Diabetes, Metabolic Syndrome and Obesity

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REVIEW

Obesity and Its Comorbidities: Current Treatment Options, Emerging Biological Mechanisms, Future Perspectives and Challenges

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Abstract: Obesity is a chronic, multifactorial disease and a major global public health challenge. Defined by excessive fat accumulation, obesity significantly increases the risk of numerous diseases, including type 2 diabetes mellitus (T2DM), cardiovascular disease, heart failure, and metabolic dysfunction-associated steatotic liver disease, contributing to rising morbidity and mortality rates worldwide. Although several pharmacological treatments have demonstrated notable efficacy in weight management, concerns regarding drug safety remain a significant challenge. Metabolic bariatric surgery (MBS) has emerged as the most effective intervention for achieving long-term and sustained weight loss; however, it is typically reserved for advanced stages of the disease. Moreover, the role of MBS in managing obesity-related comorbidities remains a topic of ongoing debate. In this review, we provide a comprehensive analysis of the epidemiology of obesity and its associated comorbidities, along with the latest insights into the mechanisms underlying obesity-induced chronic complications. Growing evidence highlights the crucial role of imbalances between white and brown adipose tissues, alterations in gut microbiota, genetic and epigenetic modifications, and immune system dysregulation in driving obesity and its related conditions. These emerging insights have unveiled numerous potential therapeutic targets with promising weight-reducing effects. Furthermore, advancements in our understanding of signal transduction pathways may pave the way for future multimodal therapeutic strategies in obesity management, ushering in a new era of precision medicine.

Keywords: obesity, comorbidity, mechanism, treatment, clinical challenges

Introduction

The prevalence of obesity has risen not only in the Western hemisphere but globally, contributing to significantly increased and persistent healthcare expenditures. The World Health Organization (WHO) identifies obesity as one of the most visibly apparent yet underappreciated public health challenges, significantly elevating the risk for multiple comorbidities, including insulin resistance (IR), type 2 diabetes mellitus (T2DM), liver steatosis, cardiovascular diseases, and certain types of cancer, particularly colorectal cancer (CRC).[1–3] Since the mid-1970s, the prevalence of obesity has nearly tripled, affecting 2 billion adults and 340 million children worldwide, with projections indicating an additional 10% increase by 2030.[4] Over the past decade, our understanding of obesity's etiology has substantially deepened, revealing that the pathogenesis of primary obesity involves a complex interplay of social, genetic, epigenetic, developmental, and environmental factors. It has become increasingly clear that this major health issue arises not solely from an increase in caloric intake coupled with decreased physical activity.[5] It is estimated that obesity contributes to 20% of all

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cancers.[6] Certain modifiable conditions, including metabolic dysfunction-associated steatotic liver disease (MASLD), chronic stress, and sleep apnea syndrome, have also been linked to an elevated risk of weight gain. A more comprehensive understanding of the complex etiology of obesity and its comorbidities is crucial for reshaping the perception of obesity as a chronic and degenerative disease. This perspective is essential for challenging the widespread belief that obesity is merely a consequence of individual lack of self-discipline.

Obesity is associated with an increased risk of various serious comorbidities.[7] Among these, cardiovascular disease (CVD) is the leading cause of mortality, followed by T2DM, chronic renal disease, certain types of cancer, and autoimmune diseases.[8–11] Furthermore, comorbidities such as diabetes can exacerbate obesity, establishing a vicious cycle that contributes to disease progression and the onset of both microvascular and macrovascular complications. It is estimated that 4–9% of all cancers may be promoted by an increased body fat percentage.[12] Additionally, being overweight is linked to reduced life expectancy, with males and females aged 20–29 years who are overweight predicted to live 4.2 and 3.6 years less, respectively.[13,14] A cohort study using prospectively collected data from "The Health Improvement Network" (THIN) database demonstrated that some individuals with obesity who are classified as "metabolically healthy" still face an elevated risk for coronary heart disease (49% increased risk), cerebrovascular disease (7% increased risk), and heart failure (96% increased risk), compared to normal-weight individuals without metabolic risk factors.[15] Based on these findings, the term "healthy obesity" may be a misnomer, as such a phenotype likely reflects varying degrees of adipose tissue plasticity, which can either expand in a healthy or unhealthy manner.

With advances in science and technology, as well as a deeper understanding of the pathogenesis of obesity, significant progress has been made in the fight against this condition. Various approaches to prevent obesity have been developed, with lifestyle modification, including changes in diet and behavior, serving as the most common starting point for weight loss. However, these approaches have had limited success in achieving long-term results.[16] Since sole optimization of lifestyle and behavior is insufficient in most cases, pharmacological and/or surgical interventions are often necessary. Pharmacotherapy offers an alternative strategy for patients who fail to achieve their treatment goals through lifestyle changes, and a growing number of innovative anti-obesity drugs are currently under development.[17,18] At present, MBS, including sleeve gastrectomy (SG), one-anastomosis gastric bypass (OAGB), and Roux-en-Y gastric bypass (RYGB), remains the most effective therapeutic option for obesity, offering long-lasting weight loss. However, its widespread application is hindered by concerns about long-term complications, high operational costs, and limited access.[19,20] Recent advances in elucidating the intricate pathogenesis of obesity are paving the way for novel treatment approaches, which may provide revolutionary prospects for therapeutic interventions aimed at weight reduction.

In this review, we examine the comorbidities of obesity, with a particular focus on several major diseases: metabolic dysfunction-associated steatotic liver disease, T2DM, cardiovascular disease, cancer, and autoimmune diseases. We also summarize current clinical strategies for the prevention and treatment of obesity. Special attention is given to the regulatory mechanisms involved in the pathogenesis of obesity, specifically the imbalance between white and brown adipose tissues, gut microbiota, genetic and epigenetic alterations, and changes in immune function. These insights offer clinicians renewed hope for more effective strategies in combating the obesity epidemic.

Comorbidities of Obesity

Metabolic Dysfunction-Associated Steatotic Liver Disease

MASLD is diagnosed when hepatic steatosis (≥5% hepatocytes with fat accumulation) coexists with ≥1 cardiometabolic risk factor, including central obesity, type 2 diabetes, hypertension, atherogenic dyslipidemia, or insulin resistance.[21] The diagnostic workflow of MASLD integrates multiple approaches:[22,23] (1) Liver biopsyremains the gold standard for evaluating steatosis grade (SAF score), lobular inflammation, and fibrosis stage (NASH CRN scoring); (2) Non-invasive scores, particularly the FIB-4 index (incorporating age, ALT, AST, and platelet count), stratify fibrosis risk (low risk: <1.3; high risk: >2.67); (3) MRI-based quantification provides comprehensive metabolic assessment, including liver fat fraction (LFF, via MRI-PDFF ≥5% for steatosis), subcutaneous adipose tissue (SAT, protective phenotype), and VAT (strongly associated with MASLD severity). These tools are indispensable for preoperative risk stratification, as VAT volume and LFF independently predict post-surgical metabolic outcomes.

