Arh. farm. 2024; 74: 335 – 347 *Review article/Pregledni rad*

Obesity Management - a Clinician's Perspective

Snežana Polovina[1,2,3], Mirjana Šumarac-Dumanović[1,3], Dragan Micić[4]

[1]Clinic for Endocrinology, Diabetes and Diseases of Metabolism, University Clinical Center of Serbia, Dr Subotića 13, 11000 Belgrade

[2]Faculty of Pharmacy Novi Sad, University Business Academy, Trg mladenaca 5, 21000 Novi Sad

[3]University of Belgrade – Faculty of Medicine, Dr Subotića 8, 11000 Belgrade

[4]Department of Medical Sciences, Serbian Academy of Sciences and Arts, Knez Mihajlova 35, 11000 Belgrade

Corresponding author: Snežana Polovina, e-mail: snezanapolovina@gmail.com

Received: 20 April 2024; Revised in revised forme: 10 June 2024; Accepted: 10 June 2024

Abstract

The global epidemic of obesity has affected almost every country in the world, causing an enormous social and health burden. Although many counter-measures have been introduced against this epidemic, obesity is still on the rise. An important step in this area was made when obesity was classified as a disease. The recognition of obesity as a disease enables governments and state agencies to develop their own plans to curb the obesity epidemic. Obesity has been recognized as a problem from ancient times, and different measures have been suggested as solutions. Modern management of obesity is currently based on the following therapeutic principles: diet, exercise, psychological support, pharmacological treatment, and bariatric surgery. The history of pharmaceutical treatment is rather long and full of withdrawals of the drugs due to various reasons. New perspectives and promising results were introduced with a class of drugs based on incretins. These drugs were developed as agonists of gastrointestinal peptides in a mono form or a combination of two or three different agonists, achieving results similar to the effects of bariatric surgery. Currently, about 70 different therapeutical principles are in the process of development. Problems related to the drugs on the market are their high prices, limited capacity for production, and lack of experience regarding long-term use.

Key words: obesity, dietary treatment, exercise, anti-obesity drugs, bariatric surgery, low grade inflammation

https://doi.org/10.5937/arhfarm74-50566

Introduction

Obesity is one of the most prevalent chronic non-communicable diseases worldwide, affecting approximately 650 million people. Excessive accumulation of visceral fat is associated with numerous comorbidities, which are major contributors to disability and global mortality (1). The obesity epidemic is still in progress and calls for strategies to curb it. Treatments that result in substantial weight reductions may improve outcomes for people living with obesity. There have been many setbacks in the development of drugs to treat obesity. Management of obesity is essential to prevent or decrease the development of comorbidities (2).

The first data on the treatment of obesity can be found in Greek medicine, then in the 10th century, when the king of Leon in northern Spain, Sancho the Fat (Sancho el Craso), had his doctor Hasdai Abu Yussuf ibn Shaprut sew up his mouth, leaving a small hole for a tube through which he could only drink fluids, and reducing his BMI by 50% (3).

Anti-obesity drugs appeared in the early 20th century and included thyroid hormones, dinitrophenol, and amphetamine. The discovery of new therapeutic principles in the second half of the 20th century was based on an attempt to understand the mechanism of regulation of food intake and energy consumption after the discovery of leptin in 1994. After it was noticed that amphetamine can cause addiction, the search for a drug that has an anorexigenic effect and does not lead to addiction began. Drugs that increased energy consumption led to higher mortality. A new era of anti-obesity drugs started after the discovery of hunger hormone ghrelin and many gastrointestinal peptides that affect metabolism and act on the gastrointestinal tract (4).

Physiologic regulation of energy balance

In order to understand the principle of treating obesity, it is necessary to know the physiology of food intake and the regulation of energy balance. The energy balance in the body is regulated by hunger and satiety, and energy consumption. The neuroendocrine system controls the hunger and satiety through bidirectional crosstalk between nucleus ventromedialis and nucleus ventrolateralis in the hypothalamus on the one side, and peripheral tissues on the other side. Proopiomelanocortin (POMC) neurons modulate food intake and energy metabolism via the melanocortin type 4 receptor (MC4R) in the brain. The MC4R is a G protein-coupled receptor whose mutation leads to a monogenic cause of obesity. After a meal, POMC neurons reduce the appetite and increase energy consumption, with the goal of maintaining a stable body mass. POMC cells are activated in response to energy input. Their activation produces melanocyte-stimulating hormone (alpha-MSH) and beta-endorphin. α-MSH leads to reduced food intake, increased energy expenditure, and weight loss by the activation of MC4R. Beta-endorphin reduces the activity of POMC cells by binding to the inhibitory mu-opioid receptor (MOP-R). On the other hand, neuropeptide Y (NPY) and agouti related protein (AgRP) are activated in a state of negative energy balance. After activation, NPY and AgRP inhibit POMC neurons and antagonize MC4R signaling, which stimulates food intake and reduces energy consumption (5). The main hormones that regulate food intake and modulate appetite are

