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Challenges and Novelties in the Treatment of Obesity in Adults. A review

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Abstract:

Introduction

Obesity is a complex, chronic disease that continues to be a significant global health challenge due to its prevalence and association with numerous comorbidities. Etiology of this disease includes different factors from genetic, environmental, and lifestyle fields, while effective management of obesity is still being studied.

Aim of the study

The aim of this comprehensive review is to examine arising innovations in the treatment of adult obesity. Deeper insight into the available database would help to provide better understanding of obesity and of its treatment.

Materials and Methods

To reach satisfying results the research was conducted on the articles referring to obesity treatment from the Pubmed databases. Articles from recent years were preferably utilized to keep the review up to date.

Results

Nowadays, pharmacotherapy can offer GLP-1 receptor agonists like liraglutide or semaglutide, and new drugs like tirzepatide that show great effectiveness. Additionally, bariatric surgery continues to offer great solution for severe obesity, combining restrictive and malabsorptive mechanisms for significant weight loss and metabolic benefits. The main procedures include gastric bypass with sleeve gastrectomy or duodenal switch. Personalized treatment, referring to different obesity phenotypes, has shown improvement in the therapeutic outcomes. Some new therapies are studied including triple agonists (retatrutide), non-peptide GLP-1 receptor agonists, and drugs reaching other receptors. All of them are promising for the effective obesity treatment in the future.

Summary

This review underlines the need for multidisciplinary and personal approach in the treatment of obesity and the need to share the knowledge about it to address the growing obesity epidemic effectively. Recognizing obesity as a chronic and complex disease is essential to improve patient's understanding of their condition as well as to reach effective treatment outcomes.

Key words: obesity; nutrition; lifestyle; bariatric surgery; pharmacotherapy in obesity

Introduction

Obesity is a complex and multifactorial chronic disease that has become a principal public health issue affecting millions of individuals worldwide [1] This condition is characterized by excessive fat accumulation and arises when energy intake consistently exceeds energy expenditure, creating a positive energy balance that finally leads to weight gain. According to WHO, in 2022, 2.5 billion

adults were overweight. Of these, 890 million were living with obesity, which means 1 in 8 people worldwide suffered from obesity [2].

Nowadays, environmental and lifestyle factors further aggravate the issue of obesity. Over the past five decades, the prevalence of this disease has increased globally to pandemic levels. According to data, since 1980, obesity rates have doubled in more than 70 countries and have continued to rise in others. It is projected that by 2030, about 38% of the world's adult population will be overweight, and 20% will be obese [3]. Moreover, COVID-19 pandemic has further accelerated these trends by facilitating obesogenic lifestyle behaviors, resulting in long-term implications of spreading obesity worldwide [4].

The most commonly utilized tool for defining and categorizing obesity is body mass index (BMI), defined as weight in kilograms divided by height in meters squared (kg/m^2). According to established thresholds, patients with a BMI of ≥ 25 kg/m^2 are classified as overweight, while those with a BMI of ≥ 30 kg/m^2 are considered obese. While BMI offers a practical method to assess the level of obesity, it is a limited tool, as it does not focus on fat distribution, while it is the abdominal obesity that is more closely linked to health risks. That is why waist circumference is frequently included alongside BMI in clinical evaluations, as both tools are accessible and reproducible for measuring body weight status [2]. More specifically, Waist-to-Hip Ratio (WHR) is used and it is calculated by dividing the waist circumference by the hip circumference in cm. A WHR greater than 1.0 in men and 0.85 in women indicates an excess of visceral abdominal fat [5].

