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Obesity management for cardiovascular disease prevention

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A B S T R A C T

Background: Obesity is a complex disease that leads to higher morbidity and mortality and its rate in the United States is rapidly rising. Targeting obesity management is one of the cornerstones of preventive medicine. Early intervention can significantly reduce the risk of developing cardiovascular disease. While it is well known that lifestyle interventions such as healthful nutrition and routine physical activity are the first and most important step in management, some do not achieve the desired results and require further therapies.

Methods: A literature review was conducted, that included clinical documents, public scientific citations and peer review articles to evaluate anti-obesity medications, endoscopic procedures and bariatric surgeries in the management of obesity. We also included effects of these interventions on weight loss, cardiovascular disease risk reduction and side effects.

Results: This clinical review summarizes recent evidence for the different approaches in obesity management including medications, common endoscopic procedures and bariatric surgeries. For more detailed review on the different management options discussed, we recommend reviewing Obesity Medicine Association Clinical Practice Statement [1].

Conclusion: Management of obesity reduces cardiovascular risk, improves metabolic parameters and other important health outcomes. Different management approaches are available, hence, a high level of awareness of the growing epidemic of obesity is needed to ensure timely referrals to obesity medicine specialists.

1. Introduction

Obesity is a complex disease that is directly associated with the risk of developing dyslipidemia, type 2 diabetes mellitus (T2DM), hypertension, and sleep disorders which are well known cardiovascular disease (CVD) risk factors. Obesity also increases the risk of CVD and cardiovascular mortality independent of the other risk factors [1]. The prevalence of obesity in the United States is on the rise, reported to be as high as 42%, according to data from the Centers for Disease Control [2]. Importantly, it is one of many modifiable CVD risk factors. Lifestyle interventions, including healthful nutrition and physical activity, are first line in the management of obesity. However, other interventions including anti-obesity medications, endoscopic procedures, and bariatric surgery have been successfully utilized in patients who do not achieve desired outcomes with lifestyle modifications alone. The impact of these interventions on CVD outcomes along with cardiovascular side effects and precautions, will be reviewed in this article (see Fig. 1).

2. Anti-obesity medications

2.1. Semaglutide

Glucagon-like peptide-1 (GLP-1) is an endogenous incretin produced in intestines after food intake that enhances insulin secretion and suppresses glucagon release [3]. Semaglutide is a GLP-1 receptor agonist (GLP1-RA) that has been approved for T2DM management and has been shown to reduce cardiovascular events in patients with T2DM [4]. The food and drug administration (FDA) approved semaglutide SC injection (2.4 mg once weekly) for chronic weight management in adults with obesity or overweight with at least one weight-related condition (such as high blood pressure, T2DM, or high cholesterol) on June 4, 2021 [5].

Semaglutide was evaluated in a series of clinical trials called Semaglutide Treatment Effect in People with Obesity (STEP) trials [6]. STEP 1 trial evaluated the safety and efficacy of semaglutide use for weight loss [7]. The dose of subcutaneous (SC) 2.4 mg weekly of semaglutide was studied in about 2000 patients with overweight or obesity (Body mass index (BMI) $\geq$27 kg/m^2 in persons with $\geq$1 weight-related coexisting condition or $\geq$ BMI 30 kg/m^2) without T2DM versus placebo both along

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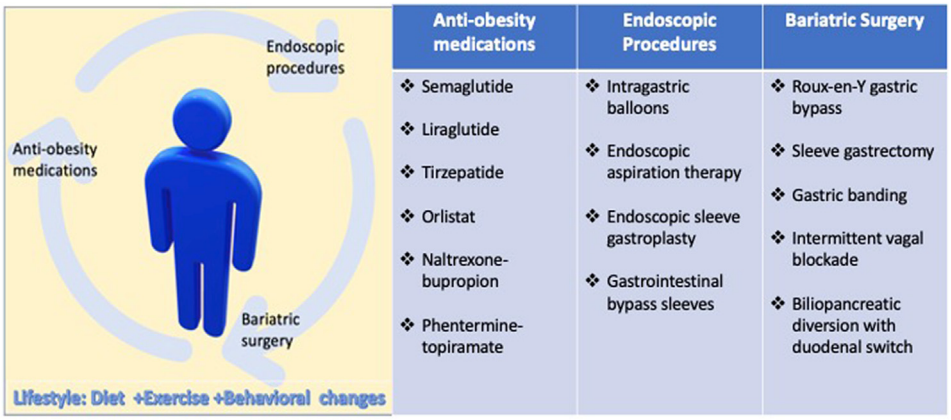

Fig. 1. Central illustration summarizes medications, endoscopic procedures and bariatric surgery for the management of obesity discussed in the article.

with lifestyle modifications who were followed for 17 months [7,8]. Most of the participants were white (75%) and female (74%) with a mean age of 46 years. Mean change in weight was 15% vs 2.4% in semaglutide vs placebo, with an estimated treatment difference of −12.4% points (95% CI −13.4 to −11.5, P<0.001). The average reduction in body weight with semaglutide was 15.3 kg, with weight loss of ≥5% achieved by 86% in the semaglutide group versus 31% in the placebo group. Patients in the semaglutide group achieved an improvement in cardiometabolic profile compared to placebo. There was a greater reduction in waist circumference (−14 cm vs −4 cm) and BMI (−6 vs −1 kg/m^2) with semaglutide vs placebo [7,8]. There was also a greater reduction in the systolic/diastolic blood pressure (−6/3 vs −1/0.4 mmHg), as well as C-reactive protein (CRP) mg/l (ratios to baseline 0.47 vs 0.85) with semaglutide vs placebo. Fasting plasma glucose (FPG) (−8 vs −0.5 mg/dl) and glycated hemoglobin (HbA1c) reductions were also greater with semaglutide compared to placebo (−0.45% vs −0.15%). Finally, semaglutide led to greater reductions in low-density lipoprotein-cholesterol (LDL-C) mg/dl (ratios to baseline 0.97 vs 1.01) and physical functioning scores [8] compared with placebo.