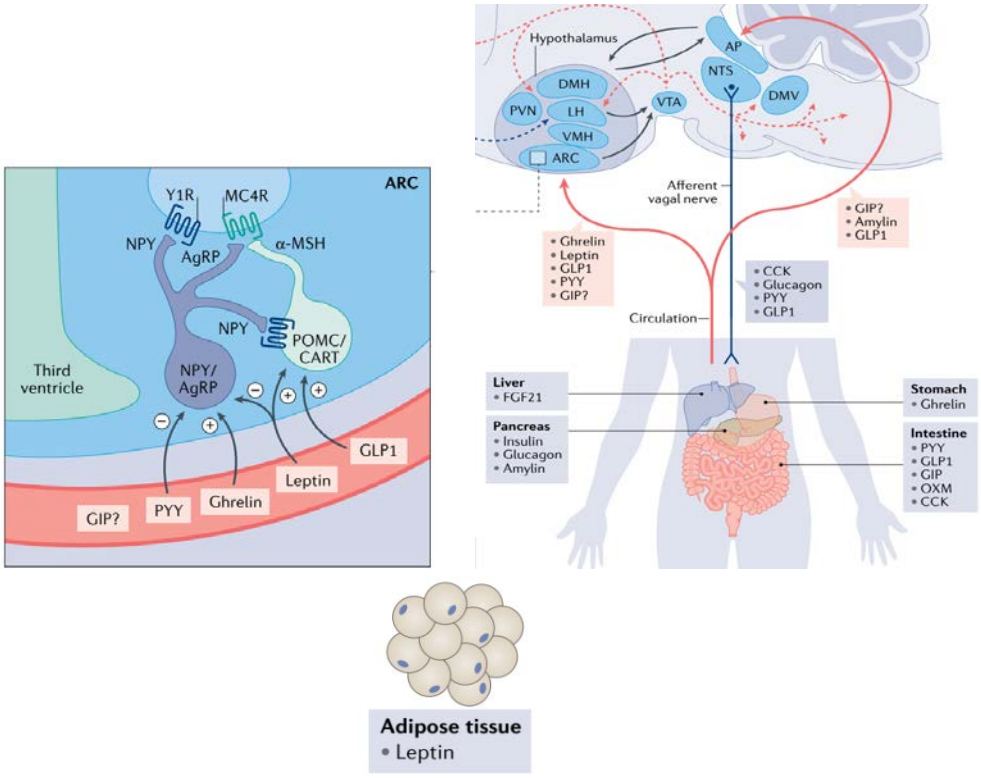

Figure 1. **Regulation of energy balance-hormones in control of homeostatic and hedonistic eating behaviour. α MSH- α melanocyte–stimulating hormone, AgRP-agouti-related peptide, AP-area postrema, ARC-arcuate nucleus, CART-cocaine and amphetamine regulator transcript, CCK-cholecystokinin, DMH-dorsomedial hypothylamus, DMV-dorsal motor nucleus of the vagus, FGF21- fibroblast growth factor 21, GIP-glucose dependent insulinotropic peptide, GLP-1-glucagon-like peptide 1, LH-lateral hypothalamus, MC4R-melanocortin 4 receptor, NPY-neuropeptide Y, NTS-nucleus tractus solitarius, OXM-oxyntomodulin, PFC-prefrontal cortex, POMC-proopiomelanocortin, PVN-paraventricular nucleus, PYY-peptid thyrosine thyrosine, VMH-ventomedial hypothalamus, VTA-ventral tegmental area, Y1R-neuropeptide Y receptor type 1. *Adapted from: (6).***

Slika 1. **Regulacija energetske ravnoteže-hormoni u homeostatskoj i hedonističkoj kontroli unosa hrane. α MSH- α melanocitni–stimulišući hormon, AgRP-agouti-related peptid, AP-area postrema, ARC-arkuatni nukleus, CART-regulatorni transkript za kokain i amfetamin, CCK-holecistokinin, DMH-dorzomedijalni hipotalamus, DMV-dorzalni motorni nukleus vagusnog nerva, FGF21- fibroblastni faktor rasta 21, GIP- glukozno zavisni insulinotropni peptid, GLP-1-peptid sličan glukagonu 1, LH-lateralni hipotalamus, MC4R-melanokortinski receptor 4, NPY-neuropeptid Y, NTS-nucleus tractus solitarius, OXM-oxyntomodulin, PFC-prefrontalni korteks, POMC-proopiomelanokortin, PVN-paraventricularni nukleus, PYY-peptid tirozin tirozin, VMH-ventomedialni hipotalamus, VTA-ventralna tegmentalna area, Y1R-neuropeptid Y receptor tip 1. *Prilagođeno iz: (6).***

