Emerging Role of GLP-1 Agonists for Weight Loss in Adults Without Diabetes

Introduction

Obesity among adults is a body mass index (BMI) of ≥30 kg/m^2. In 2022, 16% of adults globally were obese 16% obese, an increase from 8.7% in 2000.[1,2] The prevalence of obesity has increased by almost 150% in the Southeast Asia Region, up from 1.9% to 4.7%, and nearly 140% in the Western Pacific Region, up from 2.7% to 6.4%.[1]The prevalence of obesity in females is higher than in males. According to the NHANES data in 2017-2018, the age-adjusted prevalence of overweight and obesity in males was 49.9% compared to 53/4% in females. [1-3]

Overweight and obesity are global health issues that result in numerous health complications, including type 2 diabetes, cardiovascular disease, depression, and malignancy.[3-5] While lifestyle modification might improve quality of life and health outcomes, only 61% of individuals with obesity complete lifestyle programs.[6,7] Bariatric surgery, including the Roux-en-Y gastric bypass, provides long-term protection against complications in people with high BMI.[8] However, these procedures have risks, and many people might hesitate to undergo what they perceive as a major surgical procedure.[9] As a result, there is a growing interest in exploring alternative treatment options such as glucagon-like peptide 1 receptor agonists (GLP-1 RA) for weight loss in patients without diabetes.

Medication for Obesity

Pharmacotherapy is an important alternative or adjunct therapy for weight loss, in addition to lifestyle modification and bariatric surgery.[10] Currently, the following drugs are approved by the FDA for long-term use in cases of weight management:[11,12]

1) Orlistat, a lipase inhibitor
2) Phentermine/topiramate, a norepinephrine /dopamine /serotonin-releasing agent with GABA-A receptor agonist,
3) Naltrexone/bupropion, an opiate receptor antagonist with a dopamine/norepinephrine reuptake inhibitor,
4) Liraglutide and semaglutide, glucagon-like peptide 1- receptor agonists (GLP1-RA)
5) Setmelanotide: Melanocortin-4 receptor agonist.

Lorcaserin was withdrawn in 2020 as a safety clinical trial showed an increased occurrence of primary cancers.[14] The focus here will be the efficacy and safety of GLP-1RA therapy in managing obesity in adults without diabetes. The pharmaceutical industry has been increasingly interested in this class of drugs due to their ability to mimic the effects of endogenous GLP-1 release in the intestine and the brain, leading to a decrease in feeding and weight reduction.[15-18]

Glucagon-like Peptide-1

Glucagon-like peptide-1, an incretin, is a 30- or 31- amino-acid-long peptide hormone with a biphasic secretion pattern – early (within 10-15 minutes) followed by a longer (30-60 min) second phase.[19] GLP-1 is produced in the intestinal enteroendocrine L cells upon ingesting food. GLP-1 is rapidly degraded by dipeptidyl peptidase,[20] and neutral endopeptidase.[21] It is primarily eliminated through the kidneys

by glomerular filtration, tubular uptake, and catabolism.[22] Intact GLP-1 has a plasma half-life of approximately 2 minutes, making it impractical for clinical use.[23]

GLP-1 also promotes insulin secretion in a glucose-dependent manner,[24] insulin gene transcription, and mRNA stability and biosynthesis,[25-27] thereby decreasing blood sugar levels. It also inhibits glucagon (reduces the potential for hypoglycemia) and stimulates somatostatin secretion. In the brain, it has been shown to promote satiety, which reduces food and water intake and decreases body weight.[28-30]

GLP1-RAs belong to a class of drugs that mimic the action of GLP-1 in the body. Additionally, GLP1-RAs decrease appetite by inhibiting gastric emptying, acid secretion, and motility, reducing postprandial blood glucose levels in patients with type 1 and 2 diabetes.[31-33] GLP1 RAs also have cardioprotective effects attributed to their natriuretic, diuretic, and blood pressure-reducing effects and reduction of inflammation.[34]