Transient diarrhea and nausea were the most common reported adverse events leading to discontinuation of semaglutide vs placebo (59 [4.5%] vs. 5 [0.8%], respectively) [8].

The results of the first trial to assess major adverse cardiovascular events (MACE) reduction for adults with obesity but without T2DM, the Semaglutide Effects on Heart Disease and Stroke in Patients with Overweight or Obesity outcome trial (SELECT), should be released later this year [9]. This trial enrolled 17,000 adults from multiple countries with BMI ≥27 kg/m^2 and established CVD, defined as one or more of the following: prior myocardial infarction (MI), prior ischemic or hemorrhagic stroke, symptomatic peripheral arterial disease with ankle-brachial index <0.85 at rest, prior peripheral arterial revascularization procedure, or amputation due to atherosclerotic disease. The following groups were excluded: patients with type 1 diabetes mellitus or T2DM, and patient with MI, stroke, hospitalization for unstable angina pectoris, or a transient ischemic within 60 days of enrollment [9,10].

2.2. Liraglutide

Liraglutide is a GLP1-RA that shares the same mechanism of action of semaglutide, which results in delayed gastric emptying [11], and appetite suppression [12,13]. The Satiety and Clinical Adiposity – Liraglutide Evidence in non-diabetic and diabetic individuals (SCALE) program was conducted to evaluate safety and efficacy of liraglutide, which included four large scale randomized multicenter phase III trials [11,14–19]. The SCALE Maintenance trial enrolled 500 patients with a BMI ≥ 30 kg/m^2 or ≥27 kg/m^2 with a weight-related comorbid condition who lost ≥ 5% of initial weight with a low-calorie diet were enrolled to receive liraglutide 3 mg SC daily injections vs placebo [20]. Main outcomes were percentage weight change from randomization, efficacy of liraglutide in maintaining ≥5% of initial weight loss and proportion that lost ≥ 5% of body weight after randomization [20]. At 56 weeks, the liraglutide group experienced a greater decrease in body weight compared with placebo (6% vs 0.2%, p < 0.0001) [20]. A large proportion of liraglutide-treated patients maintained the initial ≥5% weight loss (81% versus 49%), achieved ≥5% weight loss (50% vs 22%), and achieved ≥10% weight loss (26% versus 6%), compared with placebo-treated patients (p < 0.0001) [16,20].

In the SCALE-Maintenance trial, several metabolic parameters improved with Liraglutide vs placebo [20]. At 56 weeks, there was a significant difference in FPG (−9 vs −3.6 mg/dl in the liraglutide group vs placebo, respectively) with estimated treatment differences for liraglutide vs placebo −0.4 (95% CI −0.5 to −0.3, P<0.0001). There were also significant changes in HbA1c (−0.1% vs 0.1%) between liraglutide and placebo groups with treatment differences of −0.3 (95% CI −0.3 to −0.2, P<0.0001) and CRP (−20 vs −1 nmol/l) with treatment of −13.0 (95% CI −23.4 to −2.6, P=0.01). There was also a significant change in systolic/diastolic blood pressure between the two groups (+0.2/1.4 vs +2.8/1.2 mmHg) with estimated treatment differences of systolic blood pressure of −2.7 (95% CI −4.7 to −0.8, P=0.007) and diastolic blood pressure differences of −0.3 (95% CI −1.7 to 1.1, P=0.64) between liraglutide vs placebo. Net changes in lipids were of negligible magnitude [16,20].

Mild to moderate gastrointestinal side effects have been reported. Nausea was transient and mainly occurred in the first four weeks of the trial, coinciding with dose escalation [16]. Symptomatic hypoglycemia was more frequent than the placebo group (5.2% vs. 2.4%), though the difference was not statistically significant [16,19]. An increase in heart rate has also been reported with the use of liraglutide [21].

Liraglutide 3.0 mg daily SC injection has been FDA approved since December 2014 as an adjunct to a reduced calorie diet and greater physical activity for chronic weight management in adults with a BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 with at least one weight-related condition [22].

GLP1-RA medications have been well studied in patients at high risk of CVD with unique benefits. One meta-analysis of 56,000 patients with T2DM on GLP1- RA showed a 12% reduction in MACE (HR 0·88; 95% CI 0·82–0·94) and a 12% reduction in all-cause mortality (HR 0.88; 95% CI 0·83–0·95). Additionally, a 9% (HR 0·91; 95% CI 0·83–0·99) reduction in admission to the hospital for heart failure was also observed [23,24]. GLP1- RA should be strongly considered in patients with existing CVD or at a high risk, irrespective of HbA1c [24]. Lower doses of GLP1-RA are recommended in older population ≥65 years to avoid hypoglycemia [24]. Liraglutide and semaglutide should be used cautiously in patients with pancreatitis, and retinopathy screening should also be undertaken.

These medications are contraindicated in pregnancy or breastfeeding, or in patients with a personal or family history of multiple endocrine neoplasia type 2 or medullary thyroid cancer [24]. The SUSTAIN-6 and PIONEER-6 trials demonstrated beneficial effects of GLP1- RA on cardiovascular outcomes among those with T2DM [25,26].

2.3. Tirzepatide

Tirzepatide is a dual-glucose-dependent, insulinotropic polypeptide and GLP1- RA that is currently FDA approved for management of T2DM. The Study of Tirzepatide [LY3298176] Versus Semaglutide Once Weekly as Add-on Therapy to Metformin in Participants With Type 2 Diabetes (SURPASS-2) trial demonstrated superiority to semaglutide with mean changes in HbA1c of 2.3%, and weight reductions of 11 kg with the highest dose of 15 mg at 40 weeks. There were no significant differences in LDL-C or blood pressure between the two study drugs [27]. Although tirzepatide has not been approved by the FDA for weight management in patients without T2DM, Eli Lilly has been granted fast track status by the FDA for its approval especially after the promising weight loss results [28]. The use of tirzepatide was associated with a 21% change in body weight from baseline after 72 weeks. The percentage of participants who had $\geq$5% weight loss was up to 91% (95% CI 88–94) with the highest dose of 15 mg weekly [29].