secreted in adipocytes, such as leptin and adiponectin, and in the gastrointestinal tract, such as peptide tyrosine tyrosine (PYY), ghrelin, cholecystokinin (CCK), glucagon-like peptide 1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP) and oxyntomodulin (oXm). The regulation of food intake would be simpler if there was only a homeostatic control mechanism. However, the process of food intake has also a hedonic component that is sensitive to palatability and food odor. The part of the brain responsible for the hedonic experience of food is located next to the hypothalamus (Figure 1). The dopaminergic reward center is located in the mesolimbic brain region and in the hippocampus, and it is responsible for the phenomenon where a person in stressful situations, and even when unhappy and dissatisfied, takes in food, perceiving it as a comfort and reward (6).

Weight loss is easier than weight maintenance

Previous experiences in the treatment of obesity have shown that it is incomparably easier to reduce excess body weight than to maintain an achieved lower weight and prevent weight regain (7). Successful treatment of obesity is considered to reduce body weight by 10% or more and maintain the achieved weight for at least 1 year. Data from the National Weight Control Registry in the UK showed that the patients who lost an average of 33 kg and maintained the loss for more than 5 years had a continuously high level of physical activity and controlled caloric intake. In addition, after 2-5 years of successful weight maintenance, their chances to avoid regaining the weight increase (8).

Psychological factors such as lack of willpower, stigmatization of society, perception of one's own body, and previous experiences with weight loss are obstacles to long-term weight loss. The main barrier to successful weight loss and weight maintenance is the inability to resist to junk food, large portions and emotional eating. These self-sabotaging actions are the result of unresolved intrapersonal conflicts and lack of motivation (9).

Physiology of weight regain after weight loss

In order to maintain a reduced body weight for a long time, it is necessary to maintain an energy deficit of approximately -500kcal/day by reducing the feeling of hunger and increasing energy consumption (10). A number of factors are involved in the mechanism of weight regain after previous weight loss, from the paraventricular nucleus in the hypothalamus (PVH) to a series of adipokines and neurotransmitters. Increased synaptic transmission of PVH to Agouti related peptide (AgRP) increases the number of active synapses of AgRP neurons in response to an energy deficit. These synapses remain active until the lost body mass is recovered (11).

Growth hormone regulates the neuroendocrine response to body weight reduction via AgRP neurons, hunger signals, and energy conservation (12). The major challenge in obesity management is weight maintenance after successful weight loss, when the mechanisms by which the body tends to restore the lost energy reserve are activated. In order to overcome these mechanisms, pharmacotherapy is often required. Potential

adipose-related mechanisms responsible for regaining body mass after weight loss are obesogenic memory and cellular stress. People whose fat tissue has a high level of leukocyte activity in the first week of weight loss are at a high risk of regaining it, while people who are resistant to adipose tissue inflammation are at a reduced risk of regaining body weight. In the process of weight regain, the role of immune cells of adipose tissue, adaptive thermogenesis, lipolysis, lipid oxidation and energy consumption at rest is significant.

Treatment focused on dysfunctional adipose tissue

The recommended strategy to prevent weight loss from affecting the function of adipose tissue includes: daily physical activity, increasing the protein content of meals from the usual 15 to 25%, taking medication for the treatment of obesity, dietary supplements with green tea or caffeine, measuring body weight during 24 months of treatment in order to determine the increase in body weight, and maintaining contact with the obesity patient group (13, 14). The beginning of the treatment of obesity is the acceptance of a proper diet, appropriate physical activity and quality sleep, and this remains the basic therapeutic approach for the rest of life. When it has been established that dysfunctional adipocytes and low-grade inflammation are the basis for the comorbidity of obesity, a treatment focused on dysfunctional adipose tissue, the so-called ABCD approach (Adiposity Based Chronic Disease), is indicated. Previous studies demonstrated that a 5 to 10% reduction in body weight has significant benefits for preventing comorbidities related to obesity, including the prevention of progression of metabolic diseases such as prediabetes, type 2 diabetes, obstructive sleep apnea, steatosis of the liver, or dyslipidemia (15).

Lifestyle change is the basic approach for management of obesity

Dietary treatment is based on lower energy intake, balanced composition of food and proper rhythm of meals. It is desirable to adapt the diet to the patient's daily activities and energy consumption.