GLP1-RA design

As discussed, GLP1 is not an ideal therapeutic agent due to rapid degradation and elimination. However, this knowledge has aided in developing other agents by two different approaches - prolonging half-life by inhibiting degradation by DPP-4 (DPP-4 inhibitors) or developing GLP-1 RAs resistant to degradation by DPP-4. While GLP-1 agonists are less likely to be degraded by DPP-4 and promote insulin secretion, DPP-4 inhibitors extend the half-life of GLP-1, thereby enhancing insulin secretion and suppressing glucagon release, which helps in achieving glycemic control. Both GLP-1 RA and DPP-4 inhibitors have been used for glycemic management.[35] However, only GLP-1 RAs have shown to have weight loss effects, and DPP-4 inhibitors are weight neutral. [36]

The first GLP1-RA – exenatide was approved by the FDA in 2005 for glycemic control in type 2 diabetes as an adjunct to diet and exercise.[37] Exenatide was inspired by exendin-4, a natural peptide hormone in the saliva of the venomous lizard Gila monster, which has similar activity to GLP-1 but a longer half-life due to resistance to DPP-4 secondary to the replacement of Ala8 by Gly-8 at the cleavage site.[38]

Lixisenatide is structurally similar to exendin-4, where six lysine residues were added to the C Terminus, and the Proline residue was deleted.[39]

By adding hydrophobic long-chain fatty acids capable of binding to albumin to GLP1, glomerular filtration, and renal clearance decrease and half-life increase. This approach aided the development of the following GLP1-RAs: liraglutide, semaglutide, and tirzepatide. Modifications made to the structure of GLP1 in liraglutide include the attachment of C-16 palmitoyl fatty acid to Lys-26 via a gamma-glutamic acid spacer and the replacement of Lysine 34 with arginine 34.[40] This modification extended the half-life to 13 hours.

Semaglutide, although resembling liraglutide, exhibits two amino acid substitutions that render it resistant to DPP-4. The first involves the replacement of Gly with 2-aminoisobutyric acid at position 2; the second is the attachment of octadecanoic diacid to the side chain of Lys-26 through a short

polyethylene glycol spacer and a γ-glutamic acid linker.[41] Furthermore, the presence of C-18 fatty acid moiety results in a high affinity for albumin, thus inhibiting glomerular filtration.[41] This translates to a half-life of approximately 168 hours in humans.[42,43]

Tirzepatide combines structural features of both GLP-1 and exenatide. It is dual-acting, GIP- RA (glucose-dependent insulinotropic polypeptide-receptor agonist), and GLP-1 RA. Amino acid 2-aminoisobutyric acid (Aib) replaces Ala-8, thus inhibiting degradation by DPP-4, and C20 fatty diacid is attached to the side chain of Lysine 20 via a linker of L-γ-glutamic acid and two 8-amino-3,6-dioxaoctanoic acids.[44]

Many GLP1-RA have been approved for the treatment of type 2 diabetes. However, only liraglutide and semaglutide are approved for long-term use in weight management.

Liraglutide

Liraglutide was the first daily injectable GLP1-RA approved in people with type 2 diabetes (Victoza®, up to a dose of 1.8 mg).[45] Liraglutide (Saxenda®) injection 3 mg was approved for weight management in adults with excess weight (BMI ≥27 kg/m^2) who also have weight-related medical problems or obesity (BMI ≥30 kg/m^2) and children aged 12-17 years with body weight above 132 pounds (60 kg) and obesity in 2014.[46] This was based on the results of various clinical trials. [47-51]