2.4. Orlistat

Orlistat is a gastric and pancreatic lipase inhibitor that is approved in the US and Europe for the long-term pharmacologic management of obesity [30].

Recently, Ardissino et al. conducted a large nation-wide propensity-score matched study with close to 37,000 patients with obesity who were matched on a 1:1 basis to orlistat vs placebo, followed for 6 years. MACE was lower in the orlistat group (HR 0.74; 95% CI 0.66–0.83) compared with placebo. The orlistat group had lower rates of MI with (HR 0.77; 95% CI 0.66–0.88), ischemic stroke (HR 0.68; 95% CI 0.56 to −0.84), new-onset heart failure (HR 0.79; 95% CI 0.67–0.94), as well as CKD stage III development (HR 0.78; 95% CI 0.73–0.83) and mortality (HR 0.39; 95% CI 0.36 to −0.41). There were no differences in revascularization rates (HR 1.12; 95% CI 0.91–1.38) [31].

Side effects of orlistat use are mostly gastrointestinal, including abdominal discomfort and soft oily stools. There is a possible decrease in fat-soluble vitamin absorption with long-term orlistat treatment. For example, one study noted ~8% decrease in 25-hydroxy-D concentrations after 2 years of orlistat use [32]. Thus, vitamin level monitoring should be considered in patients taking this medication.

Orlistat 120 mg daily oral was approved by the FDA in 1999 for obesity management in conjunction with a reduced caloric diet, and to reduce the risk of regaining weight after prior weight loss and in 2007. Orlistat 60 mg was approved as a daily oral medication for over-the-counter use for weight loss in adults with overweight, 18 years and older, in conjunction with a reduced-calorie and low-fat diet [33].

In a study comparing orlistat with liraglutide, both drugs reduced weight, FPG, systolic blood pressure, LDL-C and alanine transaminase over 7 months follow up. However, weight loss was higher with liraglutide (−7.7 kg) compared with orlistat (−3.3 kg), and more individuals lost at least 5% of their baseline weight with liraglutide (64.7%) than orlistat (27.4%) [34]. Orlistat decreased FPG by 5 mg/dl, LDL-C by 9 mg/dl and systolic/diastolic blood pressure by 4/3 mmHg points [34].

2.5. Naltrexone-bupropion

Naltrexone is a water-soluble crystalline medication that is a pure opioid antagonist. Bupropion is also a water-soluble crystalline medication that is a dopamine reuptake inhibitor related to the phenylethylamines, which are known for their stimulant effects [35]. The mechanism of this combined medication on weight loss is poorly understood. Some research suggests the hypothalamic melanocortin system and the mesolimbic reward system are the potential target of this combination [36,37].

Patients from four phase III clinical trials: COR-1, COR-II, COR-BMOD and COR-DM were pooled over a 14 month follow up period. All four studies included 4536 patients and demonstrated statistically significant and clinically meaningful weight loss of approximately 5–9 kg after 52 weeks of treatment with the extended-release form of naltrexone ER/bupropion ER compared with placebo. Significant improvements in cardiometabolic markers including waist circumference, triglycerides, and high-density lipoprotein-cholesterol (HDL-C) and HbA1c [38] were also observed.

Significant reductions in HbA1c were noted in the naltrexone ER/bupropion ER group vs placebo (−0.6% vs −0.1%), with a placebo-corrected difference of 0.5% at the end of 56 weeks ($p < 0.001$) [38,39]. In addition, a greater percentage of patients achieved a HbA1c of <7.0% (44.1 vs 26.3%) or HbA1c of <6.5% HbA1c (20.7 vs 10.2%) in naltrexone ER/bupropion ER vs placebo groups, respectively [38,39]. Triglyceride reductions were noted in the intervention vs placebo group (−11% vs −0.8%, respectively with $p=0.007$). HDL-C increases were also noted in the intervention vs placebo group (+3% vs −0.3%, respectively with $p<0.001$) [39]. No significant change in FPG, LDL-C or CRP were observed between the two groups [39].

Most side effects are gastrointestinal, including nausea which was reported in 27%–34% of patients, and constipation (15%–24% of patients). Other side effects include, headache (14%–24%), dizziness (7%–14%), and dry mouth (8%). Some patients reported modestly higher systolic blood pressure with naltrexone ER/bupropion ER, however, there was a mean overall decrease in systolic blood pressure compared with baseline at the end of the study, with mean reductions of 3.4–11.4 mmHg [36,40].

Sposito et al. performed a systematic review and meta-analysis to examine cardiovascular outcomes in randomized controlled trials that tested naltrexone, bupropion, or the combination among patients with obesity, smoking, and other clinical conditions [41]. This analysis found that these medications, or their combination, were not associated with the incidence of MACE, and no increased risk of nonfatal MI or all-cause death was observed [41].

In 2011, the FDA declined this medication's approval because of concerns regarding long-term cardiovascular safety in adults with overweight and obesity [37]. However, the combination gained FDA approval in 2014 for patients with obesity or overweight with at least one other weight-related condition or illness, such as high blood pressure or T2DM. Clinicians should consider stopping this medication at 12 weeks if at least 5% of weight loss is not achieved [42,43].

Two cardiovascular outcome trials with naltrexone-bupropion were conducted, the LIGHT and the CONVENE trial. However, both studies were halted prematurely, thus their effects on CVD remain uncertain [44].

2.6. Phentermine-topiramate

Phentermine is an amphetamine analogue which is a sympathomimetic that increases the release of noradrenaline from presynaptic vesicles in the hypothalamus [45]. It has been approved as monotherapy for the management of adults with obesity in the US for short-term use only (up to 12 weeks) in conjunction with dietary and lifestyle modifications [46].

