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REVIEW

Obesity as a Chronic Disease: A Narrative Review of Evolving Definitions, Management Strategies, and Cardiometabolic Prioritization

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ABSTRACT

Obesity is a multifactorial, complex disease that is driven by genetic, biological, environmental, and behavioral factors. In this review, we explain the key contributors to obesity, limitations in current definitions, its relationship with cardiometabolic health, and recent advancements in treatment. Obesity is characterized by the presence of excess and dysfunctional adipose tissue, driven by chronic inflammation and maladaptive energy homeostasis. Although body mass index (BMI) has historically been used to diagnose obesity, BMI provides a limited evaluation of individual patients because it fails to specifically quantify adiposity, which is the primary determinant of metabolic impact in these patients. There is an ongoing and necessary shift in treating obesity with a weight-inclusive approach that aims to address obesity upstream and prevent downstream cardiometabolic health complications. This approach is being supported by various treatment options, notably glucagon-like peptide-1 receptor agonists like semaglutide and tirzepatide, that also have promising effects on cardiovascular, renal, and liver health. Advances in precision medicine, gut microbiome research, and Multi-target therapies support personalized therapeutic approach. Despite these developments, less than 25% of individuals living with obesity are receiving evidence-based treatment. There is an urgent need to improve health care delivery to patients with obesity through timely, affordable, and multimodal treatments that promote sustainable and sustained weight loss. Increasing board certification of practicing physicians through the American Board of Obesity Medicine will be critical to improving access and quality of care.

Keywords: BMI; Cardiometabolic Health; GLP-1 RA; GIP; Obesity; Weight management

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Key Summary Points

Obesity is a chronic disease of dysfunctional adipose tissue that is driven by the dysregulation of energy homeostasis and chronic low-grade inflammation.

Body mass index, while commonly used, provides a limited evaluation of obesity and there is an ongoing push to use anthropometric measurements like waist circumference that can more specifically identify excess adiposity.

Weight-inclusive approaches to treat individuals living with obesity aim to treat upstream drivers of obesity and prevent downstream cardiometabolic health complications.

The development of pharmacological treatments like glucagon-like peptide-1 receptor agonists are transforming obesity care through their substantial and sustained weight loss and many cardiometabolic health benefits.

Future directions for obesity management may include phenotyping to provided individualized dietary, lifestyle, pharmacological, and surgical treatment strategies.

INTRODUCTION

Obesity, characterized by excess adiposity, affects 890 million adults and 160 million children worldwide [1]. By 2035, an estimated 51% of the global population will be living with overweight or obesity [2]. According to the 2021–2023 National Health and Nutrition Examination Survey (NHANES), 40.3% of adults in the United States are living with obesity with the highest prevalence in adults aged 40–59 years [3]. Childhood obesity is regarded as a major public health crisis nationally and internationally, as 37 million children aged than 5 years old and 340 million children aged 5–19 are considered overweight or obesity with 1 billion more at risk [1, 4]. It is also well known that obesity has long-term complications, and increases the risk for hypertension (HTN), type 2 diabetes (T2DM), coronary artery disease (CAD), stroke, and numerous cancers. Given the rising prevalence of obesity, a comprehensive understanding of its impact on individual, public, and global health is critical. This review examines obesity as a chronic disease, explores factors contributing to its prevalence and cardiometabolic consequences, with a focus on T2DM, and summarizes evolving treatment strategies. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

DEFINITIONS OF OBESITY

The National Institutes of Health and World Health Organization define obesity as a BMI ≥ 30 [3]. However, BMI has many limitations and provides a limited direct association with metabolic health on an individual basis [5]. Lean muscle mass is denser than adipose tissue, so more muscular patients may have an elevated BMI and frail patients with reduced lean body mass may be misclassified with a healthy BMI despite relative excess adiposity [6]. Visceral fat, or adipose tissue surrounding internal organs, is a known determinant of metabolic risk and has stronger associations with all-cause and cardiovascular disease (CVD) mortality than total body fat alone; however, BMI cannot subdivide between subcutaneous and visceral fat distributions [4]. Thus, prior research in the National Health and Nutrition Examination Study (NHANES) showed that 29% of Patients with BMI in the obesity range were metabolically healthy, whereas 30% of patients in the normal BMI range were metabolically unhealthy [7]. Lastly, BMI-based definitions typically do not account for age, sex, and race/ethnicity and do not inform providers about the origin or heterogeneity of obesity [6, 8].

Due to BMI's limitations, there has been a push towards redefining obesity, for example through assessment of anthropometric measurements, like waist circumference (WC) and waist-to-hip ratio (WHR) [9]. WC and WHR quantify

abdominal-specific adiposity, which has a stronger association with CVD, HTN, and T2DM than BMI [10–12]. Additional methods like body round index, dual energy x-ray absorptiometry, air displacement plethysmography, and bioelectric impedance can more accurately quantify body fat distribution, but they are impractical in daily clinical settings [8, 13]. Given these limitations, BMI is still widely used to define obesity, but recent guidelines suggest including measurements like WC in primary care settings to distinguish between patients with clinical versus pre-clinical obesity (e.g., with and without end organ injury), which will help guide patients towards treatment pathways that are more appropriate for their metabolic status [14].