MASLD is characterized by excessive intrahepatic fat accumulation and is defined by the presence of liver steatosis in more than 5% of hepatocytes, excluding other causes of intrahepatic fat accumulation such as excessive alcohol consumption, infectious diseases, autoimmune disorders, and metabolic diseases. As a metabolic disorder, MASLD is strongly associated with various metabolic comorbidities, including dyslipidemia, T2DM, and obesity,[24] with IR serving as the primary pathogenic link between these conditions.[25] Moreover, excessive hepatic fat accumulation can progress to inflammation (metabolic dysfunction-associated steatohepatitis [MASH]) and liver fibrosis, potentially advancing to MASH-related cirrhosis, which has become the fastest-growing indication for liver transplantation in Western countries. A recent meta-analysis by Younossi reported a 50.4% increase in MASLD prevalence over the past 30 years, rising from 25.3% (1990–2006) to 38.2% (2016–2019), closely mirroring the growing prevalence of obesity and metabolic syndrome.[26] Consequently, targeting inflammatory pathways in MASLD or reducing visceral adipose tissue (VAT) has emerged as a promising therapeutic strategy, with histological improvements demonstrated in patients enrolled in a phase IIb clinical trial.[27] There is ongoing debate about whether MASLD aligns with the current definition of liver disease. In 2020, a panel of experts proposed renaming NAFLD as metabolic-associated fatty liver disease (MAFLD), a term that more accurately reflects the hepatic manifestation of systemic metabolic dysfunction.[28] Notably, MASLD is a significant contributor to the increased all-cause mortality observed in individuals with obesity, as evidenced by population-based studies.[29] Mechanistically, obesity-associated zinc-alpha-2-glycoprotein (ZAG) inhibits the nuclear factor kappa-B (NF-κB)/c-Jun N-terminal kinase (JNK) signaling pathway, thereby suppressing obesity-related inflammation in hepatocytes.[30]

The complex pathophysiology of MASLD and its progression are driven by the interaction of multiple factors, including obesity, chronic inflammation, epigenetic modifications, endocrine disruptors, oxidative stress, and gut microbiota dysbiosis.[31,32] Indeed, alterations in gut microbiota composition and/or its metabolites may contribute to disorders of energy metabolism, including liver injury and metabolic dysfunction.[33] Our previous study also reported that obesity induces inflammation in the pituitary gland, leading to impaired pituitary inositol-requiring enzyme 1α (IRE1α)-X-box-binding protein 1 (XBP1) unfolded protein response (UPR) signaling, which is crucial for protecting against pituitary endocrine defects and the progression of MASLD.[26] Notably, targeted ablation of pituitary IRE1α has been linked to the onset of hypothyroidism and a diminished response of the thyroid hormone receptor β (THRB)-mediated transcriptional activation of Xbp1 in hepatic tissues. Conversely, activation of the hepatic THRB-XBP1 signaling axis has been shown to ameliorate MASLD in murine models with compromised pituitary UPR.[26,34] Collectively, a deeper understanding of these pathways may inform future strategies for the prevention and treatment of MASLD.

Type 2 Diabetes

T2DM is one of the leading causes of death worldwide, with projections suggesting that the number of cases will rise to 350 million by 2030.[35] The complications associated with T2DM affect nearly every tissue in the body and contribute significantly to the risk and mortality of various diseases, including neuropathy, cardiovascular disease, and certain types of cancer.[36,37] It is well established that insulin and glucagon function as antagonistic hormones to maintain glucose homeostasis in the body. Insulin is crucial for cellular glucose uptake and is secreted by pancreatic β cells when blood glucose levels rise, promoting glucose utilization in hepatocytes for glycogen production and storage, as well as converting excess glucose into fatty acids.[38] In contrast, glucagon is typically described as a counter-regulatory hormone to insulin. It is secreted by pancreatic α cells in the fasting state to raise blood glucose levels by promoting hepatic glycogenolysis and gluconeogenesis.[39] However, in T2DM, the balance between glucose uptake and utilization by peripheral tissues is disrupted. Specifically, the presence of excess weight or obesity increases the susceptibility to developing T2DM.[40] Although the pathophysiology of T2DM can vary among patients, it is generally caused by reduced insulin secretion and/or increased glucagon secretion, elevated glucose production, impaired insulin signaling, and decreased glucose uptake by skeletal muscle, liver, and adipose tissues.[41] Genetic mutations that disrupt insulin sensitivity also play a role in the development of T2DM.[42]

Weight gain is an independent risk factor for T2DM,[43] and increased body weight or waist circumference promotes insulin resistance.[44] In other words, obesity profoundly alters gastrointestinal hormone secretion, exacerbating glycemic dysregulation. Key appetite-regulating peptides such as GLP-1 and PYY are typically downregulated in obesity,

impairing postprandial insulin response and satiety signaling. Notably, metabolic bariatric surgery can reverse these defects, as demonstrated in a randomized trial where laparoscopic RYGB with fundus resection significantly increased postprandial GLP-1 and PYY levels, correlating with diabetes remission rates.[45] A cross-sectional study reported that low plasma adiponectin levels and high intra-abdominal fat are strong predictors of insulin resistance and β-cell dysfunction.[46,47] Mechanistically, various pro-inflammatory cytokines and chemokines triggered by obesity activate intracellular pathways, such as c-Jun NH2-terminal kinase (JNK) and IκB kinase-β (IKKβ), which play crucial roles in the development of insulin resistance and T2DM.[48,49] JNK activation induces serine phosphorylation of insulin receptor substrate-1 (IRS-1) at Ser-307, leading to decreased tyrosine phosphorylation of IRS-1 and disruption of its interaction with the insulin receptor, ultimately impairing downstream insulin signaling.[50] A proteomic study also assessed the effects of abdominal fat distribution on measures of insulin sensitivity and β-cell function in healthy adults, showing a strong association between increased VAT and decreased β-cell function.[51] The study further revealed a correlation between elevated levels of S100A8/9 (calprotectin) in urine and plasma and chronic low-grade inflammation and insulin resistance. Additionally, mRNA levels of S100A8 were increased in the adipocyte fraction of obese mice.[51] Patients with obesity experience T2DM at a younger age and live with the disease for a greater proportion of their lifespan compared to individuals with normal weight.[40] Consequently, it is clear that more treatment strategies targeting both obesity and T2DM need to be developed.

