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Obesity treatment - overview of pharmacological and surgical methods

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Abstract

Introduction and purpose of the work: Obesity is a chronic disease that leads to many complications. Almost a third of the world's population is now classified as overweight or obese. This is a huge global problem. The base of treatment is diet and physical activity, but fortunately nowadays we also have pharmacological and surgical treatment - which are increasingly used. The aim of this study is to draw attention to obesity disease which may lead to serious complications and compare available pharmacological and surgical treatment.
State of knowledge (brief description): Treating obesity is a difficult and often multidisciplinary challenge. Currently many drugs with different mechanisms and different efficiencies has been approved for treatment. All of them show efficiency, but the available studies show that surgical treatment produces better results than pharmacological treatment.
Summary: We currently have a huge range of obesity treatment options available. Surgical treatment produces better results than pharmacological treatment. Nevertheless, not every patient qualifies for bariatric surgery. Pharmacological methods are also effective. The treatment method should be individually selected for the patient.

Introduction

Obesity is a chronic disease that leads to many complications. WHO defines overweight and obesity as abnormal or excessive fat accumulation that may impair health. [1] We diagnose adult obesity on the basis of BMI - a simple mass-to-height ratio that is commonly used worldwide. It is defined as the weight in kilograms divided by the square of the height in meters (kg / m2). Obesity is diagnosed if the BMI value is ≥ 30 kg / m2. We distinguish between 1st degree obesity - BMI 30-34.9 kg / m2, 2nd degree obesity - BMI 35-39.9 kg / m2 and 3rd degree obesity with BMI ≥ 40 kg / m2. It should be remembered that the BMI index is not a reliable indicator in all groups of people - including athletes or the elderly. We also distinguish visceral obesity, which according to the diagnostic criteria of the International Diabetes Federation (IDF) is diagnosed in adult Europeans with a waist circumference of men ≥ 94 cm, in women ≥ 80 cm.

The prevalence of overweight and obesity worldwide has doubled since 1980 to such an extent that almost a third of the world's population is now classified as overweight or obese. The available reviews of studies show that the incidence of obesity is higher in women than in men and increases with age. [2]

Obesity is not only a disease in itself, but also worsens the prognosis of other diseases and contributes to the development of new ones. This happens through a number of mechanisms. In obese individuals, adipose tissue releases increased amounts of non-esterified fatty acids, glycerol, hormones, pro-inflammatory cytokines, and other factors that contribute to the development of insulin resistance. [3] In turn, impaired insulin sensitivity, inflammation and endothelial dysfunction may contribute to the initiation and progression of the atherosclerotic process. [4] By causing changes in the cardiovascular system, obesity contributes to the onset of heart failure [5].

In 2016, the total cost of treating adult obesity in the United States was $ 260.6 billion. Adults with obesity in the United States compared to those of normal weight experienced a higher annual cost of medical care by $ 2,505, or 100%, with costs significantly increasing in the obesity class, from 68.4% in class 1 to 233.6% in Grade 3 [6] Appropriate obesity treatment contributes not only to improve health of the patient and society, which is the most important thing, but will also significantly reduce costs.

The treatment of this disease is very difficult due to the reduced movement and the current lifestyle conducive to the storage of adipose tissue. In addition to dietary treatment and physical activity, we currently have other therapeutic methods - pharmacological and surgical.

Pharmacological methods of obesity treatment

When lifestyle modification and dietary treatment are not effective, drug treatment should be instituted. According to the guidelines of the Endocrinology Society (ES), drug treatment should be considered in people with a BMI above 27 kg/m2 in obesity-related diseases such as coronary artery disease, hypertension, lipid and carbohydrate metabolism disorders, and obstructive sleep apnea. Pharmacological treatment is also indicated in patients with existing complications and in those with a BMI above 30 kg/m2. It should be remembered that the initiation of pharmacological treatment does not exempt from the continuation of non-pharmacological measures, such as maintaining an appropriate diet and physical activity [7].

