

## Management of Obesity as a Chronic Disease: Treating Patients Beyond Weight Loss and Body Mass Index

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### Abstract

Obesity is a chronic, relapsing, multifactorial disease driven by complex genetic, neurohormonal, behavioral, environmental, and socioeconomic factors. Its prevalence in the United States exceeds 42% of adults and continues to rise, contributing substantially to type 2 diabetes, cardiovascular disease, chronic kidney disease, metabolic dysfunction-associated steatohepatitis (MASH), obstructive sleep apnea, and certain malignancies. Beyond its clinical burden, obesity imposes significant economic costs through increased healthcare expenditures and reduced productivity. Historically, management has centered on weight reduction and body mass index (BMI) thresholds; however, emerging evidence supports a broader framework focused on improving cardiometabolic and renal outcomes independent of weight loss alone.

This narrative review outlines a comprehensive approach to obesity evaluation and management, emphasizing structured clinical assessment, identification of drivers and complications, and individualized treatment planning. Intensive multicomponent lifestyle interventions, including calorie reduction, dietary pattern modification, physical activity, sleep optimization, and behavioral therapy, remain foundational. Dietary approaches such as Mediterranean, DASH, and reduced-calorie plans share common cardioprotective principles. Resistance training and adequate protein intake are particularly important for preserving lean mass, especially in patients receiving anti-obesity pharmacotherapy. However, metabolic adaptation and neuroendocrine responses frequently limit the durability of lifestyle-induced weight loss, underscoring the need for adjunctive therapies.

Pharmacologic options for long-term treatment have expanded considerably. Glucagon-like peptide-1 receptor agonists and dual glucose-dependent insulinotropic polypeptide/GLP-1 receptor agonists demonstrate clinically meaningful reductions in major adverse cardiovascular events, slowed progression of chronic kidney disease, improvement in obstructive sleep apnea, and histologic resolution of MASH in selected populations. Bariatric surgery remains the most effective intervention for severe obesity, producing substantial and sustained weight loss with remission of multiple comorbidities.

Despite therapeutic advances, barriers including stigma, limited access to multidisciplinary care, insurance constraints, and insufficient clinician training hinder effective management. Reframing obesity as a chronic disease requiring long-term, personalized, multimodal treatment is essential. Targeting metabolic, cardiovascular, and renal risk reduction “beyond the scale” represents a necessary paradigm shift to improve long-term outcomes.

**Keywords:** Obesity; Cardiometabolic Risk; Anti-Obesity Pharmacotherapy; GLP-1 Receptor Agonists; Lifestyle Intervention

### Introduction

Obesity is increasingly recognized as a serious, chronic, recurrent, and multifactorial disease influenced by genetic, behavioral, and environmental factors [1]. It is associated with a significantly increased risk of morbidity and mortality [2]. Comprehensive medical management of obesity includes lifestyle interventions (dietary modifications, increased physical activity, and behavioral changes), pharmacotherapy (anti-obesity medications), and may be complemented by metabolic bariatric surgery and endoscopic procedures [3,4]. Traditionally, the management of obesity has centered around weight reduction and BMI as primary therapeutic targets [5]. However, the emergence of novel therapeutic agents for the management of obesity has shown benefits, particularly in improving cardiometabolic and kidney outcomes, highlighting the importance of treating beyond weight loss and BMI alone [6]. In this narrative review, we will address the evaluation and management of obesity through lifestyle interventions and pharmacotherapy. We will highlight the beneficial effects of managing patients with obesity on cardiometabolic and kidney outcomes beyond the reduction of weight and BMI.

