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Obesity and Obesity-Related Diseases and Treatments

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ABSTRACT

Obesity is a disease that impairs body health as a result of abnormal or excessive fat deposit in the adipose tissue. Obesity and overweight are caused when the amount of energy taken during nutrition is higher than the amount spent during metabolism and physiological activities. Obesity is a chronic and common disease with increasing prevalence worldwide affecting both adults and children. Obesity is a multifactorial disease affected by many environmental and genetic factors and is known to be an important risk factor for early mortality, metabolic, and cardiovascular complications. The fact that obesity treatment is a long and difficult process and its cost is high emphasizes the importance of preventing obesity. For this purpose, obesity prevention studies including diet education, physical activity, and behavioral changes should be initiated and carried out. When preventive measures are insufficient, different treatment options come to the fore including diet, exercise, lifestyle changes, medication, and surgery. In this article, data on the definition of obesity, its causes, and treatment options have been compiled in order to determine the ideal methods for the prevention and treatment of obesity.

Keywords: Anti-obesity agents, drug, obesity, obesity treatment

INTRODUCTION

Obesity is defined as a chronic metabolic disease described by increased fat stores in the body.[1] According to the World Health Organization (WHO) valuation, those with a body mass index between 25 and 29.9, which is calculated by dividing the body weight by the square of the height, are considered "overweight" and those above 30 are considered "obese."[2] The proportion of body fat in people with ideal weight should be 12%-18% in men and 20%-30% in women. If the body fat ratio is more than 22%-25% in men and 32%-35% in women, the presence of obesity is mentioned.[3]

It is known that the obesity occurs as a result of the interaction of genetic, psychological, physical, environmental, and socioeconomic factors.[1,4] There are risk factors such as age, hormonal and metabolic factors, gender, sociocultural factors, income status and education level, genetic factors, sedentary lifestyle, excessive and wrong nutrition, some medications used, frequent dieting, marital status, smoking and alcohol use, and irregular sleep in the formation of obesity.[5,6] The first phase of obesity treatment is to aim an achievable body weight loss for patients. In this way, it is aimed to provide the individual with adequate and correct nutrition habits, to increase the quality of life of the individual, and to reduce the risks of obesity-related diseases and deaths in the individual.[7]

Diagnosis, Etiology of Obesity, and Affecting Factors

The body mass index (BMI) is widely used to determine obesity according to the obesity classification made by the World Health Organization. Body mass index is known as a value acquired by dividing the body weight (kg) of the individual by the square of the height (meter) (BMI = kg/m^2). Since BMI is a cheap, simple, and reliable method, it is frequently used as an obesity diagnosis method (Table 1).[8]

Obesity is a multifactorial disease and occurs as a result of the interaction of genetic, physical, psychological, environmental, and socioeconomic factors.[9] Hormonal disorders such as hypothyroidism cause an increase in fat accumulation due to a decrease in basal metabolic rate. Insulinoma, Cushing's syndrome, hypothyroidism, polycystic ovary, hypogonadism, and Binge eating disorder can cause obesity.[10] Some drug classes used in the treatment of various diseases such as antidepressants, antiepileptics, and neuroleptics can also cause weight gain as a side effect. The most important findings supporting the role of heredity in obesity have been obtained from studies with BMI in identical twins, which is a multifactorial disease.[11] The fact that the concordance found in monozygotic twins is higher than in dizygotic twins in these studies indicates the effect of heredity in obesity.[12,13] Obesity is affected by environmental factors as well as heredity. For example, it is suggested that the desire of obese patients to overeat is a habit acquired from the family environment. In addition, excessive television

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Table 1. The Ranges of Body Mass Index Values

	BMI (kg/m²)
Severe thinness	<16.0
Moderate thinness	16.0-16.9
Mild thinness	17.0-18.4
Normal range	18.5-24.9
Overweight (pre-obese)	25.0-29.9
Moderately obese	30.0-34.9
Severely obese	35.0-39.9
Very severely obese	≥40.0

watching, long-term computer use, and lack of physical activity are known as habits originating from family life.[14]