MECHANISMS OF OBESITY

The American Medical Association and other health organizations classified obesity as a disease in 2013 [15]. Obesity is a chronic disease of adiposopathy, or dysfunctional adipose tissue. It is driven by chronic low-grade inflammation and dysregulated energy homeostasis, including oxidative stress, mitochondrial dysfunction, immune dysfunction, and metabolic dysfunction [16–18]. Like other chronic diseases, obesity has a Multifactorial pathophysiology that includes complex genetic, biological, environmental, and behavioral interactions. Twin, family, and adoption studies estimate that obesity is 40–70% hereditary [13, 19, 20]. Over 20 genes drive monogenic inheritance and many of these genes influence central nervous system (CNS) pathways that control food intake [20, 21]. Analyses from 60 genome-wide association studies have shown that more than 1100 genetic loci variants interact with the environment to promote polygenic obesity through the CNS [19, 21]. While most genes in monogenic obesity are expressed in the hypothalamus and control appetite, polygenic obesity involves the hippocampus and limbic system, which are involved in learning, cognition, and emotion, and the substantia nigra and insula, which are related to addiction and reward [19, 21–23]. These findings may help explain why 80% [24] Patients with obesity who lose weight regain 50% of that weight within 1 year [25, 26]. This process is believed to be driven by "anti-starvation" mechanisms noted in individuals living with obesity and can persist after attainment of a lower BMI [25, 26]. Monogenic and polygenic mechanisms result in lower energy expenditure, imbalance of hunger-related hormones, and reduced activation of dopaminergic pathways that can influence weight re-gain [25, 26]. A patient's environment also promotes the development of obesity. NHANES studies demonstrate a higher prevalence of obesity among low income and less educated patients from historically underserved communities [27]. These findings follow previous research that have shown how well-built physical environments such as improved neighborhood walkability and recreational facility access may improve obesity rates, [28, 29] while residential segregation, food insecurity, and poor housing quality may increase obesity [28–31]. Increased stress from such socioeconomic inequality can also lead to elevated cortisol and catecholamines that can limit lipolysis [32–34]. Overall, redefining obesity as a formal disease with significant environmental and social contributors represented a significant step towards the development of evidence-based and appropriate medical therapy.

WEIGHT-CENTRIC VERSUS WEIGHT-INCLUSIVE OBESITY PARADIGMS

Historically, care around obesity has followed a "weight-centric" model of obesity: body size can be altered primarily through diet and exercise, and weight is solely responsible for the diseases associated with obesity, [35] viewing lower body weight as inherently healthier [35, 36]. While it is well-established that individuals with obesity, especially visceral obesity, have an increased risk for all-cause mortality and CVD, [37–39] this weight-centric paradigm can worsen weight stigmatization. Social rejection and devaluation based on body weight and shape can then lead to weight-based discrimination in the workplace,

education, home, and healthcare settings [40, 41]. Due to such weight-based stigma, patients may not seek timely care and present with more advanced forms of disease [35] and experience excess physiological and psychological stress [14, 42–46]. Thus, there has been a push towards adopting a "weight-inclusive" treatment approach because it focuses less on weight loss and more on overall health, non-restrictive eating patterns, and body acceptance [35, 36]. Through this model, providers can treat patients more holistically and provide treatment plans that address obesity-related conditions and not just weight.

INTERPLAY OF OBESITY AND CARDIOMETABOLIC HEALTH

The relationship between obesity, cardiometabolic health, and CVD is well established (Fig. 1). Cardiometabolic disease in obesity is typically driven by hypertrophy of visceral adipose tissue (VAT), [47, 48] which is associated with insulin resistance, hyperinsulinemia, glucose intolerance, atherogenic dyslipidemia, and chronic inflammation [11, 48–57]. These effects drive increased blood pressure and atherosclerosis, but also directly impact the heart. VAT and ectopic fat in the pericardium and epicardium result in increased circulating blood volumes and chronic inflammation, resulting in concentric left ventricular remodeling and increased risk of cardiomyopathy, particularly with heart failure with preserved ejection fraction (HFpEF) [58–62]. Arrhythmia is also increased, believed to be related to ectopic myocardial fat deposition that disrupts standard conduction patterns, [63] resulting in a 50% increased prevalence of atrial fibrillation, [64, 65] and increased risk of sudden cardiac death [11, 61, 66–70]. Ectopic adipose tissue deposits in organs like the liver, heart, kidney, pancreas, and skeletal muscle also alter cardiometabolic profile and contribute to CVD [48, 71]. A notable example is metabolic dysfunction-associated steatotic liver disease (MASLD), related to hepatic steatosis in the presence of metabolic disease, and is an independent risk factor for CVD [72]. Obesity is also an independent risk factor for the development and progression of chronic kidney disease, and this is driven by obesity-related hyperfiltration and structural changes due to higher levels of inflammation [73]. Furthermore, obesity is a recognized risk factor for the development of T2DM. There is a ~ 90% overlap between patients with T2DM and overweight or obesity, and obesity accelerates T2DM complication rates [48, 74, 75]. The complications of T2DM, particularly diabetic nephropathy and CVD, significantly contribute to obesity-related mortality [76, 77]. Thus, these manifestations of end-organ injury create pathological feedback loops which exacerbate other cardiometabolic changes associated with obesity, increasing development of other risk factors and CVD events [11, 72].

