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Semaglutide – a long – awaited cure for obesity or an elusive treatment?

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ABSTRACT

Introduction and aim. Obesity is a challenging disease that affects various organs and cannot be easily treated. Therefore, the discovery that taking semaglutide results in weight loss caused great excitement amongst patients and medical professionals. The aim of this literature review is to explore the benefits and dangers of semaglutide and its effectiveness in treating obesity.

Material and methods. Review of articles published in PubMed since 2017 until first quarter of 2024.

Analysis of literature. Obesity is an increasing problem of the world population. There are different approaches in obesity treatment. Semaglutide seems effective in treating diabetes, as well as conditions that emerge from long-lasting obesity. It showed positive influence regarding diabetic neuropathy, cardiovascular risk and more. It is important to remember about possible adverse events. The most prominent are gastrointestinal symptoms, such as nausea, diarrhea, vomiting, and abdominal pain. New reports show complications with simultaneous use of anesthesia or coexisting depression. Larger studies on semaglutide- related side effects will be published in 2025 and in 2026.

Conclusion. Semaglutide is an anti-diabetic drug showing promising effects in treating diabetes and in alleviating conditions caused by obesity. It is worth remembering that its side effects have not yet been fully investigated.
Keywords. semaglutide, treatment, weight loss

Introduction

Semaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1 RA). In its structure, it is similar to incretin glucagon-like peptide-1 (GLP-1), which is secreted in response to the food intake. GLP-1 has a short half-life in circulation (1–2 minutes) due to degeneration by the dipeptidyl peptidase-4 (DPP-4) and neutral endopeptidase (NEP). Due to modification of the chemical structure, semaglutide has a much longer half-life in the blood of about seven days (184 hours).[1-2] According to this, semaglutide can be administered either orally (Rybelsus) or by subcutaneous injection (Ozempic, Wegovy).

Semaglutide causes stimulation of pancreatic beta cell GLP-1 receptors, which leads to insulin secretion and at the same time inhibits glucagon release from alpha-pancreatic cells.[1-3] Semaglutide reduces food intake by lowering appetite, slowing down digestion in the stomach and gut mobility, improving glycemic control and activation of mechano-receptors to produce satiation signals. It also it decreases brain food reward anticipation, thus helping reduce body weight.[1,3,4,5] Semaglutide is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes (T2D), for long-term weight management in patients with overweight or obesity, and for decreasing the incidence of cardiovascular events and physical functioning.[1,3,4,5] Possible side effects include nausea, diarrhea, vomiting, constipation, abdominal pain, fatigue, hypoglycemia, gastroesophageal reflux disease (GERD), and increased risk of cholelithiasis. The U.S. Food and Drug Administration (FDA) label warns of potential association with pancreatic cancer and thyroid cancer.[5] Semaglutide can minimize urges to binge eat so it can be used to treat compulsive dysfunctional eating behaviours.[6]

Semaglutide was approved by the U.S. FDA in 2017 for the treatment of T2D; in 2021 it was the 90th most commonly prescribed medication in the US, with 8 million prescriptions.[3,7] In this article we will try to answer the question of why semaglutide is such a popular drug, what are the benefits and the potential dangers of its use.

Aim

The aim of this review is to highlight the importance of semaglutide's role in treating obesity along with its potential benefits in other areas, and, on the other hand, consider possible side effects that may impact the decision of including this medication in patient treatment.

Material and methods

A review of literature was performed to discover the latest findings on semaglutide. The scientific articles were reviewed by using PubMed. We have considered reviews and original papers from 2017 until first quarter of 2024.

Analysis of the literature

Obesity as a challenge in medicine

Obesity is one of the most common diseases in the world. The main criteria are the BMI (body mass index) value and excessive accumulation of body fat. The limit for obesity is considered BMI above 30 kg/m^2, first degree obesity is defined as that in the range of 30–34.99 kg/m^2, second degree 35–39.99 kg/m^2, third degree obesity extreme obesity above 40 kg/m^2.[8-11]

Currently, there is an increase in the number of patients suffering from obesity, as well as an increasing number of patients with complications of the disease.[8] Obesity in 2022 affected about 16% of the adult population worldwide.[10] In the 1990s, the disease affected only 8% of adults worldwide.[10]

