

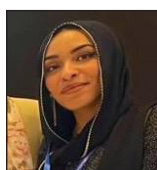


Review Article

Obesity on a Molecular Level: A Review of Pathogenesis and Treatment Approaches

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ABSTRACT

Obesity represents a multifactorial, nuanced, and global public health concern. An individual can be predisposed to obesity owing to the intricate interplay between key genes, the surrounding environment, and personal habits. Nutrigenetics offers insights into how molecular biology and diet intersect. This paper documents the reported direct and indirect effects of genes, hormones, and receptors involved in metabolic regulation, including fat mass and obesity-associated gene, melanocortin 4 receptor, ghrelin, and leptin, along with dopamine and its receptors. Additionally, this paper presents preventative measures for obesity along with currently available treatment approaches, including herbal, pharmacological, and surgical interventions, as well as lifestyle modifications affecting the body on a molecular level. Additionally, an individualised diagnostic and treatment pathway using obesity biomarkers is proposed. Lastly, this review highlights that research on obesity from a molecular biology perspective is still evolving, and that there are few to no approved genetic treatment approaches despite the growing body of research in the fields of nutrition and genetics.

Keywords: Ghrelin, Leptin, Molecular biology, Nutrigenetics, Obesity

1. INTRODUCTION

Human obesity is nuanced and typically arises from the interaction between genetic/epigenetic factors and various environmental influences.^[1] As a pressing global concern, the 'obesity epidemic' represents a challenging area of research. The World Health Organisation noted that, in 2022, approximately 2.5 billion adults (43% of the global adult population) were overweight, with over 890 million living with obesity. More recently, in 2024, an estimated 35 million children under the age of 5 were overweight.^[2] Adipose tissue, previously considered passive energy storage, is currently known as the body's largest endocrine organ.^[3] It is responsible for the synthesis and release of multiple bioactive proteins such as adipokines. Adipocytes, along with other fatty tissue components, produce molecules that exhibit a wide range of endocrine, autocrine, and paracrine activity.^[4]

Obesity has recently been characterised as a disease with a broad genetic and hereditary component. Genes like MC4R, FTO, LEP, and their receptors have demonstrated a profound effect on Body Mass Index (BMI) over many years, leading them to be subjected to a growing body of research in this area.^[5,6] Furthermore, dopamine and its receptors, especially the D2 and D3 subtypes, have been implicated in food addiction and, consequently, marked obesity.^[7] This review sheds light on the genetic causes and the diagnostic markers of obesity, as well as treatment interventions, including pharmaceutical, surgical, and lifestyle interventions.

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2. POSSIBLE GENETIC CAUSES OF OBESITY

2.1. Polymorphism and genetic variants

It has been shown that specific genes involved with appetite and energy intake regulation have multiple variants, each of which has a unique effect on appetite, manifesting as fluctuation in energy intake and a specific inclination to certain food types. Alleles/ variants of genes like MC4R, FTO, GHRL, and LEP play a distinctive role in the aforementioned dietary inclinations that usually lead to obesity, long-term. This is why these alleles are referred to as 'Risk alleles'. For instance, rs7799039 is one of the most studied leptin polymorphisms. Men possessing a risk allele of the rs7799039 variant reported higher energy, fat, and saturated fatty acids intake than those without it.^[8]

It is generally assumed that poor self-discipline is the sole culprit causing obesity. However, research by Crovesy *et al.* introduced a nuanced approach.^[8] They simplified the intricate gene-diet interactions and their impact on dietary intake and preference. They showed that polymorphisms affecting genes involved in the regulation of energy intake have been linked to particular dietary intake patterns. For instance, the presence of the variant, rs17782313, of the Melanocortin 4 Receptor (MC4R) gene is associated with increased energy and fat intake and decreased protein and carbohydrate intake [Figure 1].

