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SEMAGLUTIDE IN THE TREATMENT OF OBESITY- A NEW LOOK AT AN EFFECTIVE PHARMACOLOGICAL TOOL IN THE FIGHT AGAINST EXCESSIVE BODY WEIGHT

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ABSTRACT

Obesity is a chronic and progressive disease, the prevalence of which continues to rise worldwide, leading to a worsening quality of life, increased incidence of other diseases, and mortality. Treating obesity poses many challenges in daily clinical practice, therefore requiring a comprehensive medical approach that involves not only lifestyle changes but also pharmacotherapy and the use of bariatric surgery methods. Due to the ongoing exploration of obesity-related issues, therapy with semaglutide, belonging to the glucagon-like peptide-1 (GLP-1) receptor agonist class, has gained popularity, recently approved for treating obesity. Numerous clinical studies and observations have demonstrated that semaglutide has the most significant impact on weight loss among all drugs used in obesity therapy, accompanied by improvements in quality of life and cardiovascular risk factors.

The aim of this article is to present the current state of knowledge regarding the use of semaglutide in obesity therapy, its safety, and its correlation with other obesity treatment methods.

In this article, we used English databases such as PubMed, Google Scholar and Medline. We selected articles based on keywords such as semaglutide, glucagon-like peptide –1, obesity treatment, weight loss.

KEYWORDS

Semaglutide, Glucagon-Like Peptide-1, Obesity Treatment, Weight Loss

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1. Introduction to the issue of obesity

In recent decades, obesity has become a global challenge, associated not only with individual health problems but also with significant social and economic consequences, posing a serious issue for healthcare [1]. Body Mass Index (BMI) expresses the ratio of weight (in kilograms) to height squared (in meters) and is the most useful parameter of this kind at the population level, although it does not always accurately reflect a patient's degree of obesity. Obesity is defined as a BMI above 30 kg/m² [2].

According to the World Health Organization (WHO) report, obesity among adults has been rising since the 1970s. The problem of overweight and obesity is increasingly affecting children as well. According to WHO data from 2016, as many as 13.1% of adults worldwide were struggling with obesity, and due to the ongoing obesity epidemic, we can estimate that excess body weight affects an even wider group of people [3].

To better understand the scale of the global obesity and overweight epidemic, it is necessary to examine the most significant health consequences of excess body weight. Obesity is a chronic disease that negatively impacts psychological and social functioning, generating significant economic costs for the healthcare system. Obese individuals are at risk of numerous comorbidities, including cancer [4]. Consequently, the growing global obesity problem has influenced the epidemiology of cancer [5]. Additionally, obesity poses a significant risk in cases of Covid-19 infection, increasing the risk of severe disease, and obese individuals are at higher risk of mortality from SARS-CoV-2 infection compared to individuals with normal weight [6]. The mortality rate due to obesity is comparable to the results achieved in the case of tobacco smoking [7].

Excess body fat can lead to various health problems, including cardiovascular diseases, diabetes, lipid disorders, sleep apnea, musculoskeletal disorders (spinal degeneration), and some cancers. Excess body fat can also affect the menstrual cycle, fertility, and increase the incidence of polycystic ovary syndrome [8]. Years of dealing with the global problem of obesity have contributed to a significant increase in knowledge related to the causes, mechanisms, and treatment of obesity.

2. Mechanism of action of semaglutide

Semaglutide in a dose of 1 mg was originally approved in 2017 for the treatment of type 2 diabetes as an alternative to metformin. Semaglutide belongs to the group of glucagon-like peptide 1 (GLP-1) analogs and shares 94% structural homology with native human GLP-1 [9]. The mechanism of action of semaglutide involves reducing glucose levels by increasing insulin secretion, decreasing glucagon secretion, and delaying postprandial gastric emptying [10].

GLP-1 receptors are present in the pancreas, heart, smooth muscle of blood vessels, nervous system, immune system, gastrointestinal tract, and kidneys [11]. GLP-1 acts multifactorially not only by affecting glucose levels but also in regulating appetite and cardiovascular function. Clinical studies have shown a decrease in systolic blood pressure, favorable effects on serum lipid levels, and reduction of inflammation [12]. Due to the localization of these receptors in many tissues and organs, GLP-1 has multifaceted effects, but its impact on appetite and glucose levels is most important in the treatment of obesity, associated with receptor activation in the pancreas and brain [13].