Cardiovascular Disease

CVD remains the leading cause of mortality globally and is primarily driven by modifiable risk factors, including obesity and overweight.[52] The elevated risk of CVD associated with obesity, particularly atherosclerotic cardiovascular disease (ACVD), is largely triggered by traditional established risk factors, such as dyslipidemia, hypertension, insulin resistance, T2DM, and obstructive sleep apnea (OSA).[53] Notably, the strong relationship between obesity and the development of CVD is not solely dependent on overall body fat mass but also on complications commonly linked to excess weight, such as heart failure and arrhythmias.[54] Excess adipose tissue accumulation can lead to structural remodeling of the heart, causing both right and left ventricular (LV) hypertrophy, which may eventually progress to heart failure. For every 1 kg/m² increase in Body Mass Index (BMI), the risk of LV hypertrophy increases by 5.1%, and for every 1 cm increase in waist circumference, the risk of LV hypertrophy increases by 2.6%.[55] Obstructive sleep apnea (OSA) is a critical yet frequently overlooked contributor to right heart failure (RHF) in obesity. The pathophysiology involves three key mechanisms:[56,57] chronic intermittent hypoxia, which induces pulmonary vasoconstriction and hypertension, thereby increasing right ventricular (RV) afterload; mechanical stress from exaggerated intrathoracic pressure swings during apneic episodes, directly elevating RV transmural pressure; and neurohormonal activation, where sympathetic overdrive promotes myocardial fibrosis and RV dysfunction. Furthermore, the progression of inflammation, oxidative stress, and elevated leptin levels in obesity is closely associated with the development of CVD. Numerous studies have been conducted, most of which support the relationship between long-term obesity and increased risk of CVD.

Obesity contributes to myocardial dysfunction and increased CVD risk through multiple processes, including neurohormonal activation, hemodynamic alterations, ectopic fat deposition, lipotoxicity, and the endocrine and paracrine actions of adipose tissue.[54,58] The renin-angiotensin-aldosterone system (RAAS) is simultaneously activated in obesity, likely due to direct signaling from adipocytes.[59] The concurrent activation of the RAAS and sympathetic nervous system results in cardiac remodeling and left ventricular hypertrophy (LVH), highlighting the connection between obesity and the development of CVD.[59,60] Epidemiological studies in individuals with obesity have shown a relative increase in pro-inflammatory adipokines compared to anti-inflammatory adipokines, which play a critical role in CVD risk.[61,62] For example, a large prospective cohort study involving participants without a history of CVD demonstrated a positive correlation between dysfunctional visceral adiposity and systemic inflammation through the secretion of pro-inflammatory adipokines and cytokines. This, in turn, contributes to oxidative stress, insulin resistance, and endothelial dysfunction, all of which facilitate the development of CVD.[63] Mechanistically, adiponectin, which is secreted by the epicardial adipose tissue—a subtype of perivascular adipose tissue surrounding the coronary arteries—induces vasodilation by increasing nitric oxide concentration.[64,65] However, the vasoactive properties of epicardial adipose tissue are lost in obesity, contributing to hypoxia and oxidative stress. Additionally, increased intramyocardial fat secretes pro-

inflammatory cytokines, leading to an increase in LV mass, worsening LV function, and promoting the development of atrial fibrillation and coronary heart disease, both of which further elevate CVD risk.[66,67] In summary, obesity is a significant risk factor for the development of CVD. Compared to individuals with normal weight, those who are overweight experience CVD events at a younger age and live with this disease for a larger proportion of their lifespan.[68] Therefore, a more comprehensive understanding of CVD risk factors is crucial, as preventing and treating CVD presents significant social and medical challenges.

Cancers

Obesity has been linked to an increased risk of cancer development, with 11.9% of cancer cases in men and 13.1% in women attributed to obesity globally.[69,70] It is widely acknowledged that obesity can elevate the risk of various cancers, including breast cancer in postmenopausal women, endometrial cancer, ovarian cancer, kidney cancer, thyroid cancer, and gastrointestinal cancers (such as colorectal cancer, gastric cancer, esophageal adenocarcinoma, pancreatic cancer, and gallbladder cancer). Moreover, obesity can negatively impact the survival of individuals with cancer, particularly in those with breast, bladder, prostate, colorectal, and liver cancers. Estimates indicate that in 2019, 4.59% of cancer cases and 4.45% of cancer-related deaths and disability-adjusted life years (DALYs) were linked to a high body mass index.[71] Beyond increasing the risk of carcinogenesis, obesity can also accelerate cancer progression, hinder the effectiveness of cancer treatments, and shorten the survival of cancer patients.[72]

The connection between obesity and cancer has been extensively studied. A systematic review and meta-analysis involving 282,137 cases revealed that a 5 kg/m² higher BMI in men was associated with a modest but statistically significant increase in the risk of non-Hodgkin's lymphoma [RR (95% CI): 1.06 (1.03–1.09)] and leukemia [RR (95% CI): 1.08 (1.02–1.14)]. Specifically, for each 5 kg/m² increase in BMI, the RR for non-Hodgkin's lymphoma was 1.07 (95% CI: 1.00–1.14) and for leukemia was 1.17 (95% CI: 1.04–1.32) in women.[73] Additionally, numerous studies have reported that excess body fat in women leads to the accumulation of white adipose tissue (WAT) in the breast, which induces the release of pro-inflammatory cytokines (eg, IL-6 and TNF-α), thereby promoting inflammation associated with an increased risk of breast cancer, particularly in postmenopausal women.[74] A cross-sectional cohort study by Lyengar et al demonstrated that inflammation in breast WAT and elevated breast aromatase levels were linked to trunk fat and total body fat. Circulating metabolic and inflammatory biomarkers, such as IL-6, C-reactive protein (CRP), insulin, and leptin, were positively correlated with body fat and breast aromatase levels, while they were negatively correlated with adiponectin, sex hormone-binding globulin (SHBG), and exercise.[74] Obesity-related comorbidities substantially elevate cancer risk through diverse pathological mechanisms. For instance, MASLD contributes to hepatocellular carcinogenesis via persistent hepatocyte injury, chronic inflammation driven by TLR4/NF-κB signaling, and epigenetic dysregulation. Similarly, gastroesophageal reflux disease (GERD) facilitates the development of esophagogastric adenocarcinoma through recurrent acid-mediated mucosal damage, acquired TP53 mutations, and metaplastic progression to Barrett's esophagus.[75] Collectively, these findings support the correlations between elevated adiposity, reduced physical activity, and the promotion of pro-tumorigenic macro- and microenvironments, suggesting a multifactorial etiological framework that may contribute to cancer pathogenesis.

Several independent studies have also reported that obesity significantly impacts the synthesis and secretion of adipokines through various mechanisms, and alterations in the regulation of adipokines have been linked to different cancer types and their metastatic potential.[76] Oncogenesis and tumor progression are often accompanied by the release of inflammatory mediators into the bloodstream. In the study by Renehan et al,[77] it was identified that patients with esophageal and hepatocellular carcinomas had significantly elevated levels of leptin, which are now recognized as important factors for cancer progression due to their ability to stimulate growth hormones, promote cell proliferation, angiogenesis, and differentiation, or inhibit apoptosis through paracrine or autocrine interactions. Similarly, in another study, signaling molecules and metabolites secreted by adipose tissue, especially in the obese state, were associated with increased expression of various genes involved in pro-tumorigenic inflammatory responses and epithelial-mesenchymal transition (EMT) in pathways linked to cancer progression. These include the tumor microenvironment (TME) signaling pathways, such as TNF-α/NF-κB, KRAS, IL-6/JAK/STAT3, and transforming growth factor (TGF)-β.[78] While these adipokines hold promise, the evidence is less conclusive for other inflammatory markers. A meta-analysis conducted in

the UK, which included 18 studies involving 2,921 women diagnosed with endometrial cancer and 5,302 controls, revealed no significant correlation between the highest and lowest TNF-α or IL-6 levels and the risk of endometrial cancer.[79] Taken together, these findings provide mechanistic insights into the link between obesity and cancer risk and highlight the potential of adipose tissue biomarkers for risk assessment and prognosis.