As for the Fat Mass and Obesity-Associated (FTO) gene, its variant, rs9939609, was found to be associated with increased saturated fatty acid, snack, and general sugar intake, as well as a decrease in appetite and craving when on a high-protein diet. As such, the findings suggest that actions such as frequent eating or overeating are not the only causes of obesity.^[9]

It was found that about 20.5% of obese adults had a homozygous allele.^[10] Furthermore, it was noted that the occurrence of the polymorphism was higher among obese subjects than among lean ones, indicating that this genetic

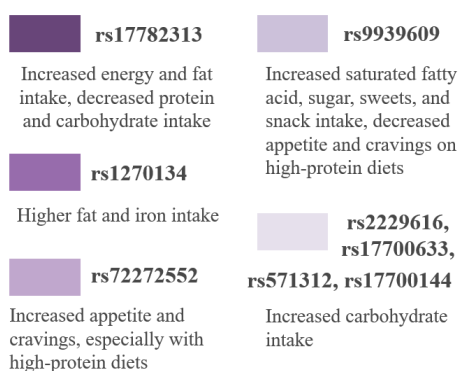


Figure 1: Influence of genetic variation on dietary preferences.

polymorphism may be a prominent driving factor for obesity. Table 1 summarises the polymorphisms involved in the pathogenesis of obesity.

2.1.1. Leptin receptor mutation

The hormone leptin, known casually as the satiety hormone, is an adipocyte-specific hormone. Linked to the obese (Ob) gene, leptin governs the mass of adipose tissue via the hypothalamic impact on energy expenditure and satiety.^[11] It acts on the single-transmembrane-domain leptin receptor. Homozygous mutations in leptin receptor 1 or 6 encoding genes have been shown to induce early morbid obesity, hyperphagia, and diminished energy expenditure in rodents.^[12] Furthermore, these rodents also exhibited hypercortisolemia and modifications in glucose homeostasis, dyslipidemia, and hypogonadotropic hypogonadism.

While these results were shown in rodents, studies done on humans reported early-onset obesity caused by leptin deficiency driven by a leptin gene mutation. This mutation leads to the loss of both the intracellular and transmembrane domains, leaving the receptor truncated and dysfunctional. Feeding behaviour in individuals suffering from this mutation is distinguished by marked hyperphagia and ravenous, insatiable hunger.^[13]

Additionally, patients affected by this leptin receptor mutation experience no pubertal development, as well as a reported reduction in the secretion of both growth hormone and thyrotropin, which also remarkably affects metabolism. These findings show that leptin is physiologically crucial in regulating various endocrine functions in humans.^[12]

2.1.2. Ghrelin gene variations

Ghrelin, which is a hormone casually referred to as the hunger hormone, is encoded by the GHRL gene. It is secreted by the bowels and promotes the release of growth hormone, appetite, and food consumption.^[8] In a 2015 study conducted on mice, obesity induction was performed by enforcing a high-fat diet for 13 weeks. The number of preproghrelin mRNA-expressing stomach cells was reportedly 15% higher in mice fed a high-fat diet than in the chow-fed control group of mice. Furthermore, a marked increase of 30% of body fat content was reported in high-fat-diet-fed mice versus only 8% in controls.^[14]

These findings show that long-term high-fat diet consumption can lead to obesity and causes a marked increase in body fat. But what warrants more attention is how this increase in body fat manifests. Ghrelin plays a key role in this mechanism. A high-fat diet was proven to increase the number of ghrelin-expressing stomach cells, leading to increased appetite and higher food intake.

Table 1: Summary of genes, polymorphisms, and their roles in obesity.

