific learning disability to guide and improve psychological and educational support. Screening and treatment of specific comorbidities associated with the genetic defect (Table 1) may also prevent further complications and should thus be given special attention. Genetic obesity is often associated with hormonal deficiency, with better outcomes if treated before becoming symptomatic. Sleep disorders, digestive disorders, and orthopedic deformations, as well as associated congenital malformations, require additional attention and often assistance from other specialized physicians. Complications of obesity may also arise and necessitate additional treatment.

Transition between pediatric and adult care may also be a critical period in such complex patients. In a retrospective cohort study, PWS patients which received transitional care had a lower BMI by 10 kg/m² and less antidepressant treatments (40). All these supports allow patients' quality of life improvement and help them to integrate with social structures and build their own lifestyle.

Pharmacological Treatments

Even though not widely used in practice and often of modest efficacy, some treatments are now approved to treat common obesity (41). In the future, these treatments could be proposed for use in patients with syndromic or monogenic obesity, but only after careful clinical evaluation. GLP1 analogs are, amongst these treatments, probably the most promising molecules being investigated. Human GLP-1, an incretin secreted by entero-endocrine cells in response to food intake, enhances insulin secretion by the pancreatic ß-cell and improves insulin sensitivity. It reduces appetite through a reduction of gastric emptying and central effects on satiety signaling. These mechanisms allow improvements of glucose metabolism and body weight. GLP-1 analogs were first developed for type 2 diabetes before being explored as a treatment for obesity. Reported side effects include frequent nausea, dizziness, pain or local reaction at the injection site, abdominal pain and low blood sugar. Other rare serious side effects have been reported, including anaphylactic reactions, pancreatitis, gallbladder and biliary diseases (42) and acute renal failure. Close attention is needed regarding the tolerance of these treatments given the 2-to-3-fold higher doses used in obesity compared to diabetes. Furthermore, less is known about their long-term safety, and these treatments may need to be prolonged to maintain a significant effect on weight.

Among GLP-1 analogs, liraglutide is supported by the most extensive scientific reports. A double-blind randomized controlled trial (RCT) was conducted for treatment of common obesity in 251 adolescents (12-17 years) with liraglutide combined with lifestyle intervention (43). The assessment after 56 weeks of treatment revealed a significant decrease in BMI-SDS of -0.22 compared to placebo. BMI reduction of more than 5% was completed more frequently with liraglutide than placebo (43.3% vs 18.7%). These results are consistent with data available for adults with a body weight change of about -5% (44). Afterwards, liraglutide (Saxenda®) was approved by the Food and Drug Association (FDA) in 2020 and by the European Medicines Agency at a dose of 3 mg per day subcutaneously for the treatment of obesity in adolescents aged 12–17 years. Given these significant but modest effects on weight loss and the mode of administration (e.g., daily subcutaneous injection), the appropriateness of using this treatment in adolescent obesity remains controversial (45,46,47).

Exenatide, another GLP-1 analog with weekly injections, showed comparable results in a double-blinded RCT against placebo in 44 obese adolescents. Six months of treatment combined with lifestyle intervention permitted a significant but mild reduction in BMI-SDS (-0.09), BMI (-0.8 kg/m^2) and weight (-3 kg) (48). Exenatide has not been approved for the treatment of obesity to date.

More recently, semaglutide showed promising results for common obesity in two RCT investigating adults on the one hand and adolescents on the other (49,50). Concerning adolescents, a double-blind RCT published in 2022 analyzed weekly subcutaneous injection of semaglutide for 68 weeks against placebo in 201 obese adolescents with at least

one weight-related comorbidity. Lifestyle intervention was proposed in both groups. The treatment resulted in a major mean change in BMI of -16.1 % (against + 0.6 % with placebo) at the end of the study period. Moreover, 73 % of patients had lost > 5 % of weight and 62 % had lost > 10 % of weight after 68 weeks on semaglutide, against 18 % and 8 % in the placebo group, respectively. There was a significant improvement of weight-related quality of life and dyslipidemia in the semaglutide group. Semaglutide has been shown to be significantly more effective in weight loss than other GLP-1 analogues. It could pave the way for new therapeutic strategies against obesity in the years to come.