### Obesity burden in the United States

#### Prevalences and health impact

Obesity in the United States has seen a dramatic rise over recent decades. In 1999 - 2000, approximately 30.5% of adults were classified as having obesity, a figure that increased to 42.4% by 2017 - 2018 [7,8]. A 2026 analysis estimated that obesity prevalence reached 42.5% (approximately 107 million U.S. adults) in 2022 and projected an increase to 46.9% by 2035 [9]. This rise in obesity is observed across all age and gender groups and is closely associated with an increase in chronic health conditions such as type 2 diabetes, heart disease, stroke, nonalcoholic fatty liver disease, sleep apnea, and various cancers [10-12]. Furthermore, people with obesity are less likely to seek medical care due to experiences of weight stigma and internalized shame, and when they do, bias among healthcare providers can lead to underdiagnosis or dismissal of legitimate medical concerns [13]. Data from 2017 - 2020 indicate that approximately 58% of adults with obesity had hypertension, and nearly 23% had diagnosed diabetes, the rates significantly higher than those observed in individuals with normal weight [7]. This reported burden of disease is likely underestimated, as these chronic conditions often go undiagnosed, particularly in their early stages. These obesity-related chronic conditions significantly impair overall health and life expectancy and often cluster together, creating a syndromic effect that complicates treatment [14]. In fact, obesity and its related complications are responsible for an estimated 300,000 premature deaths annually in the United States, making it the second-leading preventable cause of mortality, after tobacco use [15].

#### Economic impact

Recent evidence demonstrates that the economic burden of obesity continues to escalate substantially, with updated estimates showing both direct healthcare costs and indirect productivity losses far exceeding earlier projections. Direct healthcare costs attributable to obesity rose from 6.13% of U.S. national healthcare spending in 2001 to 7.91% in 2015, representing a 29% increase [16]. A 2024 systematic review found that direct medical costs account for 0.7% to 17.8% of health system expenditure across countries, with total obesity costs ranging from 0.05% to 2.42% of GDP [17].

Indirect costs now constitute the majority of the economic burden of obesity, with productivity losses several times larger than direct medical costs [18]. Obesity increases job absenteeism by approximately 3.0 days per year, with annual productivity losses ranging from \$271 to \$542 per employee with obesity, totaling \$13.4 to \$26.8 billion nationally in the U.S. [19].

A 2025 Canadian analysis found that presenteeism accounted for approximately \$6.8 billion in costs, whereas reduced workforce participation accounted for \$8.2 billion [20]. A 2025 Finnish study found that, compared with normal weight, obesity was associated with 83 - 95% higher total costs among working-age individuals, with predicted annual cost differences of €3,002-€3,443 per person [21].

**Obesity as a chronic disease**

Obesity is now considered a chronic disease, a significant driver in the global rise of chronic non-communicable diseases [22]. The increasing rate of obesity and overweight necessitates prioritizing the management of obesity with a thorough evaluation, including a detailed obesity-related history and physical examination. The 5As model offers a structured approach to guide clinicians in initiating discussions with patients about obesity management in a primary care setting [23] (Table 1).

<b>Ask:</b>	Ask for permission to discuss weight and explore readiness for change.
<b>Assess:</b>	Assess obesity class and stage, and assess for drivers, complications, and barriers
<b>Advise:</b>	Advise on obesity risks, explain the benefits of modest weight loss, explain the need for a long-term strategy, and discuss treatment options
<b>Agree:</b>	Agree on realistic weight-loss expectations, focus on behavioral goals (SMART Goals) and health outcomes, and agree on a treatment plan.
<b>Assist:</b>	Address drivers and barriers, provide education and resources, refer to appropriate providers, and arrange follow-up.

**Table 1:** The 5As model for obesity management.

Assessing a patient with obesity starts with a detailed weight history, including previous weight-loss efforts, diet history, access to healthy foods, exercise history, ability to engage in physical activity, sleep patterns, list of medications, family history, and review of systems. Gathering a dietary history can be effectively done by asking, “Walk me through your typical day.” Multiple validated dietary tools are available for use in clinics [24,25]. Providers should recognize that obesogenic medications are commonly used, and some are available over the counter. Validated questionnaires to screen for sleep apnea (STOP BANG) [26], depression (PHQ2) [27], and alcohol disorder (Audit C) [28] can help to recognize undiagnosed comorbidities that may contribute to obesity.

