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Etiology and Pathophysiology

The Genetic Blueprint of Obesity: From Pathogenesis to Novel Therapies

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ABSTRACT

Obesity is a chronic metabolic disease characterized by disturbances in energy homeostasis, leading to excessive fat accumulation. The pathogenesis of the disease is shaped by a complex interplay of genetic, epigenetic, biological, psychological, and environmental factors. These contributors affect regulatory mechanisms in the hypothalamus, hormonal signaling, and the gut-brain axis, all of which control energy intake, expenditure, and energy utilization in body tissues. In this context, particular attention is given to the role of genetic factors, which have a major impact on an individual's susceptibility to disease and support the development of personalized preventive and therapeutic approaches. Modern obesity treatment goes beyond weight reduction and

Abbreviations: AAV, adeno-associated viruses; ADCY5, adenylate cyclase 5; ADRB1, adrenoceptor beta 1; AEE, activity-induced energy expenditure; AGRP, agouti related neuropeptide (*formerly* agouti-related protein, AgRP); ALT, alanine aminotransferase; AST, aspartate aminotransferase; BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; BMI, body mass index; BS, bariatric surgery; CBT, cognitive behavioral therapy; CCK, cholecystokinin; CDKAL1, CDKAL1 threonylcarbamoyladenosine tRNA methylthiotransferase (*formerly* CDK5 regulatory subunit associated protein 1-like 1); CEP120, centrosomal protein 120; CI, confidence interval; CKD, chronic kidney disease; CNS, central nervous system; COBLL1, cordon-bleu WH2 repeat protein like 1; CRH, corticotropin-releasing hormone; CRISPR, clustered regularly interspaced short palindromic repeats; CRP, C-reactive protein; CRTC1, CREB-regulated transcription coactivator 1; CTSS, cathepsin S; DEE, diet-induced energy expenditure; DNA, deoxyribonucleic acid; DPP-4, dipeptidyl peptidase 4; DRD1, dopamine receptor D1; DRD2, dopamine receptor D2; EASO, The European Association for the Study of Obesity; FSH, follicle-stimulating hormone; FTO, FTO alpha-ketoglutarate dependent dioxygenase (*formerly* fat mass and obesity-associated); GERD, gastroesophageal reflux disease; GCGR, glucagon receptor; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1; GLP-1RA, glucagon-like peptide-1 receptor agonist; GLP-2, glucagon-like peptide-2; GRS, genetic risk score; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HMGA2, high mobility group AT-hook 2; IGF2BP1, insulin-like growth factor 2 mRNA-binding protein 1; IL-6, interleukin-6; IRS1, insulin receptor substrate 1; IV, intravenous; LCORL, ligand-dependent nuclear receptor corepressor-like; LDL, low-density lipoprotein; LH, luteinizing hormone; LPS, lipopolysaccharides; LYPLAL1, lysophospholipase-like 1; MAOA, monoamine oxidase A; MC4R, melanocortin 4 receptor; MCH, melanin-concentrating hormone; MEN-2, multiple endocrine neoplasia type 2; MR, magnetic resonance; mRNA, messenger ribonucleic acid; miRNA, micro ribonucleic acid; MSRA, methionine sulfoxide reductase A; NAFLD, non-alcoholic fatty liver disease; NCAM2, neural cell adhesion molecule 2; NEGR1, neuronal growth regulator 1; NGS, next-generation sequencing; NPY, neuropeptide Y; NRXN3, neurexin 3; NTRK2, neurotrophic receptor tyrosine kinase 2; OR, odds ratio; PAX5, paired box 5; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; PP, pancreatic polypeptide; PRS, polygenic risk score; PYY, peptide YY; rAAV, recombinant adeno-associated viruses; RMR, resting metabolic rate; RNA, ribonucleic acid; RREB1, Ras-responsive element binding protein 1; SCFA, short-chain fatty acids; SEC16B, SEC16 homolog B; SES, socioeconomic status; SLC22A18, solute carrier family 22 member 18; SNP, single nucleotide polymorphism; STAB1, stabilin 1; T2DM, type 2 diabetes mellitus; TAG, triacylglycerides; TALEN, transcription activator-like effector nuclease; TEF, thermic effect of food; TFAP2B, transcription factor AP-2 beta; THNSL2, threonine synthase-like 2; TMEM18, transmembrane protein 18; TNF, tumor necrosis factor; TOMM40, translocase of outer mitochondrial membrane 40; TRF, time-restricted feeding; TRH, thyrotropin-releasing hormone; TSC22D2, TSC22 domain family member 2; UCP1, uncoupling protein 1; US, ultrasound.

focuses on optimizing body composition by reducing fat mass and increasing lean mass. This review includes a detailed overview of the mechanisms and clinical effects of current pharmacological approaches to obesity treatment, alongside other established strategies such as lifestyle modifications and bariatric surgery. It specifically discusses lipase inhibitors, opioid antagonists, sympathomimetics, and GLP-1 receptor agonists. Looking ahead, emerging therapies—such as microbiota modulation, dual and triple drug combinations, PYY agonists, and monoclonal antibodies—are expected to play a crucial role in the management of obesity. Furthermore, this review explores the potential of CRISPR-based technology for monogenic obesity, opening new avenues for targeted obesity treatments and identifying promising research directions. In the time to come, personalized medicine might have a fundamental place in the management of obesity, providing tailored and more effective therapeutic approaches that prioritize the long-term improvement of body composition and health outcomes in patients.

1 | Introduction

The World Health Organization classified obesity as a chronic disease in 1997. According to recent estimates, 30%–70% of adults in European Union countries are affected by overweight, while 10%–30% are classified as those with obesity. Globally, 5 million people die each year due to complications associated with obesity [1]. Most of these deaths are attributed to conditions such as diabetes, cerebrovascular stroke, coronary artery disease, or cancer. A summary of obesity-related diseases is presented in Figure 1.

According to the most widely used clinical criteria, the body mass index (BMI), calculated as the ratio of body weight (kg) to the square of body height (m^2), of 25–29.9 kg/m^2 indicates overweight, while a BMI of 30 kg/m^2 or higher specifies obesity. However, in assessing nutritional status, BMI provides little information about an individual's health. Lately, newer diagnostic models, based on an excess of fat that causes organ function alterations, are being accepted. This reframing of the basic characteristics of the disease and the distinction between clinical obesity (excess fat has already caused negative health effects) and preclinical obesity (negative health effects might occur) could guide the management strategy [2]. To avoid the misdiagnosis of the disease, it is recommended to assess the patient with either anthropometric criteria (e.g., waist circumference, waist-to-hip ratio, or waist-to-height ratio) or by body composition estimation, using dual-energy X-ray absorptiometry, bioimpedance analysis, or other methods [2–4]. For holistic assessment, additional factors such as age, sex, ethnicity, concomitant diseases, and body fluid status must also be considered.

We define obesity as a disease characterized by an increased percentage of body fat to the extent that it threatens or damages individual health, usually at the level of organ dysfunction or limitations of daily activities [2]. It results from an imbalance

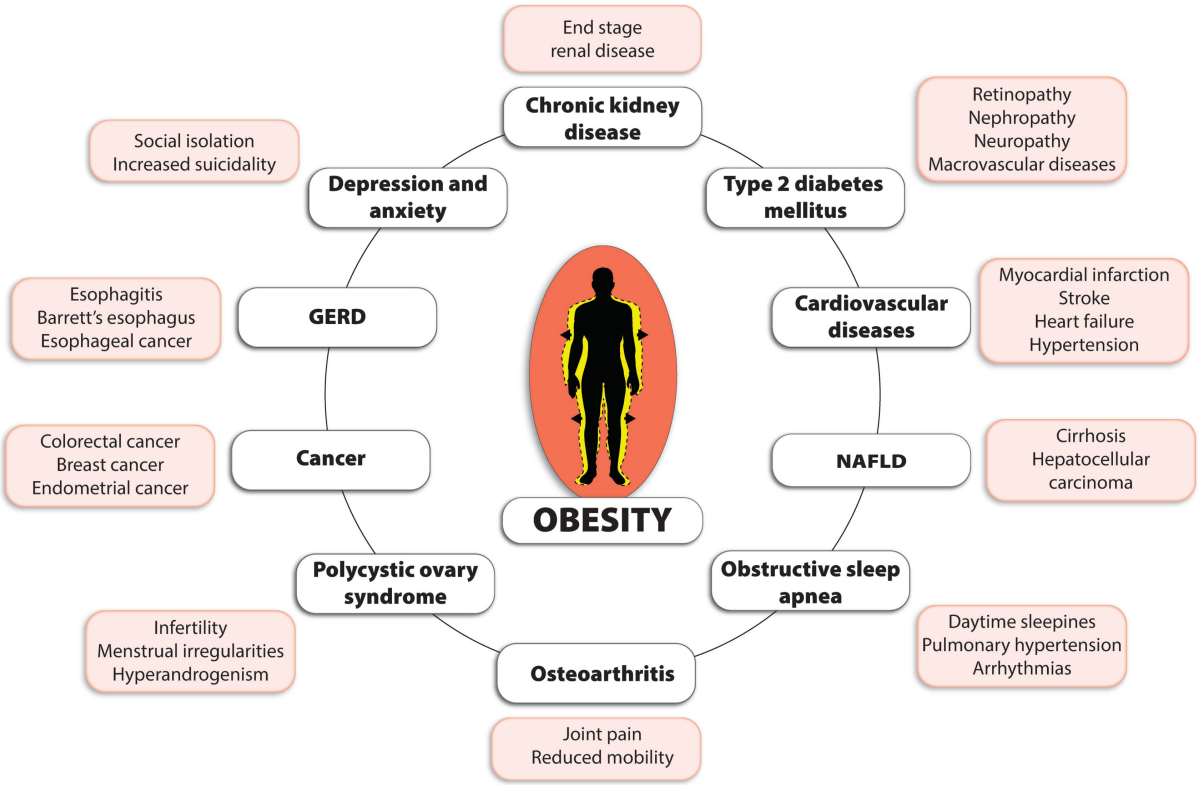

FIGURE 1 | Obesity is a major risk factor for a wide range of comorbid conditions affecting multiple organ systems. It is frequently associated with diseases such as type 2 diabetes mellitus, cardiovascular disease, non-alcoholic fatty liver disease, obstructive sleep apnea, and certain cancers, which collectively contribute to increased morbidity and mortality in individuals with obesity. GERD—gastroesophageal reflux disease; NAFLD—non-alcoholic fatty liver disease.

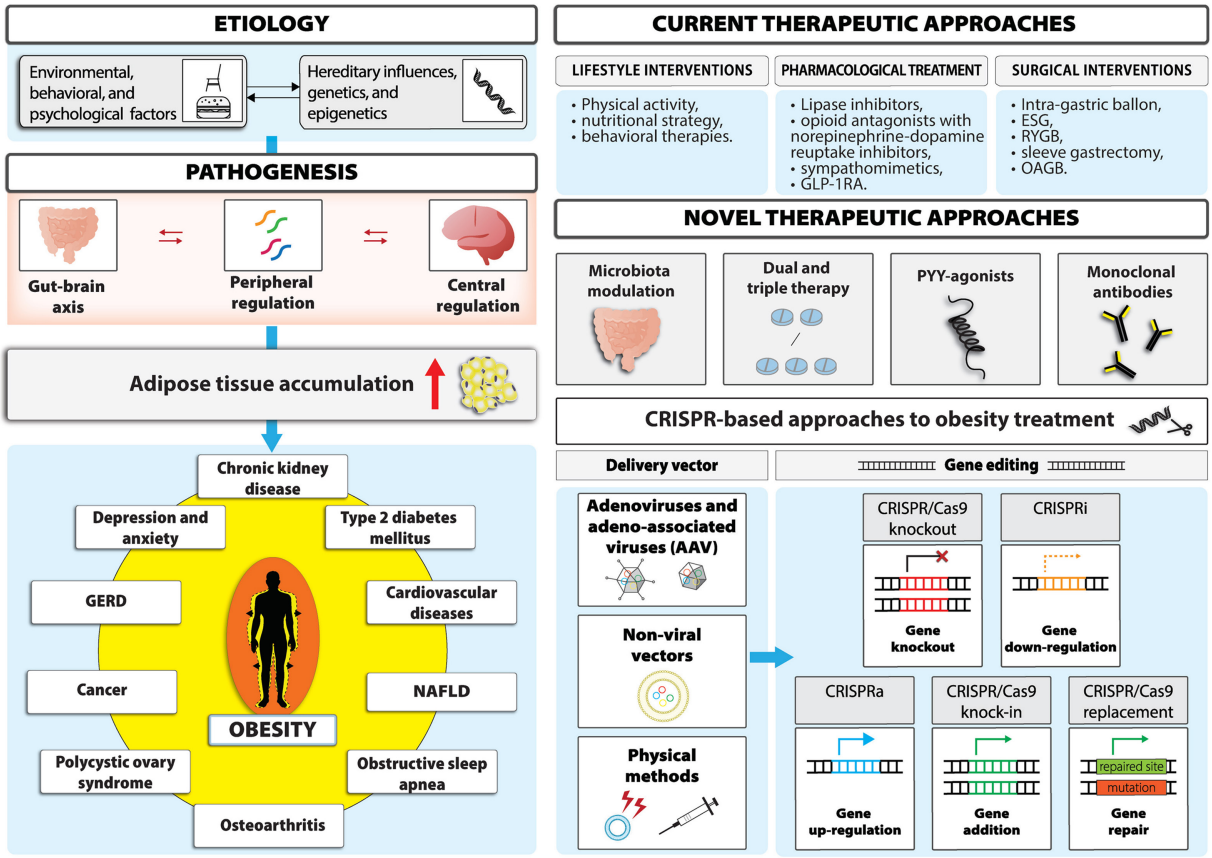

FIGURE 2 | An integrated overview of discussed topics, illustrating obesity's multifactorial etiology, pathogenesis, associated comorbidities, and evolving treatment landscape. Etiological factors include environmental, behavioral, psychological, genetic, and epigenetic influences, which interact to disrupt gut-brain communication and central and peripheral regulatory mechanisms, ultimately leading to adipose tissue accumulation. The downstream health consequences are associated with metabolic, cardiovascular, renal, respiratory, reproductive, gastrointestinal, oncological, and psychological domains. Current therapeutic strategies encompass lifestyle interventions, pharmacological agents such as GLP-1 receptor agonists, and surgical bariatric procedures. Emerging treatments include microbiota modulation, dual and triple pharmacotherapy, PYY agonists, monoclonal antibodies, and gene-editing technologies. GLP-1RA—glucagon-like peptide-1 receptor agonist; ESG—endoscopic sleeve gastroplasty; RYGB—Roux-en-Y gastric bypass; OAGB—one-anastomosis gastric bypass; GERD—gastroesophageal reflux disease; NAFLD—non-alcoholic fatty liver disease; CKD—chronic kidney disease; OSA—obstructive sleep apnea; PCOS—polycystic ovary syndrome; PYY—peptide YY; AAV—adeno-associated virus; CRISPR—clustered regularly interspaced short palindromic repeats; Cas9—CRISPR-associated protein 9; CRISPR/Cas9—CRISPR-associated system used for gene editing; CRISPRi—CRISPR interference; CRISPRa—CRISPR activation.

between energy intake and expenditure, with hormones such as leptin, insulin, estrogens, androgens, and growth hormone influencing appetite, metabolism, and fat distribution [5]. The causes of obesity are multifactorial, including biological, environmental, psychological, medical, social, behavioral, and sociodemographic factors.

In our extended review, we attempted to illustrate the pathogenesis, genetics, and new treatment approaches for obesity. Figure 2 provides an overview of the topics discussed in the present review.