Orlistat

Orlistat is one of the oldest drugs used in the treatment of obesity. It was approved by the FDA (Food and Drug Administration) in 1999 as a drug supporting the treatment of obesity. Orlistat works by inhibiting the activity of pancreatic and gastric lipase, which in turn leads to impaired absorption and digestion of fats contained in the consumed food (approx. 30%). The indication for the use of orlistat is the treatment of obesity and to reduce the risk of returning to the original weight after losing it. During treatment with orlistat, patients should follow a low-calorie diet and appropriate vitamin supplementation should be considered, due to the effect of the drug on the absorption of fat-soluble vitamins (vitamins A, D, E, K) [8].
In a meta-analysis of 28 randomized clinical trials in overweight or obese adults, orlistat compared to placebo was associated with a weight loss of at least 5% after 52 weeks [9].
In a study by Torgerson et al., During a four-year follow-up of 3305 patients, 21% of whom had impaired glucose tolerance, the use of orlistat resulted in a loss of 11% of body weight during the first year compared to a 6% reduction in the placebo group [10].
Orlistat should not be used in patients who are pregnant or suffer from malabsorption syndromes or in patients with cholestasis. Orlistat also reduces the absorption of a number of drugs, such as: levothyroxine, warfarin, cyclosporine, amiodarone and antiepileptic drugs. Orlistat is currently not commonly used in the treatment of obesity due to its troublesome side effects such as fecal incontinence, urgency, fatty stools, and persistent flatulence. However, it can be used in patients with constipation during other obesity pharmacotherapy [8].

Liraglutide

Liraglutide at a dose of 3 mg was the second FDA approved treatment for obesity in 2014. It is also approved for the treatment of type 2 diabetes, at a lower dose (up to 1.8 mg). Liraglutide works by mimicking the gastrointestinal incretin hormone, glucagon-like peptide-1 (GLP-1), which is released in response to food intake [8]. GLP-1 lowers blood glucose levels through the postprandial stimulation of insulin release from pancreatic beta cells. Another effect is the inhibition of glucagon secretion and slowing down gastric emptying. Apart from acting on the pancreas and stomach, liraglutide also acts on the subcortical areas of the brain responsible for the feeling of satiety [11].
A study by Kelly et al in obese adolescents, with 125 participants in the liraglutide group and 126 in the placebo group, showed that in obese adolescents, use of 3.0 mg liraglutide in combination with lifestyle modification resulted in greater reduction in BMI than in the placebo group with lifestyle modification after 56 weeks [12].
A study by Garvey et al. Showed that in overweight or obese patients with type 2 diabetes treated with insulin, liraglutide at a dose of 3 mg achieved better results than placebo, taking into account weight loss after 56 weeks [13].
In a meta-analysis of 28 randomized clinical trials in overweight or obese adults, liraglutide compared to placebo was associated with the greatest chance of losing at least 5% of body weight [9].
Liraglutide should be especially balanced in the treatment of obesity in patients with impaired glucose metabolism, type 2 diabetes, and taking psychiatric medications [8].

Semaglutide

Semaglutide is used in the treatment of type 2 diabetes. It is an agonist at the GLP-1 receptor and, compared to liraglutide, has a long elimination half-life, which allows it to be administered subcutaneously once a week. An oral form of semaglutide has also recently appeared, which brings even greater comfort of its use for patients. Both subcutaneous and oral preparations of semaglutide have been subjected to extensive phase III clinical trials. Regarding side effects, in comparison with placebo, semaglutide usually causes mild, transient gastrointestinal disturbances and increases the risk of gallstone disease [14].
In a study by Wilding et al. In the 1961 group with a BMI greater than or equal to 30 kg/m2, semaglutide at a dose of 2.4 mg administered once a week and lifestyle changes were associated with sustained and clinically significant weight loss [15].
In a large, multicentre, randomized study by O'Neil et al, Semaglutide in combination with dietary treatment and exercise showed a clinically significant reduction in body weight compared to placebo in people with a BMI greater than 30 kg/m2. Additionally, the group in which the dose of semaglutide was increased every 4 weeks showed a greater reduction in weight than the group receiving liraglutide at the dose of 3 mg [16].