A focused physical examination is necessary to detect underlying causes of obesity. BMI, waist circumference, and body composition scales are among the tools used in weight management clinics to classify and stage the disease. BMI is a ratio between weight and height (kg/m<sup>2</sup>) (Table 2) [22]. Although BMI has its limitations, it is currently used to define and classify stages of obesity [29]. Recent efforts, however, are shifting toward more comprehensive approaches that incorporate clinical markers, functional status, and complications, moving beyond BMI alone to better define and manage obesity. In addition to an increase in total body weight, a proportionally greater abdominal adiposity has been associated with increased risk for metabolic syndrome, type 2 diabetes mellitus, hypertension, and heart disease in both men and women. Abdominal obesity is commonly reported as a waist-to-hip ratio, but it is most easily quantified by a single circumferential measurement obtained at the level of the superior iliac crest [30]. The original US national guidelines on overweight and obesity categorized men at increased relative risk for co-morbidities such as diabetes and cardiovascular disease if they have a waist circumference greater than 102 cm (40 inches) and women if their waist circumference exceeds 88 cm (35 inches) [31].

Diagnosis	BMI (kg/m <sup>2</sup> )		Comorbidity Risk	Risk of T2DM, HTN, and CVD	
	Non-Asian	Asian		(<102 cm men / <88 cm women)	(≥102 cm men / ≥88 cm women)
Underweight	<18.5	<15.5	Low but other problems	-	-
Healthy weight	18.5 - 24.9	15.5 - 22.9	Average	-	-
Overweight	25 - 29.9	23 - 27.9	Increased	Increased	High
Class I obesity	30 - 34.9	>28	Moderate	High	Very high
Class II obesity	35 - 39.9	-	Severe	Very high	Very high
Class III obesity	≥40	-	Very severe	Extremely high	Extremely high

**Table 2:** Definition and classification of obesity (BMI categories).

### Lifestyle interventions - Challenges and strategies

The U.S. Preventive Services Task Force (USPSTF) recommends that all adults be screened for overweight and obesity, and to provide those affected with “intensive multicomponent behavioral interventions” [32]. To qualify as an “intensive multicomponent” intervention, the USPSTF recommends at least 12 sessions over 12 months where weight management is discussed. The intervention should last 1 - 2 years, followed by a 9 - 12 months “maintenance” phase [32]. The principal components of behavioral interventions include self-monitoring, goal setting, stimulus control, healthy meal planning, physical activity, stress reduction, improved sleep quantity and quality, and psychological therapy [31]. Expert panels emphasize that individuals with obesity should aim to lose 10% of their initial body weight through these behavior modifications, also called lifestyle modifications.

When discussing lifestyle modifications as a treatment for obesity, it is important to remember that 40 - 80% of obesity is genetically driven, and lifestyle modifications alone may not be sufficient for adequate or sustained weight loss [33]. The neuroendocrine regulation of body weight is overwhelmed by the toxic food environment, characterized by cheap, plentiful, and highly palatable and processed foods served in large portions [31,34]. The neuroendocrine system that defends against the perils of famine and weight loss is not adept at responding to food abundance or an environment built around energy-saving and fast-food delivery. Additionally, the body cannot distinguish between intentional weight loss and starvation; therefore, the hypometabolic response to intentional weight loss can lead to a weight plateau and weight regain [34]. Lifestyle modification, emphasizing nutrition and physical activity, is the foundation of health for all people, not just those with overweight and obesity. Patients should be made aware that lifestyle alone may not fully reverse or treat the incredibly complex behavioral, biological, cultural, economic, psychosocial, neuroendocrine, and genetic factors that influence body weight [35].

For patients with conditions like multi-organ failure or end-stage renal disease on dialysis, dietary recommendations must be tailored to their unique needs while considering their overall health [5]. Additionally, healthcare providers should offer multidisciplinary support, including physical therapists, registered dietitians, psychologists, and other health professionals, to help patients achieve their targeted goals.

### Nutrition

It is imperative to create an energy deficit when considering calorie intake and dietary recommendations for weight loss [5]. The American Heart Association/American College of Cardiology/The Obesity Society (AHA/ACC/TOS) guidelines discuss three different strategies for prescribing a reduced-calorie diet. These include 1) 1200 - 1500 kcal/day for women and 1500 - 1800 kcal/day for men, 2) 500 - 750 kcal/day energy deficit, or 3) prescribing one of the evidence-based diets that restrict certain food types to create an energy deficit (e.g. DASH, Mediterranean, or low-carbohydrate diet) [35]. The 2025 ACC Concise Clinical Guidance on Nutrition updated its dietary recommendations to highlight the importance of consuming fruits, vegetables, whole grains, healthy protein sources, low sodium, minimally processed foods, and liquid oils [36].

