Turkish Journal of Diabetes and Obesity / *Türkiye Diyabet ve Obezite Dergisi*
Review / *Derleme*

Medical Treatment in Obesity

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Cite this article as: Çetinkaya Altuntaş S. Medical treatment in obesity. Turk J Diab Obes 2023;3: 263-272.

ABSTRACT

The main aim of obesity management is to improve health. Weight loss of 5-10% or more provides improvement in obesity and obesity-related comorbid diseases (Type 2 diabetes mellitus, hypertension, dyslipidemia, fatty liver disease, etc.) as well as an increase in quality of life. As with all chronic diseases, obesity management requires a multidisciplinary approach. Individual treatment should be targeted. Obesity treatment consists of lifestyle changes, medical treatment, and bariatric surgery. Until today, many drugs have worked with the aspect of appetite reduction and energy expenditure through the nervous system. However, many drugs have been withdrawn due to safety concerns. In recent years, drugs with gut-based incretin mechanisms of action have attracted considerable interest. The first approved glucagon-like peptide-1 receptor agonist (GLP-1) analog liraglutide is promising. As a new treatment, the GLP-1 analog semaglutide 2.4 mg weekly is approved for the treatment of obesity. Another new treatment, tirzepatide, the first dual GLP-1/ glucagon-like peptide-1 receptor agonist (GIP) analog, has achieved up to 20% weight loss in obese patients and has also shown positive cardiovascular outcomes. Although promising, there is no comparative study of new effective obesity drugs with bariatric surgery, which is currently known as the most effective method, with weight loss up to 25%. Today, as the pathophysiogenesis of obesity is better understood, newer, safer molecules will continue to emerge. In this review, current information about the current and future medical treatments for obesity will be discussed.

Keywords: *Obesity, Treatment, Pharmacotherapy*

Obezitede Medikal Tedavi

ÖZ

Obezite yönetiminin temel amacı sağlığı iyileştirmektir. %5-10 ve daha fazla kilo kaybı obezite ve obezite ile ilişkili komorbid hastalıklarla (Tip 2 Diyabetes Mellitus, hipertansiyon, dislipidemi, yağlı karaciğer hastalığı vb.) iyileşme sağladığı gibi yaşam kalitesinde de artış sağlar. Tüm kronik hastalıklarda olduğu gibi obezite yönetimi multidisipliner yaklaşım gerektirir. Bireysel tedavi hedeflenmelidir. Obezite tedavisi yaşam tarzı değişiklikleri, medikal tedavi ve bariyatrik cerrahiden oluşur. Günümüze kadar pek çok ilaç sinir sistemi üzerinden iştah azaltma ve enerji harcanması yönü ile çalışmıştır. Fakat birçok ilaç güvenlik endişesi ile geri çekilmiştir. Son yıllarda bağırsak temelli inkretin etki mekanizmaları olan ilaçlar oldukça ilgi çekmektedir ve umut vaat etmektedir. Bu ilaçlardan ilk onaylanan glucagon-like peptide-1 receptor agonist (GLP-1) analogu liraglutide'dir. Yeni tedavi olarak GLP-1 analogu semaglutide 2,4 mg haftalık olarak obezite tedavisinde onaylanmıştır. Bir yeni tedavi daha olan ilk dual GLP-1/ glucagon-like peptide-1 receptor agonist (GIP) analogu olan tirzepatide obez hastalarda %20'ye varan kilo kaybı sağlamıştır ayrıca kardiovasküler sonuçları da olumludur. Yeni çıkan her ne kadar umut vaat etsede şu anda en etkili yöntem olarak bilinen %25'lere varan kilo kaybına ulaşılan bariatrik cerrahi ile yeni çıkan etkili obezite ilaçların karşılaştırmalı çalışması yoktur. Günümüzde obezitenin fizyopatogenezi daha iyi anlaşıldıkça daha yeni, güvenli moleküller ortaya çıkmaya devam edecektir. Bu derlemede obezitenin halen kullanılmakta ve gelecekte kullanılacak olan medikal tedaviler ile ilgili güncel bilgi verilecektir.

Anahtar Sözcükler: *Obezite, Tedavi, Farmakoterapi*

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DOI: 10.25048/tudod.1386433

Received / *Geliş tarihi* : 05.11.2023
Revision / *Revizyon tarihi* : 19.12.2023
Accepted / *Kabul tarihi* : 19.12.2023

INTRODUCTION

Obesity is a complex and multifactorial disease. It causes many health problems including cardiovascular diseases, hypertension (HT), hyperlipidemia (HL), cerebrovascular disease, cancer, obstructive sleep apnea syndrome, non-alcoholic fatty liver disease, gastroesophageal reflux, biliary tract disease, polycystic ovary syndrome, infertility, osteoarthrosis and depression, especially type 2 diabetes (T2DM) and prediabetes (1). The World Health Organization (WHO) has reported that obesity will be the most important health problem of the 21st century. In our country, the prevalence of obesity is increasing in both adults and children and adolescents. Therefore, obesity is now recognized as a chronic, recurrent, metabolic disease that has reached epidemic proportions and needs to be treated (2). As with all chronic diseases, obesity management requires a multidisciplinary approach. Individual treatment should be targeted. Obesity treatment consists of life style changes (LSC), medical treatment, and bariatric surgery. Until today, many drugs have worked with the aspect of appetite reduction and energy expenditure through the nervous system. However, many drugs have been withdrawn due to safety concerns. For example: Sibutramine was withdrawn due to increased cardiovascular events, rimonabant due to psychiatric side effects, and finally lorcaserin due to cancer risk. In recent years, drugs with gut-based incretin mechanisms of action have attracted considerable interest. It is promising. Today, as the pathophysiogenesis of obesity is better understood, newer, safer molecules will continue to emerge. In this review, current information about the current and future medical treatments for obesity will be given.