Semaglutide regulates the secretion of insulin and glucagon depending on glucose levels. It improves blood glucose control by reducing its levels both fasting and after meals. Additionally, it delays gastric emptying to a slight extent, which also contributes to lowering glucose levels [13]. Activation of specific GLP-1 receptors in appetite-controlling areas of the brain leads to reduced hunger and increased satiety. This action results in reduced food intake and decreased appetite for high-fat foods, leading to calorie restriction and ultimately weight reduction [14, 15].

3. The use of semaglutide in the treatment of obesity

Once-weekly subcutaneous administration of 2.4 mg semaglutide was approved by the European Medicines Agency (EMA) in November 2021 for the treatment of obesity [16]. It is recommended for use by adults with obesity or overweight who also have at least one associated condition, such as hypertension, metabolic disorders, dyslipidemia, sleep apnea, or cardiovascular diseases. According to information provided by the EMA, semaglutide is used in combination with a calorie-restricted diet and increased physical activity [17].

3.1 Current state of knowledge

Obesity therapy involves a complex process, with a key element being the lifestyle modification of patients [18]. Despite initial success in weight reduction, maintaining weight loss in the long term poses a challenge. Patients who have achieved satisfactory results through lifestyle modifications are at risk of regaining weight, a process that cannot be completely eliminated. Therefore, there is a need for pharmacological treatment to help maintain the effects achieved by patients [19].

Pharmacotherapy for obesity should be tailored to each patient individually, based on the current state of knowledge and taking into account the specificity of the drugs used and any coexisting patient conditions. The Food and Drug Administration has already approved several drugs for long-term use in obesity treatment. These include orlistat, extended-release naltrexone/bupropion, controlled-release phentermine/topiramate, and liraglutide. Phentermine/topiramate has the highest efficacy in weight reduction among the mentioned drugs, but monitoring of neuropsychiatric reactions should be considered during its use due to concerns about adverse effects [20].

Currently, studies are underway on the oral administration of semaglutide for obesity treatment. Knop et al. conducted a randomized, double-blind, placebo-controlled, phase 3 trial to assess oral semaglutide 50 mg once daily in adults with overweight or obesity, without diabetes. The mean bodyweight change was -15.1% from baseline with oral semaglutide 50 mg compared to -2.4% with placebo [21]. A meta-analysis published in 2022 compared the efficacy of semaglutide and liraglutide in weight reduction, available in two doses (semaglutide: 2.4 mg and 1.0 mg, liraglutide: 3.0 mg and 1.8 mg). The study showed that semaglutide at a dose of 2.4 mg is the most effective among the mentioned therapeutic options [22].

3.2 Safety and tolerance of semaglutide

Promising research results regarding the effectiveness of semaglutide in reducing excess body weight have encouraged researchers to further explore the topic of obesity treatment with semaglutide [23].

Semaglutide, a glucagon-like peptide-1 receptor agonist, is available in both oral and subcutaneous formulations. Despite its effective impact on weight control and maintaining normal glycemia, questions have arisen regarding the safety of semaglutide use over time. One of them concerns the potential for hypoglycemia. According to available data, the incidence of hypoglycemia appears to be minimal with semaglutide administered subcutaneously or orally alone. However, this situation may change when semaglutide is combined with other medications, such as sulfonylureas and/or insulin derivatives. Therefore, it is recommended to reduce the dose of sulfonylureas and rapid- or long-acting insulin analogs before or during the initiation of GLP-1 treatment to reduce the likelihood of severe hypoglycemic episodes [24].

Due to its effectiveness in weight reduction, semaglutide has gained popularity online. The drug manufacturer (Wegovy) has spoken out on this issue, stating that it does not endorse the independent use of semaglutide without medical consultation. However, it should be noted that despite the general enthusiasm regarding the minimal side effects of the drug, there is still a lack of sufficient research focused on the long-term use of semaglutide [25].