Regarding syndromic obesities, daily liraglutide combined with diet and exercise intervention was administrated to 55 adolescents and children with PWS in a 52 weeks multicenter RCT. There was no significant change in BMI SDS from baseline with an estimated difference around -0.1 SDS. A significant reduction in hyperphagia score was observed at week 52 for liraglutide compared to no treatment in adolescents but not in children (51). No RCT assessing PWS and the other GLP-1 agonists are available to date. The effect of GPL-1 agonists thus appears uncertain in PWS, the only syndromic obesity studied in regard of these treatments so far.

Among patients with monogenic obesity, a trial compared daily 3 mg liraglutide efficacy in 14 carriers of *MC4R* pathogenic variants against 28 non-mutated patients. An equivalent weight loss between the two groups of about 6 % of body weight after 16 weeks of treatment was observed with similar improvement in body fat mass, waist circumference, and glucose tolerance (52). These data suggest a preserved efficacy of GLP-1 agonists for genetic obesity with decreased MC4R signaling. There is no available evidence for other types of monogenic obesity and GLP-1 agonists to date. Further studies are now needed given the substantial expected benefit for these patients, especially considering its promising results in hypothalamic obesity (53).

PWS has benefited from the most intense therapeutic research among syndromic obesity due to its severity and frequency (41,54). PWS leads to a hypothalamic dysfunction involved in satiety deficiency but also results in impaired oxytocin (OXT) signaling and growth hormone (GH) deficiency (55). GH supplementation is recommended for PWS patients from diagnosis and throughout the growth phase. It has been shown to normalize height growth in children, increase lean mass, decrease body fat and improve psychomotor development (56). Continuation of the treatment during adulthood may help patients maintaining a better BMI, body composition and exercise capacity (57,58). Contradictory outcomes emerged from RCT on intranasal OXT supplementation for PWS patients (59,60), but it recently showed promising results, specifically in the youngest ones (61). The ghrelin pathway is indeed impaired in PWS and provides a potential therapeutic target. Livoletide, a non-acylated ghrelin analog, provided promising results concerning food behavior in a RCT of 40 PWS patients undergoing 14 days of treatment (62). Ghrelin O-acyltransferase (GOAT) is the enzyme catalyzing the conversion of ghrelin into its inactive form. A GOAT inhibitor is currently being evaluated in PWS (63).

Targeting the leptin melanocortin pathway has also led to development of successful innovative therapeutics, taking a great step towards personalized medicine in genetic obesity. Montague et al. (64) described the first human cases of congenital leptin deficiency, an exceptionally rare condition secondary to homozygous pathogenic variants in the *LEP* gene. When treated with recombinant leptin (metreleptin), these patients exhibited great weight loss with normalization of metabolic and neuroendocrine alterations (65,66,67). This success raised great hope for the treatment of common obesity. Unfortunately, common obesity is associated with leptin-resistance and its treatment with leptin monotherapy did not lead to sufficient efficacy (68,69,70). In addition, recombinant leptin is not indicated in other types of monogenic obesity with signal interruption downstream in the leptin-melanocortin pathway as in LEPR or POMC deficiency (71,72,73).

Since then, intense research efforts have led to the development of several MC4R agonists. Unfortunately, the first ones were responsible for cardiovascular side-effects. Recently, a better tolerated, highly selective MC4R agonist was discovered, setmelanotide (Imcivree, also initially known as RM-493). Indeed, due to the pivotal role of MC4R in weight, appetite, and energy expenditure regulation, this G protein-coupled receptor is a key target to increase energy expenditure and reduce food intake, causing a negative energy balance when activated. Daily subcutaneous injection of setmelanotide for one year resulted in significant appetite control, consequently resulting in weight loss in a trial assessing POMC and LEPR deficient patients stemming from *POMC* and *PCSK1* or *LEPR* homozygous mutations (74). In the POMC deficient group (10 patients), the mean weight loss was 25.6 % with 80 % losing at least 10 % of initial weight and induced an important decrease in the hunger score of 27 %. Regarding the 11 LEPR deficient patients, the efficiency was also significant with 12.6 % of mean weight loss, 45 % of them losing more than 10 % of weight and a decrease in hunger score of 44 %. The safety profile was characterized by frequent cutaneous hyperpigmentation,