Topiramate isa sulfamate-substituted monosaccharide used to treat epilepsy and prevent migraines. Weight loss is thought to occur because of carbonic-anhydrase inhibition on taste but the major effect is likely γ-aminobutyric acid activity (GABA) receptor activation given the interaction between GABA and leptin pathways [47].

Phentermine and topiramate extended-release (PHEN/TPM-ER) has been approved as a once-daily combination therapy for chronic weight

management in adults with obesity and overweight with at least one weight-related comorbidity as an adjunct to behavioral and lifestyle modifications [45].

Multiple trials examined the safety and efficacy of the extended-release formulation (PHEN/TPM-ER). First, the EQUIP trial (Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial) included 1267 participants with obesity (≤70 years of age and BMI ≥35 kg/m^2; excluding patients with T2DM). Second, the CONQUER trial [48] (Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults) included 2487 patients with overweight and obesity (≤70 years of age; BMI ≥27 kg/m^2 and ≤45 kg/m^2) with at least two weight-related comorbidities, including hypertension and T2DM [48]. Third one is an extension study to CONQUER (SEQUEL study) which enrolled patients for an additional 52 weeks [49]. The fourth study included adults with T2DM who were evaluated in a 28-week extension of a 28-week double-blind, placebo--controlled phase 2 trial (56 weeks total) [50].

Taken together, these trails demonstrated that PHEN/TPM-ER was associated with significant and sustained weight loss in patients with overweight and obesity when compared with placebo. Weight loss was dose dependent and ranged from 5 to 10% weight loss from baseline at 14 months compared to 1.4% with placebo. Patients achieved at least 5% weight loss after 56 weeks of treatment and significant, sustained percentage and categorical weight loss through 108 weeks in the 2-year cohort [45].

Significant reductions in systolic and diastolic blood pressures with the higher combination dose were also noted, ranging from 7 to 8/5 mmHg mean reduction compared to baseline for PHEN/TPM-ER 7.5/46 and 15/92 doses throughout 1 and 2 years of treatment. There was a transient slight increase in the heart rate that was only significant in the highest dose of the combination drug [50,51].

PHEN/TPM-ER treatment resulted in significant reductions in serum triglycerides (reduction by 5.5–40%), HDL-C (increased by 2–20%), and LDL-C (reduction by 2–5%) vs. placebo ($P < 0.05$) in patients with dyslipidemia at week 56, along with a net reduction in lipid-lowering medication use. Reductions in CRP by 1–3 mg/L were also observed [52].

Theoretical increases in heart rate and blood pressure may occur with the use of phentermine, which may be due to amphetamine-like side effects based on similarities in drug pharmacology. However, short term observational studies disproved these theoretical negative cardiovascular effects, leading to its approval for short term use [53]. Phentermine is contraindicated in patients with CVD particularly in patients with high-risk conditions such asprior coronary artery bypass grafting (CABG) or stenting, history of congestive heart failure, stroke, arrhythmias, congestive heart failure [54]. Although some studies demonstrated safety of long term (>3 months) phentermine use for "low CVD risk patients", they excluded patients with diagnoses or procedure codes for any cardiovascular outcome including MI, stroke, angina, CABG or carotid artery procedure [55]. Hence, phentermine should not be used in patients with CVD [54]. Phentermine monotherapy may be considered selectively using a patient centered approach [53,54]. Despite the precautions regarding phentermine, a retrospective cohort study suggested no increased risk of MACE in patients taking combination phentermine/-topiramate [56].

Pregnancy testing is recommended prior to starting topiramate therapy for women in childbearing age due to the risk of congenital malformations [6]. PHEN/TPM-ER is currently approved at doses of 3.75 mg/23 mg, 7.5 mg/46 mg, 11.25 mg/69 mg and 15 mg/92 mg for chronic weight management in individuals age ≥12 years with obesity and overweight with at least one weight-related comorbidity [45].

2.7. Comparison between weight loss medications

The Institute for Clinical and Economic Review (ICER) finalized its report on anti-obesity medications for effectiveness and value-evidence [57]. The authors concluded that semaglutide and phentermine/topiramate had greater weight reduction than liraglutide and bupropion/naltrexone. Also, GLP1-RA (semaglutide and liraglutide) resulted in better blood sugar and blood pressure control compared to usual care but were not superior to other anti-obesity medications [57]. In addition, the studies assessing long-term outcomes data only included adults with T2DM [57], thus outcomes among individuals without T2DM remains uncertain. Furthermore, phentermine/topiramate and bupropion/naltrexone were considered the most cost effective compared to lifestyle modification alone [57].

In a network meta-analysis comparing all aforementioned classes of medications (except semaglutide and tirzepatide) head-to-head in achieving weight loss, liraglutide was associated with an OR of 5.54 (95% CrI 4.16–7.78), orlistat with an OR of 2.70 (95% CrI 2.34–3.09), naltrexone-bupropion with an OR of 3.96 (95% CrI 3.03–5.11), phentermine-topiramate an OR of 9.22 (95% CrI 6.63–12.85) for achieving at least 5% weight loss with at least 1 year of treatment. They all were associated with higher odds of achieving 10% of weight loss from baseline compared with placebo. Liraglutide was associated with achieving at least 10% weight loss in an estimated 34% of patients, orlistat with an estimated 20%, naltrexone-bupropion in an estimated 30%, and phentermine-topiramate in 54% of participants. Phentermine-topiramate was associated with the highest probability of achieving at least 5% and 10% weight loss, followed by liraglutide, naltrexone-bupropion, and lastly orlistat. Liraglutide was most likely to be discontinued due to adverse events (OR 2.95; 95% CrI 2.11–4.23; Surface Under the Cumulative RAnking curve SUCRA, 0.20) followed by naltrexone-bupropion (OR 2.64; 95% CrI 2.10–3.35; SUCRA, 0.23) [58].