Gene	Polymorphism/Variant	Effect on Obesity	Mechanism	Reference
LEP	rs7799039	Increased energy, fat, and saturated fatty acid intake in men	Affects appetite regulation and energy intake	[8]
MC4R	rs17782313	Increased energy and fat intake; decreased protein and carbohydrate intake	Disrupts appetite and energy balance regulation	[8]
FTO	rs9939609	Increased saturated fatty acid, snack, and sugar intake; decreased appetite on high-protein diet	Affects dietary preferences and appetite control	[8]
LEPR	Homozygous mutations in receptor 1 or 6	Early morbid obesity, hyperphagia, diminished energy expenditure	Loss of leptin signaling leading to disrupted satiety	[12,16]
LEPR	Truncating mutations	Early-onset obesity, marked hyperphagia, insatiable hunger	Dysfunctional leptin receptor causing leptin resistance	[13,20]
GHRL	Arg51Gln	Associated with ghrelin activity modulation	Affects hunger hormone function	[15,21]
GHRL	Leu72Met (Met72 allele)	Earlier-onset obesity compared to wild-type Leu72	Altered ghrelin activity affecting appetite regulation	[15,21]
D2	TaqIA A1 allele	Higher risk of obesity, decreased impulse control	Reduced D2 receptor expression affecting reward pathways	[18]
D2	TaqIA A2/A2 allele	Increased susceptibility to overeating and future obesity	Enhanced striatal responses to palatable food	[18]

LEP: Leptin; MC4R: Melanocortin 4 Receptor; FTO: Fat Mass and obesity-associated; LEPR: Leptin receptor; GHRL: Ghrelin; D2: Dopamine receptor D2

Similar to the findings observed in humans with leptin gene mutation leading to marked obesity in most individuals, ghrelin gene variations and obesity may be correlated. Arg51Gln and Leu72Met are the two polymorphisms often reported in humans. People with the Met72 allele reported earlier-onset obesity compared to patients homozygous for the wild-type Leu72 allele, which suggests that polymorphism may affect ghrelin's activity.^[15]

2.1.3. Dopamine receptor variations

In a study done on rats, rapid weight gain and obesity were anticipated in the rats with access to a 'cafeteria diet' due to the marked increase in adiposity accompanied by decreased levels of striatal D2 receptors as a result of their consumption of a diet high in fat and sugar, typical of what humans with obesity would consume. Downregulation of mRNA levels for D1 and D2 receptors, as well as reduced dopamine levels in the NAc, were also observed.^[16]

D2 receptor levels in the striatum have been associated with metabolic activity in multiple cortical areas, which are critical in preserving behavioural control and managing impulsive tendencies when functioning correctly. Rats with low D2 receptors or low accumbal dopamine prefer calorically dense food, making them genetically obese.^[17] Moreover, studies performed on humans showed that individuals with the TaqIA A1 allele, which is involved with reduced expression of D2 receptors, have a higher risk of obesity. They also showed

decreased striatal activation in response to palatable food, leading to a suggested decrease in impulse control.

However, it is essential to note that the opposite can also lead to obesity. A study showed that individuals with the TaqIA A2/A2 allele increased striatal responses to a palatable milkshake, which predicts susceptibility to overeating and, as a result, future obesity. All findings combined suggest that too much or too little D2 receptor-mediated dopamine signalling can increase the risk of obesity.^[18]

3. BIOMARKERS OF OBESITY AND DIAGNOSIS: TOOLS FOR EARLY DETECTION

Research findings show that the waist circumference as a metric of fat allocation can aid prediction of obesity. More comprehensive techniques are available, such as magnetic resonance imaging. These tests are widely available for evaluating the distribution of body fat. Still, they are not readily available in clinical practice, and limitations of such tests that are important to health have not yet been identified. Measuring biomarkers representing the fundamental biological pathways for the increased risk of obesity may be an alternative approach to classifying the associated obesity phenotype.

Obesity was traditionally classified according to the BMI. However, it is now known that BMI has some major drawbacks when diagnosing obesity on an individual level.^[19] This is why the measurement of plasma biomarkers in individuals,

in theory, seems like one of the most accurate predictors of obesity or the lack thereof. However, current information on the primary role of obesity-related biomarkers in disease progression is limited, and thus, the evaluation of obesity biomarkers in clinical practice is not currently being carried out in the scope of obesity diagnosis.^[20]

3.1. Leptin-to-adiponectin ratio

Leptin-to-adiponectin (L:A) ratio has been investigated as a potential biomarker for the early detection of metabolic disturbances associated with obesity and leptin resistance. In a recent study, the L:A ratio was considered a potential biomarker for postprandial triglyceride clearance, insulin resistance (IR), or leptin resistance (LR).^[21] The study compared obese individuals, divided into metabolically healthy obese subjects (MHO) and metabolically dysregulated obese (MDO) ones, to another group of healthy subjects. The adipokines and adiponectin values were measured using ELISA kits.