but no other serious adverse events were reported. Transient digestive manifestations and local cutaneous reaction after injection were also frequently reported. These effects seem sustainable in the two first POMC deficient patients treated for more than 7 years with setmelanotide (75). The FDA approved setmelanotide in 2020, followed by the EMA in 2021, in the treatment of obesity in adults and children aged six years and older with confirmed genetic diagnosis of *POMC*, *PCSK1* and *LEPR* deficiency.

The effects of setmelanotide in *MC4R* variant carriers are more controversial. Setmelanotide is a markedly more powerful MC4R agonist than the endogenous ligand (α-MSH). In cellular models, this increased affinity allowed the rescue of intracellular signaling despite defective *MC4R* mutants. The study of rodent models has shown an intermediate response of *MC4R* heterozygous mutant to setmelanotide. These mice had less weight gain under high fat diet than the control *MC4R* heterozygous mice injected with saline. The beneficial effect of setmelanotide was less pronounced than in wild-type mice, while *MC4R* homozygous knock-out mice showed no effect of this molecule. A phase 1 RCT evaluated continuous subcutaneous infusion of setmelanotide during 28 days in eight patients carrying *MC4R* heterozygous pathogenic variants compared to 49 obese patients free of mutation. A significant change in weight loss for setmelanotide compared to placebo were observed for both *MC4R* heterozygous and obese control groups, with a similar effect of -3.48 kg and -3.07 kg, respectively (76). Further studies are required to decipher whether setmelanotide can efficiently induce significant weight loss in subjects with MC4R deficiency.

Concurrently, setmelanotide was studied in BBS patients because of its proven impaired leptin-melanocortin signaling associated to hyperphagia (28) in a 52 weeks multicenter phase 3 RCT that included 32 BBS obese patients more than six years old. The primary endpoint was significant, showing 32.3% of patients with BBS losing more than 10% of bodyweight after 52 weeks of setmelanotide, associated with a reduction in hunger scores (77). As a result of this trial, the EMA approved setmelanotide in 2021 as treatment for BBS patients older than six years, followed by the FDA in 2022.

One phase 3 RCT is in progress to assess setmelanotide treatment in Smith Magenis syndrome and 16p11.2 deletion (NCT03013543). Concerning the younger pediatric populations, a phase 3 open-label clinical trial assessing setmelanotide in PCSK1, POMC and LEPR deficient, and BBS child between 2 and 6 years of age is ongoing (NCT04966741).

Several pharmacologic therapies are now emerging, implying different affected molecular pathways. Some trials targeting hypothalamic obesity may also advance the field for genetic and syndromic obesity, given their similarities. Non-pharmacologic interventions such as deep brain stimulation are also being evaluated.

Bariatric Surgery

Presently, the most common surgical techniques are sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB). These interventions result in a sustainable weight reduction and remission of comorbidities in most of patients with common obesity (78,79). Bariatric surgery has regularly been undertaken for syndromic and monogenic obesity due to their severity, as the most effective treatment for patients with complicated severe obesity (80). These intervention outcomes remain, however, uncertain over the long term, as the evidence on its use in syndromic obesity are limited and heterogenous.