Autoimmune Diseases

Compelling epidemiological evidence underscores a robust correlation between obesity and both increased incidence and exacerbated severity of multiple autoimmune disorders. Large-scale epidemiological data demonstrate that obese individuals (BMI ≥30 kg/m²) have a significantly elevated risk (1.5–3 fold) of developing psoriasis compared to normal-weight controls,[80] with a clear dose-response relationship between increasing BMI and disease risk. The Nurses' Health Study II (n=116,430) revealed a significant dose-dependent association, demonstrating a 20% increased risk of psoriasis development per 5 kg/m² increment in BMI.[81] A meta-analysis published in 2012 further substantiated this association, demonstrating that obesity significantly increased psoriasis risk (pooled OR 1.66, 95% CI 1.46–1.89).[82] However, a notable gap in the epidemiology of psoriasis lies in the absence of data on the comorbidity rate of obesity. The precise mechanism of this relationship remains unknown but may involve adipose tissue-derived products and systemic inflammation, which will also contribute to an elevated risk of cardiovascular disease and a shortened lifespan of individuals with psoriasis. Similarly, obesity doubles the likelihood of developing rheumatoid arthritis (RA), particularly anti-citrullinated protein antibody (ACPA)-positive RA, as evidenced by the Swedish EIRA case-control study (n=2,832 cases).[83] Furthermore, emerging evidence indicates that visceral adiposity promotes RA pathogenesis through the excessive secretion of pro-inflammatory adipokines, which exacerbate systemic inflammation and amplify disease risk.[84] In this regard, adipokines represent a group of substances released by the adipose tissue, such as leptin and fibroblast growth factor 21, which can modify different organism responses. Recently, a meta-analysis presented convincing evidence of a positive association between obesity and RA, highlighting a dose–response relation between body mass index (BMI) and the risk for RA, especially in women and in seronegative cases of the disease.[85,86] Similarly, MRI-based longitudinal data demonstrate that a 10% reduction in VAT volume is associated with a clinically meaningful 27% improvement in RA disease activity (DAS28-CRP) scores.[87]

Beyond these disorders, obesity exhibits well-established associations with multiple autoimmune disorders through shared inflammatory pathways. A landmark meta-analysis of 42 prospective cohort studies (total n=2.1 million) established that adolescent obesity elevates multiple sclerosis risk by 40% (pooled OR 1.40, 95% CI 1.25–1.57), with leptin-induced neuroinflammation identified as a key pathogenic mechanism.[88] Moreover, obesity and overweight are identified as risk factors for flare in patients with systemic lupus erythematosus(SLE), by the expression of inflammatory cytokines such as TNF-α and IL-6.[89] Studies of other autoimmune diseases (rheumatoid arthritis progression and inflammatory bowel disease) have shown that obesity can also negatively affect disease activity.[90] Emerging mechanistic studies elucidate how obesity-induced metabolic inflammation fuels autoimmunity. Adipose tissue dysfunction in obesity establishes a chronic pro-inflammatory state marked by significantly elevated leptin levels (up to 4-fold higher than normal) and suppressed adiponectin secretion, creating a Th17/Treg imbalance pivotal in autoimmune pathogenesis.[91] A 2023 mechanistic study in Nature Immunology revealed that visceral adipocytes from individuals with severe obesity (BMI >35 kg/m²) drive autoimmune predisposition through dual mechanisms: (1) promoting Th17 cell differentiation via IL-6/IL-23 secretion, and (2) suppressing regulatory T cell (Treg) function through leptin-dependent STAT3 activation.[92]

Mechanism of Obesity and Its Comorbidities

Imbalance of White and Brown Adipose Tissues

Adipose tissue has traditionally been viewed as a passive tissue involved in the regulation of energy balance and homeostasis. However, it is now recognized that adipose tissue plays a more active role. It can be classified into two types based on morphological differences: WAT and brown adipose tissue (BAT). WAT primarily serves as the storage site for excess energy in the form of fat and is considered a risk factor for metabolic diseases. In contrast, BAT is a thermogenic tissue that consumes substantial amounts of glucose and fatty acids for fuel, making it an important target