2 | Pathogenesis of Obesity

The etiology and pathogenesis of obesity in adults remain subjects of ongoing debate and some confusion. Although the two terms often overlap, the main principle behind the emergence of this disease can be simply summarized. Obesity arises from a prolonged positive energy balance in the body's energy homeostasis, leading to the accumulation of excess fat, which has various negative effects on overall health. Therefore, we will distinguish the main mechanisms of development of this disease—pathogenesis—and the causes for these mechanisms to commence—etiology. Although many different factors affect the energy balance and how excess energy will be stored in the body, energy homeostasis plays a crucial role in the pathogenesis of the disease [6, 7].

2.1 | Introduction to Energy Homeostasis—Energy Intake and Energy Expenditure

Simplified, energy homeostasis encompasses the interplay between energy intake, energy expenditure, and energy storage. The body weight cannot change if the energy intake over a specified time equals energy expenditure [8]. Our energy comes from macronutrients: fat provides the most at 9 kcal/g, while proteins

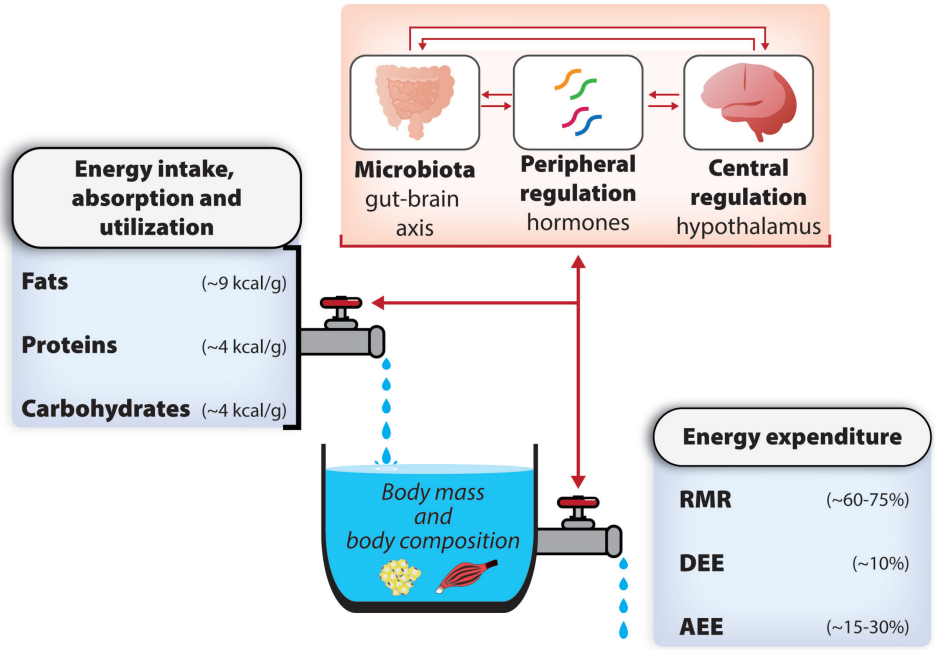

FIGURE 3 | The interplay of different factors regulating body weight and body composition. Kcal—kilocalories; RMR—resting metabolic rate; DEE—diet-induced energy expenditure; AEE—activity-induced energy expenditure.

and carbohydrates each provide 4 kcal/g [9, 10]. These macronutrients affect satiety differently, with proteins being the most satiating per calorie and fats the least [11].

Energy expenditure consists of resting metabolic rate (RMR), diet-induced energy expenditure (DEE or thermic effect of food, TEF), and physical activity-induced energy expenditure (AEE).

RMR covers essential bodily functions, such as breathing and metabolism, and is primarily dependent on the amount of fat-free mass, but can also be affected by age, medication, disease, and hormonal status [8, 12]. DEE refers to the increase in metabolic rate that occurs with food intake, generally accounting for about 10% of total energy expenditure [13]. In contrast, AEE varies widely as it is highly dependent on the physical activity level [8].

Many anti-obesity drugs work by influencing energy balance through macronutrient absorption, appetite regulation, or increasing energy expenditure. Moreover, medications can help counteract the body's natural responses to weight loss, such as decreased RMR and increased appetite, improving long-term weight loss success. Different mechanisms and their interplay are shown in Figure 3.

2.2 | Energy Homeostasis and Obesity

Energy intake, energy expenditure, and existing body energy storage are not isolated entities but influence each other profusely [14]. Additionally, they are dependent on many different factors, such as age, sex, genetic background, epigenetic changes, psychological state, behavior, and environment of the individual. Nevertheless, even small but long-term deviations from homeostasis can cause great changes in body weight [15, 16]. Even though, body weight is not the most important hallmark of obesity—excess fat accumulation is. Even if maintaining a positive energy balance through a prolonged period, a physically active individual will not accumulate energy only as fat, but also as muscle and other tissues. Moreover, patients with obesity trying to "lose weight" will lose muscle along with fat tissue if they do not support the process with physical activity and a proper nutritional strategy, diminishing the possible positive effect of weight loss. With the growing accessibility of body composition measuring methods, the concept of changing body composition rather than body weight will probably become the most important indicator of different obesity therapies in the future [17–20].

2.3 | Central Regulation of Energy Homeostasis

Food and energy intake are closely organized by the nervous, endocrine, and gastrointestinal systems.

2.3.1 | Hypothalamic Control

Most of the mechanisms affecting energy intake and expenditure are associated with central nervous system (CNS) control and different hormones affecting the metabolic pathways and satiety. The core of the central energy homeostasis control is the hypothalamus, receiving its hormonal and nervous inputs from the peripheral organs [21]. Consequently, its impairment due to structural or another type of damage can lead to hypothalamic obesity [22]. Several different neurons with different receptors for peripheral and central molecules collaborate to create the feeling of satiety or hunger. They can be divided into two groups, orexigenic and anorexigenic neurons.

Anorexigenic neurons promote satiety and inhibit hunger. Most known are those that synthesize two neuropeptides,

proopiomelanocortin (POMC) and cocaine-amphetamine-regulated transcript (CART). POMC and CART neurons can be found in the arcuate nucleus of the hypothalamus and are activated by peripheral signals, such as leptin, insulin, amylin, GLP-1, and glucose levels. POMC neurons generate several melanocortin peptides, most notably α-melanocyte-stimulating hormone (α-MSH) and γ-melanocyte-stimulating hormone (γ-MSH). α-MSH binds to melanocortin-3 receptors (MC3R), but primarily acts on melanocortin-4 receptors (MC4R), which are widely expressed in CNS regions, mainly promoting satiety but also increasing energy expenditure [23]. In contrast, γ-MSH binds preferentially to melanocortin-3 receptors (MC3R), which are involved in fine-tuning the balance of energy storage, regulating fat oxidation, and partitioning energy, particularly under conditions of nutrient flux and circadian rhythm shifts [24, 25]. The CART is frequently co-expressed with POMC in anorexigenic neurons but does not produce melanocortins. Instead, CART enhances the inhibitory effect on appetite by modulating synaptic signaling and responding robustly to leptin. While POMC-derived α-MSH directly engages melanocortin receptors, CART is thought to play a supportive role, amplifying the anorexigenic output of POMC neurons [24–27].

POMC and CART neurons are both modulated by a variety of peripheral signals. Leptin activates the neurons by triggering intracellular pathways, increasing POMC/CART gene expression and neuronal excitability [26, 28, 29]. Moreover, it also modulates micro ribonucleic acid (miRNAs) that regulate *POMC* messenger ribonucleic acid (mRNA), resulting in reduced food intake and increased energy expenditure [30]. Independent of leptin, amylin acts directly on calcitonin receptors expressed on POMC neurons, activating ERK signaling pathways. In animal models, the hormone appears to play a particularly important role in the development of POMC neurons, especially during early life [31–33]. Similarly, GLP-1 directly binds to the POMC neurons, increasing their excitatory tone [34–37]. Insulin upregulates POMC/CART expression; however, it was shown to be modulated by proteins such as Smad7 and TCPTP in animal models, enhancing or inhibiting insulin's effect based on the individual nutritional status [26, 38–40]. Lastly, higher glucose levels decrease AMPK activity and promote POMC transcription, activating these neurons [41, 42]. Together, the POMC/CART system represents a core component of the central melanocortin pathway, exerting the effects via complex and intricate pathways affecting thyrotropin-releasing hormone (TRH) and corticotropin-releasing hormone (CRH) production [26, 27, 43–46].

Central orexigenic neurons are located in the arcuate nucleus of the hypothalamus. We distinguish neuropeptide Y (NPY) and agouti-related neuropeptide (AgRP) neurons, both stimulating hunger and energy preservation [46–48]. They are influenced by several different peripheral signals, with the most important being ghrelin, which excites AgRP/NPY neurons directly and indirectly via orexin pathways.

Gamma-aminobutyric acid (GABA) neurons play both orexigenic and anorexigenic roles, depending on the specific neuronal circuit context. AgRP/NPY neurons co-release GABA and inhibit anorexigenic POMC neurons and other satiety-promoting targets [49–51]. However, GABA neurons can also participate in anorexigenic pathways, inhibiting orexigenic neurons [52, 53].

Both POMC/CART and AgRP/NPY neurons are located in the arcuate nucleus of the hypothalamus, which acts as a first-order sensor, integrating peripheral and central signals [26, 54]. These nucleus neurons project to several other brain regions, most notably the paraventricular nucleus and the lateral hypothalamus. The lateral hypothalamus receives input from the arcuate nucleus via both AgRP/NPY and POMC/CART neurons, resulting in stimulating food intake. Moreover, this area produces its own orexigenic peptides—orexin and melanin-concentrating hormone (MCH)—and is involved in the reward and arousal neural circuits. On the other hand, the paraventricular nucleus receives projections mainly from the POMC/CART neurons, causing the suppression of appetite and energy conservation via its neuroendocrine function in CRH and TRH production [54–56].

2.3.1.1 | Role of Monoamines in Regulating Hunger and Satiety. Additionally, monoamines like serotonin, dopamine, and noradrenaline play complex roles in regulating hunger and satiety. Serotonin plays a major role in anorexigenic behavior, as activation of serotonin receptors on POMC neurons, both in the hypothalamic arcuate nucleus and the nucleus of the solitary tracts, reduces food intake. It also decreases the expression of NPY and AgRP while increasing POMC expression. Moreover, it participates in several neuroendocrine signaling pathways, independent of its effect on food intake [57–60]. Dopamine is involved in both reward and homeostatic regulation of feeding, having a complex physiological role in satiety and energy balance. It can reduce food intake by downregulating AgRP expression and modulating POMC neurons through its receptors, dopamine receptor D1 (DRD1) and D2 (DRD2) [58–60]. Noradrenaline exerts a dual and opposing influence on the key hypothalamic circuits controlling feeding. It increases the activity of orexigenic AgRP/NPY neurons via excitatory α1- and β-adrenergic receptors, while simultaneously inhibiting anorexigenic POMC neurons through α2-adrenergic receptors. This coordinated modulation promotes feeding behavior and energy intake [61].

2.3.2 | Hormonal Signaling

Various peripheral signals affect the central mechanisms, the most important being various gut and fat tissue hormones. Leptin, known as the "satiety hormone," is secreted by adipocytes, influencing hypothalamic pathways to suppress hunger [48, 62–65]. Although leptin levels usually correlate with fat content and adipocyte size, they can also be influenced by other factors, such as hunger, circadian rhythms, and overeating [66–70]. In spite of typically being highly expressed in obesity, leptin resistance dampens its effectiveness via various mechanisms, such as post-translational modifications of leptin molecules, changes in transport across the blood–brain barrier (BBB), and altered receptor function [71–73]. This resistance is significant in both monogenic and multifactorial obesity, with rare genetic mutations in the leptin gene causing severe obesity [66, 74–76]. Despite plasma leptin levels rising in obesity, cerebrospinal fluid concentrations may not increase due to limited

BBB permeability [77–80]. Additionally, hyperleptinemia further reduces BBB permeability and may trigger a "leptin-induced leptin resistance," creating a feedback loop [79, 80]. It is also hypothesized that some brain areas may compensate for resistance in others, leading to wider leptin signaling issues [63].

Both insulin and amylin are satiety-promoting hormones that are secreted after a meal by the beta cells of the pancreas. Amylin has an effect on glycemic control, gastric emptying, digestive enzyme secretions, body weight, and food intake, making it one of the possible pharmacological agents for obesity and type 2 diabetes mellitus (T2DM) treatment [81, 82]. Other hormones, playing an important role in obesity pathogenesis, are a part of the gut–brain axis.

2.3.3 | Gut–Brain Axis

The gut and brain are connected via various systems, including hormonal signals, microbiota, and neural transmission [83–85].

2.3.3.1 | Gut Hormones. The gut produces several hormones, including glucagon-like peptide-1 (GLP-1), cholecystokinin (CCK), and peptide YY (PYY). These hormones act through various central and peripheral mechanisms; most, except ghrelin, are released in response to meals, promoting satiety.

GLP-1 is a peptide hormone, produced in intestinal L cells in response to nutrient ingestion. It binds to the GLP-1 receptor, localized on diverse cell types in many human tissues, pancreatic islets, gastric mucosa, intestinal L cells, regions of the central nervous system, thyroid, testis, and the cardiovascular system [86–94]. Upon receptor activation, GLP-1 stimulates insulin secretion, suppresses glucagon release, delays gastric emptying, and reduces appetite [65, 95–97]. In parallel, glucagon-like peptide-2 (GLP-2) is co-secreted with GLP-1 and plays a more specialized role in the gastrointestinal tract, where it supports mucosal integrity, enhances nutrient absorption and blood flow, and promotes intestinal epithelial growth [98].

CKK is produced in the small intestine as a response to food intake, slowing gastric emptying and increasing feelings of satiety. It has effects on the CNS and several peripheral organs, namely the pancreas, gallbladder, and muscles of the gastrointestinal tract [99–101]. Similarly, gastric inhibitory polypeptide (GIP) is released postprandially from endocrine K cells in the small intestine. It enhances glucose-stimulated insulin secretion, reduces bone resorption, and increases intestinal blood flow and lipid storage in adipose tissue. GIP acts via the GIP receptor, which is expressed in pancreatic islet cells, white adipose tissue, regions of the central nervous system, and the gastrointestinal tract [102].

PYY, secreted by the small intestine, and ghrelin, secreted primarily by the stomach, have opposing roles in appetite regulation. PYY is released from L-cells and suppresses appetite, reduces gastric motility, and boosts pancreatic secretion [103–105]. In contrast, ghrelin—an orexigenic hormone predominantly secreted by enteroendocrine cells in the gastric oxyntic mucosa—acts directly on the hypothalamus to stimulate hunger and carbohydrate metabolism, while also promoting lipogenesis, gastric motility, and acid secretion [106–109].

2.3.3.2 | Gut Microbiome. The gut microbiome consists of over a thousand bacterial species that influence nutrient digestion, absorption, and storage in the body. These bacteria also synthesize vitamins and play a role in mineral metabolism. Research suggests a link between gut microbiome composition and obesity since this pathology is associated with decreased microbial diversity and a higher Firmicutes to Bacteroidetes ratio of bacteria [110].

The gut microbiota influences satiety and hunger through various mechanisms. Metabolites and lipopolysaccharides (LPS) produced by gut bacteria can stimulate enteroendocrine cells to release more CCK [83, 85]. Additionally, GLP-1 receptor agonists (GLP-1RA) may shift the microbiota composition toward a profile associated with leanness, enhancing weight-loss effects [83, 111–113]. Furthermore, gut bacteria can produce propionate, a short-chain fatty acid (SCFA) that has been shown to stimulate GLP-1 release and work as agonists for free fatty acid receptor 2, stimulating the secretion of the appetite-suppressing hormone PYY [110, 114, 115]. The microbiome may also have an effect on leptin sensitivity in the hypothalamus through the inflammation and cytokine signaling associated with some of the species [116–118]. Microbiota in rats has been shown to affect the expression of monoamine oxidase A (MAOA) in the hippocampus, an enzyme that clears monoamines [119]. Moreover, gut bacteria can create neuroactive substances (dopamine and serotonin), which probably cannot cross the BBB but can act locally on the enteric nervous system [120].

