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Advancements In Obesity: Unravelling Pathophysiology, Treatment Strategies, And Innovative Approaches

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Obesity represents a significant global health challenge with multifactorial origins and escalating prevalence. This review examines three fundamental pathophysiological mechanisms: adipose tissue dysfunction characterized by inflammatory mediator release and metabolic perturbations, gut microbiota alterations affecting metabolic signaling and energy homeostasis, and adipose tissue hypoxia leading to cellular stress and metabolic disruption. Current pharmacological interventions demonstrate variable efficacy and comprehensive safety profiles: orlistat through lipase inhibition with gastrointestinal considerations, phentermine/topiramate via appetite suppression with monitoring requirements, and liraglutide through GLP-1 receptor agonism with established metabolic benefits, with specific focus on their limitations and long-term outcomes. MC4R has emerged as a promising therapeutic target, highlighting advances in targeted drug development for obesity management. Surgical innovations, particularly laparoscopic sleeve gastrectomy and endoscopic sleeve gastroplasty, demonstrate substantial and sustainable weight loss with improved metabolic health outcomes compared to traditional procedures, emphasizing their role in severe obesity treatment. The integration of digital health technologies - mobile applications, wearable devices, and telemedicine platforms - facilitates lifestyle modifications and enhances treatment adherence through continuous monitoring and patient engagement, revolutionizing long-term management approaches. Genetic and hormonal influences significantly impact treatment response, emphasizing the necessity for individualized therapeutic approaches. This comprehensive analysis provides an integrated framework for understanding obesity's complex pathophysiology and treatment modalities, establishing a foundation for effective, personalized intervention strategies in clinical practice.

Keywords: Adipose dysfunction; Digital health; Innovative treatments; Obesity pathophysiology; Obesity pharmacotherapy.

Obesity is a major global public health concern, impacting both developed and developing nations. Defined by the World Health Organization (WHO) as a body mass index (BMI) of 30 kg/m² or higher, obesity represents an excessive accumulation of body fat that significantly threatens an individual's health. BMI, a measure derived from an individual's height and weight,

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is widely used to assess body fat and classify obesity.[1–3]

Obesity is a multifaceted disease arising from an imbalance between caloric intake and energy expenditure. It develops when caloric consumption consistently exceeds the body's energy needs, leading to the storage of excess fat. This accumulation of adipose tissue can contribute to numerous health complications, including metabolic disorders, cardiovascular disease, and other chronic conditions.[3–5]

Global obesity prevalence has more than doubled since 1980, with over 650 million adults now classified as obese. In the United States alone, obesity rates have more than doubled in the last four decades, affecting over 42% of adults. Furthermore, the issue extends to young children, with over 38 million children under five years old worldwide considered overweight or obese.[6–10]

Recent epidemiological studies demonstrate the increasing prevalence of obesity across different regions and age groups (Table 1).[11–13]

Global Obesity Prevalence and Metabolic Impact: A Cross-Regional Analysis (2013-2019)

As shown in Table 1, global obesity rates have steadily increased from 11.5% in 2013 to 12.8% in 2016, with projections indicating continued rise, particularly in developed nations like the United States. The parallel increase in childhood obesity and associated metabolic complications underscores the urgent need for effective interventions.

The global impact of obesity is profound and far-reaching. Obesity is estimated to contribute to approximately 2.8 million deaths each year, ranking as the fifth leading cause of mortality worldwide. Moreover, it is a major risk factor for a range of chronic diseases, including type 2 diabetes, cardiovascular diseases, hypertension, and several types of cancer, underscoring its significant threat to public health.[14,15]

The causes of obesity are multifactorial, and many factors contribute to its development. The most common risk factors for obesity include genetic predisposition, sedentary lifestyle, unhealthy dietary habits, and environmental factors such as urbanization and globalization. These factors interact in complex ways, making it challenging to prevent and treat obesity effectively.[16]

Prevention of obesity is now a significant focus for public health. Early stage intervention is key to a reduction in obesity and outcomes of its health. The primary mechanisms by which lifestyle interventions, diet, and exercise prevent obesity present social barriers, including socioeconomic constraints and limited access to healthy food coupled with low levels of leisure time physical activity; such as has been reported in developing settings.[17,18]

Therefore, the treatment of obesity encompasses lifestyle changes, behavioral therapy, pharmacotherapy, and bariatric surgery. The new, novel therapies in the treatment of obesity include the stem cell therapy and gene therapy. These therapies are still very novel and are yet at a developing stage, hence further research needs to be performed before these therapies become useful.[19,20]

Conventional management of obesity is by pharmacotherapy and several classes of drugs are available presently. However, drug treatment of obesity has its problems as well, and effectiveness varies greatly among drugs. Surgery in the form of bariatric surgery-including gastric bypass and sleeve gastrectomy-is very effective in treating obesity where one gets a marked amount of weight loss with simultaneous improvements in comorbid conditions. But surgery itself involves a lot of risks, thus is not for all people[21,22]

In a nutshell, obesity is one of the most important public health issues across the globe that requires a holistic approach to prevention and treatment. Though the mainstay of obesity prevention is lifestyle modification, a lot more needs to be done to counter the environmental and social determinants of obesity. The current advances in the management of obesity, the latest therapies such as stem cell therapy, gene therapy, and others promise a better future. However, more studies are required to determine the long-term safety and efficacy of these treatments.[23]

Pathophysiology of obesity

The disease is etiologically multi-factorial, based upon interplay of genetic and environmental factors with behavioral variables, causing an imbalance due to excessive intake over expenditure, thus leading to excessive body fat deposition, elevating risks associated with the morbidities.[3]

This is one of the major components estimated to have a heritability range of 40% to 70% in the genetics of obesity. There are only a few genes identified with possible implications for obesity, largely related to appetite regulation, metabolic processes, and adipogenesis or fat cell formation. Genetic predisposition interplays with environmental triggers to modulate an individual's risk of developing obesity.[16]

Other factors contributing to the cause of obesity are environmental, including diet and exercise habits. Contribution to the risks of too much weight gain includes intakes of calories and saturated fats as well as added sugars. Sedentary behavior or insufficient physical activity also contributes to increased obesity risk. More fundamental environmental causes include the limited supply of accessible healthy food sources and opportunities for exercise, leading to exposure to obesogenic environments, which significantly affect the prevalence of obesity both in developed and developing areas.[24]

This coupled with genetics underlines the complexity to the pathogenesis of obesity and underscores multifaceted prevention and intervention strategies.[25]

Adipocyte dysfunction

Adipocyte dysfunction stands as a fundamental characteristic of obesity, characterized by both the expansion (hypertrophy) and increased formation (hyperplasia) of fat cells, or adipocytes. During obesity progression, these adipocytes undergo significant enlargement as they store excess triglycerides, often reaching sizes that compromise their normal physiological functions. This pathological expansion triggers a cascade of cellular events, notably the enhanced secretion of pro-inflammatory molecules. Key among these are tumor necrosis factor-alpha (TNF-á) and interleukin-6 (IL-6), which initiate and sustain a state of chronic, low-grade systemic inflammation throughout the body.

This inflammatory state is further amplified by the recruitment of immune cells, particularly macrophages, to the expanding adipose tissue. These macrophages, upon infiltration, undergo polarization toward a pro-inflammatory phenotype, leading to enhanced production of additional inflammatory mediators. The enlarged adipocytes also exhibit impaired insulin sensitivity and altered adipokine secretion patterns, including decreased adiponectin and increased leptin levels, contributing to metabolic dysfunction.