Patient preferences, including food types, availability, access to food, and cultural food preferences, are important to consider when developing a healthy eating plan [37]. Food properties such as satiety value, taste, and energy density are powerful determinants of total calories ingested [37]. For instance, high-fat diets tend to have higher energy density; complex carbohydrates can facilitate reductions in energy intake; and protein has a high satiety effect [38].

Meal replacements can also be incorporated into a patient’s meal plan to help them adhere to a reduced-calorie diet. Multiple studies have shown that incorporating meal replacements even for just one or two meals per day can lead to greater weight loss, compared to a meal plan consisting of the same calorie target using only “conventional” foods [39]. Meal replacements offer several benefits that support adherence to meal plans beyond calorie control, including portion control, structured eating, stimulus narrowing and control, and palatability [39].

In addition to meal replacements, two other popular strategies for creating a caloric deficit and promoting weight loss are time-restricted eating (TRE) and intermittent fasting (IF). In time-restricted eating, food is consumed ad libitum within a defined window of the day, for example, the commonly used 16:8 approach limits eating to an 8-hour period (e.g. 12 p.m. to 8 p.m.) [40]. In contrast, intermittent fasting typically involves significant caloric restriction (0 - 500 kcal) over a 24-hour period. Randomized controlled trials have evaluated protocols such as 5:2 fasting (two nonconsecutive fasting days per week) and alternate-day fasting, both of which have shown efficacy in inducing weight loss in select populations [41,42].

In general, heart-healthy dietary patterns contain primarily fruits and vegetables, foods made with whole grains, healthy sources of protein (mostly plants, fish, and seafood, low-fat or fat-free dairy products, and, if meat or poultry are desired, lean cuts and unprocessed forms), liquid plant oils, and minimally processed foods. These patterns are also low in beverages and foods with added sugars and salt. When discussing dietary patterns with patients, it is important to focus on what these “diets” have in common, rather than what separates them. For instance, a patient may prefer to consume animal protein, while others may not. Some heart-healthy dietary patterns emphasized in the Dietary Guidelines for Americans include the Mediterranean, Dietary Approaches to Stop Hypertension (DASH), Healthy US-Style, and healthy vegetarian diets [35,36,43]. For any patient attempting to lose weight, support from a registered dietitian can be valuable and may be covered by insurance.

Nutrition recommendations for patients on GLP-1 receptor agonists (GLP-1RAs) and other anti-obesity pharmacotherapies should emphasize adequate protein intake, nutrient density, and gradual, sustainable caloric reduction. These agents, including semaglutide and tirzepatide, often suppress appetite significantly, which can lead to unintentional reductions in overall food intake, including protein. To mitigate the risk of lean muscle loss and support metabolic health, patients should be encouraged to consume 1.2-1.5 grams of protein per kilogram of ideal body weight per day, particularly during active weight loss [44]. Adequate protein intake is crucial for preserving muscle mass and supporting bone health, both of which are essential for maintaining functional capacity and reducing the risk of osteoporosis and frailty, especially in older adults [45,46]. Additionally, protein promotes satiety, which may enhance adherence to calorie-controlled diets and complement the appetite-suppressing effects of weight loss medications [47].

### Physical activity

The AHA recommends at least 150 minutes of moderate-intensity aerobic activity or 75 minutes of vigorous aerobic activity each week, along with at least two days of resistance training [48,49]. There are even more benefits to being active for at least 300 minutes per week. Increasing physical activity and reducing sedentary time should be discussed at every visit for all patients, regardless of age or BMI [50]. Physical activity is important for weight loss and even more important for weight maintenance. Research shows that engaging in at least 150 minutes per week of moderate-intensity exercise can lead to weight loss when paired with a calorie-reduced diet [51]. Studies show that 200 - 300 min/week is required to prevent weight regain, and exercise is associated with longer-term weight loss [36,52]. When it comes to physical activity, especially for patients with complex medical conditions, it is important to start where the patient can start and gradually increase as tolerated. Support from physical therapists, physical medicine and rehab physicians, and/or personal trainers may be beneficial. For some patients, a reasonable first goal may be to reduce recreational screen time to reduce prolonged sitting.