In syndromic obesity, SG has been studied in one monocentric pediatric study of 24 PWS patients with a mean BMI of 46.2 kg/m² compared to 72 children with common obesity matched for age, gender, and BMI. The PWS group started regaining weight from the fourth year of follow-up, with a BMI loss of 11 kg/m² after 5 years (7 patients' data) significantly lower than the 19 kg/m² loss observed in children without PWS. More than 80% of PWS patients experienced remission of their obesity comorbidities, mainly obstructive sleep apnea, and the safety was good with no major surgical complication (81). A recent systematic review assessed bariatric surgery outcomes for 202 adults and pediatrics patients with obesity associated with hyperphagia (114 patients with PWS, 43 with *MC4R* mutations, 38 with hypothalamic obesity and 7 with BBS). Statistical analysis included 96 PWS patients with a median age of 17 years, median weight of 97 kg and median BMI of 49 kg/m^2 with duration of follow up from 6 months to 14 years. These patients had a median weight loss of 24% within one year of surgery, but showed an important weight regain leading to a non-significant weight change five years after surgery. Surgical morbidity was also problematic with 10 deaths reported out of 104 patients with PWS, including five who died within one year after surgery. Moreover, 13 PWS patients underwent a second bariatric surgery. Long-term outcomes in other hyperphagic obesities were heterogenous but showed a trend towards less weight loss and increased surgical reinterventions (82). These finding suggests that PWS patients may be more likely to regain weight long-term and more prone to surgical complications. In other type of syndromic obesity, isolated

cases of patients undergoing bariatric surgery have been reported, with varying interventions, follow-up and results. It is worth pointing out that no study assessed psychiatric and nutritional complications, more frequent in these particularly vulnerable patients. Caution should be required as patients with syndromic obesity show severe behavioral disorders, developmental disorders and compulsive food behavior which could interfere with lifestyle changes mandatory after bariatric surgery and might lead to worse outcomes. Syndromic obesity therefore appears to be an inadequate indication for bariatric surgery.

Regarding monogenic non-syndromic obesity, the most evidence concerns long-term outcome of bariatric surgery in terms of retrospective genetic analyses. The most important of these published studies assessed the effect of heterozygous variants in the leptin-melanocortin pathway on the long-term outcomes after RYGB in a retrospective case-control study with 50 heterozygous variant carriers and seven genes were analyzed: *LEPR*, *PCSK1*, *POMC*, *SH2B1*, *SRC1*, *MC4R*, and *SIM1*, while 100 matched (sex, age, BMI, and time since surgery) controls free of mutation were also assessed. Mean age was 51 ± 11 years and BMI 46 ± 7 kg/m^2 at the time of surgery. The percentage weight loss 15 years after surgery was -16.6 ± 10.7% for variant carriers against -28.7 ± 12.9% in matched controls. The weight regain after maximum weight loss was also greater in heterozygous patients with 52.7 ± 29.7 kg compared to 29.8 ± 20.7 kg for non-carriers. These data show a lower long-term efficiency of RYGB in heterozygous variant carriers secondary to more weight regain, possibly due to eating behavior disorders (83). These results were consistent with a former retrospective genetic analysis in 131 obese adults who underwent SG surgery, showing that the 10 patients carrying heterozygous variants in the leptin-melanocortin pathway had less weight loss over both the short-term and long-term (84). However, another study of 1014 patients who underwent bariatric surgery which included 30 patients with a heterozygous variant in the leptin-melanocortin pathway (12 in *POMC*, 11 in *MC4R*, 5 in *PCSK1*) showed similar weight loss among mutation carriers and controls after a short follow-up of two years (85). A recent multicenter case-control study also compared outcomes of 35 patients with heterozygous likely-pathogenic *MC4R* variants compared with 70 mutation-free controls matched for age, sex, BMI and surgical procedure. Five years after bariatric surgery, a trend towards greater weight regain after nadir was observed for the *MC4R* variant carriers, which was greater after SG than after RYGB (86).

Concerning homozygous variant carriers, the largest case series available to date reported eight patients with *POMC*, *LEPR*, and *MC4R* mutations. Long-term outcomes were unsatisfactory and experienced by every patient with a median weight regain of 24.1 kg after an initial median weight loss of 21.5 kg (87).