The sustained inflammatory environment created by dysfunctional adipocytes impacts multiple metabolic pathways. It disrupts normal adipose tissue remodeling, impairs glucose uptake, and affects lipid metabolism. Additionally, the compromised vasculature in expanding adipose tissue leads to localized hypoxia, further exacerbating the inflammatory response and cellular stress. This complex interplay between adipocyte dysfunction, inflammation, and metabolic disruption creates a self-perpetuating cycle that underlies many obesity-associated complications.[26,27]

Chronic inflammation

Persistent chronic inflammation represents a critical driver in obesity's complex pathophysiology, characterized by a sustained, low-grade inflammatory state. The adipose tissue actively secretes elevated levels of inflammatory markers, particularly tumor necrosis factor-alpha (TNF-á), interleukin-6 (IL-6), and C-reactive protein (CRP).[28] These inflammatory mediators initiate a complex cascade of metabolic disturbances. TNF-á directly interferes with insulin signaling pathways by promoting serine phosphorylation of insulin receptor substrate-1,[29] while IL-6 impairs insulin sensitivity through suppression of adiponectin production and activation of SOCS3 signaling.[30] Additionally, elevated CRP levels serve as both a marker and mediator of vascular inflammation, contributing to endothelial dysfunction through decreased nitric oxide production and increased expression of adhesion molecules.[31] This inflammatory milieu disrupts normal lipid metabolism, leading to dyslipidemia characterized by increased circulating free fatty acids and altered lipoprotein profiles. The interplay between these inflammatory markers creates a self-reinforcing cycle of metabolic dysfunction, where inflammation promotes insulin resistance, which in turn maintains the inflammatory state, perpetuating obesity-related metabolic complications.[28]

Insulin resistance

Insulin resistance emerges as a cardinal metabolic aberration in obesity, reflecting a profound disturbance in cellular glucose utilization pathways. This pathophysiological state manifests

when insulin-responsive tissues – primarily skeletal muscle fibers, hepatocytes, and adipose cells – exhibit a markedly diminished response to insulin signaling. The molecular underpinnings involve a complex cascade of disrupted signaling events: when insulin binds to its cell surface receptor, the normal phosphorylation cascade through insulin receptor substrate-1 (IRS-1) becomes compromised.[32] This disruption impairs the activation of downstream effectors, notably the PI3K/Akt pathway, ultimately preventing the essential translocation of GLUT4 glucose transporters to the cell membrane.[33]

The pancreatic â-cells respond to this cellular insulin resistance by mounting a compensatory response – dramatically increasing insulin synthesis and secretion, resulting in hyperinsulinemia. This elevation in circulating insulin, while initially adaptive, triggers a spectrum of metabolic disturbances: it enhances lipogenic pathways through SREBP-1c activation, amplifies inflammatory cascades via NF-êB signaling, and paradoxically furthers insulin receptor desensitization through increased serine phosphorylation of IRS proteins.[34]

This compensatory hyperinsulinemia establishes a detrimental feedback loop: excessive insulin promotes adipocyte expansion and dysfunction, stimulates pro-inflammatory mediator release, and perpetuates insulin resistance across multiple tissue beds. The resulting metabolic disarray creates a self-sustaining cycle of deteriorating insulin sensitivity, progressive inflammation, and worsening metabolic health.

The intricate interplay between impaired insulin signaling, compensatory hyperinsulinemia, and tissue dysfunction represents a central mechanism driving obesity's metabolic complications and disease progression.[35]

Hormonal Imbalance

Hormonal dysregulation in obesity centers on the disturbed secretion of adipose-derived hormones (adipokines), which orchestrate complex metabolic processes. The adipose tissue, functioning as an endocrine organ, secretes critical hormones: leptin, adiponectin, and resistin, each playing distinct roles in metabolic homeostasis.

Leptin, the satiety-signaling hormone, exhibits a paradoxical pattern in obesity – despite elevated circulating levels (proportional to adipose mass), target tissues develop leptin resistance.[36] This resistance involves impaired leptin transport across the blood-brain barrier and disrupted hypothalamic STAT3 signaling pathways. Consequently, the anorexigenic and energy-expenditure promoting effects of leptin become blunted, perpetuating hyperphagia and reduced energy utilization.[37,38]

Adiponectin, unique among adipokines, shows an inverse relationship with adiposity.[39] Its reduction in obesity has profound metabolic consequences, as it normally enhances insulin sensitivity through AMPK pathway activation, promotes fatty acid oxidation, and exhibits anti-inflammatory properties.[40,41] The decreased adiponectin levels contribute to impaired glucose homeostasis and exacerbated inflammatory responses.

Resistin levels become elevated in obesity, inducing a pro-inflammatory state through NF-êB pathway activation. This hormone interferes with insulin signaling cascades, particularly in skeletal muscle and hepatic tissue, thereby amplifying insulin resistance. Additionally, resistin's elevation promotes the expression of other inflammatory mediators, creating a self-reinforcing cycle of metabolic dysfunction.[42,43]

This triad of hormonal imbalances – leptin resistance despite hyperleptinemia, hypoadiponectinemia, and hyperresistinemia – creates a perfect storm of metabolic disruption, fundamentally altering energy homeostasis and inflammatory status in obesity.[44,45]

Recent research has unveiled additional molecular pathways that deepen our understanding of obesity's metabolic disturbances. For instance, a study published in Nature Communications in 2020 highlighted the role of extracellular vesicle-derived microRNA-21 (EV-miR-21), secreted by hypertrophic adipocytes. This molecule promotes inflammation in other organs, such as the liver, exacerbating metabolic dysfunction.[16]

Another entirely different consideration is gut microbiota-the massive collective community of microorganisms that live in the gastrointestinal tract. New research has established that people who are obese have an entirely different gut microbiome than non-obese individuals with less helpful bacteria and more virulent populations of harmful strains. Such dysbiosis has increasingly been linked with inflammation, insulin resistance, and other

metabolic abnormalities, thus indicating that the gut microbiome is indeed vital in the etiology of obesity.[46–48]

In essence, obesity is a complex disorder driven by a mix of genetic, environmental, and behavioral factors, along with biological influences like adipose tissue, gut microbiota, and epigenetic changes. These interactions lead to metabolic issues, including inflammation and insulin resistance, raising the risk for conditions like heart disease and type 2 diabetes. Understanding these mechanisms is key to creating effective prevention and treatment strategies.[3]

Types of obesity

Obesity is a complex condition that can manifest in various forms, each with its distinct etiology and clinical features. Broadly speaking, there are two primary types of obesity: primary (or monogenic) obesity and secondary (or polygenic) obesity.[49]

Primary Obesity is a rare genetic form of obesity caused by mutations in single genes that play essential roles in appetite control, energy balance, and body weight regulation. Mutations in genes like the melanocortin-4 receptor (MC4R), leptin receptor (LEPR), and pro-opiomelanocortin (POMC) disrupt these regulatory pathways, often resulting in severe, early-onset obesity. Individuals with primary obesity frequently have a strong family history of the condition, highlighting its genetic nature.[50,51]

Secondary Obesity is far more common and arises from a combination of genetic predisposition and environmental influences. Unlike primary obesity, which is driven by single-gene mutations, secondary obesity is polygenic, involving the interaction of multiple genes with small but cumulative effects on body weight. These genetic factors, combined with lifestyle elements such as sedentary behavior, poor dietary habits, and psychosocial stress, contribute to weight gain. Studies, including genome-wide association studies (GWAS), have identified several genetic variants linked to a heightened risk of secondary obesity, including variations in FTO, MC4R, and TMEM18 genes.[16,28]

Additionally, obesity can be classified based on fat distribution in the body. Central Obesity, also known as abdominal or visceral obesity, is marked by fat accumulation around the waist and abdomen. This form is associated with a greater risk of metabolic and cardiovascular diseases compared to Peripheral Obesity, where fat predominantly accumulates around the hips and lower limbs. The location of body fat plays a crucial role in determining health risks, as visceral fat is more metabolically active and closely linked to conditions like diabetes and heart disease.[52,53]

Another type of obesity is lipodystrophy. It is a very rare disease and involved critical genetics complication in which fatty tissues are selectively lost through predefined body areas including arms and face; but its been observed that simultaneously adiposity occurs at the areas which includes liver and muscle tissue. Lipodystrophy is further explained on metabolic complications- insulin resistant condition, dyslipidemic complication, and steatohepatitis hepatic complication.[54]

In the last couple of years, another category of obesity has been diagnosed as "metabolically healthy obesity" or MHO, referring to individuals who are suffering from obesity without the absent metabolic abnormalities usually observed, such as insulin resistance, dyslipidemia, and hypertension. MHO is said to be a rather rare phenotype that accounts for only 10-20% of all cases of obesity. However, the MHO has raised controversy whether it is benign or not, and several reports suggested that even the MHO subjects are at higher risk for metabolic complications later in life.[55,56]

In conclusion, obesity is a complex condition with varied types, including primary, secondary, and central obesity—each with distinct causes and health risks. Recognizing these forms aids in creating effective prevention and treatment strategies, addressing both genetic and environmental influences for better management of obesity's health impacts.[57]

Drug targets to treat obesity

Obesity is a complex disorder with multiple factors contributing to its development and progression. As such, there is no single drug target that can be targeted to completely cure or treat obesity. However, there are several drugs that target different mechanisms involved in the regulation of appetite, metabolism, and energy expenditure, which can be used in combination with lifestyle modifications to achieve clinically significant weight loss.[3,23]