The first phase 2 trial to study liraglutide in patients with BMI ≥30 -40 kg/m^2 was a 20-week trial and compared liraglutide at different doses (1.2 mg, 1.8 mg, 2.4 mg, and 3.0 mg, injected subcutaneously once daily) with placebo (once daily subcutaneous injection).[47] It excluded individuals with type 1 or 2 diabetes, major medical problems, drug-induced obesity, those using other weight-lowering pharmacotherapy, those enrolled in a clinical weight control study over the past three months, and bariatric surgery recipients.[47] It concluded that liraglutide treatment was well tolerated, induced weight loss, improved cardiovascular risk factors, and decreased prediabetes.[47] Participants on liraglutide lost significantly more weight compared with those on placebo (4.8 kg, 5.5 kg, 6.3 kg, and 7.2 kg for liraglutide 1.2 mg, 1.8 mg, 2.8 mg, and 3.0 mg, respectively vs 2.8 kg for placebo; $P < .01$ for all doses).[47] Additionally, participants receiving 2.4 mg and 3.0 mg liraglutide lost significantly more weight than those receiving orlistat (6.3 kg and 7.2 kg vs. 4.1 kg, $p < 0.01$ for both).[47] Seventy-six percent of individuals lost more than 5% weight with liraglutide 3.0 mg compared to 30% with placebo or 44% with orlistat.[47] In addition to reducing blood pressure at all doses, liraglutide at 1.8-3.0 mg per day decreased the prevalence of prediabetes (84-96% reduction).[47] Two-year extension data from this initial trial revealed liraglutide 3.0 mg recipients lost 5.8 kg (95% CI, 3.7-8.0) more weight than those on placebo and 3.8 kg (95% CI,1.6-6.0) more than those on orlistat.[48] At year 2, participants on liraglutide 2.4/3.0 mg for the entire two years lost 3.0 kg (95% CI,1.3-4.7) more weight than those on orlistat (P <.001).[48] Participants who completed two years on liraglutide 2.4/3.0 mg maintained a weight loss of 7.8 kg from screening.[48] The prevalence of prediabetes and metabolic syndrome also decreased by 52% and 59%, respectively, with improvements in blood pressure and lipids in participants on liraglutide 2.4/3 mg.[48]

Treatment with liraglutide 3.0 mg in the phase 3a development programme SCALE (Satiety and Clinical Adiposity – Liraglutide Evidence in individuals with and without diabetes) spanning over 56 weeks resulted in significantly greater and sustained weight loss compared to placebo and with improvements in a variety of cardiometabolic risk factors.[49-51] At week 56, the average weight loss with liraglutide 3.0 mg plus IBT was 7.5%, whereas it was 4.0% with placebo combined with IBT (estimated treatment difference -3.4%, *P = .0003*).[52] Significantly more individuals on liraglutide 3.0 mg than placebo achieved ≥ 5% weight loss (61.5% vs. 38.8%; *P = .0003*), ≥ 10% weight loss (30.5% vs. 19.8%; *P = .0469)*, and ≥ 15% weight loss (18.1% vs. 8.9%; *P = .0311*).[52]

In another study over 56 weeks, 3.0 mg of liraglutide, as an adjunct to diet and exercise, was associated with a significantly higher reduction in body weight (-8.4±7.3 kg with liraglutide vs 2.8±6.5 kg with placebo [a difference of -5.6 kg, 95% CI, -6.0 to -5.1;*P <.001*) and improvement in metabolic control when compared with placebo.[50]

The SCALE Maintenance randomized study enrolled obese or overweight patients who lost ≥5% of initial weight during a low-calorie diet.[49] They were randomly assigned to liraglutide 3.0 mg per day or placebo (subcutaneous administration) for 56 weeks.[49] A significantly greater decrease in body weight was observed in the liraglutide group than in the placebo group (6.2% versus 0.2%,*P < .0001*).[49] A significantly greater proportion of patients receiving liraglutide achieved weight loss ≥ 5% (50.5% versus 21.8%), ≥ 10% (26.1% versus 6.3%), and maintained the 5% weight loss achieved during the run-in (81.4% versus 48.9%) than patients receiving placebo (*P < .0001* for all).[49] Statistically significant improvements in cardiovascular risk factors were also noted in the liraglutide group.[49]

SCALE Obesity and Prediabetes Study Group over 56 weeks randomized patients with BMI≥30kg/m^2 or BMI ≥27kg/m^2 with treated or untreated dyslipidemia or hypertension to receive either liraglutide 3 mg or placebo in addition to lifestyle modification.[50] The liraglutide group had a greater proportion of patients who lost ≥5% (63.2% versus 27.1%) and ≥10% (33.1% versus 10.6%) of the initial body weight as compared with placebo (*p < 0.001* for both).[50] The liraglutide group had a significant decrease in the mean BMI, waist circumference, HbA1c, FPG, fasting insulin, systolic and diastolic blood pressures (cardiometabolic risk factors) as compared with placebo (*P < .001* for all).[50]