Prevalence of Obesity

Obesity, which is a health problem that has increased so much in the world, is now described as a pandemic.[15] According to the WHO data, while the probability of obesity in the 5-19 age group of children and adolescents was less than 1% in 1975, 8% of boys and 6% of girls were in the obese group in 2016.[15] According to the WHO European Region Obesity Report 2022 published by the WHO, more than 59% of the people (63% of men and 54% of women) in the European Region are considered overweight or obese. Approximately, 1 in 3 children (29% in boys, 27% in girls) is overweight or obese; it is stated that 1 out of every 10 children is obese.[16]

It is known that the prevalence of obesity in the adult population in Turkey exceeds 30%. Although the prevalence of obesity is higher in women than in men, there has been a rapid increase in male obesity recently.[17] According to the results of the studies conducted in 2016, it is stated that Turkey is one of the countries where obesity is more common with a prevalence value of 29.5% among the WHO European Region countries.[18] According to WHO's European Region Obesity Report 2022 data, Turkey is stated as the country with the highest obesity prevalence in the European Region. In Turkey, 66.8% of the adult population are considered overweight and 32.1% are obese.[19] In the Turkey Childhood Obesity Research Initiative Study (COSI-TUR 2016), it was determined that 9.9% of children in the 7-8 age group in Turkey were obese and 14.6% were overweight . In this study, it was determined that 1 out of every 4 children in the 7-8 age group in Turkey is obese or overweight.[17,20]

Health Problems Caused by Obesity

Obesity has negative effects on the cardiovascular system, endocrine system, gastrointestinal system, skin, musculoskeletal system, genitourinary system, respiratory system, and psychosocial status.[21] Insulin resistance, type 2 diabetes, hypertension, hyperlipidemia, gallbladder diseases, coronary artery disease, some types of cancer, osteoarthritis, paralysis, sleep apnea, asthma, pregnancy complications, fatty liver, menstrual irregularities, pre- and post-operative complications, musculoskeletal system problems, mental problems, anorexia nervosa, overeating, excessive hair growth, social maladjustment, skin infections due to subcutaneous fat tissue, fungal infections in the groin and feet are important health problems caused by obesity.[22] The effects of obesity on body systems are detailed in Table 2.

Treatment of Obesity

The aim of obesity treatment is to increase the quality of life of the person and to provide an adequate and balanced nutrition habit by providing a sufficient loss of body weight and by minimizing the risk of obesity-related morbidity and mortality.[23] Obesity treatment methods can be listed as medical nutrition (diet) therapy, exercise therapy, behavior modification therapy, pharmacological therapy, and surgical therapy.[24]

Medical Nutrition (Diet) Therapy

In the medical nutrition treatment of obesity, the aim is to reach the ideal weight and keep the person's weight at the ideal level by creating an energy deficit and reducing the body fat stores without loss of muscle and mass in the muscles and the vital organs.[25] According to the energy needs of the people, dietitians recommend low-calorie diets that give an average of 1200–1600 kcal/day for men and 1000-1200 kcal/day for women.[26] Diet programs should be prepared individually depending on the person's eating habits and food consumption.[27]

Exercise Therapy

Regular physical activities have an important role in regulating the energy balance, reducing the health problems caused by obesity and the mortality rate due to these health problems. Before starting a new physical activity program for obese individuals, cardiopulmonary checks should be made, chronic diseases and symptoms should be evaluated, and personalized exercise programs should be selected.[28] According to the Public Health Institution of Turkey, an individual should do physical activity for at least 5 days a week, 40-60 minutes once a day, or 20-30 minutes twice a day. Oxygen consumption should also be between 50% and 70% during exercise.[29]

Behavior Modification Therapy

One of the most important methods of obesity treatment is behavioral therapy. The aim of the treatment of obesity with behavior modification therapy is to create awareness and change in the patient's eating and activity habits and to gain positive behaviors related to physical activity and nutrition that cause excessive weight gain, lifestyle and habits. The first condition of achieving permanent weight control is to motivate the patient