DRIVERS OF MORTALITY

Obesity is a significant risk factor for heart disease and cancer. In 2015, nearly 3 million CVD-related deaths occurred among patients with obesity [78]. Obesity directly contributes to numerous cancers and excess body fat is associated with a 17% increased risk for cancer-specific mortality; the percent of cancer cases related to obesity vary according to the underlying cancer [79]. Interestingly, there is a U-shaped association between BMI and all-cause mortality from cancer and CVD, with lowest mortality in BMI range of 25–30 kg/m [39]. Obesity-related all-cause mortality rates have disproportionate effects, and are nearly twice as high for women compared to men, and highest for Black non-Hispanic adults [80]. On the other hand, obesity-associated CVD mortality rates were greater among men and patients living in rural settings, except among Black individuals who have higher age-adjusted mortality rates in urban settings [81]. Given the significant health impacts, early intervention and treatment of obesity at an individual and population level is critical to reduce downstream drivers of mortality.

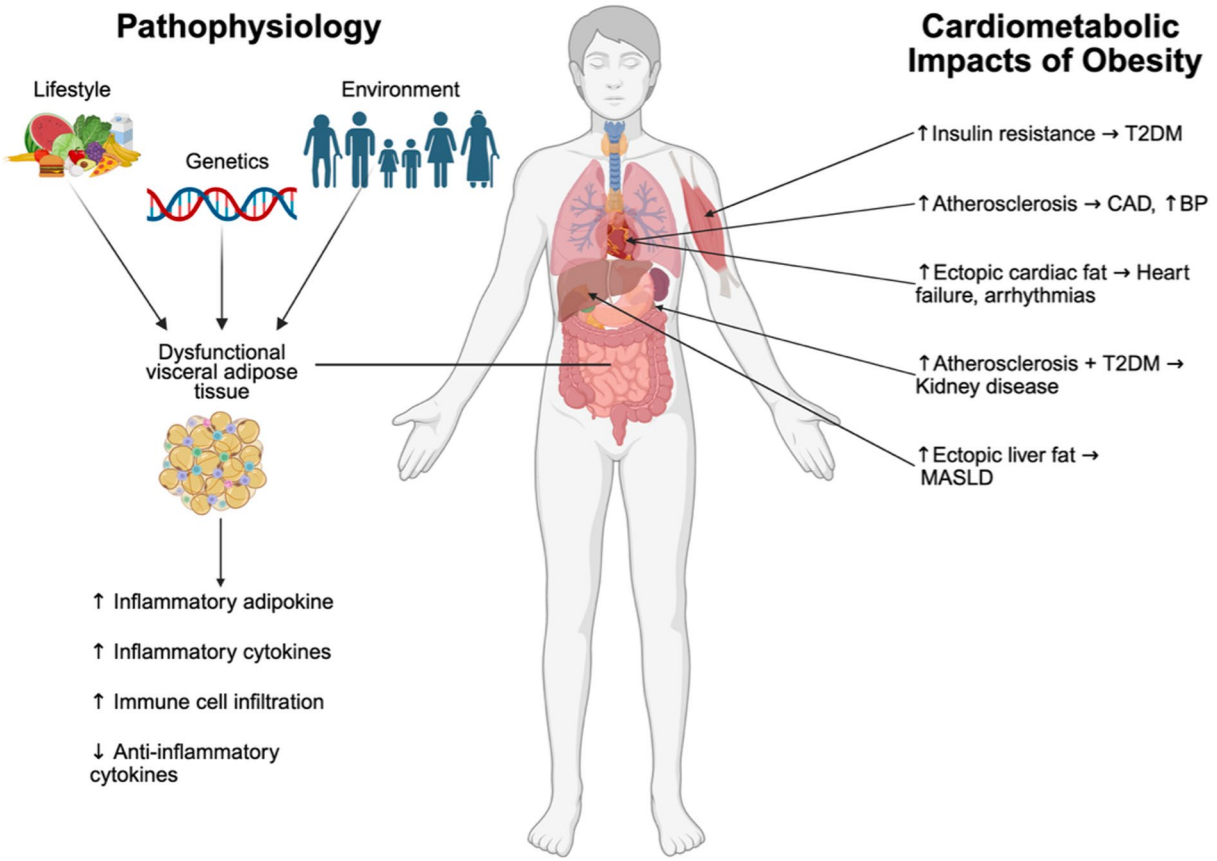

Fig. 1 The cardiometabolic effects of obesity. Obesity is a chronic disease of dysfunctional adipose tissue and chronic low-grade inflammation that is driven by genetic, biological, environmental, and behavioral factors. *BP* blood pressure, *CAD* coronary artery disease, *MASLD* metabolic dysfunction-associated steatotic liver disease, *T2DM* type 2 diabetes mellitus. Created in BioRender. Singh, V. (2025) https://BioRender.com/qb8zn98

OBESITY THERAPIES ARE CURRENTLY UNDERUTILIZED

Despite numerous medical and surgical treatment options, only 4% of individuals living with obesity are prescribed obesity management medications (OMM) [82], 0.1–2% of bariatric surgical candidates undergo surgery worldwide [83], and less than 25% of individuals living with obesity receive evidence-based treatment [84]. It has been shown that intensive lifestyle interventions and behavioral therapy can help with weight loss between 5 and 10%, but OMMs have been proven to lead to weight loss up to 25% and surgery procedures between 25 and 30% [85]. Total body weight loss of 5–10% is clinically meaningful and can reduce the risk of T2DM, decrease cardiovascular mortality, and improve metabolic profiles [86]. According to 2015 Endocrine Society Guidelines, diet, exercise, and behavioral therapy should be a part of all obesity management approaches; [87] however, for the majority of individuals living with obesity, lifestyle modification alone is inadequate. According to current guidelines, patients with a BMI ≥ 27 kg/m^2 with one or more weight related medical condition (i.e., HTN, T2DM) or BMI ≥ 30 kg/m^2 are candidates for obesity pharmacotherapy. Patients with a BMI ≥ 30 kg/m^2 with metabolic disease (i.e., T2DM), BMI ≥ 30 kg/m^2 and unsubstantial weight loss with nonsurgical methods, or BMI ≥ 35 kg/m^2 are candidates for bariatric surgery [88, 89].