Obesity pharmacotherapy should be individualized based on risk profile and amount of weight loss desired, while considering medical insurance coverage. Data from recent meta-analyses showed that the overall placebo-subtracted weight reduction with the use of anti-obesity medications for at least 12 months ranges from 2.9% to 6.8%; phentermine/topiramate (3 trials, −6.8%) liraglutide (4 trials, −5.4%), naltrexone/bupropion (5 trials, −4.0%), and orlistat (17 trials, −2.9%). However, randomized controlled trials are required to evaluate the long-term safety profile and effects on MACE [59]. Table 1A summarizes current medications for management of obesity. Table 1B summarizes the effect of anti-obesity medications on CVD risk factors.

3. Endoscopic procedures

Patients with BMI ≥ 40 kg/m^2 or BMI ≥ 35 kg/m^2 with comorbidities should be considered for bariatric surgery. However, less than 1% of all eligible patients actually undergo any operation [60]. Bariatric endoscopy encompasses malabsorption techniques, use of space occupying devices, restrictive methods, and aspiration therapies [61]. Generally, endoscopic procedures are reserved for patients with prohibitive surgical risk (patients with CVD and other significant co-morbidities) or serve as a bridge to traditional bariatric surgery [62].

3.1. Intra-gastric balloons

This endoscopic procedure includes balloons filled with saline of different sizes and shapes, developed to aid in management of obesity for patients with a BMI 30–40 kg/m^2. At 6 months, these devices can lead to reductions of 7–15% of total body weight (TBW) [62], and have been approved by the FDA [63].

The American Gastroenterological Association Practice Guidelines for obesity management cites remission of T2DM, hypertension, and dyslipidemia when using this procedure compared to a noninvasive approach. Benefits were most pronounced among patient with a FPG level >100 mg/dl, HbA1c >6.5%, and among patients with a BMI >40 kg/m^2 at baseline. Results on changes in lipid profiles were mixed [64].

Advantages include reversibility, repeatability, and more significant weight loss may be achieved when used in combination with other

Table 1A
Summary of anti-obesity medications.

Drug Name	Mechanism of action	Weight loss	Clinical trial data	Side effects	Clinical use
Semaglutide	GLP-1 receptor agonist (GLP1-RA)	Mean change in weight 15% at 17 months	STEP1 trial: 2000 patients randomized to 2.4 mg weekly Semaglutide vs placebo. At 17 months, mean weight loss 15% vs 2.4%.	Transient diarrhea and nausea	Once weekly SC injection approved by FDA 2021.
Liraglutide	GLP1-RA	6.2% at 14 months	SCALE-Maintenance: 500 patients assessed. At 56 weeks Liraglutide patients achieved 6.2% weight loss vs 0.2%.	Hypoglycemia, gastrointestinal and nausea	Daily SC injections approved by FDA 2014.
Tirzepatide	GLP1-RA and insulinotropic polypeptide	Up to 21% at 18 months	SURPASS-2 trial showed superiority to semaglutide. Mean change in A1c 2.3%, and weight 11 kg with the highest dose of 15 mg at 40 weeks.	Gastrointestinal and nausea	SC injections once weekly approved by FDA May/2022 for T2DM. Not approved for obesity management yet but one pharmaceutical company has been granted fast track status by the FDA for its approval.
Orlistat	Gastric and pancreatic lipase inhibitor	Up to 5% at 3 months	Ardissino et al., 37,000 patients to Orlistat vs Placebo. At 6 years, Orlistat group had lower MACE (HR 0,74), lower MI (HR 0.77), lower stroke (HR 0.68), lower HF (HR 0.79), lower CKDIII (HR 0.78), and lower mortalitiy (HR 0.39)	Abdominal discomfort. Fat-soluble vitamin malabsorption	Daily oral medication, approved 1999, and 2002 for over the counter.
Naltrexone-bupropion	Centrally acting (opioid antagonist- dopamine reuptake inhibitor)	5–9 kg at 13 months	COR-1, COR-II, COR-BMOD and COR-DM: 4536 patients to Naltrexone-bupropion vs placebo. At 52 weeks, Naltrexone-bupropion group had 5–9 kg weight loss. Sposito et al.: Naltrexone-bupropion was not associated with the incidence of MACE as compared to placebo. No statistical significance found in the incidence of nonfatal MI or all-cause death.	Nausea, constipation, headache, dizziness, dry mouth	Twice a day oral medication Approved by FDA 2014.
Phentermine-Topiramate ER	Amphetamine analogue-increasing GABA activity and inhibiting glutamate activity	5–10% over 14 months	EQUIP, CONQUER, SEQUEL and 28-week extension study: analysis of the four trials showed that patients with phentermine-topiramate ER had 5–10% weight loss from baseline at of 56 weeks compared to placebo.	Possible increase in heart rate.	Daily oral medication Approved by FDA 2012.

Table 1B
The effect of anti-obesity medications on CVD risk factors.

Medications	Clinical trial	LDL-C	Trial included Patients with T2DM	FPG/HbA1c (%)	Change SBP/DBP	CRP
Semaglutide	STEP-1 trial	Ratios to baseline 0.47	No	−8 mg/dl/-0.45% at 68 weeks	−6/3 mmHg	ratios to baseline 0.47
Liraglutide	SCALE-Maintenance trial	Small magnitude change	No	−9 mg/dl at 56 weeks	+0.2/1.4 mmHg	−20 nmol/l
Tirzepatide	SURPASS-2 trial	No change	Yes	−2.3% at 40 weeks		
Orlistat	XENSOR study comparing orlistat to liraglutide	−9 mg/dl	Yes (20% of orlistat patients with T2DM)	−5 mg/dl	−4/3 mmHg	N/A
Naltrexone-bupropion	COR-1, COR-II, COR-BMOD and COR-DM trials.	No change	Yes	−0.6% at 56 weeks	Overall mean reduction of 3.4–11.4 mmHg	N/A
Phentermine-Topiramate	EQUIP, CONQUER, SEQUEL and 28-week extension study.	-2-5% compared to baseline	N/A	N/A	-7-8/5 mmHg at week 56. There was a transient increase in heart rate with the highest dose.	-1-3 mg/l

weight reducing modalities. Higher rates of nausea and vomiting have been reported with intragastric balloons compared to a noninvasive approach [62].