Table 2. The Effects of Obesity on Body Systems

Cardiovascular diseases	Hypertension, coronary heart disease, deterioration in lipid profile, stroke, venous thrombosis, pulmonary embolism, varicose veins
Cancers	Urogenital (endometrium, cervix, ovary, prostate, kidney), gastrointestinal (colorectal, liver, gallbladder, esophagus, small intestine, pancreas) system tumors and leukemia, multiple myeloma, lymphoma, and breast cancer
Metabolic	Insulin resistance and type-2 diabetes mellitus, metabolic syndrome, gallstones, hyperuricemia, and gout
Hormonal	Polycystic ovary syndrome, menstrual cycle irregularities, hyperandrogenism, decreased levels of sex hormones (estrogen, testosterone), decrease in growth hormone and prolactin response, infertility, increase in cortisol synthesis, acanthosis nigricans
Rheumatological	Osteoarthritis (especially lower extremity joints), entrapment neuropathies, immobility, low back pain
Pulmonary	Asthma, decrease in total lung and functional residual capacity, increase in diffusion capacity and residual volume, sleep apnea syndrome, obesity hypoventilation syndrome (Pickwickian syndrome)
Gastrointestinal	Gallstone (cholelithiasis), fatty liver disease, reflux, esophageal hernia
Urinary	Incontinence, glomerulopathy, proteinuria, nephrotic syndrome
Psychological	Decreased self-confidence, depression, dementia, anxiety disorders, stigmatization, social exclusion and unemployment, deterioration in body image
Others	Idiopathic intracranial hypertension, skin infections (cellulitis, carbuncle, etc.), stasis, and lymphedema in the legs

Table 3. Pharmacological Drugs that Can be Used in the Treatment of Obesity

Medicines that reduce fat absorption	Orlistat
Antidiabetic drugs	Metformin, exenatide, liraglutide, pramlintide
Sympathomimetic drugs	Phentermine
Selective serotonin receptor agonists	Lorcaserin
Antiepileptic drugs	Topiramate
Combination treatments	Topiramate-phentermine, Bupropion SR-Naltrexone

to achieve the goal.[30] For a more active life, patients should be offered simple suggestions such as not snacking while watching TV, getting off the bus or minibus one stop before arriving at their destination, using the stairs instead of the elevator, and parking their vehicles at the furthest distance in places such as shopping malls. In addition, patients should be asked to monitor their weight and food intake throughout the treatment. Since frequent control and effective and long-term social support will increase the chances of success, measures should be taken to regulate the social environment of the patients.[31]

Surgical Treatment

Today, surgical treatment methods are used safely and effectively in the treatment of obesity. Surgical treatment is applied to patients who do not respond to other obesity treatment methods, have a BMI >40 kg/m^2 or a BMI in the range of 35-40 kg/m^2, and are at high risk for obesity-related diseases. In the surgical treatment method, intestinal bypass, laparoscopic gastric band application, partial biliopancreatic bypass, gastroplasty, adjustable silicone gastric band insertion, and gastric balloon application are some of the applications used.[32]

Pharmacological Therapy

Pharmacological treatment in obesity is applied if the patient has a BMI of 27-30 kg/m^2 and at least one of the obesity-related risk factors or complications. Pharmacological treatment is also applied if there is no response to behavioral change treatment that includes healthy nutrition and exercise.[33] The drugs to be used in the treatment of obesity should prevent the storage of fat in the body or to increase the use of fat to dissolve the fat stores. One of the important factors that will reduce the accumulation of fat in the body is the limitation of calorie intake, and according to this method, it is necessary to control the appetite.[34]

Another important method to reduce the fat percentage is to limit the amount of fat that passes into the systemic circulation. Methods increasing thermogenesis and basal metabolism can reduce fat stores by elevating energy consumption in the body. Such methods generally act through the activation of the sympathetic system.[35] The features that should be present in an ideal obesity drug are as follows: it should cause dose-related weight loss; it should ensure the continuity of the reached target weight; it should be safe when it is used chronically; it should not develop tolerance; and finally it should not cause abuse or addiction.[36]