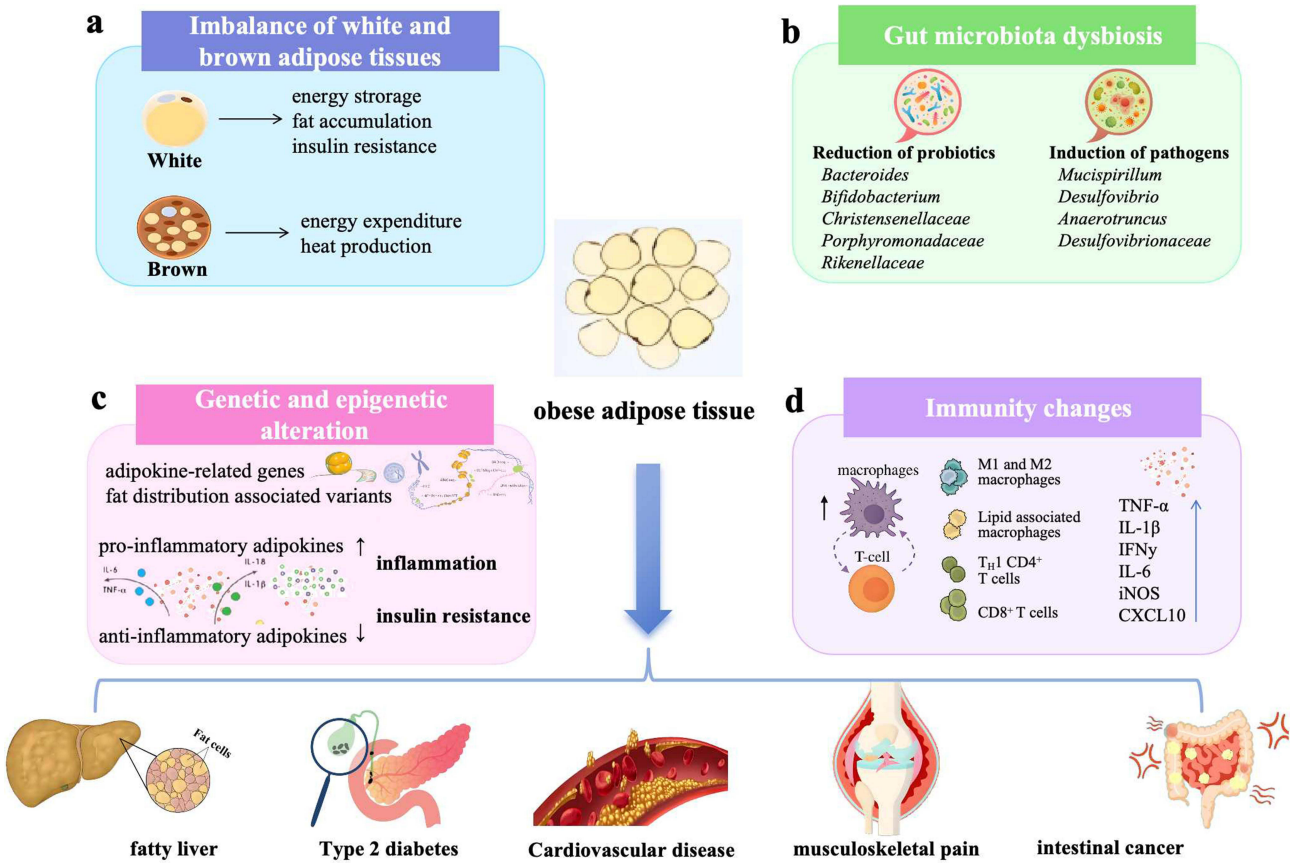

Figure 1 Mechanism of obesity and its comorbidities. Obesity is intricately associated with metabolic disorders, including NAFLD, T2DM, CVD, and CRC, through multifactorial pathophysiological mechanisms. (**a**) Imbalance of white and brown adipose tissues. WAT stores fat and promotes insulin resistance, contributing to metabolic disorders. In contrast, BAT enhances energy expenditure and thermogenesis, helping regulate metabolism and counteract obesity. (**b**) Gut microbiota dysbiosis. Obesity-related gut dysbiosis involves reduced probiotics and increased pathogenic bacteria, leading to inflammation, metabolic dysfunction, and impaired gut barrier integrity, which contribute to insulin resistance and related comorbidities. (**c**) Genetic and epigenetic alteration. Adipokine-related gene variants and fat distribution-associated polymorphisms contribute to inflammation and insulin resistance. Epigenetic modifications, such as RNA m6A methylation, regulate obesity and its complications, with FTO-dependent m6A modifications promoting adipogenesis, while METTL3 and YTHDF1 drive CRC via oncogenic pathways. (**d**) Immunity changes. Macrophage polarization and T cell alterations drive chronic inflammation, with NF-κB activation increasing TNF-α and IL-6 secretion. These interconnected mechanisms contribute to obesity-related comorbidities.

for maintaining metabolic health and protecting against obesity. The prevailing hypothesis suggests that promoting the thermogenic activity of BAT or stimulating WAT browning could reverse some of the pathological features of obesity and metabolic syndrome (Figure 1). A recent retrospective analysis of 134,529 positron emission tomography-computed tomography (PET-CT) scans from 52,487 patients found that individuals with BAT exhibited lower prevalences of cardiometabolic disorders, with an independent correlation to reduced odds of cerebrovascular disease, congestive heart failure, type 2 diabetes, hypertension, and dyslipidemia.[93] Activated BAT can utilize glucose and fatty acids as fuel for thermogenesis, thereby enhancing overall energy expenditure in both rodents and humans.[94] Additionally, a preclinical study by Bonfante et al demonstrated that the thermogenic activity of BAT was significantly increased in overweight or T2DM patients, with a marked upregulation of genes associated with thermogenesis (TMEM26, EPSTI1) in subcutaneous fat following combined training.[95] In humans, individuals with overweight or obesity may benefit from BAT activation to promote overall cardiometabolic health.

Gut Microbiota

The gut microbiota consists of numerous symbiotic bacteria that play a crucial role in regulating the host's appetite, intestinal permeability, energy absorption, and overall lipid and glucose metabolism. Therefore, it is reasonable to conclude that regulating the gut microbiota and improving intestinal dysbiosis are essential for the treatment of obesity

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(Figure 1). In a study by Le Chatelier et al, obese individuals exhibited lower gut microbiota diversity compared to healthy individuals, along with significant obesity and dyslipidemia. The structure and abundance of gut microbiota were found to be altered in obese individuals relative to healthy individuals.[96] The obesity-associated gut microbiome enhances the capacity for energy harvest from the diet, thereby contributing to increased adipose tissue storage in the host, particularly in WAT.[97] A growing body of evidence from animal studies, as well as human research, suggests a link between diet, gut microbiota, and obesity.

A growing body of evidence suggests that alterations in the gut microbiota can influence host physiology through multiple mechanisms, including enhanced energy absorption, changes in immune function, metabolic signaling, and chronic inflammation pathways. For example, dysbiosis, or imbalance in gut microbiota, has been implicated in gut inflammation, with innate immune receptors such as TLR5 and the inflammasome adaptor ASC (apoptotic speck-containing protein with a CARD) playing a role in obesity-associated dysbiosis.[98] In our previous study, we described a direct link between gut microbiota and host glycometabolism through metabolic intermediates.[99,100] The gut microbiota is responsible for producing short-chain fatty acids (SCFAs) through the fermentation of soluble dietary fiber and resistant starch. These SCFAs, by binding to G protein-coupled receptors GPR41 and GPR43, indirectly affect gene expression by modulating molecular signaling pathways, such as increasing the expression of GLP-1 and PYY in the gut. Both GLP-1 and PYY have been shown to inhibit appetite, reduce body weight, and improve insulin resistance in obese mice. Taken together, targeted interventions aimed at modulating the gut microbiota offer promising therapeutic options for promoting host health in the future.

Genetic and Epigenetic Alteration

Obesity is a complex condition influenced by numerous factors, with both genetic and epigenetic alterations playing critical roles in its development (Figure 1). A meta-analysis from the Genetic Investigation of Anthropometric Traits (GIANT) consortium, involving more than 339,000 individuals, identified 97 loci associated with BMI, 56 of which were novel. Genes near these loci showed enrichment in the central nervous system (CNS), suggesting that BMI is primarily regulated by processes such as hypothalamic control of energy intake.[101] Many proteins, produced by adipose tissue, named adipokines, have been described (leptin, resistin, TNF-α and IL−6) with a lot of relationships with metabolic parameters such as dyslipidemia and insulin resistance. For example, the APOA1 (rs670) gene has significant effects on body weight, adiposity, LDL-cholesterol levels, and insulin resistance following a 12-week dietary intervention.[102] Growth differentiation factor 15 macrophage inhibitory cytokine 1 (MIC1; also known as GDF15) is upregulated in visceral fat of obese patients with metabolic syndrome, of which it may cause energy expenditure by increasing thermogenesis, oxidative metabolism and lipolysis, thereby resulting in an decreased body weight.[103] In a clinical study, chemokine C-X-C motif chemokine ligand 10 (CXCL10) and it's receptor C-X-C Motif Chemokine Receptor 3 (CXCR3), known as important regulators of angiogenesis in different disease contexts, was reported to be produced heavily in inflamed AT with other cytokines at the onset of obesity, subsequently impairing insulin sensitivity through phosphorylation of hormone-sensitive lipase in visceral adipocytes.[104] Additionally, CXCL10 expression levels were positively correlated with several closely related CC motif chemokines found in macrophages and lymphocytes, which mediate obesity-induced chronic inflammation. These findings imply that adipose tissue distribution is a trait with significant heritability.