3.2. Endoscopic aspiration therapy

Endoscopic aspiration therapy includes a percutaneous gastrostomy tube, known as an A-Tube, that is inserted in similar fashion to a percutaneous endoscopic gastrostomy tube (PEG) tube, then the external portion is attached to the aspiration device. This therapy is approved for patients with a BMI of 35–55 kg/m^2. Long term use may result in 14–18% TBW loss after 6–24 months. Apart from reported abdominal pain and peristomal complications, this reversible therapy has minimal side effects, and can be done in the outpatient setting [61,65].

A meta-analysis including 590 patients who had aspiration therapy reported favorable effects in blood pressure: −7.8 mm Hg/−5.1 mm Hg; triglycerides: −15.8 mg/dl; HDL-C: 3.6 mg/dl; HbA1c: −1.3% at 1 year. Patients experienced 18%–19% total weight loss and 46–49% excess weight loss at 1–4 years ($p<0.0001$ for all) [66].

3.3. Endoscopic sleeve gastroplasty (ESG)

An endoscopic sleeve gastroplasty is created using a series of endoluminally placed sutures through the gastric wall from the pre-pyloric

antrum to the gastroesophageal junction (GEJ) along the greater curvature of the stomach. ESGs are reserved for patients with a BMI of 30–40 kg/m^2 [61] and may result in weight loss of 12–19% after 6–24 months [65]. These procedures usually require expertise and technical skills in specialized centers. Complications include nausea, vomiting, peri-gastric fluid collections and extra-gastric bleeding [61,65].

In a study of 91 patients undergoing ESG, 14% TBW loss was achieved at 6 months, while 18% and 21% TBW loss was achieved at 1 and 2 years, respectively. At 12 months following ESG as compared to baseline prior to ESG, there was a significant overall reduction in HbA1c (mean± SD, 6.1%±1.1% vs 5.5% ±0.48%, P=0.05). There were also significant reductions in systolic blood pressure (129 ±13.4 mm Hg vs 122.2 ±11.69 mmHg, P = 0.02) and serum triglycerides (131.84 ± 83.19 mmol/dl vs 92.36 ±39.43 mmol/dl, P =0.02). However, there was no significant change in LDL-C (P =0.79) [67].

3.4. Gastrointestinal bypass sleeves

A gastrointestinal bypass sleeve uses a liner made of Teflon that is deployed in the duodenal bulb extending into the small bowel, creating a mechanical barrier that allows food to bypass the duodenum and proximal jejunum. Duodenaljejunal and gastroduodenojejunal bypass sleeves exist as alternatives [61]. This procedure is approved for patients with BMI 35 kg/m^2 and obesity related complications or BMI of $\geq$ 40 kg/m^2. Patients achieved 49% excess weight loss at 5 years, which was sustained long term [68]. However, the overall morbidity rate is 19% at 5 years, with significant adverse events including gastroesophageal reflux disease, stricture at the gastrojejunal anastomosis, dumping, internal herniation and incisional hernia [61,68,69].

One meta-analysis showed that patients achieved 35.3% (95% CI 24.6–46.1) excess weight loss at 12 months after duodenojejunal bypass sleeve. At 12 months, HbA1c levels decreased by −0.7 (95% CI -1.76 to 0.2, P = .16) and to −1.7 (95% CI -2.5 to −0.86, P < 0.001) at 24 weeks [70].

Other small bowel endoscopic interventions include ablation technology of superficial duodenal mucosa and self-assembling magnets that can create incisionless magnetic anastomosis directing bowel contents and bypassing certain segments of the gastrointestinal system [61]. Overall, endoscopic options for management of obesity are relatively novel and may only be available in experienced centers. Long-term safety is not well established, particularly in patients with existing CVD. Thus, there is limited data or comparison studies between different endoscopic modalities in relation to CVD outcomes. Table 2A summarizes endoscopic procedures for the management of obesity. Table 2B summarizes the effect of endoscopic procedures on CVD risk factors.

Table 2A
Summary of Endoscopic procedures in management of obesity.

Endoscopic procedure	Mechanism	Weight loss	Side effects
Intra-gastric balloons	Space occupying balloons	7–15% of total body weight loss at 6 months	Nausea and vomiting
Endoscopic aspiration therapy	Percutaneous gastrostomy tube	14–18% total body weight loss between 6 and 24 months	Abdominal pain and peristomal complications
Endoscopic Sleeve Gastroplasty (ESG)	Endoluminally placed sutures through the gastric wall.	12–19% total body weight loss at 6–24 months duration	Nausea, vomiting and peri gastric fluids collections, and extra gastric bleeding
Gastrointestinal Bypass Sleeves	Liner extends into small bowel to bypass the duodenum and proximal jejunum	Achieving 49% of excess weight loss at 5 years	Overall morbidity rate of 19% at 5 years due to gastroesophageal reflux disease, stricture at the gastrojejunal anastomosis, dumping, internal herniation and incisional hernia
Ablation technology and self-assembling magnets	Novel therapies only available in experienced centers	N/A	N/A

Table 2B
Endoscopic procedures effect on cardiovascular disease risk factors.