The occurrence of obesity can be due to many factors. Main factors that may lead to obesity are monogenic mutations in *PCSK1*, *POMS*, *LEP*, and *LEPR* genes. In addition, obesity can be inherited by multiple genes, and epigenetics plays a major role in the onset of the disease.[12] The *PCSK1* gene is responsible for the processing of hormones, including POMC. Mutations in the *POMC* gene lead to hyperphagia and early-onset obesity. The *LEP* and *LEPR* genes are responsible for fat metabolism and calorie intake.[12] Other reason is gender. Women have a greater desire for sweet meals compared to men, and women are more likely to experience binge-eating disorders conducive to the development of obesity.[9,13] It also depends a lot on the environment in which the individual is raised, introducing a proper diet and cultivating healthy activity in preschool age may not lead to the occurrence of obesity.[9,14]

There are four main heterogeneous groups in patients with obesity:

- metabolically abnormal obese – this is the most common obesity phenotype. This group includes patients with a BMI >30 kg/m^2 with metabolic disorders such as diabetes, hyperlipidemia, elevated rates of inflammation, as well as fatty liver.[15-17]
- metabolically healthy obese – these include patients with a BMI >30 kg/m^2 who are metabolically healthy, that is, without insulin and lipid disorders. They have good physical endurance and less fat around the abdomen. They have a lower risk of heart disease compared to metabolically abnormal obese.[15-17]
- metabolically obese normal weight – this group includes patients with a BMI below 25 kg/m^2 who have lipid disorders, and insulin resistance and are inactive physically. They have an increased risk of developing T2D and cardiovascular disease.[15-16]

- sarcopenic obesity – is associated with a decrease in muscle mass and an increase in the amount of body fat in elderly patients who are chronically ill, and have reduced physical activity. To diagnose sarcopenic obesity, the muscle mass in the body is estimated and comapred to the body weight of the patient. Patients have increased blood pressure.[15,16,18]

One of the main complications is non-alcoholic fatty liver. It occurs, depending on the population, in about 40–70% of obese people. Lifestyle changes and weight reduction are recommended as treatment, as well as pharmacological treatment including GLP-1 agonists and currently promising sodium/glucose cotransporter 2 (SGLT-2) inhibitors not yet registered for non-alcoholic fatty liver disease (NAFLD).[19,20] Teheri et al. showed in a cohort study that the use of Empagliflozin in patients with Liver Steatosis and Fibrosis without T2D reduced the number of changes measured by elastography controlled attenuation parameter and liver stiffness measurement.[21]

Another complication affecting a patient's quality of life is the impact of obesity on bone tissue. Obese people are less likely to develop osteoporosis, but the risk of falls is high, and they have increased bone fragility, which results in a high risk of fractures.[22]

Obesity also disrupts lipid management. This is associated with decreased levels of adiponectin, and increased levels of inflammatory cytokines. This promotes metabolic disorders and thus leads to insulin resistance, which may result in T2D.[23-24]

In the course of obesity, complications from the cardiovascular system may occur. Obese people have a higher risk of heart attack, stroke, hypertension, heart failure, and atrial fibrillation.[25]

Methods of treating obesity include:

- diet, physical activity, and lifestyle change – all three components of treatment are based on changing the patient's habits. The diet should be based on the caloric deficit, as well as based on the patient's preferences.[26-27] The physical activity of the patient should be about 300 minutes of moderate to vigorous physical activity per week.[27] Cognitive-behavioral psychotherapy can help change a patient's lifestyle. The patient should be under the care of a multidisciplinary team.[28]
- bariatric surgeries – are a method of treatment for patients with a BMI above 40 kg/m^2 and over 35 kg/m2 with diseases resulting from obesity. The use of the method brings good results in patients: decreased BMI, improved health-related quality of life and improved lipid management.[9,29,30]
- pharmacological treatment – these include:
    - orlistat – reduces the absorption of fat from the gastrointestinal tract, thereby reducing the number of calories taken,
    - liraglutide – a GLP-1 receptor agonist,
    - the combination of bupropion and naltrexone – its probable mechanism of action is an effect on the hypothalamic melanocortin system and the mesolimbic reward system.
    - semaglutide – a GLP-1 receptor agonist.[31-32]

In the following two paragraphs we will discuss semaglutide's effects. We gathered some of the information described below in Table 1.