Benefits of Weight Loss in Obesity

Weight loss or body weight loss and its maintenance is very important as it reduces obesity and obesity-related health problems in both the short and long term. However, it also has economic benefits as it reduces health-related expenditures. The basic logic of weight loss is to create a negative energy balance with a calorie-restricted diet and increased physical activity (3). Obesity treatment has favorable effects on blood glucose and blood pressure regulation, improvement of lipid profile, and the course of diseases such as cancer, gout, osteoarthritis, and depression. Self-confidence, well-being, and quality of life of individuals increase as a result of successful weight loss (4).

Obesity Treatment Overview

Treatment of obesity is analyzed under 3 main headings LSC, medical treatment, and bariatric surgery. Unfortunately, it is very difficult to achieve a weight loss of at least 5% of the initial weight, which is accepted as a success criterion in obesity treatment, only with lifestyle changes (5). Bariatric surgery, which provides weight loss up to 15% of the initial weight, is indicated for patients with a body mass index (BMI) of 40 and above (grade 3) or grade 2 obese patients with comorbidities. For intermediate grade 1 and overweight patients with additional co-morbidities, the combination of LSC and medical treatment is quite appropriate in this patient group. In the process of obesity treatment, only numerical weight loss and BMI should not be focused (5). In the follow-up of the obese individual, factors such as waist circumference, neck circumference, waist-hip ratio (especially in women), body distribution (dual-energy X-ray absorptiometry, bioelectrical impedance analysis, etc.), fat loss, and muscle ratio should be evaluated. The obesity treatment should be individualized, feasible, sustainable, and realistic. Weight loss of 5-10% of the initial weight in 6 months is considered successful weight loss. More weight loss can be targeted in individuals with grade 2-3 obesity with a BMI > 35 kg/m^2 (1).

To Whom Should Medical Treatment be Applied in Obesity?

Pharmacological treatment should be considered only one part of a very broad obesity management. Pharmacological treatment added to LSC improves obesity-related health problems and quality of life. The indications and contraindications of the drug must be followed in the choice of drug treatment. Currently, pharmacological treatment should be considered in patients with a BMI > 30 kg/m^2 or a BMI > 27 kg/m^2 with at least one comorbid obesity-related disease (T2DM, HT, etc.). The efficacy of pharmacotherapy should be evaluated after 3 months. If the patient has lost more than 5% of the initial weight (3% for those with T2DM), treatment is considered successful and should be continued (1). Determination of the fat ratio in the distribution of waist circumference and/or body composition can be used as an alternative, it is more realistic and is a better indicator in the evaluation of treatment success. If there is no response to treatment, the same treatment should not be continued and alternative methods should be considered. Today, pharmacological treatment options are very diverse all over the world (6).

Pharmacological Agents Used in Obesity Treatment

Lorcaserin

Approved in 2012 by the FDA, lorcaserin was the most prescribed weight-loss agent until early 2020. However, the European Medical Agency (EMA) did not approve this drug due to possible valvulopathy, suicide attempt, and cancer risk. Lorcaserin is a serotonin receptor agonist. Serotonin receptor agonists decrease appetite by stimulating propi-

omelanocortin (POMC) receptors in the arcuate nucleus of the hypothalamus and consequently decrease food intake (7). Lorcaserin, unlike other serotonin receptor agonists, shows an anorectic effect without pulmonary hypertension and valvulopathy because it is more specific for 5-hydroxytryptamine 2c (5-HT2c) (8). Until 2009, lorcaserine was not approved by the FDA due to the risk of an increase in some tumors in rats (9). In a later clinical study with 2400 participants treated with lorcaserine, concerns were raised about the risk of cancer in 1 year despite significant weight loss. Subsequently, in 2020, the FDA emphasized the cancer risk and cancer-related mortality with lorcaserin. Shortly thereafter, lorcaserin was withdrawn from the market (10).

Phentermine-topiramate

Phentermine-topiramate (PHEN -TPM) combination has been approved as an oral medical treatment in the USA, but has not been approved in Europe due to long-term cardiovascular concerns (11). PHEN is a sympathomimetic agent, that suppresses appetite via the central nervous system, but its long-term effects on weight management are still uncertain. TPM is an anticonvulsant. It increases the appetite suppressant effects of PHEN. With PHEN-TPM extended-release (ER) combination treatment, a weight loss of 10.9% was observed in 1.6% of the diet placebo arm applied to create a 500 kcal deficit in individuals without diabetes, while 32.3% of the other group had a weight loss of more than 15% (12). Similar results were reported in the 2-year follow-up of PHEN-TPM (13). The most common side effects of PHEN-TPM are paresthesia, upper respiratory tract infection, constipation, insomnia, taste change, dry mouth, headache, insomnia, anxiety, and depression. It is teratogenic in pregnancy because it causes cleft palate- cleft lip anomaly in the fetus (12).

Naltrexone-bupropion (NB)

Naltrexone is an opioid receptor antagonist, approved for the treatment of opioid dependence and alcohol. Bupropion is a dopamine and norepinephrine reuptake inhibitor. It is used for depression and smoking cessation (14). Although the mechanism of NB combination is not fully understood, it increases satiety, decreases appetite, and increases energy expenditure via hypothalamus-mesolimbic dopamine pathways. NB combination given with a 500 kcal deficient diet resulted in a weight loss of 0.9% in the control group and 6.3% in the other group in patients without diabetes (15). In another study, the rate of weight loss of more than 10% was 28.3% in the group given NB treatment (16). The most common side effects are nausea, headache, constipation, dry mouth, and anxiety. Larger cardiovascular safety studies are needed for this drug like PHEN-TPM.