In this study, about 90% of the obese subjects had LR, while no differences were seen between the obese subgroups. Leptin is an indicator of fat mass, so it was not surprising to see high leptin levels in all of the obese subjects. While adiponectin was markedly lower in obese subjects than in healthy subjects with normal weight, no differences were observed between the MHO and MDO subgroups. On the other hand, 76% of the obese subjects (having both MHO and MDO) displayed low adiponectin values.

The obese subgroups showed delayed TG clearance, IR, and LR, indicating that almost all of the obese subjects' metabolism is dysregulated. The study findings suggest that the L:A ratio may be a good surrogate biomarker of early obesity-related metabolic disturbances. This may aid in early, directed intervention and prevention of developing metabolic disorders and their complications.

Another study done on obese women showed that leptin levels were significantly higher, but adiponectin levels were lower in women with obesity and metabolic syndrome than in those without metabolic syndrome. This shows that the L:A ratio can not only be an indicator of obesity, but it also indicates the presence of metabolic syndrome.^[22]

3.2. Free IGF-1

Insulin resistance has long been known to be associated with obesity. In the long term, insulin resistance is characterised by hyperinsulinemia. However, more recent findings suggested that obesity first induces hyperinsulinemia, followed by insulin resistance. Hyperinsulinemia increases the bioavailability of free insulin-like growth factor (IGF)-1 by downregulating

IGF binding proteins (IGFBP-1 and -2) synthesis on the one hand and through the upregulation of hepatic IGF-1 synthesis on the other hand. A small cross-sectional study found that free IGF-1, but not total IGF-1, was higher in obese than in normal-weight individuals, suggesting that it can be an indicator of obesity with underlying hyperinsulinemia.^[20]

3.3. CRP and other inflammatory biomarkers

Obesity has shown an association with chronic low-grade systemic inflammation; the production of inflammatory cytokines in the adipose tissue of individuals with obesity, such as tumour necrosis factor α (TNF- α) and interleukin-6 (IL-6) is upregulated, which stimulates the liver to secrete acute phase proteins such as C-reactive protein (CRP).^[23] Moreover, obesity-induced inflammation is mediated by the secretion of pro-inflammatory adipokines, like leptin and resistin, and a decreased production of the anti-inflammatory adiponectin. In theory, many of the mentioned inflammatory biomarkers can be used to diagnose obesity. Detecting chronic low-grade inflammation, however, requires high-sensitivity assays that can determine the concentration of CRP in subclinical ranges, i.e., <10 mg/l. Older studies employed simple assays with a detection limit of >10 mg/l, which should be interpreted with caution.^[20]

3.4. Circulating miR-216a

MicroRNAs (miRNAs), small non-coding RNA molecules, are able to remain stable in plasma and have been studied as potential predictive biomarkers for obesity and related metabolic disorders. In a recent study aimed at identifying circulating miRNAs as biomarkers for obesity status in women, 60 obese women and 60 normal weight-age-matched control women were selected. At the end of the study, circulating miR-216a was validated as a biomarker of obesity, with notably low levels in obese women. Not only that, but a negative correlation between the plasma miR-216a content and body mass index (BMI), waist circumference, triglycerides, as well as other metabolic dysregulation markers, was observed. Suggesting that the abnormally expressed circulating miRNA, miR-216a, could be a predictive marker for obesity.^[24]

3.5. Serum omentin

Another recent study enrolled 60 obese individuals and 40 normal-weight controls to find possible correlations between omentin, a secretory protein produced in visceral adipose tissue, and obesity. Omentin concentration in obese individuals was found to be significantly lower than that in controls (145.5 ± 33.3 versus 383.6 ± 92.9). Moreover, a negative correlation of omentin with waist and hip circumferences, percent of adipose tissue, body weight, and

body mass index, which is considered to be a worldwide-recognised metric for obesity.^[4] Based on the significance of the biomarkers mentioned above, a personalised diagnostic and treatment approach is suggested in Figure 2, which can serve as a basis for a more accurate and individualised treatment of obesity on a molecular level.