Table 1. Comparison of semaglutide's effects

Effects of semaglutide	Benefits	Disadvantages
Metabolic	Reduction of HbA1c Decreased fasting insulin to normal levels	Hypoglycemia (if combined with sulfonylurea and/or insulin therapy)
Gastrointestinal	Decreased liver fat content Higher reduction of liver enzymes	Nausea, diarrhea, vomiting, abdominal pain, constipation, etc.
Surgical	Decrease in odds of developing sepsis and readmission	Higher risk of aspiration due to delayed gastric emptying
Body image	Weight loss	"Ozempic face"
Synergy with other diseases	Decreased disorders in estrous cycle in polycystic ovary syndrome (PCOS)	First occurrence of depression or relapse Rhabdomyolysis Bullous pemphigoid

Positive aspects of semaglutide

Oral treatment with semaglutide leads to a reduction of HbA1c and weight in patients. A Spanish multicenter longitudinal study on 1018 people with T2D showed that ≥5% weight loss and HbA1c reduction >1% was achieved in 19.1% of patients at 6 months and 37.5% of patients at 12 months.[33] Similar findings regarding HbA1c were obtained in the IGNITE, PIONEER REAL, GLIMPLES and Japanese population studies.[34-37]

HIV positive patients

The data on semaglutide effectivity among people with HIV (PWH) is scarce. The antiretroviral therapy may be one of the causes for gaining weight, especially integrase strand transfer inhibitors (INSTI) such as dolutegravir and bictegravir are associated with weight gain.[38] As PWH are already at higher risk of cardiovascular complications and T2D, the untreated obesity further increases their risk. Haidar et al. performed a cohort observation of PWH that received semaglutide treatment. They reported a significant loss of body weight after 1 year and significant HbA1c reduction.[38] There was no difference between people receiving and not receiving INSTI proving that patients treated with INSTI also lost weight.

Diabetic neuropathy

Semaglutide seems to play a protective role in the development of diabetic peripheral neuropathy. An Australian study on 22 T2D patients treated with dulaglutide or semaglutide showed reduction of nerve cross-sectional area 1 month and 3 months post-treatment. Additionally, improvement in sural nerve conduction was reported.[39] However, due to the sample size, those findings should be confirmed by other studies.

Surgical implications

Diabetes mellitus (DM) without appropriate management increases the risk of postoperative complications. A study on knee arthroplasty in patients treated with semaglutide showed a large decrease in odds of developing sepsis and readmission.[40] Similar findings were obtained in the study on total hip arthroplasty.[41] Semaglutide also seems to be effective in the treatment of weight recurrence after bariatric surgery. In a Kuwait study of 115 patients who were treated with semaglutide after sleeve gastrectomy 62.9% achieved ≥5% weight loss and 11.4% had ≥10%. At 6 months of treatment, 80% of patients had ≥5% total body weight loss, 48.6% had ≥10% and 26% achieved ≥15% total body weight loss.[42] Those findings are consistent with the results of a Japanese study on a group of 29 patients treated with semaglutide after laparoscopic sleeve gastrectomy.[43] The findings of both studies are confirmation of the earlier results presented by Murvelashvilii et al. in which semaglutide was effective regardless of surgery type.[44]

Cardiovascular risk

Obesity is a known risk factor for cardiovascular risk factors such as dyslipidemia, T2D, hypertension and sleep disorders. It is also an independent risk factor for the development of cardiovascular disease and cardiovascular disease mortality.[45] The analysis of patients from SUSTAIN 6 and PIONEER 6 trials showed that in the group of patients, the overall hazard ratio for major cardiovascular events (MACE) and also for its components such as cardiovascular deaths (CV), myocardial infarction (MI) and strokes was lower for the patients who received semaglutide in comparison with the placebo group.[46] The post-hoc analysis of SUSTAIN 6 participants showed that the presence of polyvascular and single vascular disease was associated with a greater risk of MACE compared with no vascular disease. In those who were administered with semaglutide, the risk of MACE was lower in comparison to the placebo group thus patients with T2D might have greater absolute benefits from the treatment.[47] Semaglutide seems to reduce MACE also in non-diabetic patients. The SELECT trial analyzed a group of 17604 patients of age 45 years or older with a BMI of 27 or greater and had established cardiovascular disease. The treatment of a subcutaneous semaglutide dose of 2.4 mg once a week for a mean duration of 33 months reduced the risk of MACE by 20%.[48]