Currently Used Obesity Drugs

Orlistat

Orlistat (120 -60 mg) is the longest-used anti-obesity drug approved by the FDA and EMA in 1999. It can be prescribed over 12 years of age. Orlistat is taken with a meal and a maximum 1 hour after a meal. Although the ideal daily dose is 3x1, if the meal is skipped or a lean meal is eaten, that dose is skipped. Since it will change the absorption of the drugs used by the patient, care should be taken in their concomitant use (warfarin, antiepileptics, levothyroxine, cyclosporine, etc.). Orlistat does not affect the central nervous system. Its mechanism of action is a gastric and pancreatic lipase inhibitor, inhibits the hydrolysis of triglycerides and prevents the absorption of free fatty acids. In this way, it decreases calorie intake without any effect on appetite (17). Considering its mechanism of action, orlistat is more suitable for individuals who are overweight and consume fatty foods. There is insufficient evidence on its use after bariatric surgery and data on its use over the age of 65 are limited. The advantages of the drug are that it is not systemic, compatible with combination therapies, and can be used in patients with a history of alcohol and substance addiction. Orlistat is a generally well-tolerated drug. Side effects are generally associated with the gastrointestinal tract (oily stools, gas, flatulence, bloating, diarrhea, etc.). Supplements containing fiber such as psyllium can be used to reduce these side effects. Since orlistat reduces fat absorption, vitamins A, D, K, and E should be used as supplements as there may be a deficiency of fat-soluble vitamins in long-term use. In the largest randomized controlled trial of orlistat called XENDOS (n=3305), orlistat led to a mean weight loss of 2.4% in 4 years of use. More importantly, the risk of T2DM decreased by 9% in the group using orlistat (18,19). Orlistat improves lipid profile by decreasing intestinal fat absorption and increasing insulin sensitivity. In the same study, 91% of the patients experienced at least one of the side effects of the drug and 8% stopped the drug for this reason. A problem with orlistat is whether these fatty acids, which are not absorbed, have a malignant effect on the colon. Although premalignant lesions, apoptosis-resistant lesions, and neoplasia have been found in animal studies (20), no association was found between orlistat administration and colorectal cancer in a study conducted with a very large cohort (n = 33,625 with orlistat; 160,374 with placebo) (21).

Current Obesity Drugs Based on Intestinal Hormones

GLP-1 Receptor Agonists

Liraglutide

Liraglutide (Victoza®) was approved for the treatment of T2DM in 2010 as 1.8 mg/day subcutaneously (SC) and

later liraglutide (Saxenda®) 3.0 mg/day by the FDA in 2014 and by the EMA in 2015 for obesity. In 2021, it was also approved over 12 years of age (22). Glucagon-like peptide 1 (GLP -1) is an incretin hormone secreted from the vagal nucleus of the distal ileum and proximal colon and solitary tract. It regulates blood sugar by increasing insulin and decreasing glucagon from pancreatic beta cells in a glucose-dependent manner. It slows down the gastric emptying rate, provides a feeling of postprandial satiety and swelling, gives a feeling of satiety and satiety through the limbic and cortex in the hypothalamus, and reduces food consumption by reducing appetite (23). Unlike endogenous GLP-1 (half-life of a few minutes), it remains more stable in plasma and is long-acting because it binds strongly to plasma proteins and is resistant to metabolism by dipeptidyl peptidase (DPP)-IV enzyme. The most common side effects of liraglutide are nausea, vomiting, diarrhea, constipation, and dyspepsia. Dose titration should be done to reduce these side effects. These side effects usually start within 4-8 weeks. In addition, gallbladder and biliary tract diseases are more common. Starting from the lowest dose of 0.6 mg, the dose should be increased weekly, eventually up to 3 mg. Although these side effects are tolerated over time, according to a meta-analysis, liraglutide is the most frequently discontinued anti-obesity drug due to side effects (13%), with the NB combination in second place (12%) (24). When liraglutide was first introduced, one of the most worrying side effects was acute pancreatitis. However, it has been observed that this concern was unnecessary in time. Therefore, amylase lipase monitoring is unnecessary in patients using this drug. However, it should be requested in patients with symptoms of acute pancreatitis (25). In animals, liraglutide has been found to cause proliferation in thyroid C cells. However, although this was not found in humans, liraglutide is contraindicated in patients with medullary thyroid cancer and multiple endocrine neoplasia (family history is also sufficient) (26). Liraglutide can be used safely in neuropsychiatric patients (27). The efficacy and safety of the drug have been demonstrated in randomized controlled clinical trials. The "SCALE" clinical trial program included 4 separate studies, SCALE obesity and prediabetes, SCALE diabetes, SCALE maintenance, and SCALE sleep apnea syndrome, and a total of 5700 patients worldwide were included in the studies. (28, 29, 30) In the SCALE studies, the average rate of weight loss achieved with liraglutide ranged between 5.7-8%. In the SCALE obesity and prediabetes study, in which a total of 3731 patients were enrolled and approximately 60% of the participants had prediabetes, the rate of weight loss of over 5% in the group using 3 mg liraglutide daily (in addition to LSC and exercise) was 63.2% in the liraglutide-treated group and 27.1% in the placebo group. At the end of the study, the incidence of prediabetes was lower in the liraglutide group compared to placebo, and fewer patients developed T2DM. The rate of progression to overt diabetes was 1.8% in the liraglutide-treated group and 6.2% in the placebo group. In the SCALE diabetes study, 3 mg/day liraglutide was shown to be beneficial not only in glycemic control but also in terms of weight loss in obese diabetic patients. Therefore, 3 mg liraglutide is a drug that should be preferred primarily in obesity pharmacotherapy in overweight and obese patients with T2DM. In the SCALE maintenance study, the rate of maintaining weight lost after 1 year in the liraglutide group was 12.2%, while this rate was 6.2% in the placebo group (29). Another important study with liraglutide was the LEADER study, which showed that liraglutide at a dose of 1.8 mg reduced cardiovascular events in T2DM patients during a 5-year follow-up (31). In 24-week chronic heart failure (CHF) patients (left ventricular ejection fraction ≤45% n=241) with or without diabetes, 1.8 mg liraglutide daily did not improve left ventricular systolic function. Therefore, cardiac safety concerns have been raised in this population (32). However, in the subanalysis of the study (n=1667 patients with T2DM and CHF New York Heart Association (NYHA) functional Class I-III), there was no increase in hospitalization rates compared with patients without heart failure (33). These findings suggest that liraglutide 1.8 mg is safe in patients with T2DM and CHF. Studies are available for its use after bariatric surgery and it can also be used in patients with a history of alcohol and substance abuse. For patients over 65 years of age, data is limited, and it is disadvantageous as it requires injection. It has been shown that liraglutide treatment is beneficial in patients with obesity caused by MC4R mutation. However, liraglutide is not approved for this indication (34).