3.6. Gut microbiome

Of the numerous underlying causes of obesity, the complex relationship linking host genetics, gut microbiota, and obesity remains a remarkable one. A population-specific study has consistently identified dysbiotic patterns in children with obesity who exhibited a low proportion of Bacteroidota and an increased proportion of Firmicutes. This resulted in an elevated Firmicutes/Bacteroidota ratio, whereas Actinobacteriota were found to be higher in the gut microbiota of children with varying degrees of obesity.^[25] Higher BMI was associated with microbiota that produced short-chain fatty acids, leading to pro-inflammatory state.^[26] Additionally, transgenerational influences have been proven to result in gut dysbiosis, as well as epigenetic modifications in offspring; as such, maternal nutrition shapes the metabolism of individuals.^[27]

4. OBESITY TREATMENT APPROACHES

4.1. Molecular approaches

4.1.1. Intermittent fasting

Despite seeming as a surprisingly simple approach to such a complex problem, intermittent fasting (IF) poses a feasible way to alter gut microbiota affecting body weight. In a review by Cadena-Ullauri *et al.*,^[28] obesity was presented as a public health concern characterised by an imbalance between Firmicutes and Bacteroidetes. IF has been associated with multiple health benefits, namely weight loss and blood glucose regulation. Although the exact mechanism underlying its benefits is still unclear, it has been shown that it may involve gut microbiota alterations.^[29] A study by Su *et al.* has shown that Ramadan-associated IF diversified the gut microbiome and was associated with an increase in Clostridiales order-derived Lachnospiraceae and Ruminococcaceae.^[29] As such, IF leads to changes in the levels of microbial metabolites that act as signaling molecules contributing to a regulated circadian rhythm. This shows promise in the prevention and treatment of diseases associated with circadian rhythm dysregulation, such as metabolic syndrome and obesity.^[30] Other studies have shown that IF prompts metabolic alterations that aid