The general recommendation supported by the American College of Cardiology/American Heart Association (ACC/AHA) guideline is the reduction of caloric intake by 500 kcal up to 800 kcal per day. The European Society of Cardiology recommends the Mediterranean diet, and previously the DASH diet, for hypertension. Other diets such as plant-based diet, lower in carbohydrates and fat and higher in protein, have a short-term beneficial effect (4, 16-18). Diets should have a lower caloric intake, contain healthier foods and not exclude any food group (19, 20).

It has been established that there is a relationship between obesity and intestinal microbiota and changes in the microbiome during dietary interventions, independent of body weight reduction, which leaves open the possibility of individualizing the diet (21).

Another principle of obesity treatment is physical activity, which means any skeletal muscle activity that causes energy consumption. A subcategory of physical

activity is exercise, defined as planned, repeated structured activity with the goal of increasing or maintaining physical condition (22). For an initial reduction in body weight of 5 to 10%, the ACC/AHA guideline recommends at least 30 minutes of aerobic physical activity per day for 5 days of the week, or 150 minutes of aerobic physical activity per week. Twice as much aerobic activity is required to maintain weight loss. Combined aerobic activity and resistance exercise is recommended for elderly people with obesity for weight loss and improving metabolic status. This combination reduces the risk of muscle mass loss and sarcopenia in the elderly (16).

Antiobesity drugs

In order to achieve a reduction in body weight greater than 10%, the use of drugs is required in most cases. With new anti-obesity drugs, it is possible to reduce body weight by up to 25%, which brings them close to bariatric surgery in terms of effectiveness. The principle through which these drugs work is either enhancing satiety or inhibiting hunger, or increasing catabolism, and in order to achieve a long-term effect, their lifelong use is required, as in the treatment of any other chronic disease (23).

Since the synthesis of the first anti-obesity medications (AOM), the professional public has encountered safety issues due to which AOMs were sooner or later withdrawn from the market. Although lipase inhibitors (orlistat, cetilistat) are still popular in some countries, current drugs are mainly based on potentiating and prolonging the effect of incretins or acting on the hunger/satiety and reward centers in the central nervous system (CNS) (6, 24).

Naltrexon/bupropion (NB)

Naltrexone/bupropion (Contrave/Mysimba) is a combined oral sustained-release formulation of 8 mg naltrexone and 90 mg bupropion in each tablet, with two tablets to be taken twice a day. Bupropion is an antidepressant that increases the action of dopamine in the brain and decreases food intake. The combined effects of these two drugs reduce food cravings (25). Bupropion is a selective catecholamine reuptake inhibitor which stimulates POMC neurons, blocks opioid receptors and releases α-MSH. Binding of α-MSH to the MC4 receptor reduces food intake and increases energy expenditure. POMC and α-MSH neurons secrete beta-endorphin, an endogenous agonist of mu-opioid receptors. Binding of β-endorphin to mu-opioid receptors on POMC neurons mediates a negative feedback loop on POMC neurons, leading to a decrease in the release of α-MSH. Naltrexone inhibits negative feedback, thereby prolonging the anorexigenic activity of POMC neurons (26). Naltrexone/bupropion also acts on reward pathways, making it the drug of choice for people who eat out of emotional emptiness and dissatisfaction. Due to the blockade of reward pathways in the brain, it is recommended for people who are smokers or alcohol addicts (27). About 53% patients taking therapy with naltrexone/bupropion achieve a weight loss of at least 5%, and one third achieves a weight loss of 10% or greater, with substantial benefit on the lipid profile (27, 28).

Glucagon like peptide-1 receptor agonists (GLP-1 RA)

GLP-1 RA were developed after dipeptidyl peptidase 4 inhibitors (DPP4 inhibitors), which prolonged the half-life of GLP-1 and increased its concentration, as well as the concentration of GIP, reducing blood glucose, without an unwanted hypoglycemic effect.