One primary target is the central nervous system (CNS), specifically the hypothalamus. This brain region plays a crucial role in regulating hunger and energy expenditure. Drugs like phentermine and diethylpropion target the hypothalamus by boosting norepinephrine and dopamine release, activating the sympathetic nervous system to suppress appetite. These medications can help people lose up to 5-10% of their initial body weight. However, they come with potential side effects such as increased heart rate, high blood pressure, and insomnia.[58,59]

The gastrointestinal (GI) tract is another essential target in obesity treatment. The GI tract regulates hunger and fullness through hormones like ghrelin, glucagon-like peptide-1 (GLP-1), and peptide YY (PYY). Drugs such as liraglutide, semaglutide, and exenatide mimic GLP-1's effects, helping to reduce appetite and enhance satiety, which can lead to weight loss of 10-15% of initial body weight. These medications are generally well-tolerated, with fewer severe side effects.[60]

Finally, researchers focus on adipose tissue (fat cells) as an active participant in regulating energy balance. Adipose tissue releases hormones known as adipokines, including leptin, which signals the brain to decrease food intake and increase energy use. Some treatments, like metreleptin, aim to modulate leptin signaling to support weight management.[61]

Metreleptin is a recombinant human leptin analog that has been shown to promote weight loss of up to 10-15% of initial body weight in patients with congenital leptin deficiency. However, it is only approved for use in patients with this specific genetic disorder.[62]

In addition to the above targets, there are several other potential targets for obesity treatment, including the endocannabinoid system, the melanocortin system, and the gut microbiome. The endocannabinoid system is involved in the regulation of appetite, energy expenditure, and lipid metabolism.[59]

One of these is the endocannabinoid system, which influences appetite, energy use, and fat metabolism. This system regulates hunger signals, and drugs like rimonabant, which inhibit endocannabinoid receptors, have been effective in promoting weight loss. However, they come with notable psychiatric side effects, including depression and anxiety, which has limited their widespread use.[63]

Another emerging target is the melanocortin system, which regulates appetite and energy expenditure through melanocortin receptors. Drugs targeting these receptors, such as setmelanotide, have shown promising results in promoting weight loss, particularly for patients with rare genetic obesity disorders. While setmelanotide isn't yet widely approved for general obesity treatment, it provides a targeted approach for specific genetic cases, potentially paving the way for more precise obesity treatments in the future.[64]

Pancreatic lipase, a key digestive enzyme secreted by the pancreas, plays a crucial role in lipid metabolism through the hydrolysis of dietary triglycerides into absorbable monoglycerides and free fatty acids. This enzyme catalyzes the breakdown of approximately 50-70% of total dietary fats, making it a critical target for obesity management. The inhibition of pancreatic lipase

Table 1. Global Trends in Obesity Prevalence and Associated Metabolic Impact (2013-2019)

Year	Region	Adult Obesity (%)	Childhood Obesity (%)	Metabolic Impact
2016	Global	12.8	5.6	38% increase in diabetes prevalence
2019	United States	48.9*	19.3	65% increase in cardiovascular risk
2013	Global	11.5	4.7	33% increase in metabolic syndrome

Notes:Adult obesity: BMI ≥30 kg/m²Childhood obesity: ages 5-19 years*Projected estimateMetabolic impact based on population-attributable fraction

activity presents a therapeutic strategy by reducing fat absorption in the gastrointestinal tract, thereby creating a negative energy balance that promotes weight loss. Recognition of this mechanism has led to the development of pancreatic lipase inhibitors as pharmacological interventions for obesity treatment, with compounds like orlistat demonstrating clinical efficacy through selective enzyme inhibition.[65]

Treatments of obesity

Pharmacotherapy for Weight Loss

Pharmacotherapy for weight loss involves the strategic use of medications to aid in reducing body weight. These medications operate through various mechanisms, including appetite suppression, enhancing feelings of fullness, and altering nutrient absorption. In addition to orlistat, a pancreatic lipase inhibitor that reduces fat absorption, several other drugs have gained approval for obesity treatment, each working differently to support weight management.[66]

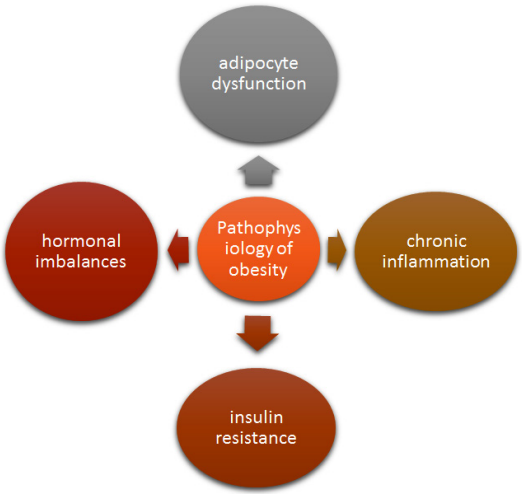

Fig. 1. Pathophysiology of Obesity

Several drugs support obesity management through distinct mechanisms are as follow:

The pharmacological landscape of obesity treatment encompasses diverse mechanistic approaches. Lorcaserin, operating via serotonin 2C receptor activation, demonstrated significant satiety enhancement but faced market withdrawal due to carcinogenicity concerns. The naltrexone/bupropion combination intervenes in reward circuitry to modulate appetite and emotional eating behaviors. Incretin-based therapies, notably liraglutide and the more potent semaglutide, act through GLP-1 receptor activation to achieve comprehensive metabolic benefits, including enhanced satiety, improved glycemic control, and significant cardiovascular risk reduction, representing a major advancement in obesity pharmacotherapy.[67]

Endoscopic Therapies

Endoscopic therapies offer minimally invasive options for weight loss by reducing stomach capacity and altering food processing. Intragastric balloons are saline-filled balloons placed in the stomach to induce fullness, reducing food intake.[68]

Endoscopic sleeve gastroplasty uses sutures to minimize stomach size, while aspiration therapy enables partial stomach content drainage

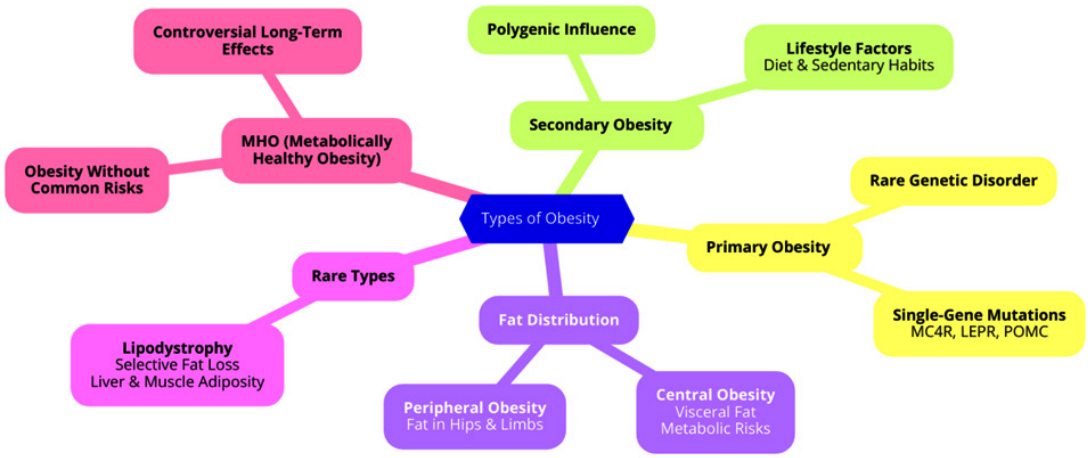

Fig. 2. Types of Obesity

post-meals. Though generally effective and safe, these procedures may lead to side effects such as nausea, vomiting, and abdominal pain. Endoscopic approaches provide alternative, non-surgical solutions for weight management with promising results for individuals seeking less invasive interventions.[69]

Gene Therapy

Gene therapy represents targeted genetic manipulation for therapeutic intervention, particularly promising for rare obesity variants like leptin deficiency. The approach involves delivering corrective genes through engineered viral vectors to restore metabolic function. Focus lies on addressing inherited defects through precise genetic modifications. These therapeutic strategies aim to compensate for specific genetic mutations causing severe obesity. Recent delivery system advancements and improved vector designs enhance potential treatment efficacy for severe genetic obesity forms, offering hope for patients with inherited metabolic disorders. This emerging therapeutic modality demonstrates significant promise in treating monogenic obesity through direct genetic correction mechanisms.[70]