Endoscopic Procedure	LDL-C	FPG/HbA1c	SBP/DBP
Intra-gastric balloons	Decreased	Decreased	N/A
Endoscopic aspiration therapy	N/A	−1.3% at 1 year	−8/ 5 mmHg
Endoscopic Sleeve Gastroplasty	No change	mean± SD, −6.1%± 1.1%	Decreased
Gastrointestinal Bypass Sleeves	N/A	−0.7% at 1 year −1.7% at 2 years	N/A

4. Bariatric surgery for obesity

The National Institutes of Health have set forth indications for bariatric surgery, recommended for patients with a BMI >40 kg/m^2 and for patients with BMI 35–40 kg/m^2 with associated comorbid conditions who failed to sustain weight loss through non-surgical means [71]. However, 30 years after these recommendations, the American Society for Metabolic and Bariatric Surgery (ASMBS) and International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) released updates in December of 2022. These updates include consideration of metabolic and bariatric surgery (MBS) for individuals with a BMI $\geq$35 kg/m^2, regardless of the presence, absence, or severity of co-morbidities. MBS should also be considered for individuals with a metabolic disease and BMI of 30–34.9 kg/m^2 [72]. Cardiac, pulmonary and other perioperative comorbidities that affect operative risk as well as psychological risk should be assessed prior to bariatric surgery. Furthermore, bariatric surgeries can be malabsorptive, restrictive or both [73].

4.1. Roux-en-Y gastric bypass (RYGB)

A Roux-en-Y Gastric Bypass (RYGB) is a procedure in which a gastric pouch is created by dissecting the stomach into a pouch followed by A Roux-en-Y gastrojejunostomy which diverts food from the body of the stomach, duodenum, and proximal jejunum [73]. This can be performed through an open, laparoscopic, or robotic technique and is considered a malabsorptive-restrictive surgery [74]. The mortality from gastric bypass is estimated to be 0.2%, which is higher than both sleeve gastrectomy and gastric banding [75]. If done laparoscopically, there is lower morbidity and mortality [76].

Early complications include anastomosis leak which may manifest in the first 24 h, bleeding, bowel obstruction and increased thromboembolic disease, which accounts for half of the early complications [74].

Late complications include herniation, stricture of anastomosis and fistula formation. Micronutrient malabsorption has been reported with calcium, iron, vitamin B12 and thiamin [73]. Weight loss generally ranges between 12% −45% of TBW at 6 months-3 years following surgery [77], which can be maintained >10 years following surgery [73].

In an observational prospective study assessing outcomes after gastric bypass surgery, adjusted mean weight loss from baseline was −45 kg, −36 kg and −35 kg at 2, 6 and 12 years after surgery, respectively. The rate of comorbidities remission at 12 years was better with surgery as compared with the non-surgery group, with favorable effects observed in T2DM (51% vs 5%), hypertension (36% vs 14%), and LDL-C (59% vs 6%)

[78]. Incidence of T2DM at 12 years was 3% in surgery group versus 26% in non-surgery group and incidence of hypertension was 16% vs 47% [78].

4.2. Sleeve gastrectomy

Sleeve gastrectomy is performed through a longitudinal resection of the stomach creating a tubular stomach based on the lesser curvature without anastomosis [73]. Sleeve gastrectomy and gastric bypass are the two most common bariatric surgeries performed in the United States [68]. Generally, patients experience slightly less weight loss with sleeve gastrectomy compared with RYGB [73].

Accelerated gastric emptying is a common risk [73]. Studies suggest that more radical antral resection leads to faster gastric emptying which may lead to reductions in the negative feedback satiety signals produced by the presence of food in the stomach, which theoretically may inhibit weight loss [79]. Vomiting, gastroesophageal reflux disease, and hernia are common complications [68].

Laparoscopic sleeve gastrectomy has shown promising long-term results. A retrospective study evaluating 578 patients with mean baseline BMI of 42.5 $\pm$ 5.5 kg/m^2 who underwent this surgery experienced mean reductions in BMI and weight loss of 33 $\pm$ 6 kg/m^2 and 59 $\pm$ 30%, respectively at roughly 10 years follow up [80]. There were significant remission rates reported for hypertension (52%), dyslipidemia (58%) and T2DM (72%) [80].

In a study comparing sleeve gastrectomy and gastric bypass, mean percentage excess weight loss at 5 years was 49% (95% CI 45%–52%) after sleeve gastrectomy vs 57% (95% CI 53%–61%) after gastric bypass [68]. At 5 years follow up, there was no significant difference between gastrectomy and bypass surgery for diabetes remission and discontinuing hypertension medications, but there was a trend towards higher remission rates in the bypass group [68]. LDL-C values were lower in the gastric bypass group compared with the sleeve gastrectomy group [68].

4.3. Gastric banding

Gastric banding is done by placing a band at the proximal portion of the stomach that is adjustable and connected with a subcutaneous balloon to control the rate of gastric emptying resulting in early satiety [73]. Weight loss of 16% TBW has been reported at after 3 years [81]. A review on adjustable gastric banding reported excess weight loss of 40–65% at 3 years and37-68% excess weight loss at 5 years. These results remained consistent over 15 years of follow up [82]. Complications include gastric pouch enlargement, which can be prevented by decreasing the size of the gastric pouch volume, erosion and gastroesophageal reflux disease. Techniques are rapidly evolving to mitigate these risks [83]. Notably, gastric banding is rarely performed at many institutions [84].

4.4. Intermittent vagal blockade

The vagus nerve plays an important role in satiety, metabolism, and autonomic control in upper gastrointestinal track function [85]. Intermittent vagal blockade has been developed to establish weight loss through this mechanism and is achieved through leads placed in vagal trunk. This results in vagal blockade leading to early satiety and may avoid neural adaptations compared with truncal vagatomy. This procedure has been approved by the FDA [86]. A randomized, double-blinded, placebo-controlled trial evaluated vagal blockade in the treatment of obesity, which included 8 sites across the United States. A total of 240 participants underwent vagal nerve blockade, which resulted in a 24% reduction in weight at 12 months, compared with 16% reduction in weight in the placebo group. Mild to moderate heartburn and abdominal pain were the most common side effects reported in the vagal blockade group [85].

4.5. Biliopancreatic diversion with duodenal switch (BPD-DS)

The biliopancreatic diversion with duodenal switch is done by creating a gastrectomy, followed by an anastomosis between the proximal duodenum and a portion of bypassed intestine [73]. Weight loss was slightly greater with this procedure compared to RYGB [73]. The excess weight loss at 2, 5 and 10 years was 80.6%, 69.3%, and 67.4%, respectively. This study reported 85% and 70% complete remission of T2DM rates at 2 and 5 years, respectively [87].