SCALE Sleep Apnea trial patients randomized to liraglutide 3.0 mg group had a significantly greater reduction in the mean body weight (5.7% versus 1.6%), had a greater proportion of patients who lost ≥ 5% (46.3% versus 18.5%) and ≥ 10% (23.4% versus 1.7%) of the initial body weight as compared to placebo (*p < 0.0001* for all three).[51] Mean HbA1c and systolic blood pressure were also significantly lower in the liraglutide group (*P < .0001*).[51]

Results from a pooled analysis of the SCALE trials suggested liraglutide 3 mg did not increase the risk and possibly had a beneficial effect on cardiovascular safety in an overweight and obese population.[53]

Overall, liraglutide 3.0 mg is well tolerated in chronic weight management.[46] Like most obesity medications, it has some common side effects like nausea, vomiting, diarrhea, mild constipation, hypoglycemia, headache, dyspepsia, fatigue, dizziness, abdominal pain, and increased lipase.[56] Gastrointestinal intolerability is common and was noted to be the most common cause of

discontinuation in patients with adverse events in clinical trials.[47-52] To mitigate these digestive effects, it is advised to initiate treatment with a daily dose of 0.6 mg subcutaneously and increase it by 0.6 mg every week until a dose of 3 mg is reached.[46] The treatment should be stopped if a 3 mg dose is not tolerable. Liraglutide should be used cautiously in patients with impaired kidney or liver function but is safe and does not affect kidney function in patients with moderate renal impairment (estimated glomerular filtration rate 30-59 ml/min/1.73 m^2).[55] Patients starting liraglutide should be cautioned about the risks of acute pancreatitis, acute gallbladder disease, serious hypoglycemia, heart rate increase, hypersensitivity reactions, and suicidal behavior.[55] Also, it is marketed with a black box warning about the risk of medullary thyroid carcinoma (MTC) as it has been shown to cause thyroid C-cell tumors in rats and mice; however, with the evidence to date including over 6000 patients, no increased risk for MTC has been observed in humans.[46] Liraglutide is also contraindicated in pregnancy and is not recommended in nursing mothers, children, patients taking insulin or other GLP-1 agonists.[46] Finally, although liraglutide (as well as other GLP-1 agonists) increases heart rate slightly, the clinical implications of this change are not known, and it does not appear to adversely affect cardiovascular outcomes at the 1.8 mg dose.[56]
Newer GLP-1RAs, such as semaglutide or other drugs in development for obesity, may have advantages over liraglutide due to lower cost and longer half-life, avoiding the need for daily injections.[57]

Semaglutide

Semaglutide is a second-generation GLP1-RA that has been studied extensively in clinical trials. The STEP (Semaglutide Treatment Effect in People with obesity) trials were a series of multicenter, randomized, double-blind, phase 3, placebo-controlled trials that examined the efficacy and safety of a higher 2.4 mg dose of semaglutide compared to the approved 0.25 mg and 0.5 mg doses for weight loss in patients with overweight or obesity.[58-63]
STEP 1 enrolled adults with obesity (BMI ≥ 30) or overweight BMI > 27 kg/m^2 with a weight-related condition who did not have diabetes and randomly assigned them to receive once weekly semaglutide or placebo in addition to lifestyle interventions for 68 weeks.[58] A mean change in body weight from baseline to week 68 of -14.9% was observed in the semaglutide group as compared with -2.4% in the placebo group, for an estimated treatment difference of -12.4 percentage points (95% confidence interval [CI], -13.4 to -11.5; P<0.001).[58] A significantly higher number of participants in the semaglutide group than in the placebo group achieved weight reductions of ≥ 5% (86.4% vs 31.5%), ≥10% (69.1% vs 12.0%), and ≥15% (50.5% vs 4.9%) at week 68 (*P<0.001* for all three comparisons of odds).[58] Participants who received semaglutide had a greater reduction in cardiometabolic risk factors from baseline than those who received a placebo.[58] In people with complications secondary to overweight and obesity, studies have recommended a weight loss of 10-15%. With Semaglutide, approximately 70% of the participants achieved at least 10%, and about 50% achieved 15 % weight loss. This study concluded that once-weekly Semaglutide, in addition to lifestyle intervention helps achieve substantial and sustained mean weight loss.[58]