Thus, melanocortin pathway heterozygous variants, in the absence of major eating or neurodevelopmental/psychiatric disorders, are not an absolute contraindication to bariatric

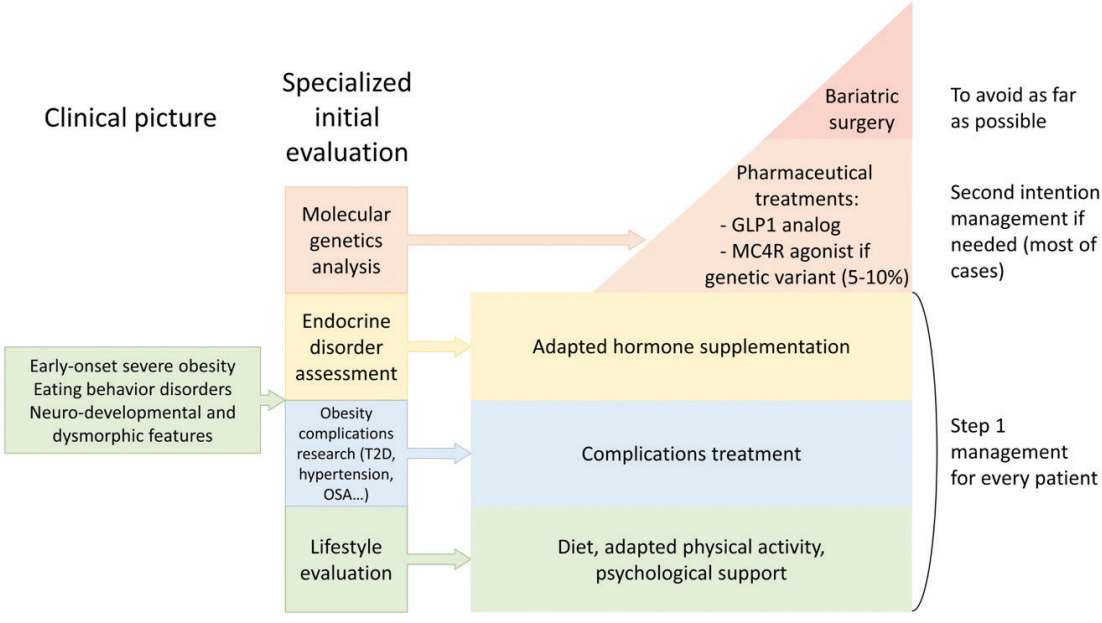

Figure 2. Emerging strategy for management of genetic and syndromic obesity.

OSA: obstructive sleep apnea, T2D: type 2 diabetes

surgery. However, with the emergence of new effective treatments, caution and multidisciplinary discussion to accurately judge the benefit-risk balance are warranted before opting for surgery (Figure 2).

Conclusion and Perspectives

Until recently, only multicomponent lifestyle interventions were proposed for patients with syndromic or monogenic obesity. While it remains the basis of their clinical management, the emergence of innovative, targeted treatments in recent years has changed this reality and paved the way for personalized medicine for these diseases in the future. Bariatric surgery now has pharmaceutical challengers for weight loss, which should probably be preferred in these situations to avoid irreversible anatomical changes and uncertain outcomes. However, further efforts are still needed to clarify the position of each treatment in each of these rare and complex clinical conditions. Early genetic diagnosis remains a major concern for these patients while it permits access to specialized multidisciplinary care, new molecules, and ongoing clinical trials to optimize their management. Genetic analyses should be offered to every child with rapid weight gain and additional clinical suggestive features. This population, confronting a lifelong struggle with obesity and its complications, certainly require special attention, which may prevent the development of obesity related complications, avoid the failure of conservative treatment approaches, and reduces the stigmatization of patients and their families. Intensive lifestyle intervention may help to improve these features, particularly when held on an outpatient basis as close to home as possible. Specific healthcare pathways are currently available in France to explore this hypothesis. This management will hopefully lead to a better prognosis for these patients in adulthood.

Research is thankfully still producing new solutions. Patients with monogenic forms of obesity may benefit in the future from CriSPr-mediated gene editing via induced pluripotent stem cell technologies (88) or direct defective gene repairing (89). Given the clinical severity of these patients, involvement and cooperation from both physicians and scientists is still required to improve their conditions and outcomes.

Ethics

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: Nathan Faccioli, Christine Poitou, Karine Clément, Béatrice Dubern, Design: Nathan Faccioli, Christine Poitou, Karine Clément, Béatrice Dubern, Literature Search: Nathan Faccioli, Christine Poitou, Karine Clément, Béatrice Dubern, Writing: Nathan Faccioli, Christine Poitou, Karine Clément, Béatrice Dubern.

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