4.6. Single anastomosis duodenal-ileal bypass with sleeve gastrectomy (SADI-S)

Biliopancreatic diversion with duodenal switch and single anastomosis duodenal-ileal bypass with sleeve gastrectomy (SADI-S) is a hypoabsorptive bariatric procedure that is generally indicated in patients with obesity and (BMI $\geq$ 50 kg/m^2) [88]. This surgery is similar to BPD-DS, but it requires only one anastomosis [89].

There is little data on long term outcomes for patients who have undergone SADI-S. Thus, the ASMBS released a statement in 2020 cautioned against this procedure, citing a lack of evidence [90].

4.7. Cardiometabolic effects of bariatric surgery

A meta-analysis of 73 studies demonstrated consistent benefits in CVD risk factors following bariatric surgery. LDL-C was reduced by 22%, triglycerides by 32%, and HDL-C was increased by 19% at 4 years of follow up [91]. Although these studies didn't report on the use of lipid lowering therapies, the benefits of bariatric surgery on reductions in LDL-C have been shown in 62%–86% of patients [92].

Another meta-analysis demonstrated reductions in hypertension rates of 46$\pm$8% especially when BMI was reduced by 10 kg/m^2 [93]. However, these impressive results may be attenuated over time, which may be due to long standing arterial wall stiffening [94].

An open label randomized controlled trial was conducted to assess diabetes control and remission rates among patients undergoing bariatric surgery with RYGB or biliopancreatic diversion vs medical management. They included patients with a BMI of $\geq$35 kg/m^2 and concomitant T2DM. Diabetes remission was defined as an HbA1c concentration of $\leq$6·5% and a FPG of $\leq$5·6 mmol/L at 2 years without pharmacological treatment for 1 year. Remission was achieved in 50% of the surgical arm versus 0% in the medical arm (p=0·0007) [95]. One other study showed recurrence of diabetes was as high as 58% at 15 years in the gastric banding arm compared to usual care that included advanced lifestyle modifications [96].

Weight loss has been shown to decrease inflammation via reductions in inflammatory markers such as CRP, erythrocyte sedimentation rate, interleukin-6 and an increase in adiponectin, an anti-inflammatory adipokine which plays a role in insulin sensitivity [97].

Flow-mediated dilation of the vasculature, a surrogate of vascular reactivity, was studied in a systematic review that included 269 patients. There was a significant improvement in FMD (Mean difference 5.65%; 95% CI 2.87–8.03, P<0.001) at 3 months-2 years following bariatric surgery [98]. The longer the duration of reduced vascular reactivity due to obesity, the higher the chance of recurrence following bariatric surgery [73]. Hence, early referral to obesity specialists may result in better outcomes.

A systematic review and meta-analysis that included more than 29,000 patients who underwent bariatric surgery, with a follow-up 8.5 years showed that weight loss varied from 15 to 30% depending on the bariatric surgery procedure performed. It has been reported that there was a 52% reduction in mortality (OR 0.48), 54% reduction in MI (OR 0.46) and 51% reduction in stroke (OR 0.49) [99,100].

Surgical weight loss also may reduce hard cardiovascular events. In a systematic review comparing surgical to non-surgical (e.g. intensive lifestyle intervention, standard of care, or no specific therapy) weight

Table 3
Summary of Bariatric surgery procedures in management of obesity:

Bariatric surgery	Mechanism	Weight loss	Side effects
Roux-en-Y Gastric Bypass (RYGB)	A gastric pouch and a bypass that diverts food from the body of the stomach, duodenum, and proximal jejunum	12% -45% of total body weight (TBW) loss at 6 months-3 years	Malabsorption, herniation, stricture of anastomosis, fistula
Sleeve Gastrectomy	Stomach is resected longitudinally creating a tubular stomach.	49% of excess body weight at 5 years	Accelerating gastric emptying
Gastric banding	A band placed at the proximal portion of the stomach and connected to a subcutaneous balloon	16% TBW at 3 years	Gastric pouch enlargement, GERD and erosion
Intermittent vagal blockade	Early satiety stimulation by vagal blockade	24% of excess body weight at 1 year	Heartburn and abdominal pain
Biliopancreatic diversion with duodenal switch	Gastrectomy and an anastomosis between proximal duodenum and a portion of bypassed intestine	15%, 18% and 18% of excess body weight at 2, 5 and 10 years	High incidence of short- and long-term complications with high degree of malabsorption

loss, surgical weight loss led to reductions in cardiovascular mortality (HR 0.59; 95% CI 0.47–0.73, P<0.001), all-cause mortality (HR 0.55; 95% CI 0.49–0.62, P<0.001), incident heart failure (HR 0.50; 95% CI 0.38–0.66, P<0.001), MI (HR 0.58; 95% CI 0.43–0.76, P<0.001) and stroke (HR 0.64; 95% CI 0.53–0.77, P<0.001). There was no significant association with atrial fibrillation [101]. Table 3 summarizes bariatric surgery procedures in management of obesity.

5. Conclusion

Obesity is a complex disease that should be evaluated by a multidisciplinary team to provide optimal care. Management decisions should be individualized based on the available data, weight loss desired, risk profile, and surgical/medical expertise. Some endoscopic and bariatric surgery options may only be performed in experienced centers, and long-term safety and efficacy data may be lacking. Outcome trials for anti-obesity medications are still ongoing in this evolving field, which will continue to expand options for patients with obesity. Although randomized controlled trial data on cardiovascular outcomes are generally poor, observational data suggests weight loss may improve cardiovascular health. While weight loss is important, sustaining weight loss is just as critical. Early referral to experienced obesity specialists is highly recommended to avoid long term morbidity and mortality related to the growing epidemic of obesity.

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Author contributions

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Conflict of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

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