OBESITY THERAPIES

Current obesity treatments, including lifestyle modification, pharmacotherapy, and procedural and surgical interventions are discussed below, with greater detail on pharmacologic interventions as these therapies represent a paradigm shift in the treatment of obesity as a chronic, cardiometabolically-driven disease.

Lifestyle Modification

Lifestyle modifications include dietary changes, physical activity, and behavioral change. About a 500–750 kcal/day deficit and 150–180 min of aerobic exercise per week can lead to mean weight loss of 0.5–0.75 kg per week [90]. These lifestyle modifications can also be paired with intensive behavioral therapy, which utilizes motivational interviewing to identify individualized self-monitoring tools for continued weight loss [90]. In the short term, high-intensity lifestyle interventions led to weight loss of ≥ 5% body weight in 35.5% and 58% of participants in the Diabetes Prevention Program and Look AHEAD trial, respectively [91–93]. However, individuals regained a mean one-third of their lost weight in the year following lifestyle interventions [94]. Thus, lifestyle interventions are frequently an adjunct to obesity pharmacotherapy, which may obtain more significant health improvements.

First Generation Obesity Management Medications

Phentermine was the first obesity medication approved in 1959 for short-term use (≤ 3 months), working by increasing the release of norepinephrine in the hypothalamus to decrease food intake (Table 1) [95]. A 6-month randomized controlled trial (RCT) using 7.5 mg and 15 mg phentermine resulted in ≥ 5% weight loss in 43.3% and 46.2% of participants, respectively, compared to 15.5% in the placebo group [96]. The most associated side effects with phentermine were xerostomia, insomnia, headaches, and constipation that were shown to improve with dose reduction [95]. The combination drug of phentermine–topiramate was approved in 2012, and the addition of topiramate provides GABA-receptor augmentation to further reduce appetite and increase satiety [97–99]. Initial placebo-controlled RCTs tested 7.5 mg/46 mg or 15 mg/72 mg phentermine–topiramate over 56 weeks [97]. While 21% of patients on placebo achieved ≥ 5% weight loss, 62% on 7.5 mg/46 mg and 70% on 15 mg/72 mg achieved similar weight loss by the end of the trial [97]. The most commonly associated side effects with the medication were paresthesia, dry mouth, constipation, and dysgeusia, and nervous system-related adverse events increased at higher doses [95].

Naltrexone–bupropion is another centrally acting agent that was approved for weight loss in 2014, which stimulates neurons in the hypothalamus to reduce food intake and increase energy expenditure [95, 100]. In an RCT of placebo, 32 mg/360 mg, or 16 mg/360 mg naltrexone/bupropion, 6%, 39%, and 48% of participants, respectively, achieved ≥ 5% weight loss over 56 weeks [101]. Interestingly, participants receiving naltrexone–bupropion had a transient increase in mean BP that eventually reduced below baseline, and follow-up studies have not determined if naltrexone–bupropion worsens CVD outcomes [101, 102]. The most common adverse events were nausea, constipation, headache, vomiting, dizziness, insomnia, and dry mouth [95].

Orlistat is an intra-gastrointestinal agent that was approved for weight loss in 1999, and it deactivates lipases that facilitate fat absorption, blocking absorption of 30% of dietary fat [95]. While a large trial of 3305 participants with BMI ≥ 30 kg/m^2 demonstrated ≥ 5% weight loss in 72.8% of Patients compared to 45.1% on placebo, [103] due to prominent adverse effects, including fecal urgency and steatorrhea, orlistat is not widely recommended for weight loss [104].

Table 1 Summary of the Food and Drug Administration (FDA)-approved pharmacotherapy for the treatment of obesity

OMM Class	Generic name	Brand name	Mechanism of action	Clinical trial	Recommended dose (s)	Mean weight loss compared to placebo at ≥ 1 year (%)	Common adverse events
Centrally acting medications	Phentermine	Lomaira (PO) Adipex (PO)	Increased norepinephrine (NER) release in the central nervous system (CNS) to decrease food intake	[96]	15 mg or 30 mg PO QD 8 mg PO TID	Not available[a]	Xerostomia, insomnia, headaches, and constipation
	Phentermine–topiramate	Qsymia (PO)	Increased NER release in the CNS to decrease food intake, GABA-receptor augmentation to reduce appetite and increase satiety	CONQUER [97], SEQUEL [98], EQUIP [99]	Dose escalation: 3.76 mg phentermine/23 mg topirmate PO QD, 7.5/46 mg PO QD, 11.25/69 mg PO QD, and titrate up-to max. dose of 15 mg/92 mg PO QD	5.1% on 3.7/23 mg and 10.9% on 15/92 mg [98]	Paresthesia, dry mouth, constipation, and dysgeusia
	Naltrexone–bupropion	Contrave (PO)	Decreased NER reuptake to reduce food intake and increase energy expenditure	COR-1 [101], COR-BMOD [102], COR-II [100]	Dose escalation: Week 1–8 mg naltrexone/90 mg bupropion PO QD in AM, Week 2–8/90 mg PO BID, Week 3–16/180 mg PO in AM and 8/90 mg in PM, Week 4–16/180 mg BID	6.4% on 32/360 mg [99]	Headache, constipation, nausea, vomiting, dizziness, insomnia, dry mouth
Intragastrointestinal medications	Orlistat	Xenical (PO) Ali (PO)	Lipase inhibitor to prevent the breakdown and absorption of fats	XENDOS [103]	60 or 120 mg PO TID with fat-containing meals	10.2% on 120 mg TID [102]	Cramps, flatulence, fecal incontinence, oily spotting