Exendin-4 was originally found in salivary glands in the lizard Heloderma suspectum. A synthetic GLP-1 receptor agonist was branded as exenatide in 2005, and its half-life was 2.5 hours. It was the first Food and Drugs Administration (FDA) approved GLP-1 receptor agonist for type 2 diabetes mellitus (DMT2), but not for weight loss. In order to increase the duration of the drug, liraglutide was developed. In the beginning, liraglutide in a dose of 1.8 mg was approved for DMT2, and later, in a dose of 3mg per day, liraglutide branded as Saxenda was approved by the FDA in 2010 for management of obesity – initially for adults only, and in 2020 for children aged 12 and older. Liraglutide exerts an anorexigenic effect by activating arcuate POMC neurons, simultaneously inhibiting neuropeptide Y/agouti related pepide (NPY/AgRP) neurons through postsynaptic gamma-aminobutyric acid (GABA) receptors, and increases the activity of presynaptic GABA neurons. Viewing pictures of food after the administration of GLP 1 RA reduces the activation of the insula, amygdala, putamen and orbitofrontal cortex of the brain, which leads to a lower food intake (24, 29). In the meantime, in 2017, semaglutide in a dose of 1mg, subcutaneously administered once weekly, branded as Ozempic, was approved by the FDA for DMT2. Four years later, in 2021, the same drug, but in a dose of 2.4mg once weekly, showed more efficacy (20% weight loss) in weight loss than Saxenda (up to 15% weight loss) (24). By implementing the ABCD approach in the treatment of obesity, based on the Satiety and Clinical Adiposity (SCALE**)** Obesity and Prediabetes Trial, the benefits of liraglutide also go beyond weight loss. About 70% of patients with prediabetes establish normoglycemia after 1 year of treatment. In 80% of patients, the risk for progression of prediabetes to DMT2 is reduced (30). One of the studies devoted to the effect of liraglutide demonstrated that the combination of liraglutide with moderate to vigorous exercise was associated with improvements in insulin sensitivity and fitness (31). A combined approach which, after 12 to 18 months of GLP-1 agonist administration, is continued with Food is Medicine (FIM), helps to maintain the initial reduction in body weight. In case that FIM is not sufficient, GLP-1 agonist can be administered as "booster therapy" from time to time (32).

GIP receptor agonist (GIP RA)

The idea of using GIP receptor agonists to treat type 2 diabetes mellitus and obesity was unusual, given the expected effect on the increase of blood glucose. Despite this physiological effect, in preclinical studies GIP receptor agonists demonstrated a beneficial effect on energy balance and blood glucose, and a possible explanation for this is an increase in leptin sensitivity. The next step in the development of anti-obesity medications is the discovery of a drug that simultaneously stimulates GLP-1, GIP and/or glucagon receptors. The single-molecule drug (Tirzepatide) showed the best effect on

reducing body weight with GIP and GLP-1 receptor agonism. One of the beneficial effects of this combination is that GIP reduces the nausea caused by the GLP-1 receptor agonist. Tirzepatide is administered once weekly as a subcutaneous injection (6). In a trial with tirzepatide, the average weight reduction in participants was -15.0% with 5 mg of tirzepatide, -19.5% with 10 mg, and -20.9% with 15 mg weekly doses (1). Another variant is a unimolecular drug with a glucagon receptor (GcgR) and GLP-1 agonism (6). The glucagon agonist stimulates thermogenesis by acting on adipocytes, and also has a lipolytic effect in the liver (27). The FDA approved tirzepatide injections for chronic weight control in obese adults in November 2023.

The triple agonist retatrutide (GLP-1/GIP/glucagon) can lead to a greater reduction in body mass (17%) than dual agonists, through reduced calorie intake and higher energy expenditure. Studies have shown that retatrutide has a comparable effect on improving the glucose profile in comparison with tirzepatide (33). The results of a phase two trial with retatrutide in the treatment of obesity were published in June 2023 in *New England Journal of Medicine* (34).

MC4R agonist

MC4R agonist, **setmelanotide**, has caused a decrease in body weight in patients with POMC or leptin receptor (LEPR) mutations. Setmelanotide was injected daily (24).

Bariatric surgery

Bariatric surgery is still the most effective way to treat obesity, indicated for patients with BMI >30kg/m^2 with unregulated type 2 diabetes, or with BMI >35kg/m^2 and at least one obesity-related disease, or with BMI >40kg/m^2 regardless of comorbidities. The most common bariatric procedures are Roux-en-Y gastric bay-pass (RYGB), sleeve gastrectomy (SG) and biliopancreatic diversion with duodenal switch (BPD/DS). Average weight loss varies from 30 to 50% depending on the type of surgery, as well as the influence on metabolic parameters (e.g., blood glucose, insulin, C-peptide, diabetes type 2 remission, lipid profile, CRP etc.). The maximum effect of bariatric surgery is achieved with a change in lifestyle, and often with the simultaneous use of anti-obesity medications (31, 33). Weight regain after bariatric surgery is most commonly the result of non-compliance with proper nutrition and physical activity (35). There are no official guidelines on pharmacotherapy aimed at weight regain after bariatric surgery. Anti-obesity medications after weight loss surgery are indicated to support weight loss and for the prevention and management of weight regain (36, 37).

Anti-obesity medications in the pipeline

Medications in phase 3 trials:

Methylphenidate acts as an inhibitor of dopamine reuptake, which reduces food intake. The main indication for this drug is the treatment of attention deficit hyperactivity disorders (ADHD). The side effects of methylphenidate include upper abdominal pain, tachycardia, sleep disturbance and headaches.