In the STEP 3 trial at week 68, participants receiving 2.4mg semaglutide experienced a mean weight loss of 16% vs. 5.7 % for placebo (difference: -10.3%; *P < .001*).[59] Furthermore, a significantly higher proportion of participants who received semaglutide lost ≥ 5% of their baseline body weight compared

to those in the placebo group (86.6% vs. 47.6%, respectively, *P* < *.001*).[59] The semaglutide group was also found to have a higher likelihood of achieving weight reduction of ≥10%, ≥15%, ≥20% by week 68 compared to the placebo group (75.5% vs 27%, 55.8% vs 13.2 %, and 35.7 % vs 3.7% respectively, *P* < *.001*)).[59] Additionally, the semaglutide arm reported a significantly higher reduction in waist circumference and blood pressure, BMI, glycated hemoglobin, C-reactive protein, total cholesterol, and LDL at week 68 than with placebo.[59]

STEP 4 concluded maintaining treatment with semaglutide compared to placebo in individuals without diabetes led to continued weight loss.[60] After 16 weeks of dose escalation to semaglutide 2.4 mg and four weeks of maintenance dose 2.4 mg, 803 participants were randomized to 48 weeks of subcutaneous semaglutide or switched to placebo, in addition to lifestyle intervention in both groups.[60] The change in mean body weight was observed to be -7.9% in the semaglutide arm compared with a +6.9% in the placebo arm from weeks 20 to 68 (difference, -14.8; *P* < *.001*).[60] Waist circumference, systolic blood pressure, and SF-36 physical functioning score also improved significantly in the subcutaneous semaglutide group vs the placebo (*all P* < *.001*).[60]

STEP 5 found that when continued for two years, semaglutide resulted in a significant and long-lasting weight reduction and improved cardiometabolic risk factors in adults with obesity (BMI ≥ 30 kg m^2) or overweight (BMI ≥ 27 kg/m^2) with at least one weight-related comorbidity without diabetes.[61] The mean change in body weight from baseline to week 104 was -15.2% in the semaglutide group versus -2.6% with placebo (estimated treatment difference of -12.6 percentage points, *P* <*.0001*).[61]

In the STEP 6 trial, semaglutide 2.4 mg once weekly resulted in a significantly higher weight reduction at week 68 compared with semaglutide 1.7 mg or with placebo (-13.2% vs -9.6% vs 2.1%; *P<.0001*) in adults from east Asia.[62] At week 68, a significantly higher number of participants were noted to have lost ≥5% weight in the semaglutide 2.4 mg (83%) and semaglutide 1.7 mg group (21%) than in the placebo group (both *P* <*.0001).*[62]

Similarly, in STEP 8, semaglutide 2.4 mg resulted in significantly greater weight loss at week 68 than once daily liraglutide 3.0 mg (-15.8% vs -6.4%; difference -9.4 percentage points [95% CI, -12.0 to -6.8]; *P* < *.001*) when combined with lifestyle modification.[63] Participants had significantly greater odds of achieving ≥10% or ≥15% and ≥20% weight loss with semaglutide vs liraglutide (70.9% of participants vs 25.6% [95% CI, 3.5 to 11.2], 55.6% vs 12.0% [95% CI, 4.1 to 15.4], and 38.5% vs 6.0% [95% CI, 3.5 to 19.1], respectively; all *P* < *.001*).[63] More gastrointestinal adverse events were reported in participants taking semaglutide compared with liraglutide (84.1% vs 82.7%).[63]

In a meta-analysis of RCTs that assessed the weight loss effect of GLP-1RAs in adults without diabetes compared with control groups, a more significant weight loss was seen in GLP-1 RA groups with an overall mean difference of -7.1 kg (95% CI -9.2 to -5.0) (I2 = 99%).[64] The comprehensive analysis found that GLP-1 RA improved glycemic control without increasing the risk of hypoglycemic events.[64] Better control of blood pressure and plasma levels of LDL, HDL, and triglycerides was seen with GLP-1 RA treatment.[64] Subgroup analysis showed a greater treatment effect of semaglutide than liraglutide.[64] Vomiting, nausea, dyspepsia, diarrhea, constipation, and abdominal pain were GLP-1 RA-associated common adverse effects.[64]