Table 1 continued

OMM Class	Generic name	Brand name	Mechanism of action	Clinical trial	Recommended dose (s)	Mean weight loss compared to placebo at ≥ 1 year (%)	Common adverse events
Glucagon-like peptide-1 receptor agonist (GLP-1RA)	Liraglutide	Saxenda (subQ)	Increase glucose-dependent insulin secretion, decrease glucagon release, and delay gastric emptying	SCALE 1–5 [45, 106–109]	0.6 mg subQ QD and increase dose by 0.6 mg subQ weekly to max dose of 3 mg subQ QD	8% on 3 mg QD [105]	Nausea, vomiting, diarrhea, and constipation
	Semaglutide	Wegovy (subQ)		STEP 1–8 [110–117]	0.25 mg subQ weekly and increase dose at 4-week intervals to max dose of 2.4 mg subQ weekly	14.9% on 2.4 mg [109]	
Glucose-dependent insulinotropic polypeptide (GIP)/GLP-1RA	Tirzepatide	Zepbound (subQ)	GLP-1 activity with enhanced GIP activity increase suppression of appetite in the CNS	SURMOUNT 1–4 [119–122]	2.5 mg weekly and increase dose by 2.5 mg subQ in at least 4-week intervals to max dose of 15 mg subQ weekly	15% on 5 mg, 19.5% on 10 mg, and 20.9% on 15 mg [118]	Nausea, vomiting, diarrhea, and constipation

mg milligrams, *OMM* obesity management medications, *PO* by mouth, *QD* dosed daily, *subQ* subcutaneous, *TID* three times a day

[a]Phentermine is only approved for up to 3 months use

Second-Generation Obesity Management Medications

Glucagon-like peptide-1 (GLP-1) receptor agonists (RA) are emerging as an extremely promising group of OMMs, especially given their effective weight loss with beneficial "off-target" effects on cardiovascular, kidney, and liver outcomes. GLP-1RA medications work by mimicking the effects of the intrinsic hormone GLP-1RA to increase glucose-dependent insulin secretion, decrease glucagon secretion, and delay gastric emptying [105]. GLP-1RAs also have activity on the brainstem, hypothalamus, and reward centers of the brain to decrease food intake, diminish cravings, and increase satiety [105]. Daily subcutaneous injection of liraglutide was the first approved GLP-1RA in 2014, and its use in the treatment of obesity has been studied in five SCALE trials [45, 106–109]. Across these trials, ~ 60% of treatment participants and ~ 25% of placebo participants lost ≥ 5% of their body weight, with a mean weight loss of 6–8%, with weight losses could sustained over longer therapy [45, 106–109]. Semaglutide was approved in 2021 as a weekly injectable subcutaneous GLP-1RA, and it has demonstrated sustained and clinically significant weight loss in eight STEP trials [110–117]. These studies typically demonstrated not just high rates of achieving clinically meaningful ≥ 5% weight loss (86.4% semaglutide 2.4 mg weekly vs. 31.5% placebo [110]) but also mean weight loss of 9.6–17.4% across multiple studies [110–117]. Common side effects of GLP-1RAs are mainly gastrointestinal, including nausea, vomiting, diarrhea, and constipation [118].

Tirzepatide is a dual GIP and GLP-1 RA. This medication was approved as a weekly subcutaneous injection in 2023 for the treatment of obesity and has been studied through four SURMOUNT RCTs [119–122]. These trials have showed a mean weight loss of 12.8–25.3%, with increasing weight loss at higher doses and longer use, and > 80% of treatment participants losing ≥ 5% of their body weight compared to < 35% on placebo [119–122]. Tirzepatide is also associated with dose-dependent gastrointestinal adverse effects [120].

Endobariatrics

Endobariatric therapies offer a less invasive alternative in the treatment of obesity, employing endoscopic techniques to promote weight loss and improve metabolic health [123]. These interventions address a critical gap in the current obesity care continuum, particularly for patients with a BMI ≥ 30 kg/m^2 who may not qualify for or prefer to avoid surgery. Several FDA-approved options are available, including intragastric balloons (IGBs), the transpyloric shuttle (TPS), aspiration therapy, and endoscopic sleeve gastroplasty (ESG) using the Apollo OverStitch system. However, TPS and aspiration therapy are not commercially available. [124, 125] IGBs are the most common endobariatric intervention practiced. This procedure involves inserting a balloon into the stomach, where it occupies space within the stomach to alter appetite and reduce food intake. This procedure has been associated with ≥ 10% total body weight loss within 6 months [126]. ESG is a minimally invasive procedure that reshapes the stomach by placing sutures along the inner gastric wall. Using a full-thickness, FDA-approved endoscopic suturing system (OverStitch; Apollo Endosurgery, Austin, TX, USA), the front and back walls of the stomach are brought together to significantly reduce its internal volume. This reduction helps Limit food intake, slows gastric emptying, and promotes positive metabolic effects. ESG is associated with a low risk of complications and has been shown to result in a 15–20% total body weight loss at 2 years, with sustained benefits lasting up to 5 years. ESG has low complication rates and reduces total body weight by 15–20% in 2 years with sustainable weight loss for up to 5 years [127, 128]. An alternative to ESG that is under investigation is the Primary Obesity Surgery Endoluminal (POSE) technique that places incisionless sutures along the stomach wall. POSE has low adverse rates and has been associated with 17% total body weight within a year and improvements in metabolic parameters [129]. Lastly, another emerging endoscopic modality is duodenal mucosal resurfacing, which targets the small intestine to reduce nutrient absorption and alter hormone