Naltrexone/Bupropion

Naltrexone is an opioid antagonist used in the treatment of opioid and alcohol dependence. Bupropion is an antidepressant that works by blocking the reuptake of dopamine and noradrenaline. Both drugs have been on the market since the 1980s, and the combination was approved for the treatment of obesity in 2014 in both adults and children. Together, naltrexone and bupropion act on two independent areas of the brain responsible for controlling food consumption (the arcuate nucleus and the reward system) and lead to a reduction in the feeling of hunger and appetite [8].
In a study by Apovian et al. In a group of 1,496 in overweight or obese people with dyslipidemia and with/without hypertension, participants taking naltrexone in combination with bupropion showed greater weight loss compared to placebo. In addition to weight reduction, the markers of cardiometabolic risk in the group treated with the drug improved, and the patients' quality of life related to body weight and food control also improved. The most common observed side effect of the therapy was mild, transient nausea, and no more frequent episodes of depression or suicidal ideation were observed when naltrexone was used with bupropion compared to placebo [17].
Naltrexone / bupropion should be considered in the treatment of obesity in patients with a tendency to addiction, including food addiction, and in patients with depression [8].

Topiramate/Phentermine

Topiramate is an anti-epileptic drug approved in 1996 with a later extension of use in migraine headache prophylaxis (2014). In 2021, Topiramate/Phentermine was approved by the FDA for the treatment of obesity as an adjunct to lifestyle modification. The effect of the drug in reducing caloric intake is believed to be mediated by modulation of gamma-aminobutyric acid receptors, blocking of carbonic anhydrase and antagonism of glutamate. The most common side effects are paraesthesia, dizziness, dysgeusia, insomnia, constipation, and dry mouth [8].
In the randomized CONQUER study on a group of 2,487 overweight or obese patients with concomitant comorbidities (dyslipidemia, diabetes, pre-diabetes, hypertension, abdominal

obesity), patients taking Topiramate/Phentermine led to significantly greater weight loss than placebo [18].
Also in the next randomized clinical trial EQUIP, patients receiving Topiramate/Phentermine showed a greater reduction in body weight with both doses compared to the placebo group [19].
Topiramate/Phentermine may be considered in the treatment of obesity in younger, unburdened patients who need assistance with appetite suppression [8].

Surgical methods of obesity treatment - bariatric surgery

Besides pharmacological treatment, bariatric surgery is a commonly used method of treating obesity. Compared to non-surgical interventions, the effect on weight loss and obesity-related diseases is greater in bariatric surgery, regardless of the method chosen [20]. According to the current NICE (guidance), the patient should be referred for bariatric surgery when the following criteria are fulfilled:

- They have a BMI of 40 kg/m^2 or more, or between 35 kg/m^2 and 40 kg/m^2 and other significant diseases (for example, type 2 diabetes or high blood pressure) that could be improved if they lost weight.
- All appropriate non-surgical measures have been tried but the person has not achieved or maintained adequate, clinically beneficial weight loss.
- The person has been receiving or will receive intensive management in a tier 3 service (for more information on tier 3 services*
- The person is generally fit for anaesthesia and surgery.
- The person commits to the need for long-term follow-up [21].

There are several methods of bariatric surgery: sleeve gastrectomy, laparoscopic adjustable gastric banding, Roux-en-Y gastric bypass, biliopancreatic diversion with a duodenal switch.

Sleeve gastrectomy (SG)

Sleeve gastrectomy involves laparoscopic removal of about 80% of the stomach, leaving a narrow fragment of the "sleeve". The reduction in the volume of the stomach prevents the patient from consuming large volumes of food at one time. This method causes a weight loss of up to 70% and lasts for at least 3 years [22]. Moreover, it increases the remission rate of arterial hypertension, diabetes, sleep apnea and dyslipidemia [23]. It is a relatively quick operation to perform. With this method, digestion is unaffected, so these complications are less common. On the other hand, patients are exposed to vomiting due to overeating and to discharge from the newly formed stomach [20].