Obesity continues to be the main risk factor for numerous health challenges including type 2 diabetes mellitus, cardiovascular disease, hypertension, dyslipidemia, and various cancers such as those of the breast, colon, and pancreas. Complications of obesity of the mechanical origin also occur. It contributes to degenerative joint changes, sleep apnea and urinary incontinence due to increased pressure on the body. [5] Additionally, obesity is associated with reduced quality of life and decreased life expectancy [6]. These complications highlight the critical need for effective obesity management. The causes of obesity are multifactorial, including a combination of genetic, environmental, behavioral, and metabolic factors. These include excessive caloric intake, physical inactivity, genetic predisposition, hormonal imbalances and psychological factors like stress or emotional eating [7].

When it comes to the treatment of obesity, the emphasis is put on more personal approach, including not only weight reduction, but also on deeper understanding the reasons of the disease in order to change the patient's mindset and daily habits. It is important to underline that obesity has different phenotypes and pathogenesis, so recognizing it and personal approach to it is crucial for therapeutical success. One of the ways to differentiate obesity phenotypes is the metabolic outcome. In some phenotypes, no complications in metabolism are observed, which is called metabolically healthy

obesity (MHO) and is related to no hormonally active ectopic visceral adipose tissue [8]**.** Yet, in the other patients metabolic difficulties occur relatively early on the disease, regardless of the lack of a high BMI – it is called the metabolically obese normal weight (MONW) phenotype [9]. Other classifications focus on muscle mass deficiency (sarcopenia and non-sarcopenia obesity) and sometimes there is a need for introducing protein intake and enhancing resistance exercise [10]. Important classification bases on the behavioral differences in the pathogenesis of weight gain like the dominance of hunger and satiety disorders, appetite issues, stress and lifestyle influence [11]. There are several main types distinguished: the „hungry gut" - characterized by the shorter feelings of fullness, leading to increased food intake; „hungry brain" - that involves impaired satiation, resulting in difficulty with feeling full, „emotional hunger" - which is driven by emotional eating with cravings, and reward-seeking behaviors, and „slow burn" - characterized by low predicted energy expenditure and a tendency to slowly gain weight. The treatment differs between the phenotypes and patients receiving personalized therapy based on their specific obesity type experienced much better results, with a higher proportion achieving substantial weight loss. This suggests that tailoring treatment to individual phenotypes improves the effectiveness of obesity intervention [12]. In this review current challenges with underlining of the personal approach in the treatment of adult obesity will be explored.

Aim of the study

The aim of this review was to summarize and elaborate on the topic of current obesity treatment options. Through deeper insight into the available therapies efficacy of them could have been analyzed alongside with side effects. Focus was put on the closer analysis on the personal treatment aspect of obesity treatment as an important foundation.

Materials and Methods

In order to reach satisfying results the analysis of the articles referring to obesity treatment from the PubMed databases was conducted. The keywords used in the research were „obesity", „obesity treatment", „nutrition", „bariatric surgery", „pharmacotherapy of obesity". Articles from recent years were preferably utilized to reach the most actual results.

Obesity treatment

1. Pharmacotherapy

Pharmacotherapy plays crucial role in the management of obesity especially for patients who do not achieve sufficient weight loss through lifestyle changes. Currently available medications target mechanisms involved in appetite regulation, caloric intake, and metabolism. Below, the fundamental

medications for obesity treatment, widely used across most countries, are described in more detail and are summarized in Table 1.