3 | Etiology of Obesity

The etiology of obesity is complex, involving an intricate interplay between genetic predispositions, epigenetic modifications, and external environmental influences. Understanding the underlying causes is critical for developing targeted prevention strategies and personalized treatment approaches that address the specific needs of individuals and communities. We have summarized the pathogenesis and the roles of various etiological factors contributing to obesity in Figure 4.

3.1 | Hereditary Influences, Genetics, and Epigenetics

Obesity inheritance is multifactorial, arising from the interplay of multiple genes and environmental factors. Rather than following simple Mendelian inheritance, obesity is a complex genetic trait, where many genetic variants contribute small effect sizes to the overall risk. Shared environmental factors affect BMI in childhood, but their influence declines by late adolescence, indicating genetics as the primary contributor to BMI variations during adolescence, regardless of ethnicity or environmental exposure [121]. A strong genetic predisposition substantially increases the risk of developing overweight during adolescence and early adulthood, often leading to an earlier onset of this condition [122].

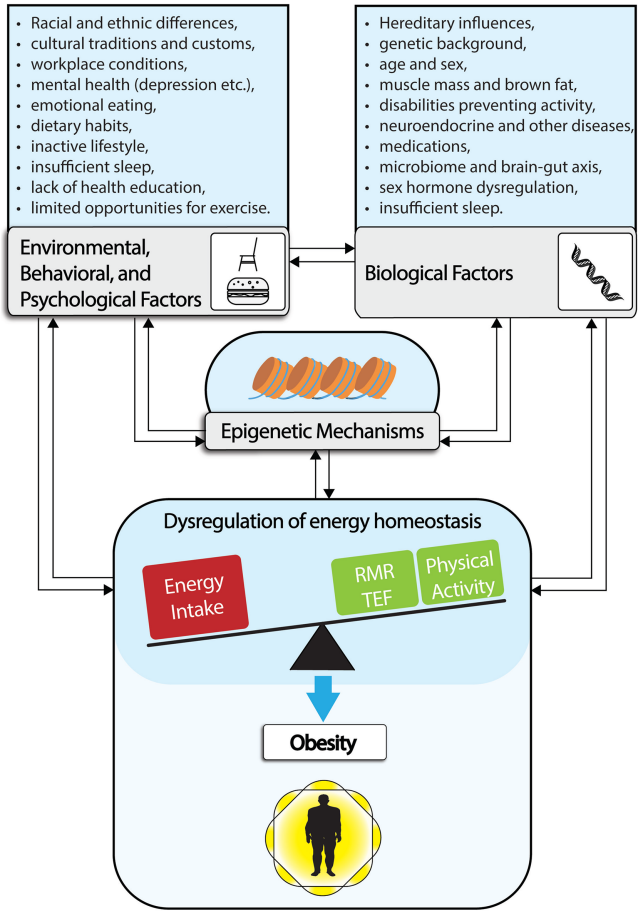

FIGURE 4 | Etiological model of obesity illustrating the multifactorial interactions among biological, environmental, behavioral, and psychological factors. These influences disrupt energy homeostasis—defined as the balance between energy intake and expenditure—thereby promoting adipose tissue accumulation and the development of obesity. TEF—thermic effect of food; RMR—resting metabolic rate.

More than 1000 loci linked to obesity-related measures, including single nucleotide polymorphisms (SNPs), have been identified through genome-wide association studies (GWAS) [123]. However, these findings explain only about 6% of the variation in BMI, highlighting the complexity of genetic influences on obesity [124]. Research has shown that many identified loci contain genes involved in critical energy homeostasis pathways, including appetite and satiety regulation (such as *BDNF*, *MC4R*, and *NEGR*), energy and lipid metabolism (including *FTO*, *RPTOR*, and *MAP 2K5*), insulin secretion and action (*TCF7L2* and *IRS1*), and adipogenesis [123].

3.1.1 | Monogenic Obesity

Monogenic obesity is a rare and severe condition that typically manifests early in life and follows a Mendelian inheritance pattern. It results from single-gene defects or chromosomal aberrations, which can vary in size and type [125]. Monogenic obesity can manifest either as a part of specific syndromes or as an isolated phenotype without associated clinical features. It is often accompanied by abnormal feeding behaviors and various endocrine disorders, primarily resulting from autosomal recessive mutations in genes involved in the leptin-melanocortin pathway. These gene alterations contribute to varying obesity severities, typically without additional significant phenotype changes. In contrast, syndromic obesity is linked to intellectual disabilities, distinct facial characteristics, and organ-specific developmental issues, with genes involved in hypothalamic and CNS development frequently implicated, though not all have yet been identified [126, 127].

3.1.1.1 | Leptin and Leptin Receptor (LEPR) Gene Mutation. The leptin gene (*LEP*) is located on chromosome 7 and encodes the peptide hormone leptin. Sequence variants of the LEP gene, especially rs7799039 and rs2167270, and its receptor *LEPR*, particularly rs1137101, can lead to leptin resistance, disrupting appetite control and contributing to severe obesity [128, 129]. Patients with *LEP* sequence variants have been shown to experience increased hunger and decreased energy expenditure [130]. Although leptin has a well-established link to obesity, leptin-based therapies to treat obesity have not yet been fully explored [131].

A study in the Vietnamese preschool population found that individuals with the AA genotype of rs7799039 had a higher risk of obesity, especially when combined with the GG genotype of *LEPR* rs1137101 [132]. Similarly, the rs2167270 A allele has been associated with elevated leptin levels and an increased risk of prediabetes, independent of BMI and waist circumference [133]. Furthermore, the Ukrainian population study suggested a heightened risk for developing metabolic syndrome in carriers of the *LEPR* rs1137101 gene polymorphism [134].

3.1.1.2 | Proopiomelanocortin (POMC) Deficiency and Melanocortin 3 Receptor (MC3R) and Melanocortin 4 Receptor (MC4R) Gene Mutation. The *POMC* gene, located on chromosome 2, encodes a precursor protein that is cleaved into several peptides, including α-, β-, and γ-melanocyte-stimulating hormones (MSH), which are integral to appetite regulation and energy expenditure [135, 136]. Variants in the *POMC*, particularly rs934778 and rs6545975, lead to errors in the cleavage of POMC, which relies on prohormone convertase to process this large protein into smaller, functional peptides. Impaired production of these peptides leads to early-onset obesity, adrenal insufficiency, alterations in pigmentation, and disrupts appetite regulation [136, 137]. A recent study further links rs934778 and rs6545975 to an increased risk of extreme obesity [136].

Melanocortin receptors (MCRs), particularly MC3R and MC4R, are G-protein-coupled receptors primarily expressed in the hypothalamus. They are activated by POMC-derived peptides, including α-, β-, and γ-MSH, which influence appetite and metabolic rate. Dysfunction in MC3R or MC4R due to genetic variants can lead to disrupted melanocortin signaling and leptin pathway dysregulation, contributing to obesity and metabolic imbalances [138].

The *MC4R* gene, located on chromosome 18, is recognized as the most frequent childhood obesity-associated gene [139]. The rs17782313 variant was identified in approximately 4% of obesity cases even before the emergence of advanced genetic testing and next-generation sequencing (NGS) [140].

Mutations in this gene can disrupt normal signaling pathways, leading to increased food intake and decreased energy expenditure [139]. A meta-analysis highlighted that individuals carrying the C allele of rs17782313 have a higher propensity for obesity and related metabolic disturbances, including hyperglycemia [141].

The *MC3R* gene, located on chromosome 20, is an important regulator of appetite [142]. Although a Brazilian study found no association between the *MC3R* rs3746619 variant and obesity or anthropometric measures—consistent with previous findings in Chilean adults—it reported that carriers of the A allele had higher HbA1c levels, suggesting a potential role in glycemic regulation [143]. Meanwhile, the rs3746619–rs3827103 haplotype, which reduces *MC3R* expression, has been associated with higher BMI, increased adiposity, and altered metabolic traits in other populations, including African Americans [144, 145]. In addition to its central role in energy regulation, a study by Patel et al. in mice demonstrated that MC3R is crucial for hepatic autophagy. Deficiency in MC3R disrupted fat metabolism and led to obesity, while restoring its expression in the liver enhanced autophagy and improved systemic metabolic outcomes [146].

3.1.1.3 | FTO Alpha-Ketoglutarate Dependent Dioxygenase (FTO) Gene Mutation. *FTO* (FTO alpha-ketoglutarate dependent dioxygenase, formerly *fat mass and obesity-associated*) gene is located on chromosome 16 and encodes a protein that plays a role in regulating energy balance, appetite, and metabolism, although the precise mechanisms are still under investigation. Variants in the *FTO*, particularly the polymorphisms rs9939609 and rs9930506, are associated with an increased risk of obesity and higher BMI. However, due to its moderate effect size and high environmental influence, *FTO* is often characterized as an important polygenic rather than a typical monogenic obesity gene [147–150].

A recent study in Korean females demonstrated that individuals with the AA genotype of the rs9939609 exhibited significantly higher BMI and body fat percentages [151]. Similarly, research in a multiethnic group in Asia reported that the rs9939609 A allele correlates with a higher risk of obesity [152]. Another study found that individuals carrying the rs9939609 risk allele consumed notably more sugar and saturated fats than those with the homozygous dominant genotype [153]. Additionally, rs9930506 has also been linked to obesity indices such as weight and hip circumference. Interestingly, a study involving male participants found that weight loss interventions were significantly less effective in individuals carrying the risk allele [154].

3.1.1.4 | Cocaine and Amphetamine Regulated Transcript (CART) and CART Prepropeptide (CARTPT) Gene Mutation. The *CARTPT* gene is located on chromosome 5 and encodes a neuropeptide CART predominantly expressed in the hypothalamus, where it plays a crucial role as an anorexigenic factor, promoting satiety and reducing food intake. Variants in the *CARTPT* gene, particularly the polymorphisms rs2239670, are associated with abnormal food intake behavior and obesity. A cross-sectional study in obese Iranian adults found that the rs2239670 polymorphism significantly interacts with diet quality indices, influencing obesity-related metabolic and anthropometric traits such as BMI, waist circumference, fat mass, glucose levels, and lipid profile [155]. Another study found that the rs2239670 polymorphism was both directly and indirectly associated with metabolic syndrome [156].

3.1.1.5 | Neuropeptide Y (NPY) Gene Mutation. The *NPY* gene is located on chromosome 7 and encodes a 36-amino acid peptide neurotransmitter that is widely expressed in the central and peripheral nervous systems. It is one of the most potent orexigenic (appetite-stimulating) peptides in the hypothalamus, particularly within the arcuate nucleus, where it is co-expressed with AgRP [157].

Several *NPY* polymorphisms have been linked to weight and metabolic changes. A study in a Brazilian cohort found that the rs16147 CC genotype was associated with a higher risk of childhood-onset obesity [158]. Another study, for example, showed that individuals with the rs5574 CC genotype showed a greater yearly increase in waist-to-hip ratio and smaller reductions in energy and carbohydrate intake, along with elevated fasting glucose and cholesterol, whereas those with the rs16147 TT genotype had higher body weight and greater increases in skinfold thickness and waist measures, despite lower carbohydrate intake [159]. The rs164147 genotype was also shown to influence changes in waist circumference, HOMA-IR, insulin, CRP, and IL-6 levels following a weight loss diet in individuals with obesity [160].

3.1.2 | Polygenic Obesity

Polygenic obesity, also referred to as common obesity, is a result of the combined effect of hundreds of polymorphisms, each contributing a small effect to overall susceptibility. Its heritability pattern is similar to other complex traits and diseases [125]. GWAS revealed that nearly all genes implicated in monogenic and oligogenic (involving a few genes) forms of obesity, such as *FTO*, *LEPR*, *POMC*, *MC4R*, and *PC1*, also exhibit common variants associated with greater BMI and polygenic obesity [161–163]. Moreover, polygenic obesity is influenced by environmental factors, including diet, lack of physical activity, ultra-processed foods, fast food, microbiome alterations, and chemical contaminants, all of which can impact gene expression [164]. Nevertheless, recent GWAS studies have shown that genetic factors may account for 40%–75% variation in BMI [165–167]. More than 1100 loci have already been linked to adult BMI [125, 168]. Some of the identified genes and their associations with obesity are summarized in Figure 5.

Genes such as *FTO*, *MC4R*, *BDNF*, *NEGR1*, and *ADCY3* have emerged as key regulators of energy balance, feeding behavior, and hypothalamic signaling. For instance, *FTO* encodes an RNA demethylase involved in N6-methyladenosine (m6A) modification; by influencing RNA methylation, it regulates appetite and adiposity. In contrast, *MC4R* plays a central role in the melanocortin signaling pathway that suppresses food intake [169–171]. *BDNF* and *NEGR1* are implicated in neurodevelopmental processes governing energy homeostasis and synaptic plasticity, and *ADCY3* is vital for leptin signaling and cAMP production in hypothalamic neurons [172–176].

Many of the identified genes converge on neuroendocrine pathways and adipose tissue function. *NRXN3*, *CRTC1*, *COBLL1*, and *TCF7L2* are key regulators of insulin signaling, adipogenesis,

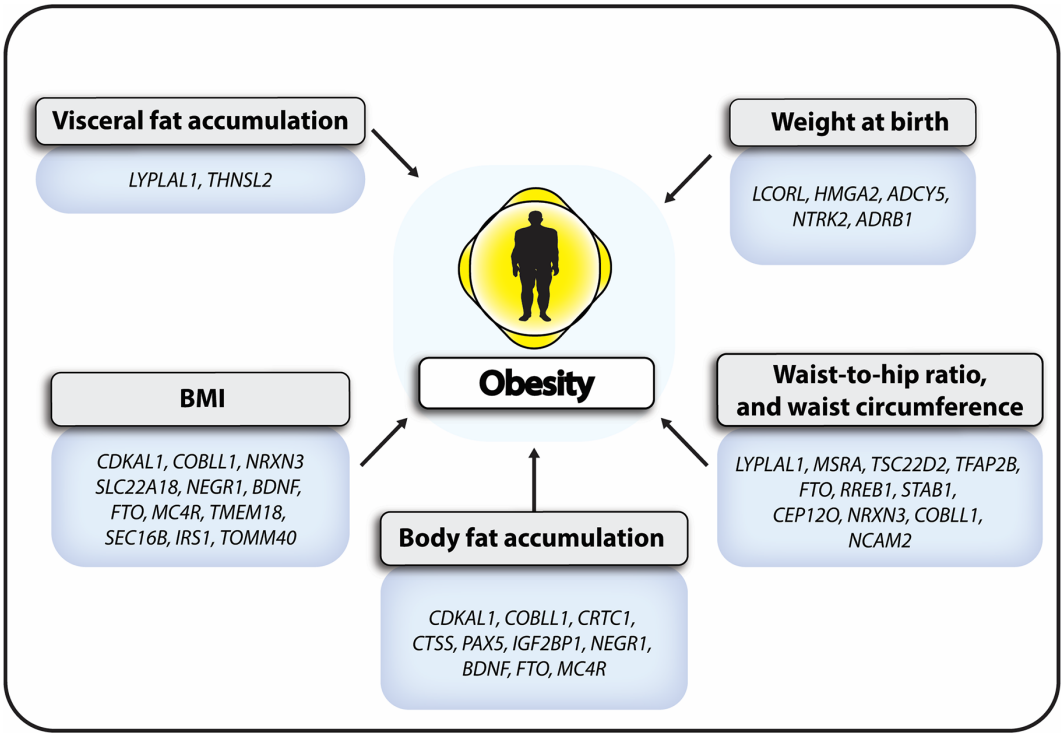

FIGURE 5 | Genetic architecture of obesity illustrating key gene loci associated with specific obesity-related traits. Distinct sets of genes are linked to visceral fat accumulation, body fat accumulation, BMI, waist-to-hip ratio, waist circumference, and birth weight, each contributing to the overall risk and development of obesity. *LYPLAL1*—lysophospholipase-like 1; *THNSL2*—threonine synthase-like 2; *LCORL*—ligand dependent nuclear receptor corepressor-like; *HMGA2*—high mobility group AT-hook 2; *ADCY5*—adenylate cyclase 5; *NTRK2*—neurotrophic receptor tyrosine kinase 2; *ADRB1*—adrenoceptor beta 1; *CDKAL1*—CDKAL1 threonylcarbamoyladenosine tRNA methylthiotransferase (*previously* CDK5 regulatory subunit associated protein 1-like 1); *COBLL1*—cordon-bleu WH2 repeat protein like 1; *NRXN3*—neurexin 3; *SLC22A18*—solute carrier family 22 member 18; *NEGR1*—neuronal growth regulator 1; *BDNF*—brain-derived neurotrophic factor; FTO—fat mass and obesity-associated protein; *MC4R*—melanocortin 4 receptor; *TMEM18*—transmembrane protein 18; *SEC16B*—SEC16 homolog B; *IRS1*—insulin receptor substrate 1; *TOMM40*—translocase of outer mitochondrial membrane 40; *CRTC1*—CREB regulated transcription coactivator 1; *CTSS*—cathepsin S; PAX5—paired box 5; *IGF2BP1*—insulin-like growth factor 2 mRNA-binding protein 1; *MSRA*—methionine sulfoxide reductase A; *TSC22D2*—TSC22 domain family member 2; *TFAP2B*—transcription factor AP-2 beta; *RREB1*—Ras-responsive element binding protein 1; *STAB1*—stabilin 1; *CEP120*—centrosomal protein 120; *NCAM2*—neural cell adhesion molecule 2.