Tesofensine suppresses the appetite by increasing dopaminergic activity in the forebrain. The main mechanism of action is the inhibition of the reuptake of serotonin, noradrenaline and dopamine.

Exenatide (2 mg) with dapagliflozin 10 mg decreases the food-related neural activity in the reward system and thus reduces the body mass by about 4kg in persons with obesity and prediabetes. A trial of metformin with dapagliflozin was conducted in a similar population, with the same effect as the previous combination.

Cagrilintide is an analog of amylin that increases satiety by acting on the satiety center in the hypothalamus and at the same time slows gastric emptying. A study examining the synergistic effect of cagrilintide and semaglutide is ongoing (25).

Medications completed phase 2

Orforglipron and danugliprone are an oral, non-peptide, potent GLP-1 receptor agonist which activates G-proteins through the recruitment of β-arrestin to GLP-1 receptor.

Bimagrumab is a human monoclonal antibody that blocks the activin type II receptor (ActRII) and thus prevents the loss of muscle mass and stimulates skeletal muscle growth. Bimagrumab could be a first-line treatment for sarcopenic obesity.

Medications in phase 1 or 2

Amylin, secreted from pancreatic β cells in response to food intake, slows gastric emptying and acts as a satiety signal in the homeostatic and hedonic brain regions.

Glabridin analogue regulates the metabolism through changing gene expression by increasing energy consumption in muscles and the liver.

Oxytocin reduces appetite, acting centrally, and leads to a reduction in food intake.

Tocotrienols acts in two ways: taste buds activators alter nutrient sensing mechanisms and therefore activate anorexigenic pathways, while another mode of action is to reduce insulin resistance by increasing the expression of adiponectin and reducing adipose tissue inflammation. Their effectiveness is being tested in obese menopausal women (25).

Numerous combination molecules for the treatment of obesity are also being investigated, such as liraglutide/setmelanotide, GLP-1RA/GcgR, leptin/pramlintide (or with FGF21, as well as with exendin 4), exendin 4/salmon calcitonin, exenatide/CCK and GLP1/PYY (6).

Conclusion

The global burden of obesity is one of the challenging social and medical problems all over world, targeting both highly developed and undeveloped countries. The enormous number of subjects with obesity, as well as the costs of obesity management and its comorbidities, represent a serious problem for each country. Currently, the following methods are the pillars of obesity management: diet, exercise, psychological intervention,

pharmacological intervention and bariatric surgery. Diet and exercise are the basic principles of treatment for every person with obesity, which they should accept as lifelong treatment. The history of anti-obesity drug use is rather long, with many ups and down, when the drugs were removed from the market due to various reasons. In last decade, there has been rapid progress in the development and therapeutic use of a novel class of anti-medications, which are based on incretins and their analogs from the gastrointestinal tract. Current problems with these new drugs are their high price, limitations in their production, and lack of experience with their effects after long-term use. However, their effects are promising, so that one can expect that in the future bariatric surgery should be reserved only for the most serious cases.

Acknowledgements

There was no financial support for this manuscript. We did not have any grant for this manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

Co-author contributions to the manuscript: Snežana Polovina: Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Roles/Writing - original draft; and Writing - review & editing. Mirjana Šumarac Dumanović: Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Roles/Writing - original draft; and Writing - review & editing. Dragan Micić: Investigation; Methodology; Project administration; Resources; Validation; Visualization; Roles/Writing - original draft; and Writing - review & editing.

References

1. Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, et al. SURMOUNT-1 Investigators. Tirzepatide Once Weekly for the Treatment of Obesity. N Engl J Med. 2022;387(3):205-216.
2. Duncan I, Kerr D, Aggarwal R, Huynh N, et alet al. New drugs for obesity, is the excitement affordable? Population Health Manag 2023;26(5):356-357.
3. Gargantilla Madera P, Arroyo Pardo N. Hasday: tratamiento de la obesidad en el siglo x. Endocrinol Nutr. 2016;63:100-101.