Semaglutide

Semaglutide is a long-acting GLP-1 analog similar to liraglutide. 1 mg once weekly SC dose was approved for T2DM in the USA in 2017 and in Europe in 2018. Later, the oral form of the maximum dose of 14 mg was approved in the USA in 2019 and in Europe in 2020 for the treatment of T2DM. A phase 3 study of oral semaglutide treatment in non-diabetic obese patients - OASIS - is ongoing. The 2.4 mg SC form used once a week is approved for the treatment of obesity (35). FDA has approved for over 12 years of age (Ozempic®). Semaglutide reduces appetite, gives a feeling of satiety, controls eating behavior, and decreases food consumption, as well as controls blood glucose through similar mechanisms to liraglutide. It also decreases gastric emptying rate. Semaglutide exerts these effects via the GLP-1 pathway and by regulating food intake and preference via

the central nervous system (35). STEP studies have been conducted in overweight and obese patients with semaglutide given 2.4 mg SC weekly. 8 are international (STEP 1-5, STEP 8, STEP 9, 10), 3 are regional (STEP 6, STEP 7, STEP 11) and 6 have been published so far. STEP-1 (36) (large pivotal study) with weight loss, STEP-2 (37) with weight loss in T2DM patients, STEP-3 (38) weight loss with intensive behavioral therapy, STEP-4 (39) status of weight loss after the end of semaglutide treatment, STEP-5 (40) 2-year maintenance status of weight loss, STEP-8 (41) liraglutide versus semaglutide breakeven comparison. STEP -TEENS-STEP young (42) in adolescents, STEP-HFpEF in patients with heart failure and obesity (43), and STEP-HFpEF-DM in patients with both heart failure, obesity, and T2DM (44), where the weekly high dose of 7.2 mg (SELECT) is ongoing. Summaries of the studies are given in Table 1. In a clinical study conducted in non-diabetic patients, 2.4 mg semaglutide and 500 kcal/day of a deficit diet were given followed by 2.4% weight loss in the placebo group and 14.9% weight loss in the treated group at the end of 56 weeks. The rate of those with 15% weight loss compared to baseline weight was 50.5%, while the rate of those who achieved 20% weight loss was 32%(36). 20% weight loss is a rate almost achieved by bariatric surgery. While almost one-third of the participants reached this rate with semaglutide, the rate of reaching this target in the control group was only 1% (36). In another study, in 2.4 mg semaglutide treatment supported with low calories, the rate of weight loss in the first 8 weeks of 68 weeks of treatment was 5.7% in the placebo group and 16% in the treatment group (38). Weight loss plateaued after 60 weeks, provided that the program was followed (40). However, weight gain gradually started to be regained. This led to the idea of continuing the treatment (45). In a study conducted in patients with T2DM, weight loss after weekly 2.4 and 1 mg semaglutide administration was 9.6% and 7%, respectively. In the Placebo group, this rate was 3.4%. In this study, the decrease in HbA1c was 1.5%, 1%, and 0.4%, respectively. Finally, in a head-to-head comparison with liraglutide given daily, weekly 2.4 mg semaglutide was superior (41). The most common side effects observed with semaglutide are mild gastrointestinal side effects including nausea and vomiting (37). The rate of discontinuation of treatment due to side effects is between 3-7%. The initial starting dose of semaglutide is 0.25 mg and is increased weekly until the final dose of 2.4 mg. In this way, side effects can be reduced by dose titration. The rate of pancreatitis related to semaglutide was 0.2% in the STEP-1 study (36). Semaglutide contraindications are similar to liraglutide (46). As a result, obesity drugs approved until 2021 (PHEN-TPM, NB, orlistat, and liraglutide) provide approximately 5-10% weight loss with LSC, while semaglutide, used as 2.4 mg SC weekly, approved in 2021, provides approximately 14.9-17.4% weight loss in patients without diabetes with LSC. It is the most potent of the available obesity drugs, almost 2 times as much as other drugs (36). In other words, the weekly semaglutide dose of 2.4 mg SC is very effective and safe in overweight and obese patients. It also improves quality of life and improves cardiometabolic problems. Gut hormones-dual agonists and triple agonists Despite the effective weight loss of GLP-1 analogs, especially semaglutide, there is still a considerable difference between the weight lost with current treatments and bariatric surgery. One of the reasons for this is that not only GLP-1 but also other gut hormones such as glucose-dependent insulinotropic peptide (GIP), glucagon, amylin, and peptide YY increase the effects of GLP-1 in the postoperative period after bariatric surgery, resulting in additional weight loss and improving metabolic results (47).

Table 1: STEP Clinical Program

Clinical Program	Study	Cases -Number (n)	Treatment Week	Comparison	Mean Weight Loss Relative to Basal Weight (compared to semaglutide 2.4 mg vs.
Step 1	Weight Loss	1961	68	Placebo	-14.9 vs. -2.4
Step 2	Weight loss in T2DM	1210	68	Semaglutide 1 mg vs placebo	-9,6 vs –7 vs -3,4
Step 3	Intensive Behavioural Treatment and Weight Loss	611	68	Placebo	-16.0 vs -5,7
Step 4	Weight loss with maintenance	903	68	Semaglutide 2.4 mg 20 weeks followed by 48 weeks with placebo	-7,9 vs +6,9
Step 5	Long-term weight loss	304	104	Placebo	-15,2 vs –2,6
Step 6	East Asia	401	68	Semaglutide 1.7 mg with placebo	-13,2 vs -9,6 vs –2,1
Step 8	Breakeven with Liraglutide	338	68	Liraglutide 3 mg with	-15,8 vs –6,4
Step Teens	Weight loss in adolescents	201	68	Placebo	