- **GLP-1 analogues - Liraglutide and Semagluitide**

Glucagon-like peptide-1 (GLP-1) is an incretin hormone released from the enteroendocrine cells in the small intestine as a response to food intake [13]. GLP-1 receptor agonists are medications that mimic this effect in two different pathways. The central mechanism of action is regulation of hunger and satiety mechanisms, which results with reduced calorie intake without affecting energy expenditure. The peripheral effect contributes to glucose-dependent regulation of insulin and glucagon secretion in pancreas, reducing the risk of both hyperglycemia and hypoglycemia [11]. In addition, GLP-1 receptor agonists help to delay the gastrointestinal emptying, which enhances prolonged satiety, reduced hunger, and stabilized blood sugar levels also leading to lower calorie intake [14]. Currently available GLP-1 receptor agonists are liraglutide at a dose of 3.0 mg and semaglutide at a dose of 2.4 mg in a form of subcutaneous injections. Both liraglutide and semaglutide show beneficial effect in the treatment of patients with the risk of cardiovascular events [15,16]. Moreover, GLP-1 receptor agonists seem to be a good choice for patients with complications related to the development of insulin resistance, type 2 diabetes mellitus and metabolic syndrome [11]. Although GLP-1 receptor agonists are highly effective in reducing body weight, they can also show some side effects. Most of them are typically mild and transient like nausea and vomiting, diarrhea or constipation, but some may persist as a chronic gastrointestinal motility disorders. Caution is advised due to the potential risk of pancreatitis [17,18].

Nowadays, GLP-1 inhibitors are one of the most effective anti-obesity drugs. In the SCALE trial, which involved use of liraglutide in a weekly dose for 56 weeks, about 63% patients that received it showed weight loss of about 5% in comparison to the placebo-group, in which only 27% of participants lost weight [19]. The effectiveness of semaglutide was checked for in the STEP trial (Semaglutide Treatment Effect in People with Obesity), where it caused from about 14 % to 17% weight reduction in obese individuals after 68 weeks of treatment. What is more, the STEP trials showed improvements in waist circumference, lipid profiles, blood pressure, and C-reactive protein, all of which are cardiometabolic risk factor [20,21,22].

- **Tirzepatide**

Tirzepatide is a new FDA-approved medication for obesity. It has silmutaneous agonistic effect on both GLP-1 receptors and glucose-dependent insulinotropic peptide (GIP) receptors. GIP receptors are

mostly located in the central nervous system and it is the central effect on energy intake that is said to be of greatest importance [23]. Tirzepatide not only lowers the calories intake but also increases energy expenditure, which helps to affect both sides of body's energy homeostasis equation [11]. To estimate the effectiveness of Tirzepatide in various dosages, SURMOUNT 1-4 trials were conducted in obese patients with or without type 2 Diabetes Mellitus. All of the trials demonstrated significant body weight reduction reaching even 20% in patients treated with tirzepatide [24,25,26].

- **Naltrexone/Bupropion**

Naltrexone is an opioid receptor antagonist used originally to treat alcohol and drug addiction. Through binding to the μ opiate receptors in the brain naltrexone demonstrated influence on central appetite control. However, in studies, it did not show any consistent results when used in monotherapy [27]. Bupropion originally is an anti-depressant drug that was used for the treatment of depression and of smoking addiction. Interestingly, it has been found that the main side effect of Bupropion is weight loss. It acts by blocking the dopamine and noradrenaline reuptake at the presynaptic cleft and so it decreases the reward-related sensation of eating [14]. In combination with naltrexone it demonstrated notable weight loss [28]. Together, naltrexone and bupropion modulate mood, appetite, and cravings, which makes them suitable for patients with irresistible need for snacking, emotional eating and diagnosed eating disorders. These combination can show some side effects from the gastrointestinal tract like constipation or nausea, and from central nervous system, for instance dizziness and headache. That is why it ceased to be used as one of the main obesity-drugs in some countries [29].

- **Orlistat**

Orlistat is a gastric and pancreatic lipase inhibitor that is used in treatment of obesity in accordance with hypocaloric diet. Due to inactivation of lipase, only 70% of the ingested fat is absorbed, and the rest is excreted as an oily diarrhea [14]. Possible side effects might occur like flatulence, a sudden need for bowel movement, malabsorption of fat-soluble vitamins and some drugs [30]. The effect of body weight reduction of about 10% can be expected, however it can be even better if fatty products are exchanged to low-fat alternatives [31]. Moreover, orlistat can also modestly reduce blood pressure and plays a significant role in Type 2 Diabetes Mellitus prevention, probably due to its weight reduction effect [32]. Orlistat might be also successfully used in combination with other anti-obesity drugs [14].