Drugs Used in the Obesity Treatment

Pharmacological treatment of obesity is applied if the patient's BMI is between 27 kg/m^2 and 30 kg/m^2 and at least one of the obesity-related risk factors or complications is present. In addition, pharmacological treatment is applied in case of failure to respond to behavioral therapy including healthy nutrition and exercise.[37] Since there is excessive fat storage in the body in obese patients, the used in the treatment of obesity should prevent the storage of fat or increase the use of fat to melt the stores. One of the most important factors that will reduce the accumulation of fat in the body is the restriction of calorie intake, that is, food intake, and in this method, it is aimed to control the appetite.[37] The success of the drug in the treatment of obesity is measured by the degree of weight loss and the reduction in associated risk factors. Weight loss of 2 kg in the first month of drug therapy, losing more than 5% of the initial body weight within 3-6 months, and maintaining this target weight indicate that the treatment is successful.[38] Pharmacological drugs that can be used in the treatment of obesity are classified as shown in Table 3.[39,40] The mechanisms of action, approval bodies, and side effects of drug-active ingredients used in the treatment of obesity are given in Table 4.[41-59] The chemical structures of some commonly used anti-obesity drugs are given in Figure 1.

Orlistat

Orlistat, can be preferred in obese people with BMI ≥ 30 kg/m^2 or can also be chosen as one of the drugs used in the treatment of excess body weight in patients with ≥28 kg/m^2.[41] Orlistat acts as a specific, potent, irreversible food lipase inhibitor, which reduces the calorie content of meals consumed by reducing the

Table 4. Generally Used Anti-Obesity Drugs

Drug	Approving Bodies	Mechanism	Adverse Effects	References
Orlistat	FDA - 1999 EMA -1998	Pancreatic lipase inhibitor	Decreased absorption of fat-soluble vitamins, oily stools, fecal urgency, bloating, gas, abdominal pain, and diarrhea	41-43
Topiramate	FDA- 2012	Anti-convulsant agent	Gastrointestinal adverse effects, increased nervousness, sweating, tremors, hypersomnia, insomnia, and fatigue	44,45
Phentermine	FDA- 2012	Sympathomimetic amine, appetite suppressant	Increased blood pressure and pulse rate, constipation, insomnia, dizziness, tremor, headache, and palpitation	45-47
Liraglutide	FDA- 2014 EMA- 2015	GLP-1 agonist	Nausea, medullary thyroid tumor in rats and mice, pancreatitis, headache, constipation, and heartburn	48,49
Semaglutide	FDA- 2017	GLP-1 agonist		49,50
Dulaglutide	FDA- 2014 EMA- 2014	GLP-1 agonist		51,52
Tirzepatide	EMA- 2022	GLP-1 agonist	Nausea, diarrhea, vomiting, dyspepsia, constipation, abdominal pain, dizziness, and hypoglycemia	56
Lorcaserin	FDA- 2012	Selective 5HT-2C receptor agonist	Depression, infection, headache, nausea, and dizziness	53-55
Bupropion and naltrexone	FDA- 2014 EMA- 2015	Naltrexone:OpioidreceptorantagonistBupropion:Norepinephrine/dopamine reuptake inhibitör	Nausea, headache, insomnia, constipation, dizziness, and vomiting	57-60

FDA, Food and Drug Administration; EMA, European Medicines Agency

absorption of fats in the gastrointestinal tract.[42] Covalent binding of gastric and pancreatic lipases with the active serine site in the gastrointestinal tract lumen prevents pancreatic and gastric enzymes from hydrolyzing dietary fat into absorbable free fatty acids and monoglycerols.

The pharmacological action of orlistat is dose dependent, with the optimal therapeutic dose recommended as 180-360 mg/day 1 hour after each main meal or divided into 3 doses up to 1 hour. In case of skipping a meal, orlistat is not required. Patients should follow a nutritious and balanced diet with a fat content of no more than 30%. It is also recommended to distribute fat intake evenly at each meal to minimize gastrointestinal side effects. If the patient's meal does not contain fat, he may skip the orlistat dose. Caution is required when it is used with cyclosporine. In cases where orlistat is used orally, it is excreted in the stool for 3-5 days. Orlistat is contraindicated in patients with pregnancy and lactation, chronic malabsorption syndrome, or cholestasis.[43] Side effects such as oily spotting, leakage with gas, sudden need to defecate, loose or watery stools, oily stools, increased frequency of defecation, and stool incontinence can be seen with the use of orlistat. Side effects increase as the fat ratio in the diet increases and the absorption of fat-soluble vitamins is impaired. Therefore, when using orlistat, a fat-soluble vitamin supplement is recommended.[42]