Epigenetic mechanisms regulate gene activity and organism development. The epigenome encompasses DNA methylation, histone modifications, and RNA-mediated processes, and disruptions in these mechanisms can lead to various pathologies, including obesity and its associated comorbidities. A large-scale study investigating DNA methylation in CD4+ T cells found eight CpG sites associated with BMI and five with waist circumference.[105] Among these CpG sites robustly linked to BMI, gene expression of CPT1A was significantly altered and overrepresented in lipid metabolism pathways.[106] Notably, the direct correlation between CPT1A and obesity-related diseases has been well documented. CPT1A encodes the enzyme carnitine palmitoyltransferase 1A, which plays a critical role in carnitine-dependent transport across the mitochondrial membrane during the oxidation of long-chain fatty acids and is involved in several metabolic processes.[107] Moreover, DNA methylation in intron 1 of CPT1A was found to be inversely associated with both waist circumference and BMI, with genetic variations previously linked to obesity. Peroxisome proliferator-

activated receptors (PPARs) are a family of ligand-responsive nuclear receptors, consisting of three members that can be activated by endogenous ligands such as fatty acids and their metabolites.[108] Upon ligand binding, PPARs form heterodimers with retinoid X receptors and bind to specific DNA response elements (PPRE) to regulate gene transcription.[108] Notably, PPAR-γ is predominantly expressed in adipose tissue and is regarded as a master regulator of adipogenesis and lipid metabolism.[109] Several studies have demonstrated the correlation between PPAR-γ and obesity development. For example, PPAR-γ agonists such as rosiglitazone and pioglitazone are clinically used as promising drug targets for managing metabolic diseases.[110,111] Collectively, epigenetic alteration provides an open field for discovery of targets for future prediction and therapeutic concepts in obesity and its related complications.

Immunity Changes

Accumulating evidence suggests that altered metabolic pathways and changes in the local immune microenvironment may drive immune cells to adopt specific metabolic programs through signaling and cellular differentiation (Figure 1). Various metabolic signals, including fatty acids (FAs), oxidized LDL, and ATP, as well as immune response elements, act as disease modifiers, accelerating the progression and complications of obesity. Adipose tissue macrophages(ATMs) are a heterogeneous population classified as M1(CX3CR1lowCCR2+) or M2(CX3CR1highCCR2-) anti-inflammatory phenotype. M2 macrophages are induced by anti-inflammatory cytokines such as IL-4 and IL-13, and secrete high levels of anti-inflammatory mediators like IL-10, IL-1 decoy receptor, and arginase, thereby inhibiting IL-1β and iNOS activity. Consistently, we have previously shown that CX3CL1 is expressed in adipocytes and upregulated in obese human adipose tissue, where it contributes to the adhesion of monocytes to adipocytes and the development of metabolic disorders.[112] Moreover, an M2 phenotypic shift can also be induced by PPARγ activation, a process crucial for maintaining metabolic homeostasis and protecting against M1-mediated inflammation, possibly by promoting lipid storage in adipocytes and preventing lipotoxicity and adipocyte death.[113]

B cells exhibiting increased expression of the transcription factor T-bet are present in the adipose tissues of obese humans. These T-bet+ B cells secrete pro-inflammatory cytokines and pathogenic antibodies, thereby exacerbating metabolic disorders in obesity by presenting antigens to T cells.[114] In the early stages of obesity, there is an increase in the number of immunoglobulin G (IgG)+ CD19+ B cells in VAT, reflecting the accumulation of class-switched, mature B cells in obese adipose tissue.[115] Furthermore, IgG produced by B cells facilitates the clearance of apoptotic and necrotic debris through antibody-mediated complement fixation, which enhances macrophage phagocytosis and may modulate adipose tissue inflammation by influencing immune cell activity.[116] Conversely, B cell deficiency results in a reduction of M1 macrophages and CD8+ T cell-mediated IFN-γ expression in VAT, which leads to improved glucose tolerance in obesity.[117] In an in vitro experiment using macrophages from adipose tissue, Nishimura et al demonstrated that CD8+ T cells infiltrated the adipose tissue of mice on high-fat diets prior to the accumulation of M1 macrophages. Additionally, a 2014 murine study revealed that depletion of CD8+ T cells using antibodies improved the inflammatory profile and enhanced insulin/glucose sensitivity, suggesting that cytotoxic T cells may serve as potential therapeutic targets in obesity and insulin resistance.[118] In line with this observation, CD4+ T cell reconstitution studies in lymphocyte-free DIO mice revealed that T cells predominantly impact glucose homeostasis by improving glucose tolerance, enhancing insulin sensitivity, and reducing weight gain.

Prevention and Treatment Strategies for Primary Obesity

Lifestyle Modifications

Lifestyle modifications aimed at reducing body weight and fat mass are recommended as the primary treatment for obesity.[119] Generally, lifestyle interventions, including physical exercise and dietary changes, exert their effects by decreasing energy intake (through diet) and increasing energy expenditure (through physical activity) (Figure 2). The Obesity Guidelines recommend that individuals who are overweight (BMI 25.0–29.9 kg/m²) or obese (BMI ≥30 kg/m²), and who would benefit from weight loss, should be advised to engage in a comprehensive lifestyle intervention for at least six months.[120] Various dietary strategies have been proposed to promote weight loss, though the optimal macronutrient composition for obesity treatment remains to be determined. Overweight and obese individuals enrolled in

Figure 2 Treatment path for obese patients. In the absence of severe metabolic comorbidities, initial obesity management focuses on lifestyle interventions, including dietary modifications, physical activity, psychological support, and sleep optimization. Pharmacological therapies may be utilized as adjuncts to enhance weight loss when necessary. In patients with metabolic disorders, early consideration of metabolic surgery is warranted. If non-invasive approaches achieve sufficient weight loss, long-term adherence to lifestyle modifications is crucial. However, if conservative treatments fail, bariatric procedures, such as sleeve gastrectomy, may be performed, with Roux-en-Y gastric bypass as a subsequent option if needed. Post-surgical care requires lifelong monitoring and supplementation of vitamins and trace elements, with potential risks including dumping syndrome, internal hernia, and anastomotic leakage.

lifestyle-modification programs are frequently advised to follow a low-fat diet (ie, <30% of total calories from fat), which emphasizes the consumption of vegetables, fruits, and whole grains, and provides between 1,500 to 2,000 kcal per day.[121,122] In line with the US Department of Agriculture's recommendations, this diet typically promotes a weight loss of one to two pounds per week.[123] Meanwhile, physical exercise is another central component of lifestyle modification, particularly for targeting excess visceral adipose tissue. Physical activity alone (without reduced energy intake) offers limited benefits in decreasing body weight and fat mass, which can be disappointing and counterintuitive for individuals who often believe that significant weight loss can be achieved solely through high levels of physical activity without any dietary adjustments.[124]