4. Bray GA, Heisel WE, Afshin A, Jensen MD, Dietz WH, Long M, et al. The Science of Obesity Management: An Endocrine Society Scientific Statement. Endocr Rev. 2018;39(2):79-132.
5. Quarta C, Claret M, Zeltser LM, Williams KW, Yeo GSH, Tschöp MH, . POMC neuronal heterogeneity in energy balance and beyond: an integrated view. Nat Metab. 2021 Mar;3(3):299-308.
6. Müller TD, Blüher M, Tschöp MH, DiMarchi RD. Anti-obesity drug discovery: advances and challenges. Nat Reviews Drug Discov. 2022;21(3):201-223.
7. Gutt S, Schraier S, Gonz S, GBagnes MF, Yu M, González CD, Di Girolamo G. Long-term pharmacotherapy of obesity in patients that have undergone bariatric surgery: pharmacological prevention and management of body weight regain. Expert Opin Pharmacother. 2019;20(8):939-947.
8. Wing RR, Phelan S. Long-term weight loss maintenance. Am J Clin Nutr. 2005;82(1 Suppl):222S-225S.
9. Gupta H. Barriers to and Facilitators of Long Term Weight Loss Maintenance in Adult UK People: A Thematic Analysis. Int J Prev Med. 2014;5(12):1512-20.
10. Melby CL, Paris HL, Foright RM, Peth J. Attenuating the Biologic Drive for Weight Regain Following Weight Loss: Must What Goes Down Always Go Back Up? Nutrients. 2017;9(5):468.
11. Grzelka K, Wilhelms H, Dodt S, Dreisow ML, Madara JC, Walker SJ, et al. A synaptic amplifier of hunger for regaining body weight in the hypothalamus. Cell Metab. 2023;35(5):770-785.e5.
12. Furigo IC, Teixeira PDS, de Souza GO, Couto GCL, Romero GG, Perelló M, et al. Growth hormone regulates neuroendocrine responses to weight loss via AgRP neurons. Nat Commun. 2019;10(1):662.
13. van Baak MA, Mariman ECM. Mechanisms of weight regain after weight loss - the role of adipose tissue. Nat Rev Endocrinol. 2019;15(5):274-287.
14. van Baak, MA, Mariman, ECM. Obesity-induced and weight-loss-induced physiological factors affecting weight regain. Nat Rev Endocrinol. 2023;19(11):655–670.
15. Garvey T. Is obesity or adiposity-based chronic disease curable: the set point theory, the environment, and second-generation medications. Endocr Pract. 2022;28(2):214-222.
16. Yurista S, Eder R, Feeley M, Kodur N, Tang WHW, Nguyen CT. A Closer Look at ACC/AHA and ESC Guidelines for Managing Obesity and Overweight in Adults. JACC Adv. 2023;2(7):100570.
17. Bloch MJ. The dietary approaches to stop hypertension (DASH) diet-promise unmet. J Am Soc Hypert. 2017;11(6):323–324.
18. Richardson LA, Izuora K, Basu A. Mediterranean diet and its association with cardiovascular disease risk factors: A scoping review. Int. J Environ Res Public Health. 2022;19(19):12762.
19. Tettamanzi F, Bagnardi V, Louca P, Nogal A, Monti GS, Mambrini SP, et al. A high protein diet is more effective in improving insulin resistance and glycemic variability compared to a mediterranean diet—a cross-over controlled in patient dietary study. Nutrients. 2021;13(12):4380.
20. Chao A, Quigley KM, Wadden T. Dietary interventions for obesity: clinical and mechanistic findings. J Clin Invest. 2021;131(1):e140065.
21. Wiechert M, Holzapfel C. Nutrition Concepts for the Treatment of Obesity in Adults. Nutrients. 2022;14(1):169.
22. Oppert JM, Bellicha A, van Baak M, Battista F, Beaulieu K, Blundell JE, et al. Exercise training in the management of overweight and obesity in adults: Synthesis of the evidence and recommendations