Semaglutide injection 2.4 mg (Wegovy®) once weekly was approved by the FDA in June 2021 for chronic weight management in adults with BMI≥30 kg/m^2 or BMI≥27kg/m^2 with at least one weight-related comorbidity and in adolescents >12 years of age with an initial BMI ≥95% for age and sex.[65] Semaglutide is initiated at a dose of 0.25 mg/week subcutaneously for the first month, followed by dose escalation to 0.5 mg /week for the second month, then 1 mg during the third month and a dose of 1.7 mg/week for the fourth month and finally patients can choose to stay at 1.7 mg or increase to 2.4 mg during the fifth month onwards based on tolerability and adverse effects.[65] Semaglutide should be used with caution in patients with hypersensitivity reactions, diabetic retinopathy, acute pancreatitis, cholelithiasis, chronic kidney disease with low GFR, medullary thyroid cancer, and multiple endocrine neoplasia (MEN).[65]

The most common adverse reactions to semaglutide in adults are nausea, vomiting, diarrhea, constipation, vomiting, and abdominal pain.[58-65] While nausea and diarrhea were the most common adverse events with Semaglutide, they were typically mild-to-moderate in severity and short in duration.[58-65] Other reported side effects include pancreatitis, gallbladder stones, increased risk of hypoglycemia in patients with type 2 diabetes, renal failure, severe allergic reactions, changes in vision in people with type 2 diabetes, increased heart rate, depression, and thoughts of suicide.[65]

In the past, GLP-1RAs were thought to be associated with an increased risk of pancreatitis and pancreatic cancer.[66] However, meta-analyses have failed to show such an association. In a meta-analysis of 113 trials,12 reported no information on pancreatitis, and 72 reported no events in all treatment groups. Furthermore, the incidence of pancreatitis and pancreatic cancer was not significantly different from that observed in the comparator groups (MH-OR [95% CI] 0.93 [0.65-1.34], *P = .71*, and 0.94 [0.52-1.70], P = .84, respectively), a significantly increased risk of cholelithiasis (MH-OR [95% CI] 1.30 [1.01-1.68], P = .041) was detected. Based on the above analysis, GLP1-RAs appear safe for patients with acute pancreatitis; therapy in patients with cholelithiasis would require further research.[66,67] Although thyroid C-cell tumors have been observed in rodents, they have not been detected in humans.[68]

The SELECT trial studied the effects of once-weekly semaglutide in addition to standard of care prevention of major adverse cardiovascular events (MACE) in people with CVD with overweight or obesity for five years. The study excluded patients with a history of cardiac disease, heart failure, and diabetes. It demonstrated a significantly higher reduction in major cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) of 20% for people treated with semaglutide 2.4 mg compared with placebo.[69-70]

Tirzepatide

Tirzepatide is a new dual GLP-1RA and glucose-dependent insulinotropic polypeptide (GIP) that has shown promising results for weight loss. Tirzepatide (Mounjaro®) was approved by the FDA in May 2022 as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[71] Tirzepatide is only approved for those with type 2 diabetes mellitus and should not be used in those with type 1 diabetes mellitus or other forms of diabetes, such as latent autoimmune diabetes in adults.[72,73]

A meta-analysis of seven RCTs involving over 12,300 patients showed that weekly tirzepatide led to greater weight loss compared to weekly semaglutide 2.4 mg, daily semaglutide 0.4 mg, and liraglutide 3 mg. Tirzepatide and weekly semaglutide had similar efficacy, but both significantly increased the likelihood of achieving a 5%-20% weight loss compared to liraglutide. Although all GLP-1RAs effectively reduced weight, tirzepatide was notably superior in efficacy, maintaining a comparable safety profile. [Alkhezi 2023]

Another meta-analysis of RCTs designed to study the efficacy of tirzepatide in patients with obesity or overweight revealed that among 5800 patients, 78.22%, 55.60%, 32.28% achieved ≥5%, ≥10%, and ≥15% weight loss, respectively.[76] Tirzepatide 5 mg demonstrated weight loss superiority relative to placebo (mean difference: -12.47 kg, 95% CI: -13.94 kg to -11.00 kg) and semaglutide (mean difference: -1.90 kg, 95% CI: -2.97 kg to -0.83 kg) with dose-dependent increase for 10 mg and 15 mg doses. [76]