and lipid metabolism, with *TCF7L2* notably implicated in both insulin secretion and adipocyte function [177–181]. *CDKAL1* and *ADCY5* are associated with beta-cell function and adipose tissue metabolism, respectively, while *ADRB1* is linked to sympathetic nervous system activity; all three genes influence metabolic rate and thermogenesis [182–185]. Genes such as *MTCH2*, which play a role in mitochondrial metabolism, and IRS1, a key component of insulin signaling, exemplify the intricate relationship between energy homeostasis and insulin resistance [186–189]. Additionally, *BBS1*, associated with Bardet-Biedl Syndrome, underscores how rare monogenic obesity disorders can shed light on the mechanisms underlying common polygenic obesity [190]. *IGF2BP1*, *SEC16B*, *LYPLAL1*, *TMEM18*, and *CTSS* contribute to adipocyte differentiation, endoplasmic reticulum function, and lipid remodeling [191–195]. *TFAP2B* is a transcriptional regulator that influences fat deposition and inflammation [196, 197]. Finally, *HMGA2* and *LCORL* are associated with anthropometric traits such as stature and lean body mass, which indirectly modulate obesity risk [198–200].

3.1.2.1 | Polygenic Risk Scores and Their Implications. GWAS have elucidated the role of common polygenic variations in obesity risk, leading to the development of polygenic risk scores (PRS) [201]. PRS integrate the effects of numerous common genetic variants into a single score that estimates an individual's genetic predisposition to obesity. A 2019 study with four cohorts found that individuals in the top 10% of PRS were significantly more likely to have a BMI > 30 kg/m^2 compared to those in the lowest 10%. High PRS was also associated with an increased risk of related conditions, such as coronary artery disease and T2DM [202].

Even so, the application of PRS and genetic risk scores (GRS, i.e., based on a small number of genetic variants) remains challenging, and future research is expected to identify additional loci involved in obesity. Although it is suggested that genetics could explain 40%–70% of the variability in BMI, current PRS explain only about 10%–20% of that variation [165–167]. This "missing heritability" could be explained by the rare genetic variants not captured by GWAS, gene–gene interactions, gene–environment interactions, and epigenetic modifications [203]. As a result, PRS are not routinely used in clinical practice, as they typically have low sensitivity and specificity [125].

Although PRS can indicate a genetic predisposition to obesity, healthy lifestyle habits—such as regular physical activity—can

significantly mitigate this risk. For instance, individuals with high fitness levels can offset their genetic susceptibility, and studies have shown that up to 17% of those in the top 10% of PRS risk maintained a normal BMI [204]. Additionally, current PRS for BMI do not distinguish between lean and fat mass, which limits their utility in understanding disease mechanisms. Consequently, GWAS studies focused on body fat percentage or fat-free mass may provide more precise insights into obesity pathogenesis [205–207]. Furthermore, the predictive power of PRS for BMI remains limited compared to traditional clinical risk factors. Namely, a recent study from 2020 showed that PRS explained a smaller proportion of BMI variation compared to clinical predictors [208].

From a clinical viewpoint, the final goal is the development of highly sensitive and specific prediction scores, enabling clinicians to anticipate obesity risk and customize lifestyle interventions focused on healthy weight management for individuals [123].

3.1.3 | Epigenetics and Environmental Modulation

Different external factors influence gene expression via epigenetic modifications, such as DNA methylation and histone acetylation, predisposing an individual to obesity [209, 210]. Some of those factors include diet, physical activity, and maternal nutrition during pregnancy and breastfeeding [211]. For instance, in individuals with certain *FTO* polymorphisms, high-calorie diets may lead to greater weight gain. Similarly, gene–physical activity interactions might affect how physical activity mitigates the genetic predisposition to obesity [212, 213]. A novel study from 2024 with 201,466 participants found out that 42.8% of the association between genetic predisposition and obesity phenotype was explained by lifestyle [214].

3.2 | Environmental, Biological, Behavioral, Psychological, and Socioeconomic Factors

Obesity is not merely a product of biology but is profoundly influenced by a person's surroundings, lifestyle, and mental well-being.

3.2.1 | Biological Sex Impact

Biological sex has a significant role in obesity risk, as different prevalence has been shown in male and female sex across various countries, with women having a higher risk and greater prevalence variability than men [215]. The LASI study in India reveals a surprising finding: Despite older women having higher obesity rates and concerning anthropometric measures, men demonstrate greater odds of multimorbidity, suggesting an interaction between sex and unhealthy behaviors that requires further investigation [216]. Nevertheless, some other studies had the opposite results, showing a greater risk for obesity-related physical and psychological comorbidities, and a two-fold higher mortality risk in women [217]. Even so, women are more likely than men to seek and receive various obesity treatments, including behavioral, pharmacological, and bariatric options. Additionally, while men generally experience greater absolute weight loss, this difference narrows when adjusted for initial weight [218, 219]. Consequently, there exists a significant need for more nuanced approaches in obesity medicine to address these differences and reduce the mortality gap between women and men with overweight [217].

3.2.2 | Racial and Ethnic Groups

The role of race and ethnic groups in the etiology of obesity is difficult to research appropriately due to the complex interplay of genetic, environmental, socioeconomic, and structural factors, as well as the risk of reinforcing biological essentialism or overlooking systemic inequities. In addition, most GWAS and other types of studies have largely been conducted on Caucasian or East Asian ancestry, making the research of the genetic role in the ethnic influence of obesity harder [220]. However, it is believed that the role of race and ethnicity is complex and multifaceted, involving biological factors, socioeconomic status, health behavior, neighborhood environment, and early childhood health factors [221].

Behavioral patterns such as dietary habits and physical activity vary between ethnic groups. Moreover, environmental factors, such as access to healthy food, safe spaces for physical activity, and quality health care, play a key role in the development of obesity. It has been shown that obesity rates are higher among certain racial and ethnic groups, particularly African American and Hispanic populations, compared to White and Asian groups. A cross-sectional study by Kirby et al. has shown that living in communities with ≥25% Hispanics was associated with higher BMI (+0.55 for Hispanic men, +0.42 for non-Hispanic white men) and higher odds of obesity (+21% and +23%, respectively) [222]. Another research study by Mills et al. has shown that non-Hispanic black men with a college degree or above had a higher prevalence of obesity than non-Hispanic white men when adjusted for various social and biological parameters [223].

3.2.3 | Mental Health, Stress and Emotional Eating

Recent research emphasizes the bidirectional relationship between mental and cognitive health and obesity, where each can exacerbate the other [224–228]. Mental health issues can affect eating behaviors as they may increase appetite or cravings for unhealthy foods, reduce motivation for physical activity, and overall worsen the patient's economic and social situation [229]. Moreover, stress-related hormonal changes, particularly increased cortisol levels, can contribute to fat accumulation, especially in visceral areas [230].

Emotional eating—a need to eat in response to emotions—is commonly associated with obesity and unhealthy dietary patterns, including frequent fast-food consumption. Implementing strategies to manage negative emotions and providing nutrition education can help mitigate this behavior [229].

Nevertheless, many patients express reluctance toward psychiatric pharmacological treatment, fearing potential weight gain. However, it remains highly debated whether such weight gain stems primarily from psychiatric disorders themselves or from

their treatment. One proposed mechanism involves activation of the hypothalamic–pituitary–adrenal (HPA) axis in depressive disorders, which may promote visceral fat accumulation, trigger inflammatory cytokine release, and induce metabolic changes—including elevated blood pressure, dyslipidemia, and impaired glucose metabolism [231]. Yet, antidepressants are known to contribute to weight gain, with a ≥5% increase in body weight observed as an adverse effect of agents such as amitriptyline, mirtazapine, nortriptyline, citalopram, trimipramine, paroxetine, and phenelzine. Prolonged usage of selective serotonin reuptake inhibitors (SSRIs) can lead to downregulation of serotonin receptors, potentially increasing cravings for carbohydrate-rich foods and promoting weight gain. Additionally, antipsychotics like quetiapine, haloperidol, trifluoperazine, risperidone, aripiprazole, olanzapine, and clozapine increased body weight by ≥7% from baseline, which is considered a clinically significant result. Tricyclic antidepressants (TCAs) tend to cause weight gain during short-term treatment, while SSRIs such as paroxetine and citalopram are more often linked to weight gain during medium- to long-term use [232]. Patients with first- and second-generation antipsychotics gain weight in 40%–80%.

3.2.4 | Dietary Habits

Modern dietary habits are characterized by an increased consumption of high-calorie, low-nutrient foods that are rich in sugar and saturated fats. The prevalence of fast food, sugary beverages, and large portion sizes leads to excessive energy intake and can contribute to obesity prevalence [233–236]. The HELENA study suggested an important association between portion sizes and obesity in European adolescents [237].

3.2.5 | Urbanization and Lifestyle Changes

Urbanization has led to lifestyle changes that promote sedentary behavior and poor dietary habits. The transition to sedentary occupations, increased reliance on motorized transportation, and the widespread availability of highly palatable, often processed foods have all been linked to rising obesity rates in urban populations [238]. In a time series analysis of neighborhoods in Ontario, the data indicated that greater neighborhood walkability was linked to a lower prevalence of overweight and obesity, as well as a reduced incidence of diabetes [239]. Moreover, a Danish study with 21,832 participants has shown that persons living more than 1 km from green space have higher odds of obesity (odds ratio, OR = 1.36) than those living closer than 300 m [240]. Similar OR values were shown by the results of the study on 25,317 Finnish employees [241].

3.2.6 | Physical Inactivity

Physical inactivity ranks as the fourth leading cause of death worldwide and significantly contributes to metabolic and endocrine diseases. Despite its prevalence in today's society, physical inactivity often receives less attention than other risk factors [242]. Clear connections have been identified between obesity and both sedentary behavior and physical inactivity, with these behaviors being significantly associated with an increased likelihood of developing obesity [243]. A meta-analysis of 23 studies involving 111,851 adults and older adults with obesity has shown an association between sedentary behavior and obesity (OR 1.45, 95% confidence interval [CI], 1.21–1.75) and physical inactivity and obesity (OR 1.52, 95% CI, 1.23–1.87).

3.2.7 | Socioeconomic Status

Lower socioeconomic status (SES) is linked to limited access to healthy food, higher consumption of energy-dense diets, and reduced physical activity, contributing to obesity occurrence [244, 245]. This inverse relationship between SES and obesity rates is even more apparent in high-income countries and more developed areas [246]. Moreover, a meta-analysis of 21 observational studies has shown that low neighborhood socioeconomic status (NSES) might be associated with a higher risk of overweight/obesity, irrespective of the individual's own socioeconomic status [247].

4 | Treatment Options for Obesity

The main goal of obesity treatment is to reduce body fat mass while preserving muscle mass, benefiting the acute and chronic influence on overall health. Until recently, the treatment primarily relied on lifestyle interventions, focusing on diet and physical activity. However, recent progress has introduced additional possible therapeutic options for these patients, enhancing their quality of life [248]. The primary treatment options for obesity must be multimodal and personalized. The possible approaches encompass three main areas: lifestyle interventions, pharmacological therapy, and bariatric surgery [249]. The most appropriate management should always be personalized and based on the patient's characteristics. In our review, we also discuss some of the emerging treatment possibilities, including microbiota modulation, novel pharmacological agents, monoclonal antibodies, and gene therapy.

4.1 | Lifestyle Interventions

4.1.1 | Physical Activity

Regular physical activity is a fundamental treatment option for obesity and plays a vital role in its prevention, especially when supported by an appropriate nutritional strategy and good sleep quality. It not only helps with body composition management but also improves metabolic markers, such as insulin sensitivity, aerobic capacity, and muscle capillarization [250]. Additionally, it improves the lipid profile, including increases in HDL cholesterol, and enhances vascular density in skeletal muscles. It also has positive effects on mental health by improving sleep quality and emotional well-being [251–253]. Furthermore, several studies have demonstrated that physical activity is associated with increased telomere length [250, 254].

Interestingly, for those with a higher genetic risk of obesity, a higher step count needs to be achieved in order to achieve the

needed physical activity to prevent obesity [255]. However, even with a high genetic predisposition, maintaining a healthy lifestyle can prevent obesity and related comorbidities [256]. Some studies are already highlighting the importance of personalized lifestyle interventions tailored to an individual's genetic predisposition to mitigate the risk of obesity [257].

4.1.2 | Nutritional Strategy

Nutritional strategy is another cornerstone of obesity management, with personalized nutritional assessment recommended for each patient to tailor the intervention to individual needs. Based on the patients' nutritional status, physical activity levels, and their diseases, an appropriate nutritional therapy can be prescribed. In obesity, the strategies focus particularly on energy and protein intake, with specific attention to supporting physical exercise. A meta-analysis on 92 studies that clustered patients into 12 groups has shown that the most effective strategy for nearly all outcomes (BMI, body weight, and muscle mass) is combining resistance training or mixed exercise, higher protein intake, and energy restriction [258]. Personal nutritional assessment includes evaluating the patient's energy needs. Meanwhile, protein needs for skeletal muscle mass preservation are calculated based on adjusted body weight [259, 260]. Self-reported food diaries often underestimate intake, especially in patients with obesity. For best accuracy, including an experienced dietitian in the nutritional team is recommended [16, 261].

Additionally, nutrition plays a significant role in shaping the gut microbiome, indirectly influencing metabolic health and obesity risk [262]. Beyond weight management, nutritional interventions have been shown to improve depressive symptoms, quality of life, and overall mental health, making them an essential part of holistic obesity care [263–265].

Nutrigenomics, a branch of omics sciences, examines how nutrients and diet affect genes, proteins, and metabolites, while nutrigenetics focuses on how genetic variations, such as SNPs, influence individual responses to nutrients. These differences can alter metabolism, nutritional needs, and disease risk. These insights support personalized dietary strategies, though ethical concerns about genetic testing persist [266, 267].

GWAS studies shed light on the influence of some SNPs on dietary interventions' outcomes, with identified genes being generally associated with lipid and glucose transportation and utilization (e.g., *RETN*, *ADIPOQ*, *UCP3, BDNF, CADM2, FANCL*, and *ADRB3*) [162, 268–276]. The discovered gene–environment interactions in association with the calculation of GRS have already been used in predicting the weight loss following dietary interventions [276, 277].