3.3 Long-term effects of semaglutide therapy: maintenance of weight loss and reduction of health complications risk

There have been publications testing the long-term effects of semaglutide therapy, including maintenance of weight loss as well as reduction of the risk of health complications.

In a double-blind randomized trial 1961 adults with body-mass index of 30 or greater who did not have diabetes were included. Participants who received semaglutide 2.4 mg as an adjunct to lifestyle intervention, had a mean weight loss of 14.9% from baseline as compared with 2.5% of placebo group who received only lifestyle intervention at 68 weeks. There was improvement in cardiometabolic risk factors with semaglutide compared with placebo, including reductions in waist circumference (-13.54 cm with semaglutide vs. -4.13 cm with placebo), systolic blood pressure (-6.16 mm Hg with semaglutide vs. -1.06 mm Hg with placebo). There was also improvement in glycated hemoglobin levels, lipid levels, a greater decrease from baseline in C-reactive protein, and a greater proportion of participants with normoglycemia (84.1% with semaglutide vs. 47.8% with placebo group) [26].

In another study, treatment weekly semaglutide 2.4 mg up to 104 weeks in conjunction with behavioral intervention with overweight or obesity, without diabetes, participants achieved a mean weight loss of 15.2% from baseline, compared to 2.6% in placebo group. This indicates the results of a previously reported study

that the significant weight loss during 68 weeks of treatment could be maintained by continuing treatment with semaglutide for 104 weeks [27].

In a large multicenter, double-blind, randomized, placebo-controlled trial 17,604 patients with preexisting cardiovascular disease and overweight or obesity but without diabetes were enrolled. Weekly semaglutide 2.4 mg was more effective in reducing weight loss (-9.39% with semaglutide vs. -0.88% in placebo group). There was significant weight circumference decreased, greater reductions in systolic and diastolic blood pressure and increase in the cholesterol HDL with decrease in triglyceride. Also cardiovascular-related deaths were lower (6.5% with semaglutide vs. 8.0% in placebo group) [28].

4. Semaglutide in the context of combination therapy: potential benefits and synergy with other obesity treatment methods.

Despite the noticeable benefits of using semaglutide in obesity therapy, the doses used are significantly higher than those used in type 2 diabetes treatment. Therefore, it seems reasonable to consider using semaglutide at lower doses in combination with other obesity treatment methods. Recently, there have been reports about the possibility of using semaglutide to maintain body weight after bariatric surgery.

Lautenbach et al. reported the effectiveness of treatment with semaglutide 0.5 mg once-weekly in non-diabetic patients after bariatric metabolic surgery. After 6 months total weight loss of 10.3% was observed [29].

In another retrospective study patients who underwent treatment with semaglutide 1.0 mg weekly subcutaneous injection or semaglutide 14 mg daily oral intake had lost 67.4% of the weight regained after the last bariatric procedure. After 6 months the median percentage of total body weight loss was 8.8% [30].

In the phase 1 trial Enebo et al. investigated cagrilintide 2.4 mg, a long-acting amylin analogue, in combination with semaglutide 2.4 mg. The weight loss was 17.1% compared to the placebo group receiving only semaglutide 2.4 mg, which had a weight loss of 9.8% [31]. However, larger randomized trials are needed to confirm this effectiveness.

Currently, studies are underway to use other drugs in combination with semaglutide for the treatment of obesity.

5. Conclusions

In recent decades, the issue of obesity has reached a global scale. The best way to counteract further obesity development remains prevention and lifestyle changes. In cases of obesity coexisting with other conditions or in individuals struggling to lose weight, pharmacological methods are permissible, among which semaglutide has been included.

This literature review demonstrates that semaglutide is a medication with proven effectiveness in reducing body weight. Numerous studies confirm its weight-loss effects, as well as its impact on other aspects of health, such as the cardiovascular system. The medication can be used in obesity therapy not only by individuals with diabetes but also as standalone pharmacotherapy. Semaglutide is a safe drug; however, its use for weight reduction should be constantly monitored by a doctor.

There is no doubt that semaglutide has become a breakthrough in obesity treatment and has helped many patients regain health and improved functionality. Further research on the effects of semaglutide in obesity treatment should focus on methods to maintain a more long-term weight loss effect and on investigating potential long-term adverse effects.

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