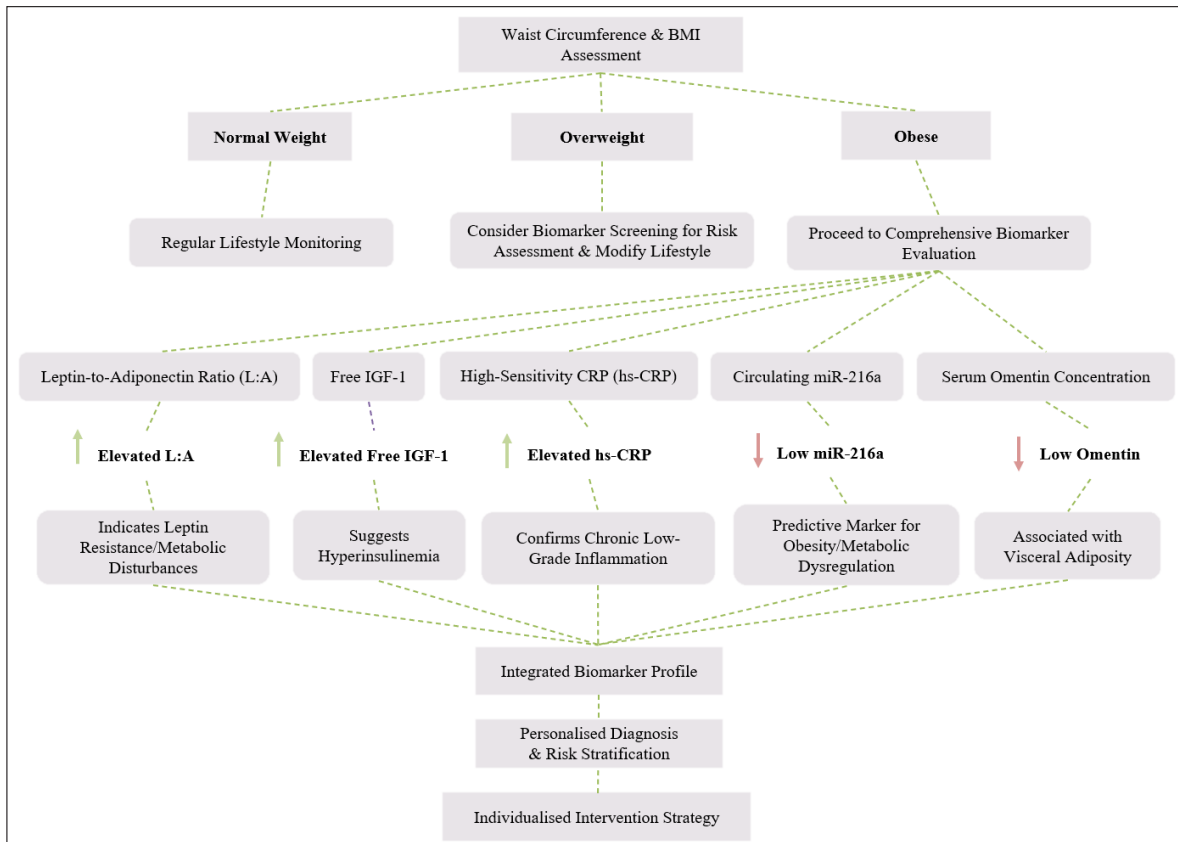


Figure 2: Flowchart of an individualised diagnostic and treatment pathway using obesity biomarkers. BMI: Body mass index; IGF-1: Insulin-like growth factor 1; CRP: C-reactive protein; miRNA: microRNA.

in fat utilization. Notably, specific bacterial taxa exhibited complex interactions with serum metabolites involved in amino acid metabolism, focusing particularly on tryptophan derivatives and fatty acylcarnitines.^[31] Thus, IF was proposed as a promising weight-management approach that favors fat utilization. Despite having proven an association between IF and gut microbiota diversity and alterations, findings of such studies are inconsistent; the bacteria that were found to be affected by IF varied across studies, warranting further research.^[32]

4.1.2. Gene therapy

The goal of gene therapy for obesity is to increase or decrease gene product in favour of lipolysis and energy expenditure, aiming at fat reduction and weight loss. It comprises the successful delivery and expression of therapeutic genes in target cells. As discussed before, leptin is the most studied gene directly associated with obesity; it plays an important role in regulating energy intake, affecting appetite and hunger cues. It acts through binding to its receptor in the brain.^[33]

Multiple attempts have been made to make functional copies of genes to compensate for the loss of functional protein due to the previously mentioned hereditary defects in leptin receptors. Gao and Liu summarised gene therapy approaches for the prevention and treatment of obesity.^[34] For example, adenovirus-mediated leptin gene delivery effectively reversed obesity in leptin-deficient mice, although diet-induced obesity exhibited leptin resistance, which limited the treatment efficacy.^[35] Other approaches include gene transfer of BDNF, FGF21, and adiponectin, which limit weight gain and enhance glucose metabolism via improving energy expenditure and reducing inflammation. Moreover, RNA interference targeting JNK1, HIF1, and pro-inflammatory cytokines has also shown promise in alleviating obesity-related metabolic disorders. These findings provide a pre-clinical basis for treating obesity genetically.

4.1.3. Gut microbiota alteration

Novel treatment strategies for obesity based on microbiome modulation to mimic that of healthy individuals have been proposed.^[36] For instance, prebiotic fiber intake may benefit individuals with obesity and associated disorders by regulating gut microbiota. Prebiotics are generally posed as a safe and cost-effective approach to modulating the microbiota for improved host–bacterial interactions and reduced insulin resistance.^[37]

Additionally, less-studied approaches like fecal microbiota transplantation (FMT) have been proposed as promising therapeutic tools for obesity and metabolic disorders. To

understand the rationale for FMT, we should first consider that obesity compromises gut microbiota diversity and increases microbial species linked with inflammation.^[38] FMT acts by directly transplanting healthy donor gut microbial strains to recipients with dysbiotic gut microbiota.^[39] Though promising theoretically, clinical studies on this approach are lacking.