Recent experimental research demonstrated significant therapeutic potential in gene therapy for obesity through targeted leptin gene delivery. Using an engineered adenoviral vector system, researchers successfully transferred functional leptin genes to hepatic tissue in leptin-deficient murine models. This intervention resulted in measurable hepatic leptin expression, leading to substantial weight reduction and improved metabolic profiles, including enhanced glucose homeostasis and lipid metabolism. The viral vector demonstrated efficient gene transfer with minimal immunogenic response. However, translational challenges persist, including optimal vector design, tissue-specific targeting, long-term expression stability, and comprehensive safety assessments. Clinical application requires extensive validation through controlled trials to establish therapeutic efficacy and safety parameters in human subjects.[2]

Gut Microbiota Modulation

Gut microbiota modulation represents a novel therapeutic approach targeting the complex microbial ecosystem within the human gastrointestinal tract. This intervention strategy focuses on altering microbial composition and metabolic activity through specific interventions. Recent scientific evidence demonstrates significant correlations between gut microbiota dysbiosis and obesity pathogenesis, particularly through altered energy harvest, metabolic signaling, and inflammatory pathways. These findings illuminate the microbiota's crucial role in metabolic homeostasis and potential therapeutic applications in obesity management.[71] Strategies to modify gut microbiota composition are emerging as potential obesity treatments. Three primary approaches - probiotics, prebiotics, and fecal microbiota transplantation - have demonstrated notable outcomes in preclinical research, suggesting

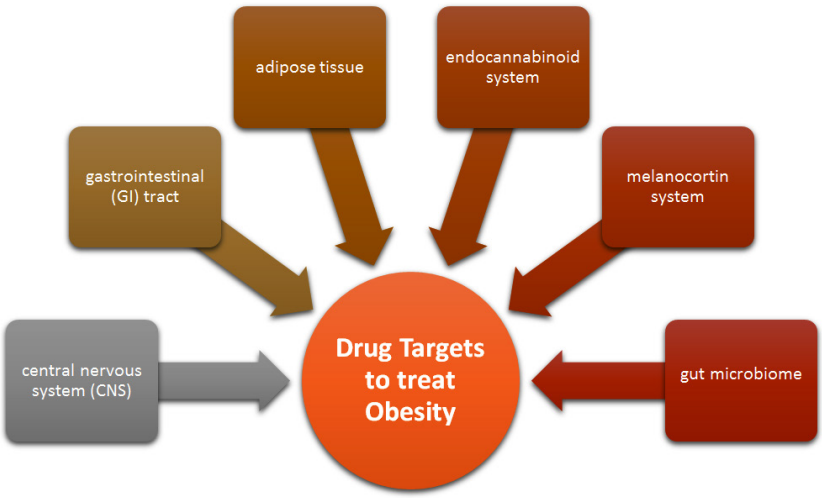

Fig. 3. Drug Targets to treat Obesity

their capability to influence weight management mechanisms. These interventions show promise in modulating metabolic pathways through microbiota modification. However, comprehensive clinical trials and longitudinal studies remain essential to thoroughly evaluate their safety profiles, therapeutic effectiveness, and long-term outcomes in human populations before considering widespread clinical implementation in standard obesity treatment protocols.[72,73]

In summary, obesity treatment is evolving with advancements in drug therapies, endoscopic methods, gene therapies, and gut microbiota modulation. These innovations show promise, yet further research is crucial to ensure their safety, effectiveness, and optimal clinical use.[74]

Drugs to use in obesity

Recent years have seen exciting progress in obesity treatment, with new medications transforming options for weight management. Drugs like phentermine/topiramate, naltrexone/bupropion, and liraglutide are already available, helping many people tackle obesity. Meanwhile, innovative therapies are under development, offering fresh hope for more effective weight loss solutions. This discussion explores the latest

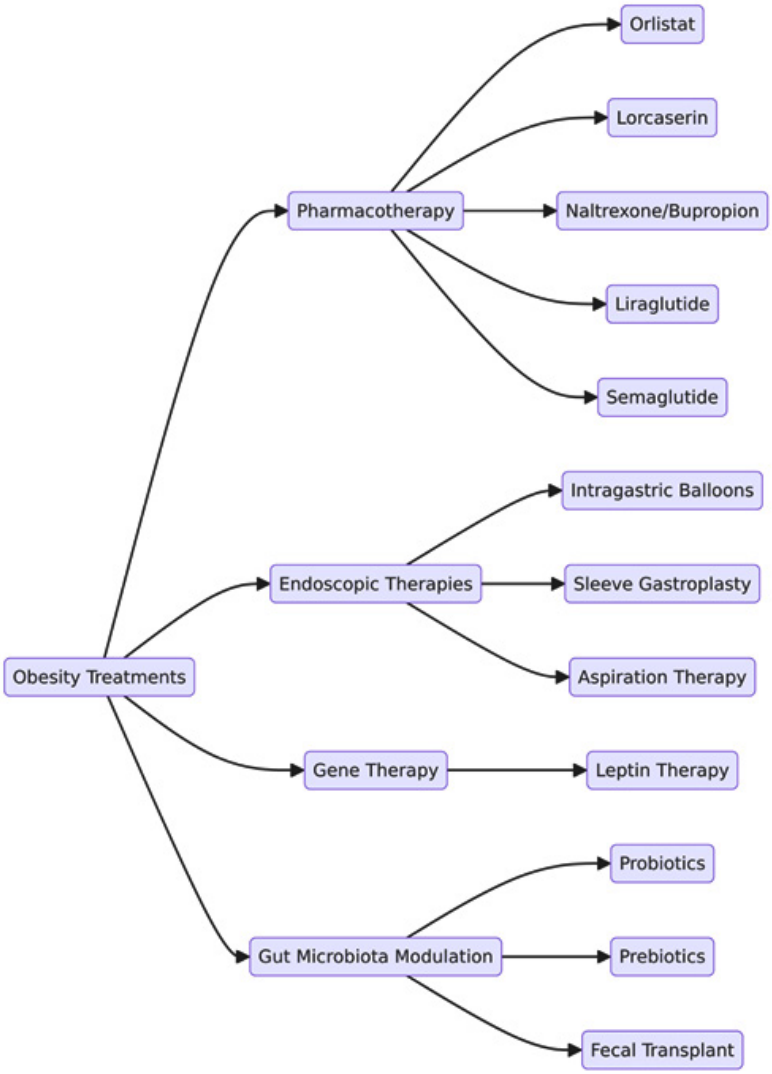

Fig. 3. Treatment of Obesity Overview

advancements in obesity medications and how they're shaping the future of treatment.[21,75]

Semaglutide

Semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, has gained approval as an effective obesity treatment. Clinical trials have demonstrated significant results, with patients achieving an average weight loss of 15-20%. Beyond weight reduction, semaglutide offers additional benefits, including improved blood sugar control and a lower risk of cardiovascular events in individuals with type 2 diabetes. Administered as a once-weekly subcutaneous injection, semaglutide is emerging as a valuable tool in the comprehensive management of obesity and related metabolic conditions.[76,77]

Fig. 4. Drugs used in obesity

Setmelanotide

Setmelanotide, a melanocortin-4 receptor (MC4R) agonist, is currently being studied in clinical trials as a treatment for obesity, particularly in individuals with rare genetic forms of the condition. MC4R is a crucial regulator of appetite and energy expenditure, and mutations in the MC4R gene are commonly associated with monogenic obesity. Setmelanotide has demonstrated efficacy in promoting weight loss among patients with specific genetic disorders, such as pro-opiomelanocortin (POMC) deficiency and leptin receptor (LEPR) deficiency, where traditional obesity treatments are often ineffective. Administered via subcutaneous injection, setmelanotide offers a targeted approach that could provide meaningful therapeutic benefits for patients with these rare genetic forms of obesity.[78,79]