A recent European RCT involving 5562 participants compared three groups: one following standard healthy eating guidelines, one with a diet tailored to individual dietary intake and anthropometric data, and one further personalized using genotypic information. The genotype-based group showed a greater reduction in saturated fat intake, particularly in individuals with *APOE* variants, compared to conventional advice [278]. In another study of 1287 individuals with overweight or obesity, Garaulet et al. found that variants in the *PLIN1* influenced weight-loss response to a Mediterranean diet. Specifically, carriers of the minor C allele at 6209T > C showed greater weight loss and were 33% more likely to achieve ≥ 7.5% weight reduction compared to TT carriers ($p = 0.017$) [279]. In a recent study of 188 participants, Di Renzo et al. examined whether the *FTO* rs9939609 polymorphism influenced body composition changes following a 4-week Mediterranean diet intervention. They found a significant gene–diet interaction affecting total body fat ($p = 0.04$) and total body water ($p = 0.02$), though the role of *FTO* in dietary response remains uncertain [280].

4.1.3 | Behavioral Therapies

Behavioral therapy aims to modify lifestyle behavior such as maladaptive eating patterns and low physical activity levels to support weight loss.

Various approaches to changing behavior in these patients exist. However, one of the important parts involves setting realistic, achievable goals to encourage gradual, sustainable lifestyle changes over time [281, 282]. Another crucial element of behavioral therapy is self-monitoring, with patients being encouraged to record their food intake and physical activities to increase their awareness and accountability. Stimulus control techniques are also used, helping patients avoid situations or environments that stimulate overeating (e.g., easy access to large food portions). Additionally, strategies such as slower eating have been shown to decrease overall energy intake [281–284]. Nevertheless, the improvement of mindless eating habits had a stronger effect than behavioral change in stress-related eating habits [283].

Cognitive behavioral therapy (CBT) has proven effective in weight reduction and in tackling emotional eating issues [285, 286]. A successful approach relies on setting attainable goals, providing social support, encouraging regular physical activity, and fostering patient education, all of which improve engagement and adherence in obesity treatment programs [281, 282].

Studies show that interventions targeting emotional eating have demonstrated potential in reducing this behavior and contributed to modest weight loss among adults with overweight or obesity [285]. However, a meta-analysis of 30 studies of youth with low SES has shown that the behavioral change techniques seem to have a small to negligible effect on BMI change. The effect seemed to be bigger with longer follow-up periods (≥ 12 months) and with the use of more than six behavioral change techniques [287].

A study by Shiwaku et al. on 76 perimenopausal women with no clinical symptoms found that the polymorphism Trp64Arg of the beta3-adrenergic receptor gene *ADRB3* was associated with difficulty in losing weight through a 3-month behavioral intervention [288]. Another study by Kim et al. assessing the response to 8-month digital healthcare lifestyle modification in 45 young participants showed that some SNPs might

predict super-responders and poor-responders. Moreover, they also found that SNPs were associated with significant differences in eating behavior changes, healthy diet diversity, and emotional eating [289]. Interestingly, pooled analysis of four studies testing four obesity-associated SNPs found no reliable evidence of significant links between the examined obesity-related SNPs and weight loss during a behavioral intervention, indicating that other factors (such as environmental, social, and behavioral) may have a greater influence on body weight regulation [290]. Similarly, a study by Heitkamp et al. found only a mild effect of some of the tested SNPs on the outcomes of the 4- to 6-week standardized in-hospital lifestyle intervention program [291].

Although behavioral therapy has an important role in the treatment of obesity, a recent systematic review found that most research about this field fails to examine whether participation, adherence, drop-out rates, or outcomes differ between different social groups. These programs often require significant personal commitment—such as time, resources, and education—which may unintentionally exacerbate health disparities. Inequalities can arise at different stages of an intervention and are often related to factors identified in the PROGRESS-Plus framework (place of residence, race/ethnicity, occupation, gender, education, socio-economic status, social capital, and other potential sources of discrimination, such as age and sexual orientation) [292].

4.1.4 | Time Restricted Feeding (TRF) and Chrono-Exercise

Time-restricted eating (TRE) is a dietary approach that limits food intake to a window of 4 to 10 h per day, with the remaining 14 to 20 h reserved for fasting. During the eating window, individuals can eat ad libitum, while hydration is encouraged throughout the fasting period. One of the key advantages of TRE is that it eliminates the need for daily calorie counting, yet has been shown to reduce energy intake by approximately 200 to 550 kcal per day. Short-term studies in individuals with obesity (1 to 3 months) have demonstrated modest weight loss of 1%–3%, while longer-term studies (up to 12 months) have generally not exceeded a 5% reduction in body weight. Nonetheless, recent evidence suggests that TRE may offer metabolic benefits independent of weight loss, including improvements in blood pressure, insulin sensitivity, and pancreatic β-cell function. To date, no clear relationship has been established between TRE and physical activity in people with obesity. A potential drawback of this method is the risk of compensatory intake of high-calorie foods during the eating window [293]. Moreover, the method might pose a risk for muscle loss in patients with chronic illnesses due to more pronounced catabolic metabolism. However, further studies are needed to better define this limitation [294].

Chrono-nutrition and exercise is an emerging interdisciplinary field within nutritional and kinesiologic sciences that explores the interaction between lifestyle habits—such as food intake and physical activity—and the circadian rhythm. Factors including meal timing, meal frequency, caloric distribution, nutrient composition, and the timing of exercise can all exert significant metabolic effects. Research has demonstrated that aligning food intake and physical activity with the body's internal clock may enhance insulin sensitivity, influence cardiac gene expression, and improve lipid metabolism [295].

4.2 | Pharmacological Treatments

Pharmacological therapy of obesity is essential for those whose lifestyle changes have not produced satisfactory outcomes. Pharmacological therapy should be implemented alongside all other non-pharmacological options, namely, nutritional interventions, physical activity, and behavioral therapy. The mechanisms of drugs are diverse, targeting several processes involved in energy expenditure, appetite management, and nutrient absorption. The European Association for the Study of Obesity (EASO) advocates for a nuanced, risk-based approach to managing obesity as a chronic, adiposity-based disease. They recommend prescribing anti-obesity medications, in line with official labeling, alongside lifestyle and behavioral interventions for patients with a BMI $\geq 30\,kg/m^2$, or $\geq 27\,kg/m^2$ when obesity-related complications are present. In adults of European descent, pharmacotherapy may also be considered at a BMI $\geq 25\,kg/m^2$ if the waist-to-height ratio exceeds 0.5 and there are associated medical, functional, or psychological impairments [296].

4.2.1 | Current Medications

Various agents are used for weight management, traditionally categorized by their mechanisms of action. These include lipase inhibitors (e.g., orlistat); opioid antagonists and norepinephrine-dopamine reuptake inhibitors (e.g., naltrexone/bupropion); sympathomimetics (e.g., phentermine and diethylpropion); and GLP-1RAs (e.g., semaglutide and liraglutide).

Orlistat is an irreversible inhibitor of pancreatic and gastric lipase, leading to a reduction in the absorption of ingested fat in the intestine by approximately 30%. This medication also influences the brain-gut axis by enhancing postprandial secretion of GLP-1. Common adverse effects include steatorrhea, flatulence, and fecal incontinence. To ensure adequate levels of lipid-soluble vitamins in the body, particularly vitamin D3, supplementation is recommended [297–299].

Naltrexone/bupropion is particularly effective in patients with emotional hunger—a form of hedonic eating driven by negative emotions, cravings, and reward-seeking behavior. However, its weight-reducing effect in individuals with obesity may be only modest to moderate. The combination works by enhancing the activity of POMC neurons, leading to reduced appetite and increased energy expenditure. Bupropion, an atypical antidepressant, stimulates dopamine activity in the hypothalamus, activating POMC neurons. Naltrexone blocks opioid receptors on these neurons, preventing feedback inhibition and further amplifying their activity. The drug should not be taken with a high-fat meal due to increased absorption and exposure [300, 301]. The most common adverse effects associated with the naltrexone/bupropion combination include constipation, dry mouth, headache, and insomnia [302]. Phentermine and diethylpropion are sympathomimetic agents used for short-term weight loss support; their side effects are consistent with their

mechanism of action and may include palpitations, tachycardia, arterial hypertension, and gastrointestinal disturbances [303].

GLP-1RA are synthetic analogs of the human incretin hormone that are resistant to dipeptidyl peptidase 4 (DPP-4) proteolysis, resulting in higher plasma concentrations and enhanced pharmacological effects. This class of medications stimulates insulin secretion from β-cells, reduces appetite, and slows gastric emptying. Based on injection frequency and duration of effect, GLP-1RA can be categorized into short-acting and long-acting groups. The most common adverse events associated with GLP-1RA are gastrointestinal symptoms, including diarrhea, nausea, and vomiting. Some studies have suggested that GLP-1RA may increase the risk for thyroid cancer; however, the evidence remains inconclusive [304]. Nevertheless, a recent study done by Brito et al. reported a higher risk of thyroid cancer during the first year of GLP-1RA use compared to three other classes of antihyperglycemic agents [305]. On the other hand, recent studies have found that patients with T2DM treated with GLP-1RA did not have an increased incidence of pancreatic cancer [306]. Moreover, one of the studies even suggested a lower risk for the mentioned pathology [307]. To minimize the side effects and improve patient compliance, the short-acting formulations have largely been replaced by once-weekly long-acting preparations in standard obesity treatment. All drugs in this category are administered subcutaneously; however, semaglutide can also be given orally, although this route is not yet approved for obesity treatment [298, 308, 309]. In a study conducted by Wilding et al., patients with obesity but without T2DM were randomly assigned to two groups: one receiving semaglutide once a week and the other receiving a placebo. At week 68, those treated with semaglutide experienced significant weight loss compared to the placebo group, with 86.4% achieving a weight reduction of 5% or more, 69.1% losing 10% or more, and 50.5% achieving a loss of 15% or more, in contrast to 31.5%, 2.0%, and 4.9% of patients in the placebo group, respectively [310].

4.3 | Surgical Interventions—Bariatric Surgery

Bariatric surgery (BS) might be considered for those who have not achieved satisfactory weight loss through physical activity, behavioral modifications, and pharmacological treatment. Generally, the candidates for BS must have a BMI over 40 kg/m^2 or a BMI between 35 and 40 kg/m^2 with obesity-related comorbidities, such as T2DM [311, 312]. However, some guidelines also suggest considering BS for patients with a BMI $\geq$ 30 kg/m^2. The BS encompasses several techniques, including intra-gastric balloon, endoscopic sleeve gastroplasty (ESG), Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy, and one-anastomosis gastric bypass (OAGB) [313]. These procedures utilize mechanisms such as enforced energy restriction, nutrient malabsorption, and modulation of intestinal neuroendocrine hormones [314]. Potential complications include post-operative tachycardia, respiratory issues (e.g., pneumonia, deep vein thrombosis, and pulmonary embolism), nutrition-related deficiencies (malnutrition, sarcopenia, and osteoporosis), and surgical or gastrointestinal complications (bleeding, peritonitis, fistula, mesenteric vein thrombosis, gastric ulcers, and dumping syndrome) [311, 312]. Moreover, BS has been shown to reduce lower limb–limb isometric strength and absolute handgrip strength [315].

Genetic variability plays a significant role in weight loss outcomes after BS. A study by Torrego-Ellacuria et al., involving 375 patients, found that 6 years post-surgery, eight specific SNPs were associated with weight response to BS. These SNPs are involved in key metabolic pathways, involving GIP, DPP-4, NPY, GLP-1, and the circadian rhythm [316]. Similarly, a smaller study with a 1-year follow-up demonstrated that individuals with a genetic predisposition to addiction, specifically the *DRD2* polymorphism, showed a stronger response to weight loss treatment [317]. Furthermore, research by Doyon et al. suggests that miRNAs involved in regulating fatty acid biosynthesis, adipocyte proliferation, and the pathogenesis of T2DM and obesity may also influence treatment response [318].

4.4 | Emerging Therapies

Novel obesity treatments, such as microbiota manipulation, PYY agonists, dual and triple receptor agonists, monoclonal antibodies, and gene editing techniques, are transforming obesity treatment by addressing both metabolic and genetic factors. We will examine gene therapy—particularly clustered regularly interspaced short palindromic repeats (CRISPR)—thoroughly, due to its groundbreaking potential for precise genetic modification to achieve lasting effects on obesity-related pathways. The reviewed emerging therapies are represented in Figure 6.

4.4.1 | Microbiota Modulation

The modulation of gut microbiota represents a novel approach in the treatment of obesity. Altered microbiota can affect energy balance through promoting lipid synthesis and storage, modulating central appetite, and triggering chronic inflammation [319]. Although research in this field is still in its early stages, several ongoing studies hold promise for uncovering effective interventions.

4.4.1.1 | Probiotics. Probiotics are live microorganisms that can benefit the host's health by supporting the physiology of the digestive system [320]. They can reinforce gut barrier integrity and improve metabolism by decreasing intestinal permeability and thereby reducing inflammation, down-regulating pro-inflammatory cytokines such as IL-6 and TNF, and producing SCFAs that have anti-inflammatory properties and promote the metabolism of lipids [110, 321].

Probiotics are commonly delivered through fermented foods or oral capsules, with milk and dairy items being the most researched carriers. Different probiotic strains have unique effects and specific dosage requirements, with *Lactobacillus* and *Bifidobacterium* being the most widely studied in relation to obesity treatment [320]. Another important bacterium that could be used as a probiotic is *Akkermansia muciniphila*. It colonizes the mucosal layer of the gut and plays an important role in regulating basal metabolism. Its reduction is associated with several diseases in humans and mouse models, including obesity. Animal and human studies confirm its beneficial activity in the treatment of obesity, exposing the possibility of its use in the next generation of therapeutic approaches for the treatment of metabolic diseases. In addition to obesity, it is also thought to

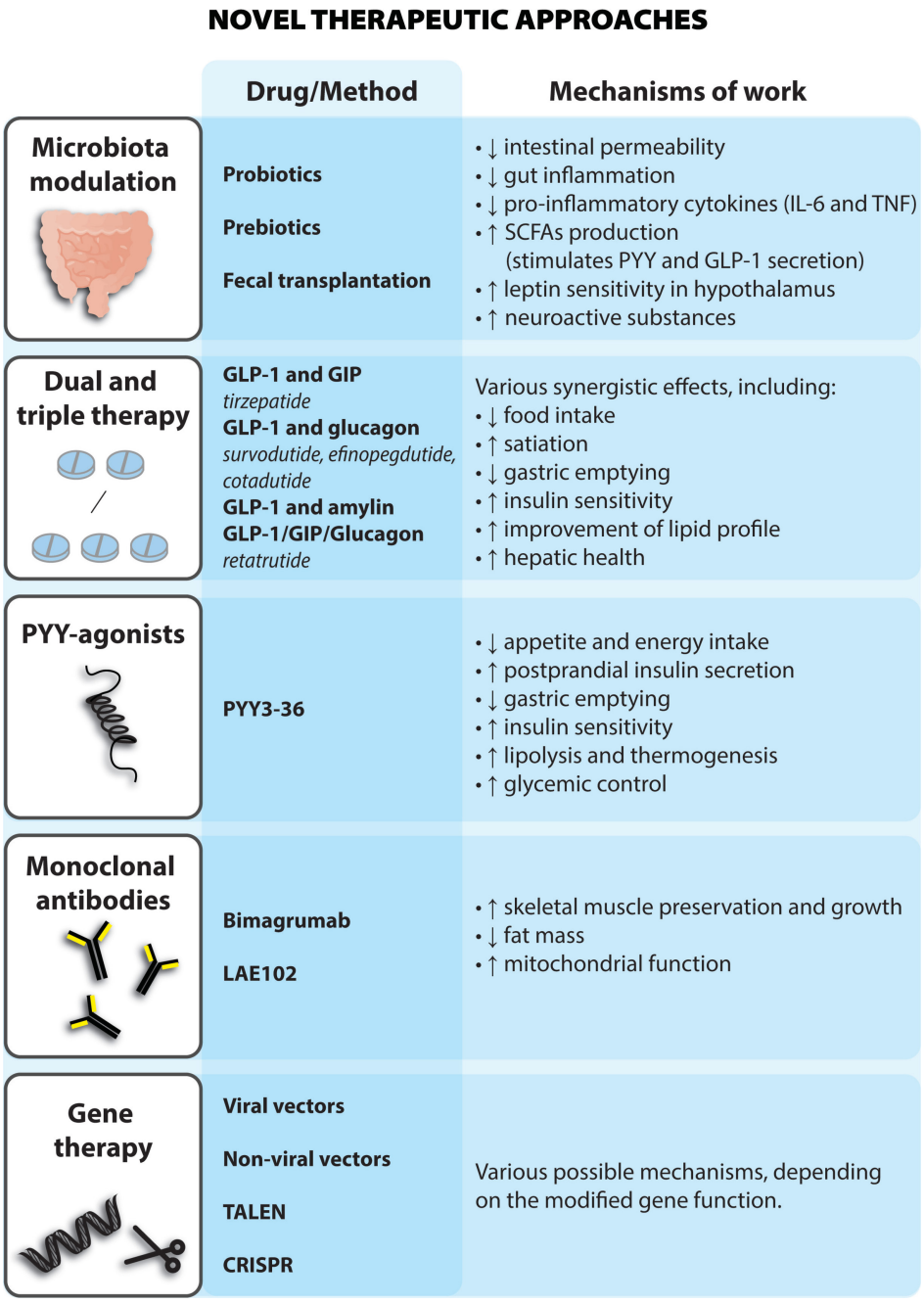

FIGURE 6 | Novel therapeutic approaches for obesity treatment. IL-6—interleukin-6; TNF—tumor necrosis factor; SCFAs—short-chain fatty acids; PYY—peptide yy; GLP-1—glucagon-like peptide-1; GIP—gastric inhibitory peptide; PYY3–36—peptide yy3–36; TALEN—transcription activator-like effector nuclease; CRISPR—clustered regularly interspaced short palindromic repeats.

have a positive effect on type 1 and 2 diabetes, hepatic steatosis, intestinal inflammation, and some cancers [322–324]. The efficacy of all of the mentioned beneficial microorganisms depends on whether they are consumed as standalone supplements or integrated into food products [320].