release, gut microbiome, and neural signal pathways. During the procedure, a catheter is used to circumferentially elevate the duodenal mucosa, followed by hydrothermal ablation. This procedures has been shown to improve glycemic control in patients with T2DM [125, 130]. Endobariatic procedural options are growing but their availability and uptake remains low. This is largely due to persistent barriers, most notably limited provider awareness of the safety and efficacy of these procedures, as well as high costs and restricted insurance coverage [125]. Advancing patient-centered care will require greater integration of promising, minimally invasive treatments that can be tailored to an individual's comorbidities and health goals.

Metabolic and Bariatric Surgery (MBS)

Currently, MBS is the most efficacious obesity treatment available for severe obesity, demonstrating the greatest durability in weight loss and the strongest evidence for inducing remission of T2DM. Patients who undergo MBS may also achieve meaningful improvements in cardiometabolic diseases such as hypertension, dyslipidemia, metabolic dysfunction-associated steatohepatitis (MASH), and microvascular complications of T2DM. Randomized controlled trials have consistently shown that MBS leads to significantly greater short- and mid-term improvements in glycemic control, cardiovascular risk factors, and chronic kidney disease compared with lifestyle and pharmacotherapy treatment. Also, observational and randomized studies have demonstrated that MBS is associated with reduced risks of CVD, certain cancers, and all-cause mortality. These compelling findings have led international diabetes organizations to support MBS as a treatment option for individuals with T2DM and BMI as low as 30.0–34.9 [131]. Despite this, only about 1% of eligible patients in the United States undergo MBS annually [132].

The most common MBS procedures performed in the US are laparoscopic sleeve gastrectomy (LSG) and Roux-en-Y gastric bypass (RYGB). All MBS procedures are commonly performed using a minimally invasive, laparoscopic approach [131], and RYGB has been the traditional 'gold standard' of MBS, involving separating the upper and lower stomach to reduce the size of the upper stomach, so the shortened stomach can be connected to the jejunum, bypassing the duodenum [133]. In contrast, LSG is a simpler procedure, in which 75–85% of the stomach along the greater curvature is removed and reshaped to a narrow, tubular structure [133]. These procedures lead to weight loss through numerous proposed mechanisms, including reduced food intake through neural adaptations, altering levels of hormones like ghrelin and GLP-1, and changing microbiota and bile acids [134, 135]. Following MBS, the body appears to recalibrate its weight "set point" after surgery, defending a lower body weight by an approximately 20–30% reduction [134].

Perioperative mortality rates range from 0.1% to 1.1% and perioperative morbidity ranges from 2 to 20%, depending on procedure type and patient characteristics. Potential post-operative complications after MBS are rare. Early complications include leaks, bleeding, hypoglycemia, vitamin deficiencies, stenosis, and venous thromboembolism. Late complications manifest as gallstones, marginal ulcer, internal hernia, perforation, intussusception, and bleeding [136]. Five-year comparative outcomes suggest that reintervention, hospital admission, and endoscopic procedures are more frequent after RYGB than LSG, though long-term mortality rates do not differ significantly between procedures [131], While RYGB is a more complex procedure than LSG, it may be preferred in patients with poorly controlled gastroesophageal reflux disease and multiple obesity-related comorbidities, especially T2DM [137]. Ten years after LSG and RYGB, 43.5% and 50.7% of patients had sustained weight loss, respectively [138]. However, weight regain occurs in more than 50% and between 26.3% and 76% of patients with RYGB and LSG, respectively, which maybe appropriate to consider adjuvant pharmacotherapy and continued lifestyle support to be utilized in those cases [139, 140].

Ultimately, shared decision-making is essential in determining whether MBS is appropriate, guided by patient-specific factors such as comorbidities and surgical eligibility. However,

major barriers remain, including limited insurance coverage, lack of awareness about MBS, unclear provider roles, and insufficient training and institutional support [131]. Addressing these challenges is critical to advancing more informed, equitable, and patient-centered use of MBS.

OFF-TARGET EFFECTS OF OBESITY MEDICATIONS: GLP-1RAS TO HEART, LIVER, AND KIDNEY

Obesity pharmacotherapy, particularly GLP-1RA and GIP/GLP-1 RA treatments, can not only assist with weight loss in individuals with obesity but they have also been shown to reduce cardiovascular event risk, decrease liver fat and inflammation, and provide kidney protection independent of their original indications for diabetes (Table 2). This has become an area of intensive research, as RCTs have looked at the effect of using liraglutide, semaglutide, and tirzepatide on the reduction of major adverse cardiovascular events [141–147]. While the overall mechanisms independent of improving obesity and cardiometabolic health are poorly understood, GLP-1RA receptors have been reported in the human atria and ventricles, and mice models have shown GLP-1RA receptors in endothelial and vascular smooth muscle cells of blood vessels [148–151]. GLP-1RAs also have anti-inflammatory effects in the cardiovascular system and decrease intestinal lipid absorption which may reduce atherosclerosis [152]. Semaglutide was approved by the FDA in 2024 as the first GLP-1RA to reduce CVD mortality in individuals with overweight and obesity regardless of diabetes status, following the SELECT trial that showed Patients with obesity and preexisting CVD on 2.4 mg semaglutide had lower MACE than placebo (6.5% vs. 8.0%) [143]. Both semaglutide and tirzepatide appear to have benefits in composite cardiovascular outcomes within patients with obesity and HFpEF, although the mechanisms are currently unclear [144, 146, 153].