- **Phentermine/topiramate**

The combination of phentermine and topiramate continues to be additional therapy to lifestyle modifications as a treatment for obesity. Phentermine is a sympathomimetic amine, that acts by increasing the release of norepinephrine in the brain promoting appetite suppression and reduction of food intake. What is more it stimulates the dopamine and serotonin release, which regulate mood and apetite. Topiramate is and antiepileptic drug and it acts on different neurotransmitter systems in the brain, including gamma-aminobutyric acid (GABA) and glutamate and by affecting these, it reduces the rewarding properties of food also leading to decreased food intake. In combination they reduce the body mass to about 9.8-11% within one year [33,34]. However, the combined therapy with these drugs was associated with increased heart rate, sleep disorders, mood changes, and gastrointestinal complications [35]. Due to these adverse effects, many countries have refused to grant marketing authorization for this therapy [7].

Medication	**Mechanism of treatment**
GLP-1 analogues - Liraglutide, Semaglutide	- regulation of hunger and satiety mechanisms in the brain - glucose-dependent regulation of insulin and glucagon secretion in pancreas - delaying of the gastrointestinal emptying and promoting prolonged satiety
GLP and GIP agonist - Tirzepatide	- lowering the calories intake - increasing energy expenditure
Naltrexone/Bupropion	- influence on central appetite control through μ opiate receptors - blocking the dopamine and noradrenaline reuptake at the presynaptic cleft (decreases the reward-related sensation of eating)
Orlistat	- inactivation of lipase and absorbing less fat, the rest excreted as an oily diarrhea
Phentermine/topiramate	- increasing the release of norepinephrine in the brain which promotes appetite suppression - stimulation of the dopamine and serotonin release, which regulates mood and appetite - reduction of the rewarding properties of food also leading to decreased food intake

Table 1. Anti-obesity medications and their mechanisms of action.

2. Bariatric Surgery

Bariatric surgery is a well-established and effective intervention for the treatment of severe obesity and its associated complications. The surgical procedures aim to reduce caloric intake and, in some cases, change hormonal responses by modifying the gastrointestinal anatomy. There are two mechanisms in which patient after surgery can loose weight: restriction and malabsorption of ingested

food. A restrictive approach is physically limiting the quantity of food that can be ingested by limiting the size and capacity of the stomach while leaving the remains of the gastrointestinal tract intact. Malabsorption of calories and nutrients occurs when a portion is bypassed or removed. Kilocalories and nutrients are less able to be absorbed because ingested food remains in the gut to a shorter distance [36]. Two most common surgical procedures are gastric bypass with sleeve gastrectomy or duodenal switch. Gastric bypass with sleeve gastrectomy is a combination of two bariatric techniques, in which a sleeve gastrectomy is performed first, removing a large portion of the stomach to reduce food capacity. Then a gastro-intestinal bypass is created, the passage of food is redirected and omits part of the small intestine, which reduces the absorption of calories and nutrients. This procedure combines the advantages of both techniques – restriction of the amount of food and malabsorption, leading to great weight loss. Duodenal switch is a more advanced procedure that goes after sleeve gastrectomy. After reducing the size of the stomach, a larger portion of the small intestine is bypassed, creating a new connection between the stomach and the rest of the bowel. This makes the procedure both restrictive and strongly malabsorptive, leading to the greatest weight loss of any bariatric surgery. However, this technique is associated with the risk of serious nutritional deficiencies and the need for lifelong supplementation [14]. Today, almost all procedures are performed by laparoscopic technique, which means through minimally invasive surgery. This technical revolution has resulted in reduced post-operative pain, quicker recovery, and less complications than open surgery [37]. What is more, health-related quality of life occurs to demonstrate large improvements after surgery, especially in physical domains [38]. In general, all of surgical procedures lead to significant weight loss, but, importantly, patients with lifestyle changes before surgery were more likely to lose more weight after the procedure [39].