Semaglutide was associated with changes of multiple biomarkers of cardiovascular risk such as blood pressure, waist circumference, glycemic control, nephropathy, levels of lipids and C-reactive protein.[48]
The cross-national study showed that in non-diabetic patients with heart failure with preserved ejection fraction (HFpEF), semaglutide not only decreased body weight but also improved patient outcomes in the 6-minute walk test in comparison to the placebo. Additionally, the patients were asked to complete a Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) which is a standardized instrument that quantifies heart failure-related symptoms. The score reflects health status. After 52 weeks of semaglutide treatment patients achieved a significantly higher score in KCCQ-CSS than in the placebo group.[49]

Polycystic ovary syndrome (PCOS)

In rodent studies, semaglutide seems to have a positive impact on PCOS outcomes. Xiong et al. reported that in PCOS mice the semaglutide treatment restored imbalance in gut microbiota induced by PCOS resulting in metabolic parameters improvement.[50] Another study showed that semaglutide reduced increase of body weight caused by dehydroepiandrosterone-induced PCOS. Additionally, semaglutide decreased fasting insulin to normal levels and showed a trend toward ameliorating glucose tolerance.[51] Histological analysis showed that semaglutide decreased disorders in estrous cycle. In addition, semaglutide increased the quantity of corpus luteum and decreased the quantity of cystic follicles.[51] Those studies show promising results of semaglutide in PCOS and were partially confirmed by Carmina et al. In a group of 27 obese patients with PCOS who were unresponsive to a lifestyle modification after three months treatment BMI, body weight, fasting glucose and insulin significantly decreased.[52] In 21 of the patients, menstrual disorders improved and 15 of women achieved normal menses.[52]

Non-alcoholic liver diseases

A multinational randomized study treatment of non-alcoholic steatohepatitis (NASH) related cirrhosis with semaglutide for 48 weeks showed that there is no significant improvement in fibrosis compared with placebo.[53] However in patients without cirrhosis, semaglutide led to significantly greater number of patients with NASH resolution with no worsening of fibrosis compared to placebo.[54] In Flint et al. study of NAFLD semaglutide did not shown difference in comparison to placebo in change of liver stiffness assessed by magnetic resonance elastography. However, semaglutide significantly decreased liver fat content at each timepoint. Compared to the placebo semaglutide group achieved a higher reduction in liver enzymes.[55]

Negative aspects of semaglutide

The recent rise of Ozempic and Wegovy intake by patients without a diagnosis of diabetes or pre-diabetic state is raising concerns within the medical community. While its efficacy in treating diabetes was

demonstrated by many researchers and potential adverse effects do not outweigh the positive results of that specific therapy, there is a demand for putting in order reported adverse events so that the medical professionals who are prescribing semaglutide would be more aware of the safety of mentioned drug.[56]

Gastrointestinal symptoms

To begin with, the most common adverse effects are associated with the gastrointestinal system.[57] They are also often the reason for the discontinuation of the drug.[58] The most common are: nausea, diarrhea, vomiting, abdominal pain and constipation, however, it must be noted that their intensity is connected to the dose escalation (during the period of escalation or shortly after) and a few days later they tend to resolve.[57-60] There have been reports suggesting an increased occurrence of pancreatitis and pancreatic carcinoma, although further research on that subject is necessary, as some researches challenge the link between those diseases and described drug.[56] Other examples of gastrointestinal problems after taking semaglutide include: impaired gastric emptying, gastritis, oropharyngeal discomfort, dry mouth, hiccups, abnormal feces and more.[57] Studies showed that a patient's age and body weight have a connection with a higher occurrence of the events mentioned above. On the other hand, patient's sex does not seem to have an impact in that subject, Prevalence of the gastrointestinal adverse effects is significantly higher in the middle- aged group than in the elderly group (>65 years).[57] Moreover, in defiance of a theory that gastrointestinal adverse events enhance the weight loss effect, it was proved that they do not have a great input in that matter.[60]