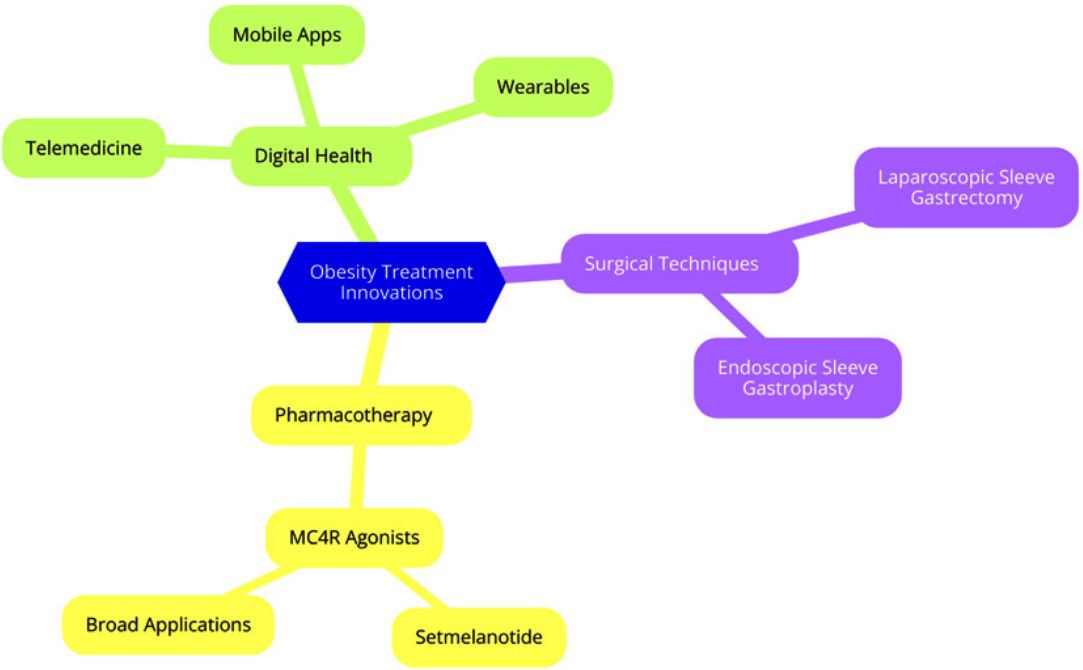

Fig. 5. Overview of latest innovation in obesity

Mirabegron

Originally approved for treating overactive bladder, mirabegron is a beta-3 adrenergic receptor agonist. Beyond its primary use, it has shown promise in promoting weight loss by boosting energy expenditure and reducing fat storage. In a recent clinical trial, mirabegron led to an average weight loss of 3.6 kg over 12 weeks in patients with obesity. Administered orally, it offers a convenient alternative for weight management, although further research is needed to understand its long-term effects on obesity.[80,81]

Exenatide

Exenatide, a glucagon-like peptide-1 (GLP-1) receptor agonist approved for type 2 diabetes treatment, has also demonstrated weight loss benefits in patients with obesity. Clinical studies have shown an average weight loss of 4.8 kg over 24 weeks with exenatide therapy. Administered via subcutaneous injection, exenatide aids weight management by enhancing satiety and regulating glucose, making it beneficial for patients with obesity, particularly those with metabolic dysfunctions.[82,83]

Beloranib

A methionine aminopeptidase 2 (MetAP2) inhibitor, beloranib has shown weight-loss potential by targeting fatty acid metabolism and fat formation (adipogenesis). Phase 2 trials revealed an average weight loss of 6.4 kg over 12 weeks among obese patients. However, despite its efficacy, beloranib's development was discontinued due to safety concerns, specifically related to thrombotic events, highlighting the importance of balancing effectiveness with patient safety in obesity treatments.[84–86]

Cannabinoid Receptor Antagonists

Cannabinoid receptor antagonists represent a significant pharmacological approach targeting the endocannabinoid system's role in appetite and energy homeostasis. These agents, specifically rimonabant and taranabant, were designed to antagonize CB1 receptors, which modulate food intake and energy metabolism. Initial clinical trials demonstrated promising weight reduction outcomes, yet subsequent safety monitoring revealed severe neuropsychiatric adverse effects, including major depression, anxiety disorders, and suicidal ideation. The withdrawal of these agents from therapeutic use highlighted a critical lesson in obesity pharmacotherapy: the necessity for comprehensive safety evaluation, particularly regarding mental health impacts, when developing centrally-acting appetite suppressants. This experience has profoundly influenced the drug development landscape for obesity treatments, emphasizing the paramount importance of thorough safety assessment alongside efficacy considerations.[87,88]

In summary, drug therapies like semaglutide, liraglutide, and phentermine/topiramate show promise in obesity treatment, alongside options like bupropion/naltrexone and orlistat. While effective, these drugs carry side effects, and long-term safety is still under study. Lifestyle changes—healthy diet and regular exercise—remain essential for sustainable weight management.[89]

Latest innovation to cure obesity

In recent years, there have been several innovative approaches for the treatment of obesity. These include new drug targets, novel surgical techniques, and the use of digital health technologies.[90]

Recent innovations in obesity pharmacotherapy have focused on the melanocortin-4 receptor (MC4R) pathway, a pivotal neuroendocrine regulator of energy homeostasis and appetite control. MC4R, predominantly expressed in hypothalamic neurons, integrates critical signals in the central melanocortin pathway. The receptor's activation typically promotes satiety, increases energy expenditure, and regulates glucose homeostasis through sympathetic nervous system modulation.

Genetic evidence underscores MC4R's importance – loss-of-function mutations in the MC4R gene represent the most common monogenic cause of severe early-onset obesity, affecting 2-3% of individuals with severe obesity.[91,92] This genetic validation has spurred development of MC4R agonists. Setmelanotide, a selective MC4R agonist, demonstrates particular promise in treating rare genetic forms of obesity linked to MC4R pathway defects.[93] Clinical trials have shown significant weight reduction and improved hyperphagia in patients with POMC, PCSK1, and LEPR deficiencies.[94]

Beyond rare genetic disorders, novel MC4R agonists are being investigated for broader

therapeutic applications in obesity. These agents aim to enhance MC4R signaling while minimizing off-target effects on related melanocortin receptors, potentially offering a more targeted approach than current anti-obesity medications. Early-phase clinical trials suggest favorable safety profiles and meaningful weight reduction, though long-term efficacy and safety data remain pending.[95,96]

Additionally, digital health technologies are emerging as valuable tools in obesity management. Interventions such as mobile apps, wearable devices, and telemedicine enhance patient engagement, supporting adherence to lifestyle changes and medication regimens. For instance, a recent study showed that a smartphone app delivering personalized diet and exercise recommendations led to significant weight loss among obese individuals. These innovations offer accessible, personalized, and effective support for those managing obesity.[97]

Bariatric surgery has evolved substantially, with laparoscopic sleeve gastrectomy (LSG) emerging as a transformative metabolic intervention. This minimally invasive technique involves precise resection of approximately 80% of the stomach along its greater curvature, creating a restricted tubular pouch. The procedure's efficacy stems from dual mechanisms: physical restriction of food intake and profound metabolic alterations through modulated gut hormone secretion, particularly reduced ghrelin production. LSG induces significant changes in gut-brain signaling pathways, affecting satiety, glucose homeostasis, and energy metabolism. Recent surgical refinements have enhanced safety profiles while maintaining substantial and sustainable weight loss outcomes through these combined restrictive and neuroendocrine effects.[98]

Laparoscopic sleeve gastrectomy achieves metabolic benefits through vertical resection of 75% gastric tissue, creating a restricted stomach volume. This anatomical modification triggers significant alterations in gut hormone profiles, notably decreased ghrelin and modified GLP-1 levels. Clinical outcomes demonstrate sustained weight reduction exceeding 60% excess weight loss and improved metabolic parameters, including enhanced glycemic control and reduced cardiovascular risk factors.[99]

Endoscopic sleeve gastroplasty (ESG) represents an innovative, minimally invasive bariatric procedure utilizing advanced endoscopic suturing technology. The technique involves precise placement of full-thickness sutures along the greater curvature of the stomach using an endoscopic suturing device, creating a tubular configuration that significantly reduces gastric volume by approximately 70%. This anatomical modification not only restricts food intake but also influences gut hormone secretion patterns, particularly ghrelin levels, affecting satiety signaling. Recent clinical studies demonstrate promising outcomes with mean total body weight loss of 15-20% at one year, coupled with a favorable safety profile. ESG bridges the therapeutic gap between pharmacological interventions and traditional bariatric surgery, offering a reversible option for patients with moderate obesity or those unsuitable for more invasive procedures.[100]

In conclusion, recent advances in obesity treatment, including MC4R-targeting drugs, digital health tools for better patient support, and new surgical methods like LSG and ESG, bring hope for more effective, personalized care. Ongoing research aims to enhance their safety and long-term success.[16,67]

CONCLUSION

Obesity's complex pathophysiology, characterized by adipose tissue dysfunction, inflammatory cascades, and metabolic disturbances, necessitates multifaceted therapeutic approaches. The interplay between adipocyte hypertrophy, altered adipokine secretion, and systemic inflammation creates a self-perpetuating cycle of metabolic dysfunction. Recent research highlights the critical roles of gut microbiota dysbiosis and adipose tissue hypoxia in disease progression.