3. Lifestyle treatment

Lifestyle modification is the foundation of obesity management, focusing on sustainable changes in diet, physical activity, and behavioral habits. While lifestyle treatment requires long-term commitment, it enhances the effectiveness of pharmacological or surgical interventions. Lifestyle changes are aimed to create a negative energy balance through reduction of caloric intake and increasing the energy expenditure [14]. Energy balance in the organism involves energy intake, expenditure and storage, with positive energy balance leading to weight gain. A daily energy deficit of 500 kcal is recommended for weight loss, and it can be reached by reducing consumption of energy-dense foods. The high energy macronutrient is fat, which provides more than double the energy of carbohydrates or protein. Thus, consequently, lowering fat intake can significantly reduce daily calories consumption. However, research indicates that it is the energy content of the diet, rather than its macronutrient composition, that plays the central role in weight management. Therefore, irrespective of the macronutrient source, consuming fewer calories facilitates weight loss [40, 41]. The best approach to

dietary treatment is taken by individualizing the plan for a specific patient with frequent evaluation of the outcomes. On the contrary, advice such as „eat more vegetables" or „workout regularly" seems insufficient and might have reverse effect [14]. In recent years, personalized nutrition has become increasingly popular, driven by tools like genetic testing. Studies reveal significant differences in how individuals metabolize identical meals, suggesting personalized diets could improve blood glucose control and related metabolic outcomes. These findings support the potential of gene-based and microbiome-based dietary strategies to enhance health [42]. What is more, to help patients loose weight, multidisciplinary weight loss programs take place, that often combine nutrition, physical activity and behavioral strategies delivered regionally or national by health insurers or companies. The largest of them are Weight Watchers and OPTIFAST. Moreover, self-monitoring of diet and physical activity such as smartphone apps can be supportive for individuals willing to loose weight and it is an accessible option for the patients [36]. Interventions in lifestyle changes do not only involve dietary modifications and increased physical activity, but also on management of sleep deprivation and stress overload. Personalized approach involves taking care of psychological factors like stress and mental health as well as consumption of any drugs and alcohol, as they can contribute to weight gain [14]. Thus, lifestyle interventions involve focus on wide range of areas of life and through small steps can cause favorable outcomes of weight loss.

4. Studies on new therapies

The research on new anti-obesity therapies continues and focuses on new variants of pharmacotherapy, personalized treatment and therapies with new mechanisms. One of the medications that is being studied is retatrutide, a triple agonist of GIP, GLP-1 and glucagon receptors. Stimulation of glucagon receptors demonstrates extra effects of increasing energy expenditure and amplifying thermogenesis. Studies show that treatment with retatrutide helped to reduce >5% of body weight in 100% participants, which is a promising result for future patients that would not respond to other drugs [43]. Other examinations are conducted on the other forms of administrations of incretin drugs, commonly used in injections, for instance oral form of semaglutide. This drug is also being researched to check its efficacy and safety in higher dosages. Interestingly it has been found that the frequency of side effects of semaglutide increases with higher doses of its oral form only to some point. However, above 25 mg a plateau in side effect occurrence is demonstrated. Thus, adverse events stop at some point, unlike the drug's anti-obesity and hypoglycemic effects [44]. Different incretin is also being studied called orforglipron, which is the first non-peptide GLP-1 receptor agonist. Drug demonstrates high effectiveness, but its use is associated with a higher frequency of side events, affecting more participants than the ones treated with GLP-1 analogs [45]. Survodutide is another interesting drug that is under research. It is a selective synthetic dual agonist of the glucagon receptor (GCGR) and the