from the European Association for the Study of Obesity Physical Activity Working Group. Obes Rev. 2021;22(S4):e13273.
23. Gjermeni, E, Kirstein AS, Kolbig F, Kirchhof M, Bundalian L, Katzmann JL, et al. Obesity-An Update on the Basic Pathophysiology and Review of Recent Therapeutic Advances. Biomolecules. 2021;11(10):1426.
24. Brandfon S, Eylon A, Khanna D, Parmar MS. Advances in Anti-obesity Pharmacotherapy: Current Treatments, Emerging Therapies, and Challenges. Cureus. 2023;15(10):e46623.
25. Chakhtoura M, Haber R, Ghezzawi, Rhayem C, Tcheroyan R, Mantzorosc C. Pharmacotherapy of obesity: an update on the available medications and drugs under investigation. eClinicalMedicine. 2023;58:101882.
26. Kosmalski M, Deska K, BK, B, RB, R K, BK, Besk M, Pietras T. Pharmacological Support for the Treatment of Obesity-Present and Future. Healthcare (Basel). 2023 Feb 2;11(3):433.
27. Onakpoya IJ, Lee JJ, Mahtani KR, Aronson JK, Heneghan CJ. Naltrexone-bupropion (Mysimba) in management of obesity: A systematic review and meta-analysis of unpublished clinical study reports. Br J Clin Pharmacol. 2020;86(4):646-667.
28. Thomas B, Lindblad AJ, Luu T, Paige A. Naltrexone-bupropion for weight loss. Can Fam Physician. 2023;69(9):627.
29. Drucker DJ. GLP-1 physiology informs the pharmacotherapy of obesity. Mol Metab. 2022 Mar;57:101351.
30. Le Roux CW, Astrup A, Fujioka K, Greenway F, Lau DCW, Van Gaal L, et al. SCALE Obesity Prediabetes NN8022-1839 Study Group. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. Lancet. 2017;389(10077):1399-1409.
31. Lundgren JR, Janus C, Jensen SBK, Juhl CR, Olsen LM, Christensen RM, et al. Healthy weight loss maintenance with exercise, liraglutide, or both combined. N Engl J Med. 2021;384(18):1719-1730.
32. Mozaffarian D. GLP-1 Agonists for Obesity—A New Recipe for Success? JAMA. 2024 Mar 26;331(12):1007-1008.
33. Melson E, Ashraf U, Papamargaritis D, Davies MJ. What is the pipeline for future medications for obesity? Int J Obes (Lond). 2024 Feb 1. doi: 10.1038/s41366-024-01473-y. Epub ahead of print.
34. Naeem M, Imran L, Banatwala UESS. Unleashing the power of retatrutide: A possible triumph over obesity and overweight: A correspondence. Health Sci Rep. 2024 Feb 5;7(2):e1864.
35. Roomy MA, Hussain K, Behbehani HM, Abu-Farha J, Al-Harris R, Ambi AM, et al. Therapeutic advances in obesity management: an overview of the therapeutic interventions. Front Endocrinol (Lausanne). 2024 Apr 23;15:1364503.
36. Busetto L, Bettini S, Makaronidis J, Roberts CA, Halford JCG, Batterham RL. Mechanisms of weight regain. Eur J Intern Med. 2021;93:3-7.
37. Lucas E, Simmons O, Tchang B, Aronne L. Pharmacologic management of weight regain following bariatric surgery. Front Endocrinol. 2023;13:1043595.

Lečenje gojaznosti iz perspective kliničara

Snežana Polovina[1,2,3], Mirjana Šumarac-Dumanović[1,3], Dragan Micić[4]

[1]Klinika za endokrinologiju, dijabetes i bolesti metabolizma, Univerzitetski klinički centar Srbije, Dr Subotića 13, 11000 Beograd

[2]Farmaceutski fakultet Novi Sad, Univerzitetska privredna akademija, Trg mladenaca 5, 21000 Novi Sad

[3]Medicinski fakultet Univerziteta u Beogradu, Dr Subotića 8, 11000 Beograd

[4]Odeljenje medicinskih nauka, Srpska akademija nauka i umetnosti, Knez Mihajlova 35, 11000 Beograd

*Autor za korespondenciju: Snežana Polovina, e-mail: snezanapolovina@gmail.com

Kratak sadržaj

Globalna epidemija gojaznosti zahvatila je skoro svaku zemlju na svetu, izazivajući ogromno opterećenje socijalnog i zdravstvenog sistema. Iako su u mnogim zemljama uvedene brojne mere za obuzdavanje epidemije, gojaznost je i dalje u porastu. Važan korak u ovoj oblasti napravljen je kada je gojaznost prihvaćena kao bolest. Prepoznavanje gojaznosti kao bolesti omogućava vladama i državama da razviju sopstvene planove za mera za kontrolu epidemije gojaznosti. Gojaznost je prepoznata kao problem od davnina i predlagane su različite mere. Savremeni tretman gojaznosti se trenutno zasniva na sledećim terapijskim principima: dijeta, vežbanje, psihološka podrška, farmakološko lečenje i barijatrijska hirurgija. Istorija farmakološkog lečenja je prilično duga i puna povlačenja lekova zbog raznih razloga. Nove perspektive i obećavajući rezultati stigli su sa klasom lekova na bazi inkretina. Ovi lekovi su razvijeni kao agonisti gastrointestinalnih peptida u monopeptidnom obliku ili kao kombinacija dva ili tri različita agonista, postižući rezultate slične onima koje postiže barijatrijska hirurgija. Trenutno je u procesu razvoja oko 70 različitih terapijskih principa. Problemi na tržištu lekova za lečenje gojaznosti su njihove visoke cene, ograničen kapacitet za proizvodnju i nedostatak iskustva po pitanju efekata nakon dugotrajne primene.

Ključne reči: gojaznost, dijetoterapija, vežbanje, lekovi za lečenje gojaznosti, barijatrijska hirurgija, inflamacija niskog stepena