Therapeutic interventions have evolved substantially, incorporating precision medicine approaches. Pharmacological advancements extend beyond traditional agents to include targeted therapies like GLP-1 receptor agonists and MC4R modulators, demonstrating enhanced efficacy profiles. Surgical innovations, particularly laparoscopic sleeve gastrectomy and endoscopic sleeve gastroplasty, offer minimally invasive options with documented metabolic benefits and sustained weight reduction.

The integration of digital health technologies has revolutionized patient care through real-time monitoring and enhanced engagement. Emerging therapeutic frontiers include gene therapy approaches targeting metabolic pathways and microbiota modulation strategies. These innovations, combined with traditional interventions, create a comprehensive treatment framework.

Success in obesity management relies on recognizing its heterogeneous nature and implementing personalized therapeutic strategies. Continued research focuses on identifying novel drug targets, understanding treatment resistance mechanisms, and developing biomarkers for therapeutic response prediction. The future of obesity care lies in integrating emerging technologies with evidence-based interventions while addressing individual patient factors for optimal outcomes.

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This research does not involve any clinical trials**.**

Author contributions

The authors of this paper have met the guidelines of the International Committee of Medical Journal Editors (ICMJE), made significant intellectual contributions to the study, and approved the final manuscript for publication. Neil B. Panchal: Conceptualization, Methodology, Data Collection, Analysis, Writing – Original Draft; Vipul M. Vaghela: Review & Editing, Supervision, Constructive Feedback; Both authors have given their final approval for submission and publication.

REFERENCES

1. Hruby A, Hu FB. The Epidemiology of Obesity: A Big Picture. *Pharmacoeconomics*. 2015;33(7):673-689. doi:10.1007/s40273-014-0243-x
2. Obradovic M, Sudar-Milovanovic E, Soskic S, et al. Leptin and Obesity: Role and Clinical Implication. *Front Endocrinol (Lausanne)*. 2021;12. doi:10.3389/FENDO.2021.585887/FULL
3. Lin X, Li H. Obesity: Epidemiology, Pathophysiology, and Therapeutics. *Front Endocrinol (Lausanne)*. 2021;12:1070. doi:10.3389/FENDO.2021.706978/BIBTEX
4. Swinburn BA, Sacks G, Hall KD, et al. The global obesity pandemic: Shaped by global drivers and local environments. *Lancet*. 2011;378(9793):804-814. doi:10.1016/S0140-6736(11)60813-1
5. Bray GA, Kim KK, Wilding JPH. Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation. *Obes Rev*. 2017;18(7):715-723. doi:10.1111/OBR.12551
6. Ahirwar R, Mondal PR. Prevalence of obesity in India: A systematic review. *Diabetes Metab Syndr*. 2019;13(1):318-321. doi:10.1016/J.DSX.2018.08.032
7. Mukhra R, Kaur T, Krishan K, Kanchan T. Commentary perspective overweight and obesity: A major concern for health in India. *Clin Ter*. 2018;169(5):E199-E201. doi:10.7417/CT.2018.2078
8. Singh RB, Pella D, Mechirova V, et al. Prevalence of obesity, physical inactivity and undernutrition, a triple burden of diseases during transition in a developing economy. The five city study group. *Acta Cardiol*. 2007;62(2):119-127. doi:10.2143/AC.62.2.2020231
9. Luhar S, Timæus IM, Jones R, et al. Forecasting the prevalence of overweight and obesity in India

to 2040. *PLoS One*. 2020;15(2). doi:10.1371/JOURNAL.PONE.0229438

10. Pradeepa R, Anjana RM, Joshi SR, et al. Prevalence of generalized & abdominal obesity in urban & rural India- the ICMR-INDIAB study (Phase-I) [ICMR-INDIAB-3]. *Indian J Med Res*. 2015;142(AUGUST):139-150. doi:10.4103/0971-5916.164234
11. Di Cesare M, Bentham J, Stevens GA, et al. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. *Lancet (London, England)*. 2016;387(10026):1377-1396. doi:10.1016/S0140-6736(16)30054-X
12. Ward ZJ, Bleich SN, Cradock AL, et al. Projected U.S. State-Level Prevalence of Adult Obesity and Severe Obesity. *N Engl J Med*. 2019;381(25):2440-2450. doi:10.1056/NEJMSA1909301
13. Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet (London, England)*. 2014;384(9945):766-781. doi:10.1016/S0140-6736(14)60460-8
14. Koliaki C, Liatis S, Kokkinos A. Obesity and cardiovascular disease: revisiting an old relationship. *Metabolism*. 2019;92:98-107. doi:10.1016/j.metabol.2018.10.011
15. Powell-Wiley TM, Poirier P, Burke LE, et al. Obesity and Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Circulation*. 2021;143(21):E984-E1010. doi:10.1161/CIR.0000000000000973
16. Loos RJF, Yeo GSH. The genetics of obesity: from discovery to biology. *Nat Rev Genet 2021 232*. 2021;23(2):120-133. doi:10.1038/s41576-021-00414-z
17. Chan RSM, Woo J. Prevention of Overweight and Obesity: How Effective is the Current Public Health Approach. *Int J Environ Res Public Health*. 2010;7(3):765. doi:10.3390/IJERPH7030765
18. Public Health Considerations Regarding Obesity - PubMed. Accessed April 22, 2023. https://pubmed.ncbi.nlm.nih.gov/34283488/
19. Wadden TA, Tronieri JS, Butryn ML. Lifestyle modification approaches for the treatment of obesity in adults. *Am Psychol*. 2020;75(2):235-251. doi:10.1037/AMP0000517
20. Yearwood L, Masood W. Behavioral Approaches To Obesity Treatment. *Quest*. 2022;56(1):142-149. doi:10.1080/00336297.2004.10491819
21. Williams DM, Nawaz A, Evans M. Drug Therapy in Obesity: A Review of Current and Emerging Treatments. *Diabetes Ther*. 2020;11(6):1199-1216. doi:10.1007/S13300-020-00816-Y
22. Srivastava G, Apovian C. Future Pharmacotherapy for Obesity: New Anti-obesity Drugs on the Horizon. *Curr Obes Rep*. 2018;7(2):147-161. doi:10.1007/s13679-018-0300-4
23. Safaei M, Sundararajan EA, Driss M, Boulila W, Shapi'i A. A systematic literature review on obesity: Understanding the causes & consequences of obesity and reviewing various machine learning approaches used to predict obesity. *Comput Biol Med*. 2021;136:104754. doi:10.1016/J.COMPBIOMED.2021.104754
24. Kahan LG, Mehrzad R. Environmental factors related to the obesity epidemic. *Obes Glob Impact Epidemiol*. Published online January 1, 2020:117-139. doi:10.1016/B978-0-12-818839-2.00010-7
25. Mingrone G, Castagneto M. The Pathophysiology of Obesity. *Minim Invasive Bariatr Metab Surg*. Published online 2015:17-23. doi:10.1007/978-3-319-15356-8_3
26. Kawai T, Autieri M V., Scalia R. Adipose tissue inflammation and metabolic dysfunction in obesity. *Am J Physiol Cell Physiol*. 2021;320(3):C375-C391. doi:10.1152/AJPCELL.00379.2020
27. Liu F, He J, Wang H, Zhu D, Bi Y. Adipose Morphology: a Critical Factor in Regulation of Human Metabolic Diseases and Adipose Tissue Dysfunction. *Obes Surg*. 2020;30(12):5086-5100. doi:10.1007/S11695-020-04983-6/FIGURES/2
28. Khanna D, Khanna S, Khanna P, Kahar P, Patel BM. Obesity: A Chronic Low-Grade Inflammation and Its Markers. *Cureus*. 2022;14(2). doi:10.7759/CUREUS.22711
29. Alipourfard I, Datukishvili N, Mikeladze D. TNF- á Downregulation Modifies Insulin Receptor Substrate 1 (IRS-1) in Metabolic Signaling of Diabetic Insulin-Resistant Hepatocytes. *Mediators Inflamm*. 2019;2019. doi:10.1155/2019/3560819
30. Kwon H, Pessin JE. Adipokines Mediate Inflammation and Insulin Resistance. *Front Endocrinol (Lausanne)*. 2013;4(JUN):71. doi:10.3389/FENDO.2013.00071
31. Amezcua-Castillo E, González-Pacheco H, Sáenz-San Martín A, et al. C-Reactive Protein: The Quintessential Marker of Systemic Inflammation in Coronary Artery Disease—Advancing toward Precision Medicine. *Biomedicines*. 2023;11(9):2444. doi:10.3390/BIOMEDICINES11092444
32. Saltiel AR. Insulin signaling in health and