Tirzepatide

Tirzepatide is the first dual co-agonist (GLP-1/GIP receptors). With this combination, the effect of GLP-1 is increased by GIP. It has a synergistic effect. Adding GIP to the GLP-1 analogue creates synergy. As mentioned above, both the central (reducing cravings and increasing satiety) and peripheral (slowing gastric emptying) weight loss effects of GLP-1 are enhanced by GIP. GIP receptors are found both in the brain and in subcutaneous white adipose tissue. Thus, activation of GIP receptors increases energy expenditure and improves the function of white adipose tissue. In addition, GIP reduces the nausea side effect of GLP-1 and increases its anorectic effect. In this way, GLP-1 tolerability and efficacy are further increased (45). The efficacy and safety of tripeptide were evaluated in the SURMOUNT studies, 6 of which were international and 2 of which were regional, in nondiabetic obese adults. Summaries of the studies are given in Table 2. In 5 cynical studies, tripeptide was given weekly at 5,10, and 15 mg was compared with placebo, 1 mg semaglutide, and long-acting insulin. The highest dose of tirzepatide provided an HbA1c reduction of 1.6% compared to placebo. Therefore, tirzepatide was approved as a glucose-lowering agent in 2022 as a once-weekly SC in addition to diet and exercise (48). Apart from its glucose-lowering effect, tirzepatide has a dose-dependent weight-loss effect. (5,10,15 mg 7%, 8.6% and 10.9% respectively) In the SURMOUNT-1 study, weight loss was 3.1% in the placebo (n=643) group followed up with LSC in the non-diabetic population at 3 different doses of 5,10,15 mg in 72 weeks follow-up, while weight loss was 15-20.9% in the group receiving tirzepatide (n=1896) (49). In a study with semaglutide 1mg (treatment dose for T2DM) and tirzepatide 15 mg, tirzepatide caused 5.5 kg more weight loss. 36% of participants achieved a weight loss of 15% or more at 40 weeks (SURPASS-2). Tirzepatide 15 mg of semaglutide 1 mg of tirzepatide reduced Hba1c by 0.45% more than 1 mg (50). After high doses of tirzepatide. HbA1c decrease is more than 1.6% more than placebo. With tirzepatide 5-15 mg, 30-57% of non-diabetic people lost 20% or more of their weight and 15-36% lost 25% or more (SURMOUNT-1). In the same study, while 95.3% of prediabetics returned to normoglycemia, this rate was 61.9% in the placebo group (49). The most important side effects of tirzepatide are nausea, vomiting, and constipation. These side effects are mild and transient. There is no risk of hypoglycemia. The risk of pancreatitis is similar to the placebo group, but the risk of cholecystitis is more frequent with tirzepatide (< 0.6%), probably due to both medication and weight loss (49). As a result, tirzepatide, the first co-agonist GLP-1/GIP analog, is the first co-agonist GLP-1/GIP analog approved at the first high dose (15mg) for T2DM, and studies have shown that it has a weight loss effect of more than 10% in 52 weeks (even though LSC was not performed in the SURPASS study). When given in combination with LSC in non-diabetic patients, it has a weight loss effect of approximately 20%. In addition, it is a safe drug with a low risk of side effects.

Setmelantodite

It is a new molecule approved over 6 years of age and in adults. It is an MC4R receptor agonist. It is used in conditions caused by deficiency of the MCR4 pathway. These pathways are POMC, proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency. Setmelantodite suppresses hunger by activating MC4R, increases the feeling of satiety, and increases energy expenditure (51). In a study of 21 patients with severe obesity resulting from either POMC/PCSK1 or LEPR deficiency after 1 year. At least 10% weight loss occurred in 80% of those with POMC/PCSK deficiency and 45% of those with LEPR deficiency. There was a decrease in hunger scores (52). The most common side effects were hyperpigmentation at the injection site, nausea, and vomiting. Other than

Table 2: SURMOUNT Clinical Study.

Clinical Study	Study Subject	Number of Cases	Treatment Duration	Comparison
Surmount-1	Weight Loss	2539	72 weeks	Placebo
Surmount-2	Weight loss in T2DM	900	72 weeks	Placebo
Surmount-3	Intensive Behavioural Treatment and Weight Loss	800	72 weeks	Placebo
Surmount-4	Weight loss with maintenance	750	88 weeks	Placebo 52 weeks after 36 weeks tirzepatide
Surmount-J	Japan	261	72 weeks	Placebo
Surmount- Cn	China	210	52 weeks	Placebo
Surmount- Mmo	CVOT	15000	5 years	Placebo
Summıt	HFpEF	700	120 weeks	Placebo

T2DM: Type 2 Diabetes, **CVOT:** Cardiovascular outcome trial, **HFpEF:** Heart failure with preserved ejection fraction

Table 3: Summary of Anti Obesity Drugs.