For patients taking GLP-1RA, physical activity guidelines align with general obesity management recommendations, with some specific considerations given the medication’s effects on appetite, gastrointestinal symptoms, and energy balance. Muscle mass and bone density preservation through physical activity, especially resistance training and impact loading, is critical to maintain skeletal muscle mass and function, especially for older adults who use these pharmacotherapies for any indication [53,54]. It may be advisable to adjust patients’ exercise intensity or timing (avoid strenuous exercise after injections or meals) until side-effects of the medications (such as nausea, early satiety, or fatigue) stabilize [44].

### Behavior modification

Behavior therapy provides tools that facilitate changes in eating and physical activity patterns. One well-known example of an intensive multicomponent intervention is the Diabetes Prevention Program (DPP), which was originally provided as one-on-one sessions and has been adapted to group sessions [55]. Healthcare system-based weight management programs, such as the MOVE! Weight management programs in the Veterans Health Administration (VHA) or in commercial settings, such as Weight Watchers and Noom, have also been shown to improve patients' health [56,57]. A technique often used in these programs is self-monitoring (i.e. recording) of calorie intake, physical activity, and body weight. This technique helps patients become more mindful of their habits, hold themselves accountable, and provides critical information on progress toward their goals. More frequent self-monitoring of food intake has been associated with greater weight loss [58].

Stimulus control is another behavioral technique that involves removing a stimulus or controlling when it occurs. Examples include recommending that your patient grocery shop only when they are not hungry, use a list, avoid bringing hyperpalatable foods into the home, eat only at meals or predefined snack times, and eat only preplanned foods.

Motivational interviewing techniques have demonstrated efficacy in multiple studies, but many clinicians may lack comfort using them [58]. One of the greatest challenges in behavioral treatment is identifying the specific eating, activity, cognitive, and emotional factors that contribute to an individual's obesity and then focusing on these targets. This is especially true for patients who have other complex medical conditions. Individuals frequently encounter a uniform approach to lifestyle modification that prioritizes broad generalizations over personalized recommendations tailored to each patient's specific needs. When it comes to lifestyle and behavior modifications, individualized plans are best.

### Anti-obesity pharmacotherapy

Anti-obesity pharmacotherapy has become an essential tool in the management of obesity. These medications reduce appetite and help individuals modify their eating behaviors to be more consistent with lifestyle changes [59]. However, the use of anti-obesity medications in patients with complex medical conditions requires careful consideration of their contraindications and potential side effects.

There are currently six anti-obesity medications approved by the FDA for long-term management of obesity: orlistat, phentermine/topiramate, naltrexone/bupropion, liraglutide, semaglutide, and tirzepatide. Phentermine is a commonly used medication that is FDA-approved for short-term treatment of obesity. The long-term use of phentermine, when prescribed individually, varies by state law [60,61]. Other medications that may aid in obesity management, although they do not have FDA indications for this purpose, include metformin and the SGLT-2 inhibitor class [62,63]. Metformin can be used in combination with other medications with a relatively low risk of drug-drug interactions. Side effects typically involve the gastrointestinal tract, such as bloating and diarrhea, which may limit its use in patients with obesity and inflammatory bowel disease or other complex GI conditions. Additionally, metformin is generally not recommended in individuals with stage 4 and contraindicated in stage 5 chronic kidney disease [64].

Orlistat was the first FDA-approved long-term medication for the treatment of obesity. It is also an attractive option, as its mechanism of action is limited to the small intestine rather than affecting central appetite regulation pathways. The side effects of orlistat are primarily gastrointestinal. Patients may experience abdominal pain, flatulence, bowel urgency, and steatorrhea, all of which can be mitigated by consuming a low-fat diet [65]. However, orlistat should not be used in individuals with known gallstones or a history of calcium oxalate kidney stones, as some patients may experience increased urinary oxalate levels [66]. Additionally, orlistat should be used with caution in individuals with significant liver disease, as rare cases of severe liver injury requiring transplantation or fatal liver injury have been reported [67].