Topiramate

Topiramate [2,3:4,5-Bis-*O*-(1-methylethylidene)-β-D-fructopyranose sulfamate] acts as a glutamate antagonist, carbonic anhydrase inhibitor, and gamma-aminobutyric acid (GABA) agonist. It is an antiepileptic drug and causes weight loss as a side effect in epilepsy patients. The exact reason why it causes weight loss is not known.[44,45]

Phentermine

Phentermine (2-methyl-1-phenylpropan-2-amine) acts as a central sympathomimetic leading to increased secretion of norepinephrine, dopamine, and serotonin. It was discontinued in 1997.[45,46] Phentermine is an appetite suppressant belonging to the amphetamine and phenethylamine class. It is known that short-term use of appetite suppressants, together with exercise, diet, and behavior changes, provides weight loss. Phentermine is generally used in obese individuals with serious weight problems. It has the potential to be addictive because its structure is similar to amphetamines.[47]

Liraglutide

Liraglutide can be given subcutaneously once daily in patients with type 2 diabetes mellitus (T2DM) at a target dose of 1.8 mg as a short-acting glucagon-like peptide-1 (GLP-1) analog. In patients with prediabetes, T2DM, dyslipidemia and OSAS (obstructive sleep apnea syndrome) and abnormal body weight, BMI ≥30 kg/m^2 or 27 kg/m^2 to <30 kg/m^2, the indication has been expanded to a target dose of 3 mg once daily since 2014 in the USA and 2015 in Europe.[48] Liraglutide, when used at a dose of 3 mg daily for 32 weeks, has been reported to contribute not only to significant weight loss but also to the androgen index and increase in menstrual frequency or regulation of menstrual frequency.[49]

Semaglutide

Semaglutide, which is a long-acting GLP-1 analog approved by the FDA and EMEA, is used in patients with a BMI of ≥30 kg/m^2 or ≥27 kg/m^2 and at least one weight-related condition.[49] Studies have shown that the use of 2.5 mg semaglutide for 68 weeks resulted in a >20% reduction in body weight in 13.1%-36.6% of patients, and a 1.0 mg dose causes weight reduction in 4.7% of patients. Orally administered semaglutide has proven to have a

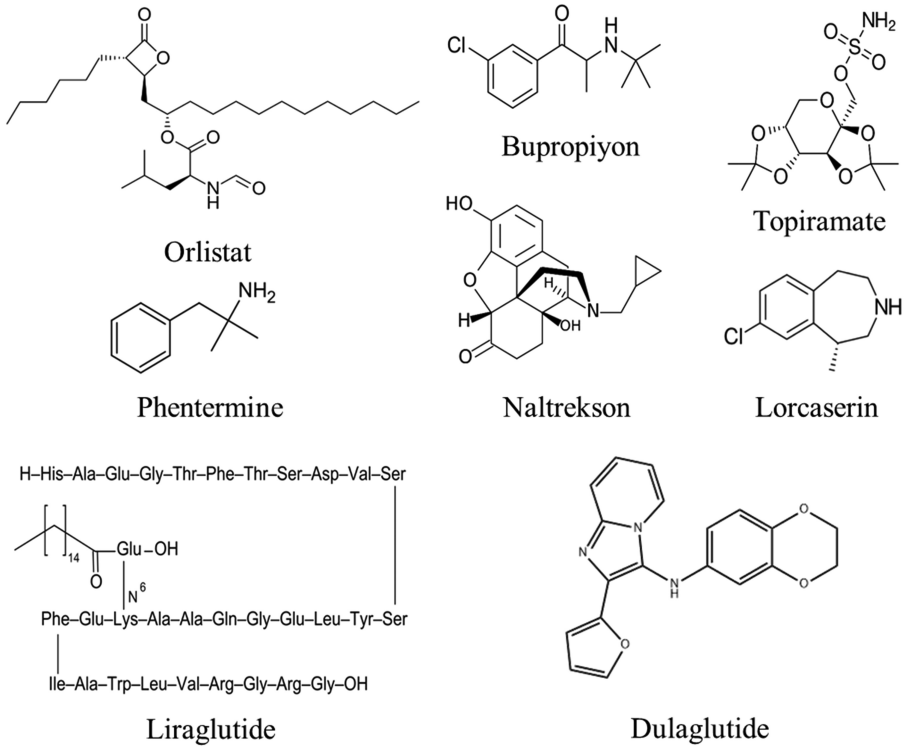

Figure 1. The chemical structures of some commonly used anti-obesity drugs.