A meta-analysis by Perna et al., including 1411 patients with overweight or obesity and related metabolic conditions, found no reduction in body weight from probiotic interventions. However, a decrease in BMI (−0.73 [−1.31, −0.16] kg/m^2), waist circumference (−0.71 [−1.24, −0.19] cm), and hip circumference (−0.73 [−1.16, −0.30] cm) was observed [325]. Another larger meta-analysis with 12,603 participants reported that probiotics or synbiotics significantly reduced body weight (−0.91 [−1.08, −0.75] kg), BMI (−0.28 [−0.36, −0.21] kg/m^2), waist circumference (−1.14 [−1.42, −0.87] cm), fat mass (−0.92 [−1.05, −0.79] kg), and body fat percentage (−0.68 [−0.94, −0.42]%) without affecting fat-free or lean body mass [326]. A 2024 meta-analysis by Duan et al., involving 391 adolescents, showed that probiotics lowered BMI (−2.53 [−4.8 to −0.26] kg/m^2), fasting blood glucose (−0.80 [−1.13 to −0.47] mmol/L), and C-reactive protein (CRP) (−0.24 [−0.43 to −0.05] mg/L). However, no significant changes in weight, waist circumference, waist-to-hip ratio, or insulin levels were observed. Notably, the intervention also increased total cholesterol, triacylglycerides (TAG), and low-density lipoprotein (LDL) cholesterol levels [327].

In many cases probiotics have been reported to cause immunoreactivity, sepsis, and antibiotic resistance caused by gene transfer. These negative effects are most common in immunodeficient patients. Some probiotic effects are associated with a highly specific strain of microorganism, making it difficult to assess the appropriate dose and treatment schedule. Therefore, more studies are needed to create an adequate protocol and guidelines regarding probiotic usage in patients [320]. Currently, over 10 studies on the use of probiotics in obesity treatment are registered on ClinicalTrials.gov.

4.4.1.2 | Prebiotics. Prebiotics are indigestible components that promote the proliferation of gastrointestinal microbes, such as *Bifidobacterium* and *Lactobacillus*. Gut bacteria convert prebiotics into SCFA and other metabolites, enhancing host health by increasing regulatory T-lymphocyte activity, mineral absorption, and immunoglobulin A secretion by B-lymphocytes. Prebiotics primarily comprise fibrous foods such as onions, garlic, asparagus, and barley. They are categorized based on their polymerization stage and food source, including fructans (subdivided into fructo-oligosaccharides and inulin), polydextrose, xylooligosaccharides, lactulose, galactooligosaccharides, triphala, and cyclodextrins. Additionally, they lower intestinal pH, inhibiting the proliferation of pathogenic bacteria such as *Escherichia coli* and *Clostridium perfringens* [299, 320].

A single-centered placebo-controlled trial of 7- to 12-year-old children with overweight or obesity has researched the effect of 16 weeks of intervention with either oligofructose-enriched inulin or maltodextrin placebo. Those who consumed prebiotics had a greater reduction in body weight (3.1%), body fat (2.4%), and trunk fat (3.8%). Moreover, a greater TGA decrease (19%) was observed in this group [328]. Another study in 45 adults with obesity with three study groups (diet only; prebiotics; probiotics) has shown that 1 month after intervention, all groups achieved a significant decrease in weight, BMI, and waist circumference. However, only the prebiotic and probiotic groups have experienced a significant decrease in fat mass and an increase in muscle strength. Moreover, the prebiotic and probiotic significantly improved the insulin profile compared to the diet-only group [329].

4.4.1.3 | Synbiotics. Synbiotics are combinations of probiotics and prebiotics, having a synergistic effect on gastrointestinal microbiota. The prebiotics enhance the survival rate of probiotics and support their colonization in the digestive tract [320].

A 2020 meta-analysis of 23 randomized trials found that synbiotic intervention led to a reduction in body weight (−0.80 [−1.56 to −0.03] kg) and waist circumference (−2.07 [−3.11 to −1.03] cm). However, no significant effects on BMI or body fat were observed. Additionally, the dosage of probiotics did not influence the treatment response [330].

4.4.1.4 | Fecal Microbiota Transplantation. While fecal microbiota transplantation (FMT) is primarily indicated for antibiotic-resistant *Clostridium difficile* infections, recent studies have also explored its potential in treating obesity, with lean donor selection being the key to success [331–333]. FMT includes transferring fecal matter from a healthy donor to the recipient's digestive tract through various methods, including colonoscopy, nasojejunal tubes, enemas, or oral capsules [331–333]. Numerous studies have examined the effects of FMT on weight loss and glycemic homeostasis in patients with obesity. Current findings indicate that FMT has no significant impact on weight or weight control. Further research is needed to assess its potential efficacy in obesity and other metabolic diseases [331–333].

4.4.2 | Dual Therapy

Dual therapy for obesity offers greater effectiveness in weight reduction and metabolic enhancement than monotherapy, as it simultaneously engages multiple biological pathways.

4.4.2.1 | Dual GLP-1 and GIP Agonism. Recent developments in dual agonists targeting both GLP-1 and GIP receptors aim to enhance their effects synergistically. Initially, many researchers viewed GIP-based treatments with skepticism [334]. However, preclinical models suggested that simultaneous activation of GLP-1 and GIP receptors leads to more substantial weight reduction and improved glycemic control compared to the activation of each receptor individually [335, 336]. Moreover, the combined agonism of GLP-1 and GIP receptors has demonstrated remarkable efficacy in glycemic control and weight loss [337]. Additionally, some dual agonists are currently being researched in humans, showing promising results.

Tirzepatide is an unimolecular dual GLP-1 and GIP receptor agonist consisting of 39 amino acids. GIP, a hormone secreted by K-cells in the jejunum after food intake, primarily boosts glucose-stimulated insulin secretion, increases blood flow to adipose tissue and the digestive organs, and reduces bone resorption. GIP also stimulates glucagon release during low blood glucose levels in the fasting state [102]. Tirzepatide has a GIP receptor binding affinity like the native GIP molecule, whereas its binding affinity for GLP-1 is 5 times lower compared to native GLP-1 [337–339]. It has been shown to have superior effects on specific aspects of the lipid profile compared to dulaglutide [340]. The efficacy of tirzepatide as a treatment for T2DM was assessed through multiple SURPASS trials, which will not be discussed in detail here [341–346].

In 2023, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved tirzepatide for chronic weight management in patients with a BMI over 30 kg/m^2 or over 27 kg/m^2 with weight-related comorbidities [347, 348]. The pharmacokinetics of the drug are dose-dependent. It is administered subcutaneously once a week, starting with an initial dose of 2.5 mg, which is increased to 5 mg after 4 weeks. The maximum dose is 15 mg per week [337]. The drug exhibits a high affinity for plasma albumin and has a half-life of 5 days. Pharmacokinetics are not influenced by factors such as age, race, sex, body weight, or liver and kidney function [349–352].

The most common adverse effects are gastrointestinal, with nausea and diarrhea being the most frequent. These effects are dose-dependent and are typically more pronounced at the beginning of treatment but tend to decrease in frequency and severity over time. Mild hypoglycemia has also been reported due to its antihyperglycemic effects. Serious adverse effects, such as acute

pancreatitis, cholecystitis, cholelithiasis, and severe hypoglycemia, occur at a very low rate (< 1%) [353].

The concurrent use of GLP-1RA and tirzepatide should be avoided due to their synergistic effect on GLP-1 receptors. Moreover, the medication also reduces the efficacy of oral contraceptives, so alternative methods should be used. It is contraindicated in patients with severe hypersensitivity reactions (e.g., anaphylaxis and angioedema), multiple endocrine neoplasia type 2 (MEN-2), or medullary thyroid cancer [349, 350, 354].

The clinical characteristics of the drug are summarized in the study review presented in Table 1.

4.4.2.2 | Dual GLP-1 and Glucagon Agonism. In 2009, initial animal model studies revealed that dual agonists targeting GLP-1 and glucagon receptors (GCGR) produced greater weight reduction than GLP-1RA alone [363]. Since then, the therapeutic benefits of this dual receptor activation have been confirmed across various species, including rodents, monkeys, and humans [364]. Glucagon, a peptide hormone secreted by pancreatic-α cells in response to low blood sugar, plays a central role in glucose regulation by promoting hepatic glucose production. It also influences lipid and protein metabolism in the liver and helps reduce food intake [365].

Several dual GLP-1 and CGCR agonists, including survodutide, efinopegdutide, NNC9204-1177, and cotadutide, are currently being explored for their potential in altering weight management and metabolic health. These drugs are designed with extended half-lives, allowing for convenient once-weekly subcutaneous administration. They generally follow a titration protocol, with an initial lower dose that is gradually increased to reach the maximum therapeutic dose [366–370].

In a Phase 2 trial led by Le Roux et al., survodutide's safety and efficacy were evaluated. Administered subcutaneously once a week, survodutide showed significant dose-dependent weight reductions over 46 weeks, ranging from −6.2% to −14.9% with doses of 0.6, 2.4, 3.6, and 4.8 mg, compared to −2.8% in the placebo group. The most common adverse effects reported were gastrointestinal, affecting about 75% of participants [350, 370]. A recent 12-week study on 99 adults with overweight or obesity evaluated the safety, tolerability, and efficacy of NNC9204-1177, revealing clinically meaningful weight loss of up to 12.6%. However, some concerning side effects were noted, including increased heart rate, decreased reticulocyte count, elevated inflammation markers, and impaired glucose tolerance [371]. Another study by Nahra et al. investigated cotadutide in 834 adults with a BMI ≥ 25 kg/m^2 and T2DM on metformin. The results indicated reductions in HbA1c and body weight, along with improvements in lipid profile, ALT, and AST levels, propeptide of type III collagen, fibrosis-4 index, and nonalcoholic fatty liver disease fibrosis score, demonstrating cotadutide's potential benefits for metabolic and hepatic health [369].

4.4.2.3 | Dual GLP-1 and Amylin Agonism. Amylin is an anorexigenic hormone co-secreted with insulin by pancreatic β-cells in response to food intake. Its primary functions include promoting satiation, inhibiting postprandial glucagon release, slowing gastric emptying, and reducing digestive enzyme secretion through multiple pathways [81, 82, 372–374]. Pramlintide, a short-acting amylin analog, is used in both type 1 diabetes and T2DM treatment and is administered via subcutaneous injection once a week [375]. Cagrilintide, a longer-acting amylin analog, is currently under investigation in combination with the GLP-1RA semaglutide (marketed as CagriSema) for managing obesity and overweight conditions. A Phase 2 study by Frias et al. compared the effects of the cagrilintide-semaglutide combination with each agent alone in participants with T2DM. The combination therapy showed superior weight reduction (−15.6%) compared to cagrilintide alone (−8.1%) and semaglutide alone (−5.1%) [81, 376–378].

4.4.3 | Triple Therapy (GLP-1/GIP/Glucagon)

GLP-1/GIP/glucagon triple agonist therapy aims to combine glucagon's metabolic effects with the double incretin action of GLP-1 and GIP to achieve greater weight reduction. In a phase 2 randomized trial led by Jastreboff et al., the efficacy and safety of retatrutide, a once-weekly GLP-1/GIP/glucagon receptor agonist, were assessed. After 48 weeks, weight loss was observed in a dose-dependent manner: 92%, 75%, and 60% of participants receiving 4 mg of retatrutide achieved at least 5%, 10%, and 15% weight loss, respectively. Higher doses yielded even better outcomes: with 8 mg, 100%, 91%, and 75% reached 5%, 10%, and 15% weight loss; and with 12 mg, 100%, 93%, and 83% achieved these targets. In comparison, only 27%, 9%, and 2% of placebo participants saw equivalent weight reductions. The most frequent side effects were gastrointestinal and generally increased with higher doses [299, 350, 377, 379].

Although GLP-1RA, dual therapy, and triple therapy have shown to lead to the inevitable lean mass loss, resistance training and adequate protein intake can help preserve muscle, leading to more favorable changes in body composition [380, 381].

There are currently many ongoing studies researching triple agonism. We have summarized them in Table 2.

4.4.4 | PYY-Agonists

PYY is a peptide co-secreted with GLP-1 by intestinal L-cells following food intake. It exists in two main forms: PYY1-36 and PYY3-36. PYY1-36, the less active form, is cleaved by DPP-4 to produce PYY3-36, which is the primary circulating form [382]. The two differ in their effects and receptor binding. Both types exert their physiological effects via Y-receptors (Y1, Y2, Y4, Y5, and Y6), which also bind NPY and pancreatic polypeptide (PP) with varying affinities [103, 299, 377]. However, PYY3-36 is more often used in body weight regulation as it is more specific since it does not bind to all known Y-receptor types as PYY1-36 but only has a high affinity for Y2-receptors and some affinity for Y1 and Y5-receptors.

The Y2 receptor, located in the hypothalamic arcuate nucleus, is the primary target of PYY3-36, through which it reduces caloric intake, enhances postprandial insulin secretion and

TABLE 1 | Summary of the completed interventional studies in patients with obesity treated with tirzepatide. T2DM—type 2 diabetes mellitus.