For the past 11 years, the combinations of phentermine and topiramate, as well as bupropion and naltrexone, have been FDA-approved pharmacotherapeutic options for treating obesity. These medications should be considered with caution and under close monitoring. Phentermine and bupropion both have stimulant properties, which can lead to similar adverse effects such as dry mouth, constipation, insomnia, and headaches [68]. Therefore, these combinations should be used with caution in patients with significant cardiovascular disease, particularly arrhythmias [69]. Topiramate can increase the risk of kidney stones, so its use is contraindicated in patients with a history of nephrolithiasis [70]. Furthermore, when phentermine/topiramate is prescribed to individuals concurrently taking diuretic medications, it is imperative to closely monitor electrolyte levels. This is due to the potential for the combination of topiramate and a diuretic to increase urinary potassium excretion, thereby leading to hypokalemia [71].

GLP-1 RAs and combination GIP/GLP-1RAs are two classes of anti-obesity medications that have shown promise in patients with complex medical conditions. These alternatives are appealing because they target the neurohormonal mechanisms governing appetite regulation without interacting with cardiac or psychiatric pharmacotherapy and without causing increases in blood pressure or heart rate [72,73]. However, healthcare providers must carefully consider potential contraindications and side effects when prescribing these medications. GLP-1 and dual GIP/GLP-1 receptor agonists are contraindicated in patients with a family history of medullary thyroid carcinoma or a personal history of multiple endocrine neoplasia syndrome type 2. They should be used with caution in patients with gallstones and a history of pancreatitis of unclear etiology [74,75]. GLP-1 and dual GIP/GLP-1 RAs most commonly cause GI side effects such as nausea, vomiting, and constipation because of the slowing of gastric emptying [76]. However, just as many or more patients have been reported to experience diarrhea. It is important to carefully monitor these symptoms in medically complex patients for not only these classes of medications but also any anti-obesity agents that affect satiety. The combination of nausea, vomiting, and decreased appetite can cause dehydration and acute kidney injury [77]. Frequent monitoring and a slower-than-recommended dose titration can prevent excessive dehydration while still achieving weight-management goals.

Weight loss pharmacotherapy is generally contraindicated in women who are pregnant, breastfeeding, or trying to conceive, due to limited safety data, potential harm to the fetus or infant, and the physiologic demands of reproduction [78]. Clinical decisions in these populations must weigh maternal health goals against fetal and infant safety. Weight loss before pregnancy can improve fertility, especially in women with obesity-related anovulation or PCOS. It is advisable to discontinue weight loss medications at least 1 - 2 months before planned conception to allow for drug clearance. There are no FDA-approved weight loss medications recommended during lactation, due to limited safety data on drug transfer into breast milk and potential neonatal effects. Orlistat is minimally absorbed but may interfere with fat-soluble vitamin absorption in both mother and infant [79]. Sympathomimetic agents, such as phentermine, may reduce milk supply and have stimulant effects on the infant [80]. GLP-1 receptor agonists have not been adequately studied in lactating women; animal studies show secretion into milk [81]. Pharmacotherapy can be initiated once a woman has fully stopped breastfeeding and is no longer expressing or providing breast milk for consumption (Table 3).

Reproductive Status	Recommendation
Pregnant	Contraindicated; discontinue immediately if pregnancy occurs
Trying to Conceive	Discontinue prior to conception; use contraception during treatment
Breastfeeding	Avoid pharmacotherapy; prioritize lifestyle changes and support lactation

**Table 3:** Recommendations for obesity medications during pregnancy, conception, and lactation.

Careful patient selection and close monitoring are essential when prescribing anti-obesity medications to this patient population. Patients should be informed of the potential risks and benefits of treatment, and their preferences should be considered when developing a treatment plan. Despite these challenges, the benefits of successful weight loss in patients with complex medical conditions can be significant. Anti-obesity medications are believed to play a role in mitigating chronic inflammation and modifying disease, particularly in cardiovascular diseases, pulmonary disease, and chronic kidney disease (CKD), both through weight loss and other mechanisms [64,82,83].