The SURMOUNT clinical trial program was a multicenter, randomized, double-blinded, parallel, placebo-controlled trial evaluating the efficacy and safety of tirzepatide.[77] In SURMOUNT 1, once-weekly tirzepatide (5 mg, 10 mg, or 15 mg) over 72 weeks demonstrated substantial and sustained weight loss compared to a placebo. The mean percentage change in weight at week 72 was -15.0% with 5-mg weekly doses of tirzepatide, -19.5% with 10-mg doses, and -20.9% with 15-mg doses and -3.1% with placebo (*P<0.001* for all comparisons with placebo).[78] The percentage of patients who lost ≥5% bodyweight was 85%, 89%, and 91% with 5 mg, 10 mg, and 15 mg of tirzepatide, respectively, and 35% with placebo.[78] Approximately 50% and 57% of participants in the 10-mg and 15-mg groups had a reduction in body weight of ≥20%, compared with 3% in the placebo group (P <.001 for all comparisons with placebo).[78] Tirzepatide was also shown to impact all the cardiometabolic factors positively.[78]

The SURMOUNT-2 trial showed an average weight reduction of 13.4% (13.5 kg) on 10 mg and 15.7% (15.6 kg) on 15 mg compared to placebo 3.3% (3.2 kg).[71] Additionally, 81.6% (10 mg) and 86.4% (15 mg) of people taking tirzepatide achieved at least 5% body weight reduction, the other co-primary endpoint, compared to 30.5% of those taking placebo.[71]

The SURMOUNT-3 and 4 trials showed adults with obesity who received tirzepatide lost >25% of their body weight and could maintain the weight loss for 88 weeks.[79] In SURMOUNT-3, tirzepatide and intensive lifestyle modification led to an additional 21.1% mean weight (for a total weight loss of 26.6%) over the 84-week study.[79] Approximately 94.4% taking tirzepatide lost ≥ 5% body weight reduction compared to 10.7% in the placebo groups over 72 weeks.[79] In SURMOUNT-4 participants achieved 21.1% weight loss during a 36-week tirzepatide lead-in period and an additional 6.7% weight loss during a 52-week continued treatment period, for a total mean weight loss of 26.0% over 88 weeks.[79]

Another study compared tirzepatide versus semaglutide in patients with T2DM.[72] A more significant weight loss was reported with tirzepatide over semaglutide (− 7.6 kg, −9.3 kg, −11.2 kg, and − 5.7 kg with 5 mg, 10 mg, 15 mg of tirzepatide and 1 mg of semaglutide, respectively).[72] Tirzepatide also showed overall greater improvements in blood glucose (−2.01 %, −2.24 %, −2.30 %, and − 1.86 % of hemoglobin level reduction, respectively) with fewer adverse effects than semaglutide.[72]

Tirzepatide should be avoided in patients with personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2, gall bladder disease, or diabetic retinopathy.[80] The most common adverse events associated with tirzepatide were mild to moderate gastrointestinal events, nausea, diarrhea, and vomiting. No significant hypoglycemia was reported in the SURMOUNT clinical trials.[77-80]

Conclusion

In conclusion, GLP1-RAs have emerged as a promising treatment for chronic weight management in adult patients without diabetes. Their ability to promote weight loss, suppress appetite, and improve cardiometabolic risk factors in this population makes them a valuable tool.
Most studies have shown that some weight loss occurs even without treatment with medication. GLP1-RA should supplement lifestyle modification, including diet and exercise, and be used under medical supervision. Medication should be considered only when non-pharmacologic therapies have been ineffective. Further research is needed to explore the long-term effects and safety profile of GLP-1 RA. While the SELECT trials recently published the initial finding of a reduction in MACE by 20% with long-term use of semaglutide, a full review of the study results is awaited. Nonetheless, current evidence supports using GLP1-RA as an effective pharmacologic option for weight loss in adults without diabetes.

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