Anaesthesiological dangers

Another danger resulting from taking semaglutide is a delayed gastric emptying. The report about a 31-year-old female undergoing the esophagogastoduodenoscopy (EGD) procedure showed that this procedure had been stopped due to a large amount of food found in the stomach during the procedure. That finding was associated with a high risk of aspiration, therefore the endoscopic examination had to be discontinued. It was stated that the patient took prescribed Ozempic and fasted for over 10 hours prior to the EGD. Next examination was scheduled a month after and the patient's last dose of Ozempic was taken a week before the EGD – that time there was no food in the stomach and the procedure was successful.[61] There is also a case report about a 66-year-old man who was qualified for an elective treatment of a renal nodule. He fasted for 9 hours and his last dose of semaglutide had been taken 6 days prior the operation, however, the doctors were not informed about the patient taking that medication. The outcome was similar to the previous example: solid food was found in the stomach; the doctors did not continue the procedure and the pulmonary aspiration was avoided due to the anaesthesiologist's choice of a rapid sequence induction. However, had there been a pulmonary aspiration, the patient could have been permanently disabled or he might have even died.[62] As it was shown in the examples above, the usual 8-10 hours fasting period before an operation is

not enough to ensure proper patient preparation, thus there was a call for specific guidelines in anaesthesiology concerning patients on Ozempic. Those were announced by the American Society of Anaesthesiologists and according to them, patients who take a daily dose should skip a dose one day prior to the operation and those with a weekly dose should discontinue Ozempic a week prior to the operation.[59]

Aesthetic controversies

After anaesthesiologists, the next group of doctors who raise concerns about Ozempic, are plastic surgeons. Many of them reported a new phenomenon that is a much older look of patients who took Ozempic. It is caused by a rapid facial fat loss. In usual circumstances, facial fat provides a volume that makes face look young. Sudden fat loss observed in Ozempic intake but also in diseases that contribute to malnourishment, attributes to changes in key face areas which are responsible for youthful look. For example, wrinkles get deeper, skin loses its turgor in cheeks, nasolabial folds, tear troughs and more. The size of lips and cheeks may change and that impacts the primary face structure. It is worth noting that in case of regaining weight, fat will not be redistributed to the face, so the aging effect is permanent and a very prominent adverse event of taking Ozempic.[59]

Diabetic retinopathy

Furthermore, there are researches that make medical society aware of possible danger of diabetic retinopathy complications (DRC) that might be enhanced by Ozempic. Some reports say it may be even the main cause for retinopathy in up to 5% of patients.[58] So far, there have been published results of the SUSTAIN 6 research with 3297 patients being involved, divided into semaglutide or placebo group. In that trial there was no exclusion associated with diabetic retinopathy (DR). It was shown that DRC were significantly higher in the semaglutide group; more patients developed vitreous hemorrhage; more of participants were in need of retinal photocoagulation in comparison to placebo group.[63-64] Further investigations of that subject – the FOCUS trial – will be released in 2025 or in 2026.[58,64]

Another group of adverse events, less frequent, but worth noticing, are psychiatric related issues such as first occurrence of depression or deteriorated mood in a patient with a long psychiatric treatment history. In both cases symptoms of fatigue, sleep relapse, disturbed concentration and decision making showed up after about a month of semaglutide treatment. Improvement of patients' state was observed after discontinuation of semaglutide. This effect is suspected to be caused by semaglutide interfering with dopaminergic neuron activity.[65] Moreover, there are singular reports of the following problems that appeared after patients started semaglutide therapy: bullous pemphigoid, rhabdomyolysis and hypoglycemia. In the first two examples, interference from other drugs was excluded and symptoms were relieved after stopping semaglutide intake, whereas hypoglycemia occurred only when accumulated with sulfonylurea and/or insulin therapy.[56,66,67]

Conclusion

Semaglutide is a very promising medication that could be used not only to reduce glucose level but also for other various ailments. It gives hope especially to patients that suffer from obesity complications. For years, there were many attempts to treat obesity, however, with different results. Semaglutide stands out because of its pleiotropic effects, of which the most desired are decreased glucose level, reduction of HbA1c and weight loss. It is worth noting that this medication comes with some side effects. The most well-known are those from gastrointestinal system, such as nausea, vomiting, constipation. There is a need of further investigation on possible negative outcome of semaglutide treatment. Many researches on that topic are announced to be released in 2025, 2026 or later.

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Author contributions

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Conflicts of interest

The authors declare no competing interests.

Data availability

Not applicable.

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