Nevertheless, the management of obesity in patients with complex medical conditions is a complex and multifaceted challenge. While anti-obesity pharmacotherapy can be a valuable tool in the treatment arsenal, healthcare providers must carefully weigh the potential benefits against the risks and consider the patient's individual medical history and preferences. A personalized, multidisciplinary approach is essential to ensure the safe and effective use of these medications in this patient population.

GLP-1 agonists have been shown to significantly reduce albuminuria and slow the decline of eGFR in type 2 diabetes with moderate to severe CKD, with the results of the FLOW trial released in 2024 - weekly 1 mg dose of Semaglutide versus placebo showed a 24% reduction in the primary kidney outcome (> 50% decline in eGFR, eGFR < 15 mL/min, dialysis or transplant, death due to kidney disease or CVD) with a hazard ratio of 0.76 (95% CI of 0.66 - 0.88) with consistent findings across multiple subgroups [84]. The SELECT trial of Semaglutide 2.4 mg weekly vs placebo in patients with overweight or obesity with preexisting cardiovascular disease and without diabetes also reported a positive result on its primary outcome of major adverse cardiovascular events with a relative risk reduction of 20%. The "secondary" nephropathy outcome (onset of macroalbuminuria, > 50% eGFR decline, kidney failure, or death due to kidney disease) was reduced by 22% with an HR of 0.78 (CI 0.63 - 0.96) [85].

Beyond cardiovascular and renal outcomes, GLP-1 and dual GIP/GLP-1RAs have shown benefits in other obesity-related conditions. In obstructive sleep apnea (OSA), the SURMOUNT-OSA trial demonstrated that tirzepatide significantly reduced the apnea-hypopnea index (AHI) by 25 - 29 events per hour compared to just 5 events per hour with placebo [86]. Thus, tirzepatide is now FDA-approved for the treatment of OSA in patients with obesity. In heart failure with preserved ejection fraction (HFpEF), semaglutide has shown improvements in functional status in the STEP-HFpEF trial, and tirzepatide has demonstrated early promise in the SUMMIT trial, although GLP-1-based agents are not yet FDA-approved for HFpEF [87].

Additionally, Semaglutide received accelerated FDA approval in August 2025 for the treatment of MASH with moderate to advanced fibrosis (stages F2-F3), based on results from the phase 3 ESSENCE trial [88]. At 72 weeks, semaglutide achieved resolution of MASH without worsening of fibrosis in 62.9% of participants compared with 34.3% with placebo, and improvement in fibrosis without worsening of MASH in 36.8% versus 22.4% with placebo. In contrast, Tirzepatide remains under investigation for MASH. In the phase 2 SYNERGY-NASH trial, tirzepatide demonstrated resolution of steatohepatitis without worsening of fibrosis in 44 - 62% of participants (vs 10% with placebo) and improvement in fibrosis stage in 51-55% (vs 30% with placebo), but it has not yet received FDA approval for this indication [89-93].

### Bariatric surgery

Bariatric surgery is a highly effective intervention for individuals with severe obesity (BMI  $\geq$  40 kg/m<sup>2</sup>), those with a BMI  $\geq$  35 kg/m<sup>2</sup> and obesity-related comorbidities such as type 2 diabetes, hypertension, or obstructive sleep apnea, or individuals with a BMI  $\geq$  30 kg/m<sup>2</sup> who have uncontrolled type 2 diabetes [94]. It offers substantial and sustained weight loss, with most patients maintaining 50 - 70% of their excess weight loss over the long term [95]. The procedure significantly improves metabolic health, including remission of type 2 diabetes in many patients, even before substantial weight loss [96]. In addition to weight loss, bariatric surgery improves cardiovascular health, including reduced blood pressure and cholesterol levels, thereby lowering the risk of cardiovascular disease. It also alleviates

obesity-related conditions such as osteoarthritis by reducing joint strain, improves liver function in those with non-alcoholic fatty liver disease, and significantly reduces the severity of sleep apnea.

The psychological benefits are notable as well, with many patients reporting improvements in body image, mood, and self-esteem, which can lead to better overall mental health [97]. Furthermore, bariatric surgery has been shown to enhance fertility and pregnancy outcomes, particularly in women with obesity-related infertility [98]. Another benefit is the reduction in long-term healthcare costs, as the procedure can decrease the need for medications and hospitalizations related to obesity-related comorbidities [16]. Despite its effectiveness, bariatric surgery requires long-term lifestyle changes, including dietary modifications and physical activity, to maintain weight loss and prevent complications.