significantly beneficial effect in reducing hunger, body fat, and body weight in patients with T2DM.[50]

Dulaglutide

Dulaglutide is used as a GLP-1 agonist in the treatment of T2DM in addition to its weight-reducing effect. In addition to insulin therapy, it has been reported to significantly reduce body weight.[51] It has been reported that patients with a diagnosis of eating disorders showed a reduction in the number of eating episodes after 12 weeks of treatment, and a significant reduction in body weight, glycated hemoglobin levels, and BMI during dulaglutide treatment compared to placebo.[52]

Lorcaserin

Lorcaserin acts as a selective agonist of the [(5R)-7-chloro-5-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine] 5-HT serotonin receptor.[53] FDA approves this drug for the purpose of promoting weight loss in obese patients with or without T2DM in long-term use with lifestyle modification. However, this drug cannot be approved due to EMEA's safety concerns. Studies show that lorcaserin reduces the incidence of DM by 19% in pre-diabetic patients and by 23% in patients without DM.[38] In diabetic patients, a 21% reduction in diabetic microvascular complications has been observed and it is known that there is an improvement in quality of life independent of dose.[54] It is emphasized that lorcaserin is effective both in the first year and in the second year of treatment. According to the FDA, lorcaserin should be discontinued if at least 12% of weight loss is not achieved within the first 5 weeks.[55]

Tirzepatide

Tirzepatide is a new drug that has been approved by the FDA in 2022 for the treatment of obesity and acts as a double GLP-1 and Gastric Inhibitory Polypeptide (GIP) receptor agonist. Subcutaneous application once a week is sufficient because it has a half-life of about 5 days. According to studies, when semaglutide and tirzepatide are compared, it is seen that tirzepatide has a much higher efficacy in weight loss.[56]

Bupropion and Naltrexone Combination

In patients with BMI ≥ 30 kg/m^2 or ≥27 kg/m^2 and T2DM, bupropion in combination with naltrexone can be used as another therapeutic option for patients with at least one co-morbidity such as dyslipidemia.[57] According to a study, it has been proven that in obese patients with BED (patient with binge eating disorder), using a long-acting preparation of the combination of naltrexone and bupropion not only significantly reduces body weight but also improves pathological eating behavior.[58] This drug combination is not to be used in patients with a history of seizures, eating disorders, or patients using alcohol. It should not be used with central nervous system depressants, especially opioids.[60]

DISCUSSION

Obesity is becoming a growing problem in children and adults around the world. According to studies on obesity, besides factors such as genetic structure, age, gender, dietary habits, sedentary lifestyle, socioeconomic and cultural level, media and screen exposure are the most important factors causing obesity. In this context, it is recommended to plan nutrition education to be given to both parents and children. Type 2 diabetes mellitus and obesity are among the well-established diseases that do not have a specific treatment so far but can be kept under control by including the appropriate treatment as well as lifestyle changes. The alarming increase in obese patient numbers worldwide requires new scientific advances to streamline administration, reduce dosing frequency, and address multiple issues in a single drug.

The fact that the drugs used in the treatment of obesity have undesirable side effects, the effects are within certain limits, and the patient regains weight when the drug is discontinued limits the long-term use of the drugs in the market. When obesity drugs are used in the treatment, the benefit/harm ratio is taken into account in the treatment with these drugs, since they have more side effects than diet and exercise. In this article, we have compiled data on obesity treatment methods and antiobesity drugs used in treatment. As the knowledge about the causes of obesity and the diseases it causes increases, it will be easier to discover more active pharmaceutical ingredients for medical treatment and to develop other treatment methods. Pharmacotherapy modalities of diabetes and obesity are developing rapidly around the world, and an increasing number of drug targets have been identified. Although these drugs are associated with clinically significant weight loss, clinical trials are ongoing. It is anticipated that more drugs will be approved for the treatment of obesity as clinical trials of candidate and existing drugs continue. These methods are very promising as they will reduce the tendency to prefer more risky methods such as bariatric surgery.

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