Caracteristics	Orlistat	Phentermine–topiramate extended release	Naltrexone–bupropion	Liraglutide 3,0 mg	Semaglutide 2,4 mg
Dose	60–120 mg three times per day, with meals, oral	3.75 mg/23 mg, 7.5 mg/46 mg, 11.25 mg/69 mg, 15 mg/92 mg: once daily, oral	8 mg/90 mg; Weekly Dose increase	First week: 0.6 mg; second week: 1.2 mg; third week: 1.8 mg; fourth week: 2 mg; and fifth week: 3 mg, once daily, subcutaneous	First month: 0.25 mg; second month: 0.5 mg; third month: 1·0 mg; fourth month: 1.7 mg; fifth month: 2.4 mg, once weekly, subcutaneous
Mechanism	Gastric and Pancreatitis Lipase Inhibitor	Sympathomimetic/ central appetite suppressant (phentermine)+GABA receptor activation (Topiramate)	Naltrexone: Opioid Receptor Antagonist/ Bupropion: Dopamine and noradrenaline reuptake inhibitor	Centrally acting (decreases appetite) + GLP -1 increases + Gastric emptying slows down + Insulin increases + Glucoagon decreases	Centrally acting (decreases appetite) + GLP -1 increases + Gastric emptying slows down + Insulin increases + Glucoagon decreases
eGFR requirement (mL/min per 1·73 m^2)	No need to adjust the dose	GFR > 15 ml/min If 15-30 ml/min, the dose should be adjusted	GFR > 15 ml/min If 15-30 ml/min, the dose should be adjusted	GFR> 15 ml/min	GFR> 15 ml/min
Terms of Us	BMI >40 kg/ m^2 and above for our country Maximum 2 years of use	BM > 30 kg/m^2 or BMI > 27 kg/m^2 with comorbid obesit	Those with a BMI > 30 kg/m^2 or a BMI > 27 kg/m^2 and obesity-related comorbidities	Those with a BMI > 30 kg/m^2 or a BMI > 27 kg/ m^2 and obesity-related comorbidities No Refund yok	Those with a BMI > 30 kg/m^2 or a BMI > 27 kg/ m^2 and obesity-related comorbidities are not available in Turkey.
Special Cas	Suitable for use over 12 years old	Suitable for use over 12 years old	Suitable for use over 18 years of age	Suitable for use over 12 years old	Suitable for use over 12 years old
Cardiovascular Effects	Undefined	Undefined	Undefined	Reduces cardiovascular disease events and mortality at low doses in patients with T2DM.	Reduces cardiovascular disease events and mortality at low doses in patients with T2DM.
Contra indications	Pregnancy, breastfeeding, gallstones.	Pregnancy, breastfeeding, uncontrolled hypertension, arrhythmia, hyperthyroidism	Pregnancy, breastfeeding, alcohol use, anticonvulsant drug use	Pregnancy, breastfeeding, Medullary thyroid Ca, MEN syndromes and family history	Pregnancy, breastfeeding, Medullary thyroid Ca, MEN syndromes and family history
Weight loss in patients with T2DM	2-5%	6-7%	2-3%	0-4%	2-6%
Average weight loss in 12 months	4%	9%	5%	6%	12.5% in 68 weeks

these, no serious side effects were found. POMC/PCSK1 / LEPR gene deficiency should be confirmed by genetic testing before treatment

New Pharmacotherapies

Other co-agonist GLP-1/ amylin analog and GLP-1/ glucagon analogs, GLP-1/GIP /glucagon triple agonist phase studies on obesity treatment are still ongoing, it is too early to comment on the results, and data are very limited. Safety and efficacy studies are needed. Among these, mazdutide is a GLP-1/glucagon analog and uses the thermogenic and catabolic effects of glucagon. In ongoing studies, it was shown that 11.57% of weight was lost in 24 weeks (GLORY-1) (53). AMG 133 is a molecule that has been shown to provide weight loss of up to 14.5% in 12 weeks by acting as a co-agonist (54). The combination of semaglutide, a GLP-1/ amylin analog, and cagrilintide (Cagrisema), a human amylin analog, resulted in 17.1% weight loss in 20 weeks of treatment (55).

CONCLUSION

In conclusion, obesity is a progressive chronic disease that is caused by chronic genetic and environmental factors such as HT and diabetes mellitus and requires lifelong struggle. Mortality and morbidity are increased in obesity. Whichever treatment (medical and/or surgical) method is chosen for obesity, the patient must be motivated for LSC (exercise, healthy eating habits, medical nutrition program, cognitive and behavioral training). Medical treatment should be planned for patients with a BMI > 30 kg/m^2 or a BMI > 27 kg/m^2 with at least one additional comorbid obesity-related disease (T2DM, HT, etc.). As the pathophysiology of obesity is understood, new drugs will continue to offer hope. It is thought that anti-obesity drugs based on GLP-1 and other intestinal hormones, which are currently being investigated and recently released, will act as a bridge between bariatric surgery and currently used anti-obesity drugs. Many factors such as efficacy, cost, safety, and comorbidities should be considered in drug selection. Whichever treatment (medical and/or surgical) method is chosen for the patient, the patient must be motivated for LSC. LSC is the most important but most neglected step in obesity.

Acknowledgments
None.

The Authors Contributions
Investigation, references, literature scanning, writing by **Seher Çetinkaya Altuntaş**.

Conflict of Interest
There ise no conflict of interest.

Financial Support
There is no financial support.

Ethics Committee Approval
There is no need the ethics committee aproval for review.

Peer-Review Proces
Extremely peer-reviewed and accepted.