disease. *J Clin Invest*. 2021;131(1):e142241. doi:10.1172/JCI142241

33. Meyts P De. The Insulin Receptor and Its Signal Transduction Network. *Endotext*. Published online April 27, 2016. Accessed December 3, 2024. https://www.ncbi.nlm.nih.gov/books/NBK378978/
34. Li M, Chi X, Wang Y, Setrerrahmane S, Xie W, Xu H. Trends in insulin resistance: insights into mechanisms and therapeutic strategy. *Signal Transduct Target Ther 2022 71*. 2022;7(1):1-25. doi:10.1038/s41392-022-01073-0
35. Tong Y, Xu S, Huang L, Chen C. Obesity and insulin resistance: Pathophysiology and treatment. *Drug Discov Today*. 2022;27(3):822-830. doi:10.1016/J.DRUDIS.2021.11.001
36. Izquierdo AG, Crujeiras AB, Casanueva FF, Carreira MC. Leptin, Obesity, and Leptin Resistance: Where Are We 25 Years Later? *Nutrients*. 2019;11(11). doi:10.3390/NU11112704
37. Münzberg H. Leptin-signaling pathways and leptin resistance. *Forum Nutr*. 2010;63:123-132. doi:10.1159/000264400
38. Gruzdeva O, Borodkina D, Uchasova E, Dyleva Y, Barbarash O. Leptin resistance: underlying mechanisms and diagnosis. *Diabetes, Metab Syndr Obes Targets Ther*. 2019;12:191. doi:10.2147/DMSO.S182406
39. Sharma M, McClung JA, Abraham NG. Adiponectin: A Mediator of Obesity, Insulin Resistance, Diabetes, and the Metabolic Syndrome. *Transl Res Coron Artery Dis Pathophysiol to Treat*. Published online January 1, 2016:33-42. doi:10.1016/B978-0-12-802385-3.00004-8
40. Han Y, Sun Q, Chen W, et al. New advances of adiponectin in regulating obesity and related metabolic syndromes. *J Pharm Anal*. 2024;14(5):100913. doi:10.1016/J.JPHA.2023.12.003
41. Nigro E, Scudiero O, Monaco ML, et al. New Insight into Adiponectin Role in Obesity and Obesity-Related Diseases. *Biomed Res Int*. 2014;2014:658913. doi:10.1155/2014/658913
42. Siddiqui K, Scaria Joy S, George TP. Circulating resistin levels in relation with insulin resistance, inflammatory and endothelial dysfunction markers in patients with type 2 diabetes and impaired fasting glucose. *Endocr Metab Sci*. 2020;1(3-4):100059. doi:10.1016/J.ENDMTS.2020.100059
43. Tripathi D, Kant S, Pandey S, Ehtesham NZ. Resistin in metabolism, inflammation, and disease. *FEBS J*. 2020;287(15):3141-3149. doi:10.1111/FEBS.15322
44. Goldsammler M, Merhi Z, Buyuk E. Role of hormonal and inflammatory alterations in obesity-related reproductive dysfunction at the level of the hypothalamic-pituitary-ovarian axis. *Reprod Biol Endocrinol*. 2018;16(1). doi:10.1186/S12958-018-0366-6
45. Oswal A, Yeo G. Leptin and the control of body weight: A review of its diverse central targets, signaling mechanisms, and role in the pathogenesis of obesity. *Obesity*. 2010;18(2):221-229. doi:10.1038/OBY.2009.228/FULL
46. Cunningham AL, Stephens JW, Harris DA. A review on gut microbiota: a central factor in the pathophysiology of obesity. *Lipids Heal Dis 2021 201*. 2021;20(1):1-13. doi:10.1186/S12944-021-01491-Z
47. Islam MR, Arthur S, Haynes J, Butts MR, Nepal N, Sundaram U. The Role of Gut Microbiota and Metabolites in Obesity-Associated Chronic Gastrointestinal Disorders. *Nutrients*. 2022;14(3). doi:10.3390/NU14030624
48. Hardin BI, Keyes D. Enterohormonal and Microbiota Pathophysiology Of Obesity. *StatPearls*. Published online February 13, 2023. Accessed April 23, 2023. https://www.ncbi.nlm.nih.gov/books/NBK578204/
49. Obesity - Symptoms and causes - Mayo Clinic. Accessed April 22, 2023. https://www.mayoclinic.org/diseases-conditions/obesity/symptoms-causes/syc-20375742
50. Mahmoud R, Kimonis V, Butler MG. Genetics of Obesity in Humans: A Clinical Review. *Int J Mol Sci*. 2022;23(19). doi:10.3390/IJMS231911005
51. Clément K, Mosbah H, Poitou C. Rare genetic forms of obesity: From gene to therapy. *Physiol Behav*. 2020;227. doi:10.1016/J.PHYSBEH.2020.113134
52. Goossens GH. The Metabolic Phenotype in Obesity: Fat Mass, Body Fat Distribution, and Adipose Tissue Function. *Obes Facts*. 2017;10(3):207-215. doi:10.1159/000471488
53. Koenen M, Hill MA, Cohen P, Sowers JR. Obesity, Adipose Tissue and Vascular Dysfunction. *Circ Res*. 2021;128(7):951-968. doi:10.1161/CIRCRESAHA.121.318093
54. Patni N, Garg A. Lipodystrophy for the Diabetologist—What to Look For. *Curr Diab Rep*. 2022;22(9):461-470. doi:10.1007/S11892-022-01485-W/METRICS
55. Tsatsoulis A, Paschou SA. Metabolically Healthy Obesity: Criteria, Epidemiology, Controversies, and Consequences. *Curr Obes Rep*. 2020;9(2):109-120. doi:10.1007/S13679-020-00375-0
56. Genovesi S, Antolini L, Orlando A, et al. Cardiovascular Risk Factors Associated With

the Metabolically Healthy Obese (MHO) Phenotype Compared to the Metabolically Unhealthy Obese (MUO) Phenotype in Children. *Front Endocrinol (Lausanne)*. 2020;11:27. doi:10.3389/fendo.2020.00027