Laparoscopic adjustable gastric banding

An inflatable silicone band is placed around the top of the stomach to constrict the stomach, restricting the flow of food. This creates a proximal pouch of the stomach that limits the amount of food consumed. Additionally, the patency of the band can be regulated (the degree of narrowing) by administering the fluid through the subcutaneous port [24]. Laparoscopic adjustable gastric banding results in weight loss of up to 55% 2 years after surgery. Additionally, it causes remission of diabetes, dyslipidemia, sleep apnea and arterial hypertension [25]. There are complications such as gastroesophageal reflux, as a result of

oesophageal pouch dilatation, while serious complications are rare: band slippage and erosion [26].

Roux-en-Y gastric bypass

The Roux-en-Y gastric bypass method creates a small proximal pouch of the stomach by dividing the upper stomach. At the jejunum level, a small intestine is separated, the distal part of which will be attached to the new pouch of the stomach. The smaller pouch of stomach created in this way reduces the amount of food consumed. Moreover, the absorption of consumed food is limited, as it bypasses the proximal part of the small intestine and flows directly to the distal part of the intestine. The distal part of the stomach and the proximal part of the small intestine are attached to the distal part of the small intestine, causing the food to mix more distally with digestive enzymes [27]. As in previous methods, Roux-en-Y gastric bypass also increases the rates of diabetes remission, sleep apnea, hypertension and dyslipidemia [22]. Complications observed after Roux-en-Y gastric bypass were rare, the literature mentions: postoperative hernia, internal hernia, marginal ulcer; iron deficiency, anemia requiring transfusion, vitamin B12 deficiency, gastrointestinal bleeding [28].

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

Biliopancreatic diversion with a duodenal switch is a two-step treatment. In the first stage, as in SG, a gastrectomy is performed, leaving the tubular bag. In the next stage, the small intestine is cut proximally - right behind the pylorus; and distal about 250 cm in front of the ileocecal valve. Then the distal small intestine is anastomosed with the duodenum, the distal end of the middle fragment is anastomosed about 100 cm before the ileocecal valve with the small intestine [29]. An increased remission rate of comorbidities has been demonstrated [30]. The complications of this surgical method include: anastomotic leakage, hemorrhage, and nutritional deficiencies [31].

Bariatric surgery has a positive effect on body composition, metabolic parameters, physical functioning, and modulation of the autonomic nervous system. In the event that non-surgical methods were exhausted, weight loss was achieved through bariatric surgery. Improvements in metabolic parameters were achieved through bariatric surgery over a long period of time (less than 1 month) and over a longer period (more than a year). However, some studies have shown that the benefits of bariatric surgery are lost at a later date, so further studies are needed to identify appropriate post-bariatric recommendations that are not clear at this time. Appropriate postoperative recommendations are likely to bring significant benefits and better long-term results [32]. Bariatric surgery is a more effective treatment for obesity than pharmacological methods. Moreover, higher rates of diabetes remission, metabolic syndrome and improvement in quality of life and metabolic parameters have been demonstrated. It should be remembered that each method of surgery is associated with the possibility of complications and the risk of reoperation [33].

Summary

Obesity is a complex problem that requires a broad and often multidisciplinary approach. Diet and exercise are the mainstay of treatment, but very often they may not be enough. Fortunately, nowadays we also have pharmacological and surgical methods that we can use in the treatment of obesity. Research shows that compared to non-surgical interventions, the effect on weight loss and obesity-related diseases is greater in bariatric surgery, regardless of the method chosen [20]. However, the treatment should be consulted and adjusted

individually to the patient. Not all obese patients qualify for bariatric surgery, but all patients should be treated in some way. After successful weight reduction, the risk of weight gain again should not be forgotten. Unfortunately, however, it may even affect a significant percentage of patients, which results in frustration, depression and recurrence of obesity-related comorbidities.[34] Treating obesity is extremely important as it reduces the risk of complications, including premature death. We have to remember not to treat obesity only as a cosmetic defect, but as a serious disease - it is crucial to inform and educate the patient about the effects and treatment options at each patient's contact with medical care.

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