Basic information	Research design(primary goal and duration)	Number of patients	Results	Main conclusions
SURMOUNT-J [355] NCT04844918 Study start: 2021 Study completed: 2023	Randomized study. The safety and efficacy of tirzepatide administered once a week	267 participants with obesity	After 72 weeks patients with 10 mg tirzepatide reduced weight by −17.8%, patients with 15 mg tirzepatide by −22.7% and placebo by −1.7%. After 72 weeks, 70% of patients with 10-mg tirzepatide, 79.69% of patients with 15-mg tirzepatide and 11.11% of placebo patients improved health problems related to obesity.	Tirzepatide resulted in weight loss and improvement in obesity-related health issues compared to placebo. The effect was more pronounced in patients receiving 15 mg, compared to those on 10 mg.
[356] NCT04081337 Study start: 2020 Study completed: 2022	Randomized study. The efficacy of tirzepatide once weekly on food intake	55 patients with obesity	After 18 weeks, patients with 15 mg tirzepatide had a lower food intake (−914.51 kcal) compared with placebo (−58.57 kcal). After 18 weeks, patients with 15 mg tirzepatide had an energy expenditure of −300.07 kcal/day, in comparison to placebo (−296.85 kcal/day).	Tirzepatide reduced appetite and caloric intake, and improved energy expenditure
SURMOUNT-1 [357] NCT04184622 Study start: 2019 Study completed: 2024	Randomized study. Safety and efficacy of once-weekly tirzepatide in patients without T2DM.	2539 patients with obesity or overweight without T2DM	After 72 weeks, patients with 5-mg tirzepatide reduced weight by −16.0%, patients with 10-mg tirzepatide by −21.4% and placebo patients by −2.4%.	Tirzepatide significantly reduces body weight, with the highest dose showing the greatest results.
SURMOUNT-4 [358] NCT04660643 Study start: 2021 Study completed: 2023	Randomized study. Safety and efficacy of once-weekly tirzepatide in patients without T2DM.	783 participants with obesity or overweight without T2DM	After 64 weeks, patients with tirzepatide (10 or 15 mg) reduced body weight (−6.0%) compared with placebo patients who increased body weight (+9.9%). At week 88, tirzepatide patients continued with weight loss (−6.7%), whereas patients with placebo continued with weight gain (+14.8%).	Tirzepatide therapy led to weight loss. Continued tirzepatide treatment helped maintain the weight loss achieved during the initial treatment phase.
SURMOUNT-3 Wadden TA et al. [359] NCT04657016	Randomized study. Safety and efficacy of once-weekly tirzepatide after intensive lifestyle intervention without T2DM.	579 patients with obesity or overweight without T2DM	After 72 weeks, 94.37% of patients with tirzepatide and 10.65% of patients with placebo demonstrated body weight reduction of more or equal than 5%.	Tirzepatide resulted in additional weight reduction in patients who had achieved ≥ 5.0% weight loss with intensive lifestyle program.

(Continues)

TABLE 1 | (Continued)

Basic information	Research design(primary goal and duration)	Number of patients	Results	Main conclusions
SURMOUNT-2 Garvey WT et al. [360] NCT04657003	Randomized study. Safety and efficacy of once-weekly tirzepatide in patients with T2DM	938 patients with T2DM and obesity or overweight.	After 72 weeks, patients with 10 mg tirzepatide reduced weight by −12.8%, patients with 15 mg tirzepatide by −14.7% and placebo by −3.2%.	Tirzepatide treatment resulted with substantial body weight reduction in patients with T2DM and obesity or overweight.
[361] NCT04311411 Study start: 2020 Study completed: 2022	Randomized study. The effect of tirzepatide on appetite and energy intake, reward-related brain areas	114 participants with obesity or overweight	After 3 weeks, caloric intake in patients with tirzepatide decreased (−523.15 kcal) in contrast to placebo (10.95 kcal).	Tirzepatide therapy resulted in caloric intake reduction compared to placebo.
SURMOUNT-CN Zhao L et al. [362] NCT05024032	Randomized study. Safety and efficacy of once-weekly tirzepatide in Chinese participants without T2DM.	210 participants with obesity or overweight and without T2DM	After 52 weeks, patients with 10 mg tirzepatide reduced weight by −13.6%, patients with 15 mg tirzepatide by −17.5% and placebo by −2.3%.	Tirzepatide (10 and 15 mg) resulted in weight loss with an acceptable safety profile in Chinese participants

sensitivity, promotes lipolysis and thermogenesis, and slows gastric emptying [299, 377]. Additionally, the hormone binds to the Y1 receptor in the pancreas and CNS, where it affects appetite regulation in the area postrema and nucleus tractus solitarius [383]. Additionally, it reduces the rate of insulin secretion and promotes β-cell survival, as studies indicate that Y1 receptor signaling is crucial for restoring impaired *β*-cell function post-bariatric treatment [384–386]. Interestingly, mouse studies suggest Y1 receptor activation may even facilitate α-cell transdifferentiation into β-cells [386, 387].

It has been shown that individuals with obesity have lower blood concentrations of PYY3–36, which is reversible and can be returned to physiological concentrations after obesity treatment. When administered, the PPY3-36 crosses the BBB and binds to the Y2 subclass of NPY receptor in the brain, which is mostly situated on the presynaptic part of the synapse [388]. PYY3-36 administration improves glycemic and lipid regulation, as well as insulin sensitivity. However, it has a short half-life of approximately 12 min, with its impact on weight loss typically lasting around 2 weeks. This limited duration may be due to rapid activation of physiological mechanisms that counterbalance reduced caloric intake or the development of receptor tolerance [386]. Additionally, intranasal administration of PYY agonists in humans has shown limited efficacy and has been associated with gastrointestinal side effects such as nausea and vomiting. In light of these findings, long-acting PYY agonists are being developed as weekly subcutaneous injections, aiming to decrease side-effect incidence and improve efficacy [299, 377].

Although PYY3-36 may not be highly effective as a monotherapy, its combination with GLP-1R agonists demonstrates a synergistic impact on appetite-regulating nuclei and enhances glycemic control [386]. In a randomized study, Schmidt et al. evaluated the effects of intravenous PYY3-36 and GLP-1 agonist infusions, administered separately and in combination, on appetite, energy intake, and expenditure in patients with obesity. Neither drug significantly reduced energy intake when given individually, but the combination led to a 30% decrease in energy intake compared to placebo [389]. Similarly, Steinert et al. examined the effects of oral GLP-1, PYY3-36, and their combination on food intake in healthy participants in an ad libitum test meal. While GLP-1 alone reduced energy intake, PYY3-36 did not show this effect when administered alone. When combined, the two peptides reduced immediate meal intake by 21.5% and increased feelings of fullness before eating, although they did not reduce total 24-h energy intake [390].

4.4.5 | Monoclonal Antibodies

Monoclonal antibodies are laboratory-engineered molecules derived from cloned immune cells, designed to replicate the function of natural antibodies. Bimagrumab, a human monoclonal antibody, targets and blocks the type 2 activin receptor (*ACVR2*), promoting skeletal muscle growth, enhancing mitochondrial function, and reducing fat mass [299, 350, 377].

Bimagrumab can be administered subcutaneously weekly or intravenously once a month. In a randomized, double-blind study by Petricoul et al., the effects of intravenous versus subcutaneous

TABLE 2 | Summary of the ongoing studies researching triple agonism in patients with obesity. MACE—major adverse cardiovascular events; BMI—body mass index; ACD—atherosclerotic cardiovascular disease; CKD—chronic kidney disease; CVD—cardiovascular disease; T2DM—Type 2 diabetes mellitus.

Authors	Research design (primary goal and duration)	Number of patients	Stage
NCT06383390 Study start: 2024	Randomized study on retatrutide's effects on MACE and kidney function in patients with ACD and/or CKD.	Estimated enrollment of 10,000 participants	Recruiting
NCT05882045 Study start: 2023	Randomized study on the safety and efficacy of once-weekly retatrutide in patients with established CVD.	Estimated enrollment of 1800 participants	Recruiting
NCT05931367 Study start: 2023	Randomized study on the safety and efficacy of once-weekly retatrutide in patients with knee osteoarthritis	Estimated enrollment of 405 participants	Active, not recruiting
NCT05929066 Study start: 2023	Randomized study on the safety and efficacy of once-weekly retatrutide in patients without T2DM.	Estimated enrollment of 2100 participants	Recruiting
NCT05936151 Study start: 2023	Randomized study on the effects of retatrutide on renal function in patients with CKD, with or without T2DM.	Estimated enrollment of 120 participants	Recruiting
NCT05929079 Study start: 2023	Randomized study on the safety and efficacy of once-weekly retatrutide in patients with T2DM	Estimated enrollment of 1000 participants	Recruiting

infusions were compared over a 20-week period. Both administration methods reduced body fat mass by 2–3 kg, showing equivalent efficacy [391]. Heymsfield et al. reported that bimagrumab led to significant body composition improvements in 78 individuals with obesity. Participants receiving bimagrumab experienced a substantial reduction in fat mass (−20.5%) compared to the placebo group (−0.5%). This reduction was accompanied by a lean mass increase (+3.6%) in the bimagrumab group, whereas the placebo group showed a slight decline (−0.8%). Additionally, waist circumference decreased by an average of 9.0 cm, contrasting with a minor increase of 0.5 cm in the placebo group. HbA1c levels also improved significantly, with a reduction of −0.76% for bimagrumab versus −0.04% in the placebo group, indicating positive effects on glycemic control. The incidence of adverse events was similar between the bimagrumab and placebo groups. However, a higher number of participants in the bimagrumab group experienced specific adverse effects, including muscle spasms, mild diarrhea, upper respiratory infections, nausea, hypertension, and increased lipase levels. Notably, muscle spasms and diarrhea were the most frequent side effects, with diarrhea being more common after the first dose and less frequent with subsequent doses [392]. Furthermore, bimagrumab affects gonadotropic cells in the adenohypophysis, leading to alterations in follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels in the bloodstream. This effect, however, does not influence gonadal hormone or adrenal androgen secretion and is reversible [393].

Nunn et al. compared the effects of bimagrumab, semaglutide, their combination, and placebo in mice with obesity. Bimagrumab administration resulted in a 10% increase in skeletal muscle mass, with a concurrent reduction in fat mass. Semaglutide, on the other hand, decreased both fat and lean mass. The combination of bimagrumab and semaglutide led to greater body weight loss, specifically through fat mass reduction while preserving lean mass. Additionally, this combination resulted in improved metabolic outcomes [394].

Another monoclonal antibody targeting the actin receptor type II is LAE102. In preclinical models, LAE102 has demonstrated potential for reducing fat mass while preserving lean muscle. Recently, it was approved for clinical study by the Centre for Drug Evaluation of the National Medical Products Administration of China. Currently, the drug is in the phase of assessing its safety, pharmacokinetics, and immunogenicity in healthy volunteers [395, 396].

A summary of ongoing studies investigating bimagrumab as a treatment for obesity is provided in Table 3.

4.4.6 | Gene Therapy Approaches

Gene therapy involves the delivery of genetic material into a cell to cause a therapeutic effect, such as correcting an error in the genome or giving the cell a new function. This is achieved by using a vector to deliver the gene to the correct cell, where protein expression produces the desired effect. The type of vector that is used is influenced by its tissue tropism, packaging ability, vector production ability, and immunogenicity [299].

Gene therapy for obesity utilizes viral vectors (and adenovirus-associated vectors), non-viral vectors (lipids and proteins), transcription activator-like effector nucleases (TALEN), and targeted genome editing, including the CRISPR system.

TABLE 3 | A summary of ongoing studies investigating bimagrumab as a treatment for obesity. T2DM—type 2 diabetes mellitus; HbA1C—hemoglobin A1C; i.v.—intravenous.

Authors	Research design (primary goal, duration)	Number of patients	Main conclusions
[397] NCT05616013 Study start: 2022	Randomized study. Safety and efficacy of intravenous bimagrumab, alone or in combination with subcutaneous semaglutide.	Estimated enrollment of 507 participants	Ongoing study
[398] NCT05933499 Study start: 2024	Randomized study. The effect of bimagrumab on insulin sensitivity, body composition, and bone structure compared to placebo, semaglutide, and calcium/vitamin D.	Estimated enrollment of 65 participants	Not yet recruiting
[395] NCT06493084 Study start: 2024	Randomized study with i.v. and subcutaneous cohorts, evaluating the safety, and efficacy of LAE102.	Estimated enrollment of 72 healthy participants	Ongoing study

In the following section, we focus on the two most promising approaches for obesity treatment—viral vectors and the CRISPR system—providing a detailed overview of the latter.

4.4.6.1 | Viral Vectors and Adenovirus-Associated Vectors. Adenoviruses are non-enveloped, double-stranded DNA viruses with an icosahedral capsid, acting as episomes without integrating into the host genome. Their main drawback as vectors in gene therapy is high immunogenicity. Therefore, once used for the therapy, the body's immune system may recognize the viral vector as a pathogen and mount an immune response, preventing the reuse of the same vector for another gene therapy [399–401]. Adeno-associated viruses (AAV), on the other hand, are single-stranded, non-enveloped DNA viruses with an icosahedral capsid. They also act as episomes and are less immunogenic than adenoviruses, consequently generally provoking a weaker immune response compared to viral vectors [299].

As noted, viral and AAV therapy can enhance the properties of specific molecules for obesity treatment. For example, fibroblast growth factor 21 (FGF21) plays a crucial role in the pathophysiology of obesity, and its therapeutic potential has already been explored. However, FGF21 has a short half-life of 1–2 h, limiting its use in treatment. Jimenez et al. investigated the application of gene therapy using AAV vectors in mice to produce FGF21 in adipose tissue, liver, or skeletal muscle. This approach resulted in weight loss, reduced inflammation, and improved insulin resistance in mice [402].

4.4.6.2 | CRISPR-Cas9 in Obesity Research: Identifying Target Genes for Potential Therapies. Research on CRISPR-Cas9 gene editing in obesity animal models and in vitro studies on human cells has provided valuable insights into the genetic factors contributing to obesity. By knocking out or modifying gene sequences and expression, researchers can study the effects of these changes on metabolism and fat storage. This process not only identifies viable gene targets for potential human therapies but also enables the exploration of gene–environment interactions and the impact of gene edits on obesity-associated metabolic disorders like diabetes. Animal models are crucial in this research, allowing for assessing safety, effectiveness, and potential off-target effects of gene editing before translating findings into human treatments. Through these studies, we gain a deeper understanding of the genetic basis of obesity, providing a foundation for developing targeted therapies. The CRISPR/Cas9 system, its delivery routes, and the genes studied are summarized in Figure 7.

One notable study by Zhu et al. successfully used CRISPR/Cas9 to correct a mutation in the *Lep* gene of *ob/ob* mice, a model for morbid monogenic obesity in humans [403]. The correction of a single base pair mutation (C to T) was performed specifically in adipose tissue only. Although the allele replacement rate was relatively low (1.67%), it was sufficient to restore leptin production. This restoration effectively suppressed appetite and improved insulin resistance. This study underscores the potential of CRISPR-Cas9-mediated genome editing as a therapeutic strategy for treating monogenic obesity in humans by targeting peripheral tissues like adipose tissue.

Another important aspect of CRISPR-Cas9 research is its ability to replicate human-specific genetic variations associated with obesity. For example, by introducing human-like mutations into animal models, researchers can simulate how these genetic changes affect metabolism, fat storage, and energy balance. This approach can also help identify the impact of SNPs linked to obesity. Editing these SNPs in animal models allows for a direct assessment of their role in obesity and metabolic disorders, paving the way for targeted therapies.