**Barriers and challenges in obesity management**

Current clinical practice diagnoses obesity based on BMI and weight, but there are no uniform guidelines or measurements that incorporate a holistic approach to obesity management. Obesity treatment lacks personalization, and clinicians often do not have adequate training to address this stigmatized healthcare condition. Additional barriers include limited insurance coverage and a lack of resources, such as diet education, healthy food sources, and diet coaches. Obesity is a chronic recurrent multifactorial disease with an increasing risk for weight regain even after effective weight loss. This necessitates a vigilant, patient-centered approach in which clinicians continuously monitor and set realistic expectations, based on other metabolic and psychological conditions rather than solely on weight and BMI.

Fastenau, *et al.* [99] discussed a disease model advocating a personalized approach that incorporates the patient’s weight and other disease indicators, along with patient preferences, lifestyle, beliefs, and goals. This results in a patient-centered approach to obesity that is both sustainable and attainable [99]. Ludwig DS, *et al.* [103] address the complexity of the psychosocial etiology of obesity, illustrating the effectiveness of behavior modification and supporting a multimodal approach [100]. The classical approach to obesity, which emphasizes eating less and exercising more, is often unsuccessful due to metabolic adaptations that conserve energy, ultimately leading to a plateau in weight loss or even weight regain [101] (Table 4).

Outcome Category	Specific Outcomes	Key Interventions
Metabolic	↓ HbA1c, improved insulin sensitivity, ↓ fasting glucose, ↓ glucagon, delay/prevention/remission of T2DM, improved lipid profile (↓ LDL, ↓ TG, ↑ HDL)	GLP-1 RAs, tirzepatide, SGLT2i, lifestyle, bariatric surgery
Cardiovascular	↓ Systolic/diastolic BP, ↓ MACE, ↓ HF hospitalizations, improved endothelial function, ↓ resting HR	SGLT2i, GLP-1 RAs, lifestyle, surgery
Renal	Slowed eGFR decline, ↓ albuminuria, delayed CKD progression, ↓ need for dialysis	SGLT2i, GLP-1 RAs
Hepatic	↓ Hepatic steatosis, ↓ inflammation, and ballooning, ↓ fibrosis progression	GLP-1 RAs, tirzepatide, lifestyle, bariatric surgery
Inflammatory	↓ CRP, ↓ IL-6, ↓ TNF-α, reduced systemic inflammation	GLP-1 RAs, lifestyle, diet, weight loss
Thrombotic	↓ Risk of DVT/PE, ↓ platelet activation, ↓ pro-thrombotic markers	Weight reduction, physical activity, GLP-1 RAs
Neurohormonal / Autonomic	↓ Sympathetic tone, ↓ leptin resistance, improved autonomic balance	GLP-1 RAs, lifestyle, surgery
Other / Metabolite Clearance	↓ Serum uric acid, ↓ gout flares	SGLT2i, lifestyle, weight loss

**Table 4:** Benefits of obesity management beyond weight loss.

## Conclusion

Obesity is a chronic, multifaceted disease that necessitates a comprehensive, multimodal treatment approach. While reducing BMI remains an important therapeutic target, obesity management should emphasize sustained lifestyle modifications alongside evidence-based pharmacotherapy and bariatric surgery. This approach yields marked benefits in cardiometabolic risk factors, cardiovascular event rates, and kidney function that exceed those expected from weight reduction alone. In other words, the goal is to improve cardio-metabolic kidney outcomes. This paradigm shift of treating obesity as a chronic disease is strongly supported by expert guidelines and recent clinical trials [5,35]. By aiming “beyond the scale,” clinicians can profoundly improve long-term outcomes in patients with obesity [5,35]. Future research should address long-term outcomes and real-world challenges, with particular focus on improving long-term adherence and strategies to sustain weight loss after achieving the target body weight.

## Conflict of Interest

The authors declare that they have no conflict of interest related to this study.

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