4.2. Herbal treatment

A pattern identification-based meta-analysis of herbal medicine showed that herbal treatment lowered body weight (mean difference = -4.10 kg, 95% CI: -5.14 to -3.06, $I^2 = 2\%$) and BMI (mean difference = -1.53, 95% CI: -1.88 to -1.19, $I^2 = 25\%$) without remarkable adverse events compared to control groups.^[40]

4.2.1. Appetite-suppressing herbs

Garcinia cambogia and Green tea (*Camellia sinensis*) are two of the most extensively studied herbal appetite suppressants. Catechins, found abundantly in green tea, especially epigallocatechin gallate, have demonstrated thermogenic and fat-oxidizing effects. Combined with exercise, recent research suggests significant weight-reduction activity of certain herbs,^[41] for instance, green tea, caffeine, and yerba mate have been shown to expedite metabolic rate and augment fatty acid metabolism. Additionally, these herbs increase energy expenditure, particularly from fatty acid sources, during low and moderate-intensity exercise.

Similarly, *G. cambogia* extract, rich in hydroxycitric acid, is a main ingredient of various weight loss regimens.^[42] Studies have shown that *G. cambogia* demonstrated positive effects on weight reduction, appetite suppression, percentage of body fat, cholesterol, triglycerides, and glucose levels.^[43] However, caution should be exercised with the intake of both herbs in terms of their dosage and safety, given that the ideal dosage has not been established yet.^[43] Despite the notable popularity of these natural weight-loss supplements, their therapeutic doses and safety remain a concern.^[42]

4.3. Pharmaceutical treatment

4.3.1. Drugs that control appetite

Ghrelin administration was noted to stimulate hunger and feeding acutely, as well as chronically promote adiposity in rodents.^[44] Subsequently, the first study investigating ghrelin administration in human subjects found a strong stimulation of appetite following the administration.^[45] Therefore, ghrelin antagonism seemed like a potential target for anti-obesity therapies.

Some pharmaceutical products target ghrelin itself, whether by neutralizing it with antibodies or oligonucleotides or by affecting its synthesis in the first place by blocking O-acyltransferase.^[46] Others spare ghrelin while targeting its receptor, GHS-R1a. As a potential pharmaceutical preparation, GHS-R1a antagonists enter the central nervous system and have already shown a decrease in body weight in mice with diet-induced obesity, as well as improved glucose tolerance, following administration for 10 days.^[47] Molecules like piperidine-substituted quinazolinone derivatives were effective antagonists that lowered body weight and improved glucose tolerance.^[19]

However, not all antagonists have shown equal success; other antagonists showed little CNS penetration; CLB-678 and CCY-2308 exhibited brain concentrations of as little as 22% and 0.001% of their plasma concentrations, respectively. They still improved glucose tolerance but barely affected body weight. In fact, all tested antagonists, regardless of their apparent brain concentration, improved glucose tolerance, suggesting that the effects on glucose homeostasis may be due to the blockade of the GHS-R1a receptors in pancreatic islets.^[46] But it ultimately shows that for antagonists to be effective in lowering body weight, they have to cross the blood-brain barrier, ensuring they suppress appetite centrally.

4.3.2. Drugs that interfere with metabolism

One of the many approaches to weight loss and obesity prevention is limiting energy intake, especially by limiting fat consumption, mainly owing to its caloric density. This should be a simple solution for the obesity problem; however, restrictive diets show low compliance and only short-term results due to frequent relapses.^[48] Therefore, there have been many pharmacological interventions to prevent the absorption of certain macronutrients or generally alter their metabolism in favor of obesity prevention and treatment;^[49] like in the case of metformin, which alters glucose metabolism on a molecular level via multiple mechanisms; for instance, it activates AMP-activated protein kinase (AMPK), a cellular energy sensor that downregulates hepatic glucose output.^[50]

Orlistat (Xenical) is an example of a drug that interferes with fat absorption through the inhibition of gastric, pancreatic, and pancreatic carboxyl ester lipase, which is an enzyme that breaks down fat into absorbable parts. It performs its action mainly in the lumen of the small intestine with little to no systemic absorption. Clinical studies showed that long-term therapy with Orlistat demonstrated the highest weight loss activity compared to other agents.^[49] However, it still has some drawbacks, like inhibiting fat-soluble vitamin absorption.