The beneficial effects of GLP-1RAs on kidney health are believed to be mediated through reduction of oxidative stress, renal inflammation, and glomerular HTN, and indirect effects on HTN, T2DM, obesity, and dyslipidemia [154–156]. RCTs in T2DM of semaglutide and liraglutide have shown reduction in prespecified renal endpoints [157, 158]. This is further supported by a meta-analysis of 11 GLP-1RAs that found GLP-1RA reduced kidney failure, reduction in eGFR by ≥ 50%, or death for kidney failure by 18% compared to placebo [159].

While there are currently no approved GLP-1RA medications for MASLD or MASH, the more advanced and inflammatory stage of MASLD that represents the transition to fibrosis, phase 2 RCTs of liraglutide, semaglutide, and tirzepatide have shown resolution of MASH without worsening of fibrosis [160–162]. More recently, a phase 3 trial in semaglutide has been reported to demonstrate an improvement in steatohepatitis and fibrosis, which would represent a major clinical impact, though the final results have not been published at this time [163]. While body weight loss of at least 10% has shown to improve steatosis, fibrosis, and inflammation in patients with MASH, [164, 165] there may be direct underlying mechanisms of GLP-1RAs in improving MASH which include reductions in steatosis, oxidative stress, and hepatic de novo lipogenesis [159].

CHALLENGES TO THERAPEUTIC ACCESS IN THE UNITED STATES AND ABROAD

Access to obesity treatment is a major challenge in clinical practice, especially with obesity medications that come with limited coverage, high costs, and supply shortages in the US These issues are present worldwide but vary in degree and form. In Western countries, the cost of pharmacotherapy agents is the primary concern [166]. Many of the newer pharmacologic agents cost > US$1000 per month, making it difficult for many patients to afford them long term, as insurance plans may not cover these medicines [167]. In China, over 50% of adults have overweight or obesity, contributing to a rising prevalence of related complications and

Table 2 Summary of the effects of GLP-1RA/GIP agonists on heart, liver, and kidney outcomes

Medication	Mean change in systolic blood pressure (mmHg)	Mean change in LDL-C (%)	Major adverse cardiovascular event (MACE) with GLP-1 RA/GIP, placebo (%, %)[a]	Effect of GLP-1 RA/GIP medication on left ventricular (LV) heart failure	Effect of GLP-1 RA/GIP medication on renal function	Resolution of metabolic dysfunction-associated steatohepatitis (MASH) with GLP-1/GIP, placebo (%, %)[a]
Liraglutide	− 4.2 [106]	− 3 [106]	4.7, 6.0 [141]	LIVE and FIGHT trials did not report significant improvement in LV systolic function with liraglutide versus placebo [142, 145]	LEADER trial showed decreased renal outcomes (HR: 0.78, 95% CI 0.67–0.92) with liraglutide versus placebo [158]	39, 9 [160]
Semaglutide	− 6.2 [110]	Not reported	6.5, 8.0 [143]	STEP-HFpEF trial reported significant improvements in symptoms measured by KCCQ-CSS[b] (between-group difference, 7.8 points; 95% CI 4.8–10.9) and exercise tolerance with semaglutide versus placebo [146]	FLOW trial showed decreased major kidney disease events (HR: 0.76, 95% CI 0.66–0.88) with semaglutide versus placebo [157]	44 (5 mg)/56 (10 mg)/62 (15 mg), 10 [162]
Tirzepatide	− 7.6 [119]	− 8.6 [119]	9.9, 15.3[c] [144]	SUMMIT trial reported significant improvements in KCCQ-CSS (between-group difference, 6.9; 95% CI 3.3–10.6) and exercise tolerance with tirzepatide versus placebo [144]	Not available, ongoing clinical trial TREAURE-CKD	62.9, 34.1[d] [161]

GIP glucose-dependent insulinotropic polypeptide, *GLP-1RA* glucagon-like peptide-1receptor agonist, *LDL-C* low-density lipoprotein cholesterol

[a]There was a statistically significant difference between placebo and GLP-1 RA/GIP treatment groups

[b]Kansas City Cardiomyopathy Questionnaire clinical summary score (*KCCQ-CSS*) measures symptoms, physical and social limitations, and quality of life in Patients with heart failure. Score ranges from 0 to 100, with a higher score indicating improvements in overall health quality

[c]Data presented from SUMMIT trial, which studied the effect of tirzepatide on heart failure with preserved ejection fraction among patients with obesity. SURPASS-CVOT is an ongoing clinical trial that is evaluating MACE in patients taking tirzepatide

[d]Data are from a Phase 2 trial SYNERGY-NASH. There is an ongoing clinical phase 3 trial ESSENCE

mortality rates [168, 169]. However, China historically had only one approved pharmacologic treatment of obesity, orlistat, dating back to 2000. GLP-1RA drugs have been available since 2011 but approved only for T2DM indications [166] until 2024, when semaglutide and tirzepatide were approved for obesity treatment by the National Medical Products Administration in China; however, cost and limited coverage still remain a challenge [170, 171].