57. Lim Y, Boster J. Obesity and Comorbid Conditions. *StatPearls*. Published online February 8, 2023. Accessed April 23, 2023. https://www.ncbi.nlm.nih.gov/books/NBK574535/
58. Kim MS. The neural basis of weight control and obesity. *Exp Mol Med 2022 544*. 2022;54(4):347-348. doi:10.1038/s12276-022-00759-3
59. Parmar RM, Can AS. Physiology, Appetite And Weight Regulation. *StatPearls*. Published online August 29, 2022. Accessed April 23, 2023. https://www.ncbi.nlm.nih.gov/books/NBK574539/
60. Chun JH, Butts A. Long-acting GLP-1RAs: An overview of efficacy, safety, and their role in type 2 diabetes management. *JAAPA*. 2020;33(S8 Suppl 1):3-18. doi:10.1097/01.JAA.0000669456.13763.bd
61. Richard AJ, White U, Elks CM, Stephens JM. Adipose Tissue: Physiology to Metabolic Dysfunction. *Endotext*. Published online April 4, 2020. Accessed April 23, 2023. https://www.ncbi.nlm.nih.gov/books/NBK555602/
62. Paz-Filho G, Mastronardi CA, Licinio J. Leptin treatment: facts and expectations. *Metabolism*. 2015;64(1):146-156. doi:10.1016/J.METABOL.2014.07.014
63. Murphy T, Foll B Le. Targeting the Endocannabinoid CB1 Receptor to Treat Body Weight Disorders: A Preclinical and Clinical Review of the Therapeutic Potential of Past and Present CB1 Drugs. *Biomolecules*. 2020;10(6). doi:10.3390/BIOM10060855
64. Abenavoli L, Scarpellini E, Colica C, et al. Gut Microbiota and Obesity: A Role for Probiotics. *Nutrients*. 2019;11(11). doi:10.3390/NU11112690
65. Kumar A, Chauhan S. Pancreatic lipase inhibitors: The road voyaged and successes. *Life Sci*. 2021;271:119115. doi:10.1016/J.LFS.2021.119115
66. Shi Q, Wang Y, Hao Q, et al. Pharmacotherapy for adults with overweight and obesity: a systematic review and network meta-analysis of randomised controlled trials. *Lancet*. 2022;399(10321):259-269. doi:10.1016/S0140-6736(21)01640-8
67. Müller TD, Blüher M, Tschöp MH, DiMarchi RD. Anti-obesity drug discovery: advances and challenges. *Nat Rev Drug Discov 2021 213*. 2021;21(3):201-223. doi:10.1038/s41573-021-00337-8
68. McGuire AL, Gabriel S, Tishkoff SA, et al. The road ahead in genetics and genomics. *Nat Rev Genet 2020 2110*. 2020;21(10):581-596. doi:10.1038/s41576-020-0272-6
69. Novikov AA, Afaneh C, Saumoy M, et al. Endoscopic Sleeve Gastroplasty, Laparoscopic Sleeve Gastrectomy, and Laparoscopic Band for Weight Loss: How Do They Compare? *J Gastrointest Surg*. 2018;22(2):267-273. doi:10.1007/S11605-017-3615-7
70. Landhuis E. The Definition of Gene Therapy Has Changed. *Nature*. Published online October 26, 2021. doi:10.1038/D41586-021-02736-8
71. Fan Y, Pedersen O. Gut microbiota in human metabolic health and disease. *Nat Rev Microbiol*. 2021;19(1):55-71. doi:10.1038/S41579-020-0433-9
72. Hasan N, Yang H. Factors affecting the composition of the gut microbiota, and its modulation. *PeerJ*. 2019;7(8). doi:10.7717/PEERJ.7502
73. Fong W, Li Q, Yu J. Gut microbiota modulation: a novel strategy for prevention and treatment of colorectal cancer. *Oncogene 2020 3926*. 2020;39(26):4925-4943. doi:10.1038/s41388-020-1341-1
74. Williams DM, Nawaz A, Evans M. Drug Therapy in Obesity: A Review of Current and Emerging Treatments. *Diabetes Ther*. 2020;11(6):1199-1216. doi:10.1007/S13300-020-00816-Y/METRICS
75. Müller TD, Blüher M, Tschöp MH, DiMarchi RD. Anti-obesity drug discovery: advances and challenges. *Nat Rev Drug Discov 2021 213*. 2021;21(3):201-223. doi:10.1038/s41573-021-00337-8
76. Mahapatra MK, Karuppasamy M, Sahoo BM. Semaglutide, a glucagon like peptide-1 receptor agonist with cardiovascular benefits for management of type 2 diabetes. *Rev Endocr Metab Disord*. 2022;23(3):521-539. doi:10.1007/S11154-021-09699-1
77. Smits MM, Van Raalte DH. Safety of Semaglutide. *Front Endocrinol (Lausanne)*. 2021;12. doi:10.3389/FENDO.2021.645563
78. Markham A. Setmelanotide: First Approval. *Drugs*. 2021;81(3):397-403. doi:10.1007/S40265-021-01470-9
79. Clément K, van den Akker E, Argente J, et al. Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMC deficiency: single-arm, open-label, multicentre, phase 3 trials. *lancet Diabetes Endocrinol*. 2020;8(12):960-970. doi:10.1016/S2213-8587(20)30364-8
80. Dawood O, El-Zawahry A. Mirabegron. *StatPearls*. Published online September 7, 2022.

Accessed April 26, 2023. https://www.ncbi.nlm.nih.gov/books/NBK538513/

81. Bridgeman MB, Friia NJ, Taft C, Shah M. Mirabegron: â3-adrenergic receptor agonist for the treatment of overactive bladder. *Ann Pharmacother*. 2013;47(7-8):1029-1038. doi:10.1345/APH.1S054
82. Hinnen D. Glucagon-Like Peptide 1 Receptor Agonists for Type 2 Diabetes. *Diabetes Spectr*. 2017;30(3):202-210. doi:10.2337/DS16-0026
83. Trujillo JM, Nuffer W, Smith BA. GLP-1 receptor agonists: an updated review of head-to-head clinical studies. *Ther Adv Endocrinol Metab*. 2021;12. doi:10.1177/2042018821997320
84. Greydanus DE, Agana M, Kamboj MK, et al. Pediatric obesity: Current concepts. *Disease-a-Month*. 2018;64(4):98-156. doi:10.1016/J.DISAMONTH.2017.12.001
85. Pickett-Blakely O, Newberry C. Future Therapies in Obesity. *Gastroenterol Clin North Am*. 2016;45(4):705-714. doi:10.1016/J.GTC.2016.07.008
86. Rodríguez JE, Campbell KM. Past, Present, and Future of Pharmacologic Therapy in Obesity. *Prim Care Clin Off Pract*. 2016;43(1):61-67. doi:10.1016/J.POP.2015.08.011
87. Janero DR, Makriyannis A. Cannabinoid receptor antagonists: pharmacological opportunities, clinical experience, and translational prognosis. *Expert Opin Emerg Drugs*. 2009;14(1):43-65. doi:10.1517/14728210902736568
88. Vemuri VK, Janero DR, Makriyannis A. Pharmacotherapeutic targeting of the endocannabinoid signaling system: Drugs for obesity and the metabolic syndrome. *Physiol Behav*. 2008;93(4-5):671-686. doi:10.1016/j.physbeh.2007.11.012
89. Tak YJ, Lee SY. Long-Term Efficacy and Safety of Anti-Obesity Treatment: Where Do We Stand? *Curr Obes Rep*. 2021;10(1):14-30. doi:10.1007/S13679-020-00422-W/TABLES/2
90. Angelidi AM, Belanger MJ, Kokkinos A, Koliaki CC, Mantzoros CS. Novel Noninvasive Approaches to the Treatment of Obesity: From Pharmacotherapy to Gene Therapy. *Endocr Rev*. 2022;43(3):507-557. doi:10.1210/endrev/bnab034
91. Brandfon S, Eylon A, Khanna D, Parmar MS. Advances in Anti-obesity Pharmacotherapy: Current Treatments, Emerging Therapies, and Challenges. *Cureus*. 2023;15(10). doi:10.7759/CUREUS.46623
92. Yeo GSH, Chao DHM, Siegert AM, et al. The melanocortin pathway and energy homeostasis: From discovery to obesity therapy. *Mol Metab*. 2021;48:101206. doi:10.1016/J.MOLMET.2021.101206
93. Kamermans A, Verhoeven T, van het Hof B, et al. Setmelanotide, a Novel, Selective Melanocortin Receptor-4 Agonist Exerts Anti-inflammatory Actions in Astrocytes and Promotes an Anti-inflammatory Macrophage Phenotype. *Front Immunol*. 2019;10. doi:10.3389/FIMMU.2019.02312
94. Clément K, van den Akker E, Argente J, et al. Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMC deficiency: single-arm, open-label, multicentre, phase 3 trials. *lancet Diabetes Endocrinol*. 2020;8(12):960-970. doi:10.1016/S2213-8587(20)30364-8
95. Hinney A, Körner A, Fischer-Posovszky P. The promise of new anti-obesity therapies arising from knowledge of genetic obesity traits. *Nat Rev Endocrinol 2022 1810*. 2022;18(10):623-637. doi:10.1038/s41574-022-00716-0
96. Gonçalves JPL, Palmer D, Meldal M. MC4R Agonists: Structural Overview on Antiobesity Therapeutics. *Trends Pharmacol Sci*. 2018;39(4):402-423. doi:10.1016/J.TIPS.2018.01.004
97. Patel ML, Wakayama LN, Bennett GG. Self-Monitoring via Digital Health in Weight Loss Interventions: A Systematic Review Among Adults with Overweight or Obesity. *Obesity*. 2021;29(3):478-499. doi:10.1002/OBY.23088
98. Yan K, Balijepalli C, Druyts E. The Impact of Digital Therapeutics on Current Health Technology Assessment Frameworks. *Front Digit Heal*. 2021;3:59. doi:10.3389/FDGTH.2021.667016/BIBTEX
99. Digital and the future of drug discovery and development | McKinsey. Accessed April 29, 2023. https://www.mckinsey.com/industries/life-sciences/our-insights/how-new-biomolecular-platforms-and-digital-technologies-are-changing-r-and-d
100. JW W, CY C. Current status of endoscopic sleeve gastroplasty: An opinion review. *World J Gastroenterol*. 2020;26(11). doi:10.3748/WJG.V26.I11.1107