In the study by Claussnitzer et al., the CRISPR/Cas9 approach was used to investigate the effects of the human *FTO* gene variant rs1421085, a risk factor for obesity. The study revealed that this variant affects a preadipocyte enhancer, impacting the expression of Iroquois homeobox 3 and 5 (*IRX3* and *IRX5*) during early adipocyte differentiation. While *Irx3*

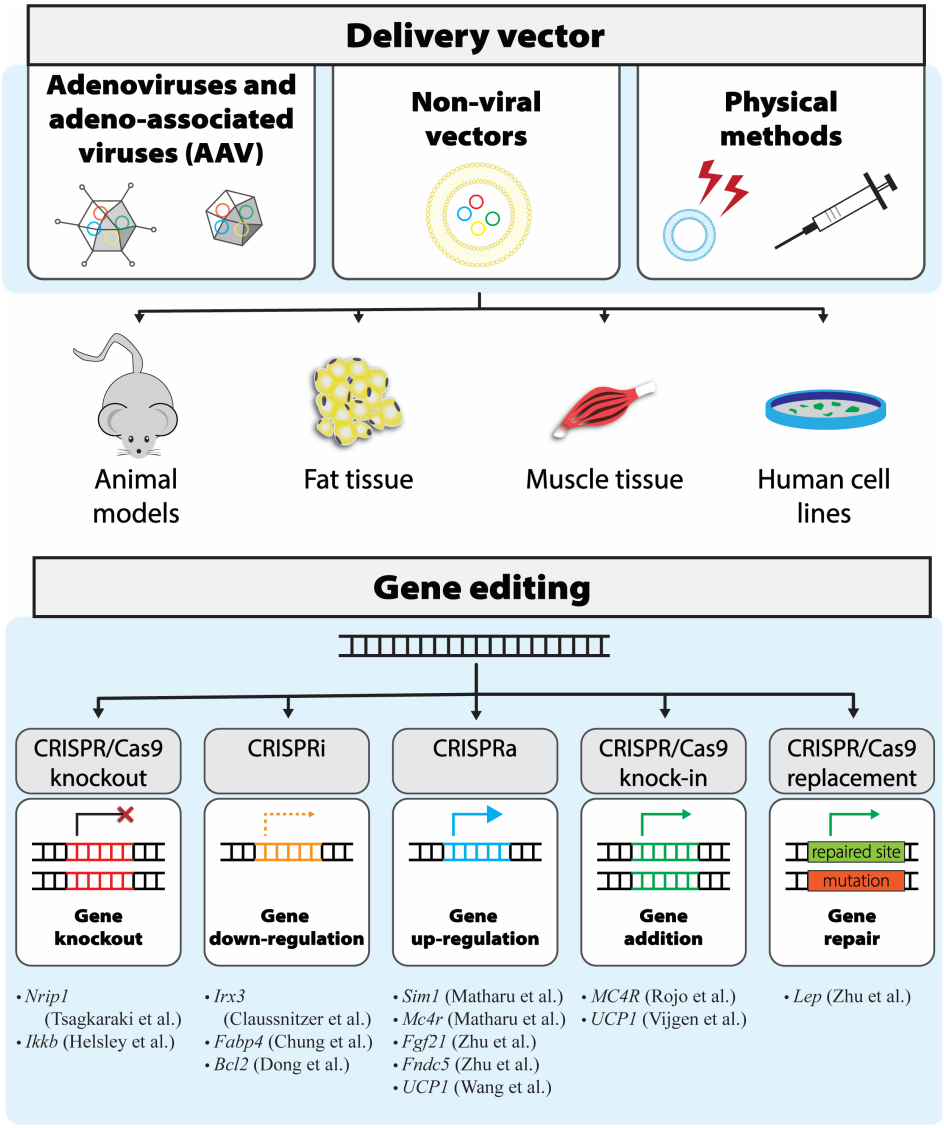

FIGURE 7 | CRISPR-based approaches to obesity treatment. Currently, studies are still being conducted on animal models and human cells in vitro. Different delivery vectors (adenoviruses, non-viral vectors, and physical methods) are used in these models. The lower part of the figure explains the basic approaches to genome editing with CRISPR technology, including gene knockout, down-regulation, up-regulation, and gene addition or repair. Key target genes involved in metabolism, fat storage, and thermogenesis are listed, along with corresponding research references. CRISPR—Clustered Regularly Interspaced Short Palindromic Repeats; CRISPRi—CRISPR interference; CRISPRa—CRISPR activation; AAV—adeno-associated viruses; *Nrip1*—nuclear receptor-interacting protein 1; IKKβ—an inhibitor of nuclear factor kappa-B kinase subunit beta; *Irx3*—Iroquois homeobox 3; *Fabp4*—fatty acid-binding protein 4; *Bcl2*—B-cell lymphoma 2; *Sim1*—single-minded 1; *Fgf21*—fibroblast growth factor 21; Fndc5—fibronectin type III domain-containing protein 5; *UCP1*—uncoupling protein 1; *LEP*—leptin; *MC4R*—melanocortin 4 receptor.

inhibition in mouse adipose tissue increased energy expenditure and reduced body weight, editing human adipocytes carrying the *FTO* risk allele promoted fat browning, offering a translational route to anti-obesity therapies [404]. Similarly, CRISPRi-mediated repression of *Fabp4* in obese mice using a dCas9-sgRNA system delivered via non-viral intraperitoneal injections led to 20% weight loss and improved glycemic and liver markers [405].

Dong et al. also applied CRISPR/Cas9 to investigate the functional role of a risk variant (SNP rs12454712) associated with obesity. They demonstrated that this intronic SNP acts as an allele-specific enhancer regulating the expression of the B-cell lymphoma 2 gene (*Bcl2*). Deleting this enhancer region in human adipocytes using CRISPR/Cas9 significantly reduced *Bcl2* expression. In a mouse model, the lower *Bcl2* expression in adipose tissue was linked to higher weight gain on a high-fat diet, while the knockdown of *Bcl2* in adipocytes led to increased apoptosis and reduced fat accumulation. This study highlights the potential of *Bcl2* as a therapeutic target for regulating central obesity [406].

Expanding the investigation of genetic variants, a separate study utilized CRISPR/Cas9 to introduce human *MC4R* gene mutations, *V103I* (valine-to-isoleucine substitution at position 103) and *I251L* (isoleucine-to-leucine substitution at position 251), into mice. These variations are known to reduce obesity risk in humans, and female mice with these gain-of-function genetic

changes exhibited less body fat. Both male and female mice carrying these mutations showed improved glucose tolerance and, in some cases, better insulin sensitivity. However, these protective mutations did not protect the mice from obesity when exposed to a hypercaloric diet, indicating that healthy eating remains important even if we want to use these favorable genetic mutations in future human therapies [407].

Haploinsufficiency, where one functional gene copy is insufficient to produce normal levels of gene expression, presents another challenge in treating genetic obesity. One study addressed this issue using CRISPR-mediated activation (CRISPRa), a technique that enhances the expression of the remaining functional allele. By targeting regulatory regions of the Single-minded 1 gene (*Sim1*) or *Mc4r* using a dCas9 (dead Cas9) protein fused with a transcriptional activator, researchers successfully increased the gene expression of both genes. They used both a knock-in approach to insert the CRISPRa transgene construct into the genome and a delivery of the transgene by a recombinant adeno-associated virus (rAAV) vector. In both cases, upregulation of *Sim1* or *Mc4r* by the CRISPRa transgene rescued a haploinsufficient obesity phenotype. This innovative approach could be a foundation for future gene therapies targeting obesity caused by gene dosage sensitivity [408].

The therapeutic potential of myokines, such as *Fgf21* and fibronectin type III domain-containing protein 5 (*Fndc5*), in obesity was also investigated using the CRISPRa approach. Myokines are proteins secreted by skeletal muscles that play significant roles in lipid metabolism. Researchers employed CRISPRa to selectively activate *Fgf21* and *Fndc5* in muscle cells, which promoted the browning of adipocytes and reduced obesity in diet-induced mice with obesity. These results suggest that myokine activation using CRISPRa could be a promising strategy for future obesity treatments [409].

Uncoupling protein 1 (UCP1) plays a key role in thermogenesis, the process that converts energy into heat, primarily occurring in brown adipose tissue (BAT). As such, UCP1 and BAT have been the focus of several studies exploring their therapeutic potential. In one study, Romanelli et al. used an AAV8-sgRNA-Cas9 construct to knock out multiple genes in the brown adipose tissue of mice. This local treatment transduced more than 90% of adipocytes, ablated genes like adiponectin, fatty acid synthase, and perilipin 1, and resulted in increased circulating FGF21 and enhanced thermogenesis [410]. Similarly, in pigs, which naturally lack UCP1 expression and struggle with thermoregulation, CRISPR/Cas9 was used to insert functional UCP1. These knock-in pigs showed improved thermoregulation, reduced fat deposition, and increased lean carcass percentage, suggesting the potential for UCP1 editing in humans, as lower BAT activity correlates with higher BMI [411]. In another study, a CRISPR-edited human stem cell line was developed to track *UCP1* expression, offering promise for future research in human brown fat development and disease modeling [412]. Additionally, Wang et al. engineered UCP1-overexpressing human white adipocytes, turning them into brown-like cells. Transplanting these cells into mice led to improved glucose tolerance, prevention of diet-induced obesity, and increased energy expenditure, opening up possibilities for cell-based therapies for metabolic diseases. These studies collectively highlight the therapeutic potential of targeting UCP1 for obesity treatments through enhanced thermogenesis and fat browning [413].

The nuclear receptor-interacting protein 1 gene (*Nrip1*) acts as a transcriptional co-repressor that regulates energy metabolism by inhibiting the browning of white adipocytes and reducing thermogenesis. Overexpression of *Nrip1* is associated with decreased fat burning and increased fat storage, while its ablation in mice under high-fat diet conditions has been shown to produce a leaner phenotype with enhanced energy expenditure, improved glucose tolerance, and increased insulin sensitivity. This makes *Nrip1* an important factor in obesity development and a potential therapeutic target. Tsagkaraki et al. introduced a novel method using CRISPR/Cas9 ribonucleoproteins (RNPs) to efficiently disrupt the *Nrip1* gene in human adipocytes, promoting their browning and thermogenic activity. The technique used electroporation for efficient gene editing, minimizing cell loss and reducing the risk of off-target effects. The edited adipocytes were implanted into glucose-intolerant mice with obesity, resulting in reduced adiposity, improved glucose tolerance, and lower liver triglycerides. These findings suggest that *Nrip1* repression in human adipocytes could be a promising therapeutic strategy for treating obesity and related metabolic disorders by increasing energy expenditure and improving metabolic health [414].

Another study explored the role of IKKβ (inhibitor of nuclear factor kappa-B kinase subunit beta, gene symbol *Ikbkb*) in adipocytes using a combination of CRISPR-Cas9 and antisense oligonucleotides (ASO). In cell lines, CRISPR-Cas9 was used to disrupt *IKKβ*, and experiments showed that knocking down *Ikbkb*in the mouse 3T3-L1 adipocytes reduced their differentiation into mature fat cells. In vivo, *Ikbkb*ASO was administered in mice to reduce diet-induced obesity, improve insulin sensitivity, and decrease fat mass, particularly in visceral fat pads. This highlights the potential of targeting IKKβ for obesity treatment and related metabolic disorders. CRISPR/Cas9 was instrumental in elucidating the role of IKKβ in adipocyte biology in cell culture, while ASO-based therapy was applied to test its metabolic effects in mice [415].

4.5 | Future Directions in Gene Therapy Approaches

CRISPR/Cas9 technology has proven to be a valuable tool in obesity research, offering precise gene editing capabilities that allow researchers to explore the genetic underpinnings of obesity. Studies targeting key genes such as *Lep*, *Fto*, *Bcl2*, *Mc4R*, *Sim1*, *Fgf21*, *Ucp1*, *Fabp4*, and *Nrip1* have shown promising results in animal models and human cells. These genes play critical roles in metabolism, fat storage, and thermogenesis, with their modification leading to beneficial effects such as improved insulin sensitivity, increased energy expenditure, and reduced fat accumulation. Peripheral adipose tissues, such as brown and white fat, are promising targets for CRISPR-based editing of genes like *Ucp1*, *Fabp4*, and *Nrip1* due to their metabolic relevance, accessibility, and lower systemic risk. Approaches such as CRISPRa and CRISPRi provide additional flexibility by enhancing or repressing gene expression without altering the underlying DNA, further improving safety profiles. Furthermore, targeting genetic variations like those found in *FTO* and *MC4R*

offers opportunities for personalized therapies. Moving forward, refining CRISPR-based delivery systems and addressing safety concerns will be essential for translating these findings into effective human treatments. The continued exploration of these target genes, especially in peripheral tissues, holds significant potential for developing novel, gene-based therapies to combat obesity and its related metabolic disorders. A major milestone in CRISPR-based gene therapy in humans is the first clinical trial, reported in 2024, to treat patients with familial hypercholesterolemia [416]. A single peripheral infusion targeting the *PCSK9* gene in the liver successfully repressed its expression, leading to a significant reduction in low-density lipoprotein cholesterol levels. Although not directly targeting obesity, this trial exemplifies the feasibility of in vivo CRISPR delivery to metabolic tissues and sets a precedent for future interventions targeting shared pathways in metabolic diseases. While concerns about long-term effects and safety remain, the results of this inaugural clinical trial provide encouraging evidence that CRISPR-based in vivo gene editing may hold substantial promise for future obesity treatments. However, the clinical application of gene therapy for obesity requires thorough evaluation and the development of standardized guidelines addressing dosage, route of administration, pharmacodynamics, pharmacokinetics, toxicity, and potential side effects.

4.6 | Challenges in the Clinical Translation of Gene Editing

One drawback of vectors in gene therapy is their potential immunogenicity. Viral vectors such as adenoviruses or retroviruses may be recognized as foreign pathogens, prompting the immune system to mount a response and generate neutralizing antibodies that can prevent the reuse of the same vector in future gene therapies. This limits the feasibility of repeated dosing, which may be necessary for chronic conditions. In contrast, AAVs are relatively low-immunogenic DNA viruses that persist as episomes. While they are generally less immunogenic than adenoviruses, AAV can still elicit immune responses, particularly against their capsid proteins, posing challenges for redosing. Similarly, when viral vectors are used to deliver CRISPR/Cas systems, they may trigger immune reactions not only against the vector itself but also against bacterial-derived proteins such as Cas9. Non-viral delivery systems, such as lipid nanoparticles or electroporation, tend to provoke weaker immune responses and may therefore allow repeated administration, although the immunogenicity of the Cas proteins remains a concern.

Off-target mutations remain a key safety concern in the clinical application of CRISPR-Cas technologies. This issue is particularly important in therapeutic settings requiring high precision. To address this, several sensitive genome-wide detection methods have been developed. CIRCLE-seq enables reproducible in vitro identification of off-target sites, while DISCOVER-Seq detects in vivo off-target activity by tracking recruitment of DNA repair proteins [417, 418]. The VIVO system also provides a robust method for identifying off-targets directly in living organisms [419]. The application of these tools has revealed mixed outcomes. In some cases, such as CRISPR-Cas9 editing for sickle cell disease and the use of paired Cas9 nickases for Hao1 gene targeting, no off-target mutations were detected [420, 421]. However, other studies show persistent concerns. For example, promiscuous guide RNAs led to substantial off-target mutations in vivo, and paired nickases, while reducing off-target effects, still caused large on-target rearrangements [419, 422]. Minimizing off-target activity requires optimized guide RNA design, as demonstrated by Akcakaya et al., who achieved high on-target editing efficiency with no detectable off-target effects using carefully selected gRNAs [419]. Additionally, the use of high-specificity Cas9 variants like Sniper-Cas9 and transient delivery formats such as RNPs can further reduce off-target activity by limiting the duration and promiscuity of Cas9 activity in cells [423]. Continued improvement of detection tools and design algorithms will be essential for enhancing the safety and precision of CRISPR-based therapies.

5 | Conclusion

Instead of a traditional conclusion, we look ahead to the promise of multi-omics approaches to deepen our understanding of obesity and enable more effective prevention, diagnostics, and treatment. By integrating data from genomics, epigenomics, transcriptomics, proteomics, and metabolomics, researchers can investigate the biological complexity underlying obesity at multiple regulatory levels [424]. This systems-level insight supports the development of individualized clinical strategies and uncovers novel molecular targets involved in metabolic regulation and immune function [425]. Although challenges such as data integration and interpretation remain, the continued advancement of multi-omics holds substantial potential to improve the precision and efficacy of obesity management. The inclusion of additional levels, such as lncRNAomics, glycomics, and lipidomics, may further refine this approach and reveal new opportunities for intervention [426].

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Conflicts of Interest

The authors declare no conflicts of interest.

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