4.3.3. Drugs that increase energy expenditure

Pharmacological agents that have a thermogenic effect can also be used in the treatment of obesity without dietary restriction. These agents include: ephedrine with caffeine and Beta agonists. Caffeine potentiates the adrenergic effect of ephedrine, which raises the metabolic rate, promoting weight loss. However effective these agents are, they also have many adverse effects, including cardiovascular complications.^[49]

4.4. Surgical treatment

Bariatric surgery has been proven to be an effective tool for weight reduction in obese individuals, especially when other interventions have shown little to no improvement. Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy, and adjustable gastric banding are the most commonly performed bariatric procedures.^[51] The gold standard is RYGB surgery, which results in an average loss of 70% of excess weight. It involves the creation of a small gastric pouch along with intestinal rerouting. Gastrojejunostomy is performed, thus diverting ingested nutrients from the body of the stomach, duodenum, and proximal jejunum.^[52]

Buchwald *et al.* demonstrated the results of bariatric surgery performed on obese individuals.^[53] Following the surgery, patients experienced a marked improvement in comorbidities associated with obesity (i.e., diabetes mellitus, hypertension, and sleep apnea), with many of the patients experiencing full resolution [Supplementary Figure 1]. Furthermore, patients with hyperlipidemia also saw substantial post-surgery improvement. This underscores the positive impact of bariatric surgery on obese patients' health beyond weight reduction.

The exact physiological mechanism underlying weight loss following gastric bypass surgery is still not exactly clear, but the following points have been suggested as potential underlying causes of the observed weight loss: Caloric malabsorption,^[54] mechanical restriction,^[54] alterations in gut hormone levels,^[55] increased bile acid concentrations,^[56] and altered composition of gut microbiota.^[57,58]

Gastric bypass surgery is also associated with notable dietary preference alterations; for instance, decreased preference for fat or sugar. But this has not yet been proven to be the major driving factor underlying the success of the surgery.^[59]

5. CONCLUSION

The notable rise in obesity, both nationwide and worldwide, has sparked the search for alternative therapeutic solutions, including pharmacological agents, surgical interventions, and, more recently, gene therapy. In this review, key genetic

variants (e.g., MC4R, FTO, LEP, GHRL, and DRD2) that affect metabolism, appetite, and reward pathways were highlighted, and an individualised diagnostic and treatment pathway was proposed. Among the documented treatments that affect obesity on a molecular level, bariatric surgery has shown tremendous improvement in morbidly obese individuals when combined with long-term lifestyle alterations. However, lifestyle and dietary changes remain the cornerstone of treatment for obesity owing to their safety and broad applicability compared to other approaches.

Overall, the ‘obesity epidemic’ remains a pressing issue that requires conclusive studies. Future research should prioritize several key gaps: Firstly, there is an urgent need for large-scale, longitudinal studies that integrate multi-omics data to fully explain the complex underlying gene–environment interactions promoting obesity. Secondly, clinical trials are lacking and are crucial for validating the safety and effectiveness of molecular and microbiome-modulating therapies in humans. Thirdly, the challenges preventing the application of gene therapy (e.g., methods of delivery, potential off-target activity, and safety) warrant investigation. Lastly, incorporating nutrigenomics into clinical practice and empowering healthcare providers can aid in the development of personalised dietary and lifestyle interventions based on the unique genetic makeup of the obese individual. By overcoming these gaps, we can move closer to developing effective, tailored, and lasting strategies that combat the global staggering rise in obesity.

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