The Obesity Guidelines recommend that obese patients follow a diet designed to induce a daily energy deficit of 500–750 kcal, leading to a weight reduction of approximately 0.5–1.0 kg per week. These guidelines acknowledge the benefits of evidence-based dietary approaches that restrict the intake of specific macronutrients to achieve an energy deficit.[125] Long-term adherence to the Mediterranean diet, which is rich in monounsaturated fatty acids, fiber, antioxidants, and glutathione, has been shown to reduce the risk of obesity, T2DM, and coronary heart disease, as well as lower cardiovascular mortality. Moreover, the Mediterranean diet has demonstrated superior efficacy in weight loss compared

to several other dietary approaches, such as the Zone, Ornish, or LEARN diets.[126] Similarly, another study reported that a 12-month dietary intervention resulted in moderate weight loss among non-diabetic overweight and obese patients, accompanied by a significant reduction in pro-inflammatory cytokines and adipokines.[127] The long-term benefits of physical activity for successful weight management have been well-documented in numerous studies. A randomized controlled trial (RCT) lasting nearly two years investigated the efficacy of higher levels of physical activity for sustained weight loss. The study found that obese individuals prescribed a higher level of physical activity (2,500 kcal/week) maintained their weight loss significantly better at 18 months compared to those with an energy expenditure goal of only 1,000 kcal/week.[128] Data from the National Weight Control Registry also indicate that overweight patients who successfully lose substantial amounts of weight and maintain their weight loss typically follow a reduced-calorie diet (~1,400 kcal/day) that is high in carbohydrates but low in fat while engaging in high levels of physical activity.[129] Furthermore, multiple observational studies have reported beneficial effects of high levels of physical activity (eg, 200–300 minutes per week) on weight maintenance and metabolic health.[130,131] Nevertheless, the optimal composition and dosage of lifestyle interventions remain inadequately defined, partly due to the lack of systematic reviews and meta-analyses capable of identifying the most effective treatment strategies. In general, the most critical factor for successful obesity treatment is the creation of an energy deficit to reduce excess visceral fat, regardless of the specific dietary or exercise regimen adopted.

Pharmacotherapy

Although lifestyle intervention is typically the first line of treatment for obesity, its effects often fail or are short-lived, leaving pharmacotherapy or surgical techniques as feasible alternatives (Figure 2). In 2021, the US Food and Drug Administration (FDA) approved five medications for long-term weight management in adults with a BMI ≥30 or ≥27 with comorbid conditions. These include appetite suppressants such as pancreatic lipase inhibitors (orlistat), noradrenergic drugs (phentermine/topiramate and naltrexone/bupropion), and glucagon-like peptide-1 receptor (GLP-1R) agonists (liraglutide and semaglutide).[132,133] According to US and EU guidelines, anti-obesity medications are recommended for adults who are unable to achieve or sustain weight loss with comprehensive lifestyle modifications and who have either a BMI ≥30 or ≥27 kg/m² with one or more obesity-related comorbidities.[120,134]

Orlistat (tetrahydrolipstatin) is an oral treatment for obesity and obesity-related conditions approved by the National Institute for Health and Care Excellence (NICE) in the UK. It induces weight loss by inhibiting pancreatic and gastric lipases, preventing the hydrolysis of absorbable free fatty acids and monoglycerides from dietary triglycerides.[135] Orlistat is typically administered in doses of 30, 60, 120, and 240 mg, three times daily before meals in clinical trials, leading to approximately a 30% reduction in systemic dietary fat absorption.[136] Notably, since Orlistat acts locally in the wall of the gastrointestinal tract, absorption is neither required nor related to its effectiveness as a weight-reducing agent. Consequently, undigested triglycerides are excreted in the feces. When combined with diet and behavior modifications, Orlistat results in a significant reduction in body weight compared to placebo and induces modest improvements in blood pressure, glucose control, and lipid profiles.[137] Although side effects (eg, flatulence, oily stools, abdominal pain) occur regularly, and the achievable weight loss is moderate, Orlistat remains the safest and only drug available for obesity treatment in adolescents.[138] In contrast, Naltrexone/bupropion is an investigational combination therapy for weight loss and maintenance, working by suppressing appetite in patients who are obese (BMI ≥30 kg/m²) or have a BMI of ≥27 kg/m². Bupropion increases the concentration of pro-opiomelanocortin (POMC) neuropeptides to decrease appetite, while Naltrexone further enhances the efficacy of melanocortin stimulation with bupropion by preventing β-endorphin-mediated autoinhibition of hypothalamic POMC neurons.[139] Overall, Bupropion/Naltrexone not only promotes weight reduction but also leads to significant improvements in several cardiometabolic risk factors, including waist circumference, triglycerides, insulin sensitivity, and reduced blood pressure.[140] Pooled results from four Phase 3 trials show that the placebo-subtracted proportion of individuals achieving ≥5% weight loss with Naltrexone/bupropion ranged from 26% to 33%.[141]

Analogs of the incretin hormone, glucagon-like peptide-1 (GLP-1), are secreted from the upper gastrointestinal tract in response to carbohydrate and fat digestion and induce satiety.[142] Liraglutide is a long-acting GLP-1 receptor agonist that works by binding to the GLP-1 receptor and directly stimulating hypothalamic receptors, thereby inducing satiety

and reducing food intake.[143] Additionally, Liraglutide can slow gastric emptying after meals and balance the secretion of insulin and glucagon to reduce the risk of cardiovascular disease, as well as reduce body weight and visceral adiposity.[144] A dose of up to 3.0 mg of liraglutide was first recommended in December 2014 for obesity treatment in the United States, while a lower dose of 1.8 mg is approved for second-line treatment of T2DM.[145] In a study conducted in Canada, it was found that the maintenance dose of liraglutide (3.0 mg) was typically administered for an average of only 2–2.5 months, regardless of the amount of weight loss.[146] For individuals with a BMI of 30 kg/m² or at least 27 kg/m², liraglutide is recommended as an adjunct to a reduced-calorie diet and increased physical activity for weight loss.[147] Beyond being an appetite suppressant, Liraglutide has recently been explored for its potential to induce visceral fat loss in humans. A randomized, double-blind, Phase 4, single-center trial reported that once-daily subcutaneous liraglutide 3.0 mg significantly reduced VAT after 40 weeks of treatment in patients with a BMI of at least 30 kg/m² or at least 27 kg/m² with metabolic syndrome but without diabetes.[144] These findings underscore that Liraglutide is not only an effective anti-obesity treatment but also has significant potential in addressing visceral fat, thereby alleviating obesity and its associated comorbidities. However, further comprehensive research, particularly clinical trials, is needed to clarify the effectiveness of directly targeting visceral fat in combating obesity.