REFERENCES

1. Toplak H, Woodward E, Yumuk V, Oppert JM, Halford JC, Frühbeck G. 2014 EASO position statement on the use of anti-obesity drugs. Obes Facts. 2015;8(3):166-174.
2. Frühbeck G, Toplak H, Woodward E, Yumuk V, Maislos M, Oppert JM: Obesity: the gateway to ill health - an EASO position statement on a rising public health, clinical and scientific challenge in Europe. Obes Facts. 2013;6:117-120.
3. Canuto R, Garcez A, de Souza RV, Kac G, Olinto MTA. Nutritional intervention strategies for the management of overweight and obesity in primary health care: A systematic review with meta-analysis. Obes Rev. 2021;22(3):e13143.
4. World Health Organisation: Fact Sheet No.311 (May 2012). www.who.int./mediacentre/factsheets/fs311/en/
5. Blundell JE, Dulloo AG, Salvador J, Frühbeck G, on behalf of the EASO SAB Working Group on BMI: Beyond BMI phenotyping the obesities. Obes Facts. 2014;7:322-328.
6. Yumuk V, Frühbeck G, Oppert JM, Woodward E, Toplak H, for the Executive Committee of the European Association for the Study of Obesity: An EASO position statement on multidisciplinary obesity management in adults. Obes Facts. 2014;7:96-101.
7. Gustafson A, King C, Rey JA. Lorcaserin (Belviq): a selective serotonin 5-HT2C agonist in the treatment of obesity. PT. 2013;38(9):525-534.
8. Meltzer HY, Roth BL. Lorcaserin and pimavanserin: emerging selectivity of serotonin receptor subtype-targeted drugs. J Clin Invest. 2013;123:4986-4991.
9. Food and Drug Administration. Summary minutes of the Endocrinologic and Metabolic Drugs Advisory Committee meeting. May 10, 2012
10. Tak YJ, Lee SY. Anti-Obesity Drugs: Long-Term Efficacy and Safety: An Updated Review. World J Mens Health. 2021;39(2):208-221.
11. Smith SM, Meyer M, Trinkley KE. Phentermine/topiramate for the treatment of obesity. Ann Pharmacother. 2013; 47:340-349.
12. Allison DB, Gadde KM, Garvey WT, Peterson CA, Schwiers ML, Najarian T, Tam PY, Troupin B, Day WW. Controlled-release phentermine/topiramate in severely obese adults: a randomised controlled trial (EQUIP). Obesity. (Silver Spring) 2012; 20:330-342.
13. Garvey WT, Ryan DH, Look M, Gadde KM, Allison DB, Peterson CA, Schwiers M, Day WW, Bowden CH. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomised, placebo-controlled, phase 3 extension study. Am J Clin Nutr. 2012;95:297-230.
14. Apovian CM. Naltrexone/bupropion for the treatment of obesity and obesity with type 2 diabetes. Future Cardiol. 2016;12:129-138.
15. Greenway FL, Fujioka K, Plodkowski RA, Mudaliar S, Guttadauria M, Erickson J, Kim DD, Dunayevich E. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2010;376:595-605.
16. Apovian CM, Aronne L, Rubino D, Still C, Wyatt H, Burns C, Kim D, Dunayevich E. A ran- domised, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). Obesity. (Silver Spring) 2013;21:935-943.
17. Tak YJ, Lee SY. Long-term efficacy and safety of anti-obesity treatment: where do we stand? Curr Obes Rep. 2021;10(1):14-30.
18. Özdamar EN, Mutlu HH. Assessment of Potential Drug-Drug Interactions in Obese Patients. Turk J Diab Obes. 2023;7:137–144.

19. Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomised study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. Diabetes Care. 2004;27(1):155-161.
20. Garcia SB, Barros LT, Turatti A, Martinello F, Modiano P, Ribeiro-Silva A, Vespúcio MV, Uyemura SA. The anti-obesity agent orlistat is asso- ciated to increase in colonic preneoplastic markers in rats treated with a chemical carcinogen. Cancer Lett. 2006;240:221-224.
21. Hong JL, Meier CR, Sandler RS, Jick SS, Stürmer T. Risk of colourectal cancer after initiation of orlistat: matched cohort study. BMJ. 2013;347:f5039.
22. Kelly AS, Auerbach P, Barrientos-Perez M, Gies I, Hale PM, Marcus C, Mastrandrea LD, Prabhu N, Randomised ASA. Controlled trial of liraglutide for adolescents with obesity. N Engl J Med. 2020;382:2117-2128.
23. Velazquez A, Apovian CM. Updates on obesity pharmacotherapy. Ann N Y Acad Sci. 2018;1411(1):106-119.
24. Khera R, Murad MH, Chandar AK, Dulai PS, Wang Z, Prokop LJ, Loomba R, Camilleri M, Singh S. Association of pharmacological treatments for obesity with weight loss and adverse events: a systematic review and metaanalysis. JAMA. 2016;315(22):2424-2434.
25. Steinberg WM, Rosenstock J, Wadden TA, Donsmark M, Jensen CB, DeVries JH. Impact of liraglutide on amylase, lipase, and acute pancreatitis in participants with overweight/obesity and normoglycemia, prediabetes, or type 2 diabetes: secondary analyses of pooled data from the SCALE clinical development programme. Diabetes Care. 2017;40(7):839-848.
26. Patel DK, Stanford FC. Safety and tolerability of new-generation anti-obesity medications: a narrative review. Postgrad Med. 2018;130(2):173-182.
27. O'Neil PM, Aroda VR, Astrup A, Kushner R, Lau DCW, Wadden TA, Brett J, Cancino AP, Wilding JPH; Satiety and Clinical Adiposity - Liraglutide Evidence in individuals with and without diabetes (SCALE) study groups. Neuropsychiatric safety with liraglutide 3.0 mg for weight management: results from randomised controlled phase 2 and 3a trials. Diabetes Obes Metab. 2017;19(11):1529-1536.
28. Davies MJ, Bergenstal R, Bode B, Kushner RF, Lewin A, Skjøth TV, Andreasen AH, Jensen CB, DeFronzo RA; NN8022-1922 Study Group. Efficacy of Liraglutide for weight loss among patients with type 2 diabetes: the SCALE diabetes randomised clinical trial. JAMA. 2015;314(7):687-699.
29. Wadden TA, Hollander P, Klein S, Niswender K, Woo V, Hale PM, Aronne L; NN8022-1923 Investigators. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE maintenance randomised study. Int J Obes. 2013;37(11):1443-1451.
30. Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, Lau DC, le Roux CW, Violante Ortiz R, Jensen CB, Wilding JP; SCALE Obesity and Prediabetes NN8022-1839 Study Group. A randomised, controlled trial of 3.0 mg of Liraglutide in weight management. N Engl J Med. 2015;373(1):11-22.
31. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM Buse JB. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375:311-322.
32. Jorsal A, Kistorp C, Holmager P, Tougaard RS, Nielsen R, Hänselmann A, Nilsson B, Møller JE, Hjort J, Rasmussen J, Boesgaard TW, Schou M, Videbaek L, Gustafsson I, Flyvbjerg A, Wiggers H, Tarnow L. Effect of liraglutide, a glucagon-like peptide-1 analogue, on left ven- tricular function in stable chronic heart failure patients with and without diabetes (LIVE)-a multicentre, double-blind, randomised, placebo-controlled trial. Eur J Heart Fail. 2017;19:69-77.
33. Marso SP, Baeres FMM, Bain SC, Goldman B, Husain M, Nauck MA, Poulter NR, Pratley RE, Thomsen AB, Buse JB. Effects of liraglutide on cardiovascular outcomes in patients with diabetes with or without heart failure. J Am Coll Cardiol. 2020;75:1128-1141.
34. Friedrichsen M, Breitschaft A, Tadayon S, Wizert A, Skovgaard D. The effectofsemaglutide 2.4 mg once weekly on energy intake, appetite, control of eating, and gastric emptying in adults with obesity. Diabetes Obes Metab. 2021;23:754-762.
35. Bergmann NC, Davies MJ, Lingvay I, Knop FK. Semaglutide for the treatment of overweight and obesity: A review. Diabetes Obes Metab. 2023;25(1):18-35.
36. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, McGowan BM, Rosenstock J, Tran MTD, Wadden TA, Wharton S, Yokote K, Zeuthen N, Kushner RF; STEP 1 Study Group. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med. 2021;384(11):989-1002.
37. Davies M, Færch L, Jeppesen OK, Pakseresht A, Pedersen SD, Perreault L, Rosenstock J, Shimomura I, Viljoen A, Wadden TA, Lingvay I; STEP 2 Study Group. Semaglutide 24 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. Lancet. 2021;397(10278):971-984.
38. Wadden TA, Bailey TS, Billings LK, Davies M, Frias JP, Koroleva A, Lingvay I, O'Neil PM, Rubino DM, Skovgaard D, Wallenstein SOR, Garvey WT; STEP 3 Investigators. Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity: the STEP 3 randomised clinical trial. JAMA. 2021;325(14):1403-1413.
39. Rubino D, Abrahamsson N, Davies M, Hesse D, Greenway FL, Jensen C, Lingvay I, Mosenzon O, Rosenstock J, Rubio MA, Rudofsky G, Tadayon S, Wadden TA, Dicker D; STEP 4 Investigators. Effect of continued weekly subcutaneous semaglutide weekly vs placebo on weight loss maintenance in adults with overweight or obesity: the STEP 4 randomised clinical trial. JAMA. 2021;325(14):1414-1425.
40. Garvey WT, Batterham RL, Bhatta M, Buscemi S, Christensen LN, Frias JP, Jódar E, Kandler K, Rigas G, Wadden TA, Wharton S; STEP 5 Study Group. Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial. Nat Med. 2022;28(10):2083-2091.