Barriers to accessing incretin-based therapies extends beyond the US and China. Socioeconomic disparities are a common thread across many countries that impact who and receives GLP-1 RA treatment. In both Australia and the United Kingdom (UK), for example, individuals from lower socioeconomic backgrounds are significantly less likely to be prescribed GLP-1RA medications. Within the US, these disparities are further compounded by racial and ethnic inequities. Studies have shown that Asian, Black, and Hispanic individuals are less likely to receive GLP-1RA therapies compared to white counterparts. It is important to note that the population label "Asian" is broad and should be interpreted cautiously, given the heterogeneity in genetic, metabolic, and sociocultural factors across Asian subgroups. To date, no clinical trial or real-world dataset provides sufficient geographic or ethnic granularity to meaningfully differentiate treatment access or outcomes within distinct Asian populations. And even in countries with universal healthcare systems, inequalities persist due to restrictive reimbursement criteria. The UK, for instance, only allows GLP-1RA prescriptions for patients who have both T2DM and obesity, excluding individuals with obesity alone, which unfortunately Limits early intervention. In contrast, other European nations have adopted more inclusive prescribing practices. Finally, even if individuals get a prescription, adherence is only 27% after 1 year due to high sustainability costs, resulting in weight regain among those who stop using GLP1-RAs [172].

Despite their clinical promise, GLP-1RA therapies remain out of reach for many individuals living with obesity around the world. Obesity medicines alone are inadequate to drive lasting improvements in cardiometabolic health. Integrating policy-level changes with nutrition-focused, Patient-centered lifestyle support is critical to optimizing health outcomes, equity, and sustainability. A recent 2024 *JAMA* Viewpoint calls for a rethinking of obesity care, emphasizing that OMMs are not a long-term solution and proposing a framework of short-term, intermittent GLP-1RA therapy paired with sustained lifestyle and nutrition interventions known as a "Food Is Medicine" approach. However, this model does not fully account for the intergenerational nature of obesity nor the persistent, multifactorial drivers beyond nutrition, such as chronic stress, endocrine-disrupting chemicals, and broader environmental changes that will continue to perpetuate the obesity epidemic. Even with transformative food and nutrition policies, a biologically predisposed majority is likely to remain, reinforcing the need for long-term pharmacotherapy for many individuals [172].

FUTURE DIRECTIONS

With advancements in genetic mapping, microbiology, and novel pharmacological therapies, the future of obesity management is shifting toward more personalized and targeted approaches that may address the complex and heterogeneous nature of obesity [173–175]. Phenotyping analyzes body characteristics such as body weight, fat distribution, and metabolic rate, and it helps classify obesity into subtypes like central, peripheral, sarcopenic, and metabolically abnormal obesity [176]. This approach will provide information about the diverse presentations of obesity and enable the selection of treatment strategies that are based on individual profiles. Artificial intelligence is also being used to identify risk factors associated with childhood obesity, using data on family history, genetics, environmental risk factors, and medical history to promote early intervention [177]. The gut microbiota is also increasingly recognized as a key player in obesity and metabolic health. Fecal microbiota transplantation (FMT) is an emerging therapeutic approach that aims to modulate the gut microbiota to improve metabolic functions and reduce obesity-related inflammation [178].

Early studies show that FMT can alter the composition of the gut microbiota, increase beneficial microbial species, and potentially enhance lipid metabolism and weight loss [179]. However, the long-term safety and efficacy of FMT are still under investigation, with potential risks such as infections and ecological dysbiosis being carefully monitored. Pharmacologic innovation in obesity treatment is accelerating rapidly, with over 100 novel medications currently in clinical development. The pipeline of future OMMs encompasses a wide array of mechanistic targets, from entero-pancreatic hormone pathways to central nervous system regulators. Emerging therapies include triple receptor agonists such as retatrutide, melanocortin-4 receptor agonists, fibroblast growth factor 21 analogs, and oral GLP-1 agonists such as orforglipron [119, 180–183]. These diverse strategies reflect a shift toward more targeted, multi-system approaches to treating obesity and its metabolic complications. Additionally, innovative devices such as bioelectric stimulators targeting the vagus nerve or hypothalamic regions are being explored to regulate appetite [184]. These advancements not only offer new hope for obesity management but also have the potential to transform the treatment of related metabolic diseases like diabetes and cardiovascular disease.

CONCLUSIONS: A NEW ERA OF OBESITY UNDERSTANDING AND THERAPEUTIC OPPORTUNITIES

Obesity is a chronic, multifactorial disease with rising prevalence and significant cardiometabolic risks. While BMI remains the standard diagnostic tool, its limitations highlight the need for better measures of metabolic health, with efforts to move towards a weight-inclusive approach to care. Treatment options, including lifestyle changes, pharmacotherapy (notably GLP-1RA and GIP/GLP-1 RA), endobariatric procedures, and metabolic surgery, remain underutilized due to cost and access barriers. Newer obesity medications such as semaglutide and tirzepatide are transforming obesity care, offering substantial and sustained weight loss with cardiometabolic benefits. Advances in precision medicine, gut microbiome research, and multi-target therapies are shaping a more personalized approach. Ultimately, a multidisciplinary, multimodal treatment strategy is essential to improving outcomes in this widespread chronic health condition.

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Declarations

Conflict of Interest. Amanda Velazquez: Advisory board—Eli Lilly (current), Intellihealth, Consultant—novo Nordisk (current), Advisory board: weight watchers (previous). All other authors (Vidhi Singh, Jia Sun, Susan Cheng, Alan C. Kwan) report no relevant conflicts of interest.

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