Another new medication, Semaglutide, was initially approved for the treatment of T2DM and chronic weight management in individuals with overweight or obesity.[148] Similar to Liraglutide, Semaglutide is also a human GLP-1 receptor agonist (GLP-1 RA) that can be used for obesity and obesity-related genetic disorders, including Bardet-Biedl Syndrome and Alström Syndrome.[149] More specifically, Semaglutide reduces caloric intake by inhibiting gastric emptying and affecting appetite, and also lowers glucose levels by reducing fasting and postprandial glucagon levels.[150] When compared with a placebo, weight loss induced by Semaglutide was closely related to clinically meaningful improvements in several cardiometabolic risk factors, including glycated hemoglobin, waist circumference, and both systolic and diastolic blood pressure, as well as benefits to physical and emotional quality of life.[151] Notably, a double-blind, double-dummy, phase 3 superiority study by Davies et al demonstrated that Semaglutide 2.4 mg once a week achieved a superior and clinically meaningful decrease in body weight for obese diabetic participants, compared to a 3.4% reduction in the placebo group.[152] Recent pharmacotherapeutic advances include tirzepatide, a novel dual GLP-1/GIP receptor agonist that has demonstrated superior efficacy in clinical trials. In the SURMOUNT-1 trial, tirzepatide achieved up to 22.5% weight reduction and significant metabolic improvements compared to selective GLP-1 receptor agonists.[153] Its dual receptor agonism exerts complementary effects through both central (appetite suppression via hypothalamic action) and peripheral (enhanced insulin sensitivity in adipose and muscle tissue) mechanisms, positioning it as a particularly promising therapeutic option for obesity with metabolic comorbidities.

During obesity, there is a marked expansion of VAT, accompanied by alterations in the adipocytes themselves, their supporting matrix, and immune cell infiltrates, leading to morphological and inflammatory changes in VAT. These changes contribute to obesity, which lies at the core of metabolic syndrome and increases the risk of obesity and its comorbidities. A polycation-based nanomedicine, polyamidoamine generation 3 (P-G3), is a class of compounds recently developed to selectively target VAT due to its high charge density. Treatment with P-G3 in obese mice inhibits visceral adiposity, increases energy expenditure, prevents obesity, and alleviates associated metabolic dysfunctions.[154] Moreover, a four-week treatment of diet-induced obese (DIO) mice with established obesity resulted in a leaner phenotype, with a 15% reduction in body weight despite continuous high-fat diet (HFD) feeding.[154] The observed reduction in the size of adipose tissue depots, whether from de novo adipocyte formation or in mature adipocytes, highlights the clinical potential of visceral fat remodeling through P-G3 treatment. Considering that P-G3 targets visceral fat distribution by blocking lipid synthesis in adipocytes and by modifying P-G3 with cholesterol to form lipophilic nanoparticles, it is gradually emerging as a promising therapeutic strategy for counteracting obesity and its related metabolic syndromes.

Metabolic Bariatric Surgery

MBS is regarded as the most effective treatment option for obesity and its associated comorbidities, offering rapid and sustainable weight loss with significantly improved clinical outcomes[155] (Figure 2). The 2022 ASMBS/IFSO guidelines[156] have updated the indications for MBS, now recommending consideration for patients with either: (1) BMI ≥35 kg/m² regardless of comorbidities, or (2) BMI ≥30 kg/m² when accompanied by at least one obesity-related

comorbidity (eg, type 2 diabetes, hypertension, or obstructive sleep apnea). Three common procedures include SG, OAG, and RYGB, which are restrictive and malabsorptive surgical techniques that significantly reduce the morbidity and mortality associated with obesity.[157] In a large prospective study by Suliman et al, patients who underwent RYGB experienced significantly more weight loss than those who underwent SG (5.6% vs 3.3%, P=0.025).[158] However, MBS must be considered alongside the risks associated with surgery, including weight rebound, morbidity/mortality, potential nutritional deficiencies, and the need for lifelong support and medical monitoring.

Recently, a growing body of studies with long-term follow-up has highlighted the high effectiveness of MBS for individuals suffering from obesity and its related comorbidities. The surgical techniques involved in bariatric interventions are varied and encompass different procedures. For instance, RYGB significantly improves glycemic control, insulin sensitivity, and reduces mean adipocyte size in patients with severe T2DM as early as 4 weeks after surgery,[159] while SG is associated with improved plasma lipid profiles, including reduced total cholesterol and triglyceride levels.[160] When the duodenum is bypassed, there is also a reduction in ghrelin levels and an increase in GLP-1 and peptide tyrosine-tyrosine (PYY), which improves insulin sensitivity as well as other metabolic parameters. Similarly, two recently published meta-analyses of studies following patients for up to 5 years also showed favorable glycemic control in patients with type 2 diabetes after MBS.[161,162] Furthermore, in cases of severe obesity, undergoing such surgical interventions also reduces overall mortality.[163] A comprehensive systematic literature review reported that metabolic surgeries were associated with nearly a 50% lower risk of death from any cause compared to nonsurgical treatments.[164] It is noteworthy that, despite the clear benefits of metabolic bariatric surgery, the increased risks during surgery must also be considered. Malnutrition after metabolic bariatric surgery, though rare, is a potentially life-threatening complication, often accompanied by significant vitamin and nutrient deficiencies. This necessitates lifelong monitoring of micronutrient levels at specialized bariatric centers, as well as frequent supplementation of vitamins and nutrients. Furthermore, anastomotic leaks after metabolic bariatric surgery can potentially lead to peritonitis, with a recent prevalence ranging from 0.8% to 1.5%.[165] Post-bariatric hypoglycemia (PBH) represents a well-documented long-term complication of RYGB, affecting 10–30% of patients. PBH typically presents with neuroglycopenic symptoms including confusion and syncope, resulting from paradoxical hyperinsulinemia mediated by β-cell hyperplasia and enhanced GLP-1 secretion. A 2023 prospective cohort study (n=1,240) established preoperative insulin resistance (HOMA-IR ≥3.8) and rapid weight loss (>15% TBWL in 3 months) as independent predictors of PBH development.[166]

Conclusions

The alarmingly rising prevalence of obesity and its associated complication is undoubtedly one of the greatest challenges facing today's health services, and well-defined programs as well as intersectoral actions are required urgently to to reverse current trends. Moreover, immediate attention must be given to understanding the signaling mechanisms and interactions between obesity and its comorbidities in order to address this complex disease and alleviate the global healthcare burden. By unraveling the cellular and molecular signaling networks, and gaining a deeper understanding of the crosstalk between obesity and the signaling pathways involved in its complications, we can move toward precision medicine in the fight against obesity and its associated comorbidities. Despite considerable progress in understanding the etiology and pathophysiology of obesity, our evolving knowledge of obesity pathogenesis and personalized therapies remains insufficient. In conclusion, while progress is being made, extensive studies targeting obesity still face challenges. A comprehensive elucidation of the mechanisms underlying obesity pathogenesis, alongside the development of efficient therapeutic strategies, is critical for achieving precision obesity treatment in the future.

Data Sharing Statement

No data was used for the research described in the article.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that there are no conflicts of interest for this work.

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