41. Rubino DM, Greenway FL, Khalid U, O'Neil PM, Rosenstock J, Sørrig R, Wadden TA, Wizert A, Garvey WT; STEP 8 Investigators. Effect of weekly subcutaneous semaglutide vs daily liraglutide on body weight in adults with overweight or obesity without diabetes: The STEP 8 randomized clinical trial. JAMA. 2022;327(2):138-150.
42. ClinicalTrials.gov. A research study on how well semaglutide works in adolescents with overweight or obesity (NCT041 02189). https://clinicaltrials.gov/ct2/show/NCT04102189. Accessed November 30, 2021.
43. ClinicalTrials.gov. Research study to investigate how well semaglutide works in people living with heart failure and obesity (STEP-HFpEF)(NCT04788511). https://clinicaltrials.gov/ct2/show/NCT04788511.Accessed November 30, 2021.
44. ClinicalTrials.gov. Research study to look at how well semaglutide works in people living with heart failure, obesity and type 2 diabetes(STEP HFpEF DM) (NCT04916470). https://clinicaltrials.gov/ct2/show/NCT04916470. Accessed November 30, 2021.
45. Blüher M, Aras M, Aronne LJ, Batterham RL, Giorgino F, Ji L, Pietiläinen KH, Schnell O, Tonchevska E, Wilding JPH. New insights into the treatment of obesity. Diabetes Obes Metab. 2023;25(8):2058-2072.
46. Papamargaritis D, le Roux CW, Holst JJ, Davies MJ. New therapies for obesity. Cardiovasc Res. 2022:cvac176.
47. Alexiadou K, Anyiam O, Tan T. Cracking the combination: gut hormones for the treatment of obesity and diabetes. J Neuroendocrinol 2019;31:e12664.
48. Blüher M, Ceriello A, Davies M, Rodbard H, Sattar N, Schnell O, Tonchevska E, Giorgino F. Managing weight and glycaemic targets in people with type 2 diabetes-How far have we come? Endocrinol Diabetes Metab. 2022;5(3):e00330.
49. Astreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, Kiyosue A, Zhang S, Liu B, Bunck MC, Stefanski A. Tirzepatide once weekly for the treatment of obesity. N Engl J Med. 2022;387:205-216.
50. Frías JP, Davies MJ, Rosenstock J, Pérez Manghi FC, Fernández Landó L, Bergman BK, Liu B, Cui X, Brown K. Tirzepatide versus semaglutide once weekly in patients with type 2 dia-betes. N Engl J Med. 2021;385:503-515.
51. Van der Klaauw AA, Farooqi IS. The hunger genes: pathways to obesity. Cell. 2015;161(1):119-132.
52. Wabitsch M, Farooqi S, Flück CE, Bratina N, Mallya UG, Stewart M, Garrison J, van den Akker E, Kühnen P. Natural history of obesity due to POMC, PCSK1, and LEPR deficiency and the impact of Set- melanotide. J Endocr Soc. 2022;6(6):bvac057.
53. A Study of IBI362 in Participants with Obesity or Overweight. Available at Accessed April 12, 2022
54. Amgen presents new AMG 133 phase 1 clinical data at WCIRDC. 2022. Available at: Accessed April 12, 2022
55. Enebo LB, Berthelsen KK, Kankam M, Lund MT, Rubino DM, Satylganova A, Lau DCW. Safety, tolerability, phar- macokinetics, and pharmacodynamics of concomitant administration of multiple doses of cagrilintide with semaglutide 24 mg for weight management: a randomised, controlled, phase 1b trial. Lancet (London, England). 2021;397(10286):1736-1748.