glucagon-like peptide-1 (GLP-1) receptor. It can provide benefits by targeting multiple pathways involved in glucose metabolism and appetite regulation. This drug is currently in clinical trials for treatment of non-alcoholic steatohepatitis (NASH), a liver condition often related to the metabolic issues like obesity and Type 2 Diabetes [46]. Personalized treatment occurs to be a great trend in the obesity treatment. It is a fresh and effective way to treat obesity and is based on adjusting treatment to the phenotype of obesity, but also on comorbidities and risk profile. There was a clinical trial involving 84 patients with obesity, categorizing them into different obesity phenotypes [47]. Those with a "hungry gut" (shorter feelings of fullness) received with GLP-1 analogues, while those with a "hungry brain" (impaired satiation) were treated by phentermine–topiramate. Participants identified with "emotional hunger" (emotional eating, cravings, and reward-seeking behaviors) were given naltrexone–bupropion, and those with low predicted energy expenditure, termed "slow burn," were prescribed phentermine and encouraged to do resistance training. This important study found that phenotype-guided treatment resulted in 1.75 times greater weight loss (15.9% total) over 12 months compared to non-phenotype-guided approaches [12]. Even more personalized treatment can occur in genetic-based obesity. There have been found some options for patients with clinically confirmed monogenetic obesity. One of the options is metreleptin, a recombinant leptin analog, which is suitable for patients with congenital leptin deficiency and works by normalizing appetite [48]**.** Different option is setmelanotide— a peptide agonist of the melanocortin 4 receptor (MC4R). It can be used in patients with genetic variants of the MC4R receptor. By affecting the MC4R pathway, the appetite function is normalized [49]. Thus, the research on new therapies continues and it notably focuses on the personal aspects of treatment.

Summary

Obesity continues to be a complex, multifactorial chronic disease with deep implications for individual health and public health worldwide. Its increasing prevalence, caused by genetic, behavioral and environmental, factors, demands efficient, personalized therapeutic strategies. Currently available pharmacotherapy, such as GLP-1 analogs and emerging treatments like tirzepatide, offer promising outcomes. Targeted treatments based on the specific needs of each obesity phenotypes leads to greater weight loss. Treatment of patients with "hungry gut" is efficient with GLP-1 analogues, "hungry brain" patients can be given phentermine-topiramate, and those with emotional hunger or low energy expenditure should preferably be treated with naltrexone-bupropion or phentermine and encouraged to exercise. Bariatric surgery continues to be an effective treatment for severe obesity and the main procedures — gastric bypass, sleeve gastrectomy, and duodenal switch— continue to help people loose weigh at greatest levels. While pharmacological and surgical interventions provide critical tools, lifestyle modifications remain the foundation of obesity management. Continued research into

innovative therapies and personalized treatment holds great potential in improving long-term outcomes for individuals affected by obesity. Emerging anti-obesity therapies, such as retatrutide offer alternative mechanisms of action and efficacy profiles, while novel therapies like setmelanotide and metreleptin target genetic causes of obesity. It is essential to widen our knowledge about such wide spectrum of possible ways of treatment of our patients. Deeper understanding of the disease keeps us better connected to and understood by the patient who can be more attentive and eager to follow our therapeutic plan. Staying informed about the latest advancements and trends in obesity treatment is essential to effectively understand complexity of obesity and combat this global health issue.

Author's contribution

Conceptualization, Karolina Kuczapska, and Marek Kurowski; methodology, Anna Gliwa; software, Monika Ryglewicz; check, Dariusz Fabian, Elżbieta Leszczyńska- Knaga and Natalia Jakubczyk; formal analysis, Weronika Rutkowska- Kawalec ; investigation, Natalia Jakubczyk; resources, Paweł Moczydłowski, Karolina Michalczuk; data curation, Karolina Michalczuk; writing - rough preparation, Monika Ryglewicz, Paweł Moczydłowski; writing - review and editing, Karolina Kuczapska, Marek Kurowski; visualization, Elżbieta Leszczyńska- Knaga; supervision, Anna Gliwa; project administration, Dariusz Fabian; receiving funding, Weronika Rutkowska- Kawalec.

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