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Semaglutide in the Treatment of Diabetes and Associated Obesity

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Abstract

Introduction and objective: Diabetes represents one of the most significant healthcare challenges of the 21st century. The disease is frequently asymptomatic, with patients often remaining undiagnosed for extended periods and failing to seek assistance from healthcare professionals. A sedentary lifestyle, excessive caloric intake, and a lack of physical activity contribute to the development of obesity, which in turn leads to carbohydrate metabolism disorders. In this study, we will examine the relationship between diabetes and obesity, and discuss the drug semaglutide, which is used to treat type 2 diabetes and also promotes weight loss.

Review methods: Review and summary of research studies available in open-source format on Google Scholar, PubMed.

Abbreviated description of the state of knowledge: Numerous clinical studies have demonstrated the efficacy of semaglutide in improving lipid profiles and promoting weight loss. This effect is believed to be mediated by the drug's ability to slow gastric emptying. It is evident that semaglutide, a glucagon-like peptide-1 (GLP-1) analogue, exerts a beneficial effect on carbohydrate parameters and helps to delay the occurrence of complications associated with diabetes.

Summary: A review of clinical reports and conducted studies indicates that semaglutide has the potential to enhance parameters that directly or indirectly impact the quality of life of patients with diabetes. However, the utilisation of the aforementioned pharmaceutical is associated with adverse effects, which may impede patient-physician collaboration and potentially precipitate the development of new health complications in patients. One of the effects of semaglutide treatment is a reduction in appetite, which contributes to weight loss. This property of the drug makes it suitable for use in patients with excessive body weight.

Keywords: GLP-1 analogs; semaglutide,; diabetes; obesity;

Diabetes

Diabetes is a group of metabolic diseases characterized by elevated blood glucose levels and is associated with a malfunction in the production or action of insulin. Insulin is a peptide hormone secreted by the beta cells of the islets of Langerhans in the pancreas. Chronic hyperglycemia leads to multi-organ complications, most commonly involving the kidneys, eyes, nerves, heart, and blood vessels. Depending on the mechanism of hyperglycemia, we distinguish between type 1 diabetes, type 2 diabetes, gestational diabetes, and less common forms such as MODY 1 or MODY 2 diabetes, among others. The most common form of diabetes is type 2 diabetes, in which there is a decrease in tissue sensitivity to insulin. This leads to increased insulin production, which in the later stages of the disease results in the pancreas' inability to produce sufficient amounts of the hormone. 90-95% of all diabetes cases are of this form.

Epidemiology

Diabetes is one of the most common chronic diseases. According to World Health Organization estimates, there were 422m people living with the disease worldwide in 2014. In 2018, there were 2.9 million adults with diabetes in Poland, accounting for 9.1% of the Polish adult population. About 300,000 new cases of diabetes among adults are reported each year in Poland [1]. One of the most important risk factors for diabetes is being overweight, which affects about 64% of Polish adults [2].

Correlation between diabetes and obesity

Research clearly indicates that people with diabetes are more likely to be overweight or obese. An analysis by the CDC, using data from the National Health and Nutrition Examination Survey (NHANES) from 1988-1994 and 1999-2002, found that in 1999-2002, as many as 85.2% of adults diagnosed with diabetes were overweight or obese, and 54.8% were obese [3].

Treatment of diabetes with GLP-1 analogs

One of the newest groups of antidiabetic drugs are GLP-1 analogues. They are characterized by a favorable metabolic profile [4] and beneficial effects on the cardiovascular system. Numerous studies show the positive effect of this drug on weight reduction.

GLP-1 primarily acts through the GLP-1 receptor (GLP-1R), which, upon activation, initiates a signaling cascade through the G protein ($G_{\alpha s}$), leading to increased levels of cAMP and activation of protein kinase A (PKA). This signaling pathway enhances insulin secretion from pancreatic beta cells in a glucose-dependent manner. GLP-1 also inhibits glucagon secretion from pancreatic alpha cells, preventing excessive postprandial glucose elevation [5].

GLP-1 analogs exhibit an anorectic effect by acting on the hunger center in the brain, resulting in reduced appetite and weight loss. This mechanism is beneficial for patients with type 2 diabetes as well as obesity [6]. These effects collectively contribute to the reduction of blood glucose levels and body weight [5,7].

The first substance from this group of drugs used to treat diabetes and associated obesity was liraglutide. It is a medication administered subcutaneously with a short half-life (11-15 hours), requiring patients to take the medication daily [8,9].

A newer drug in this group is semaglutide, which has a longer half-life (183 hours), allowing it to be administered once a week.

Numerous studies have been conducted to evaluate the efficacy and side effects of semaglutide. The most important of these include: SUSTAIN (Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes), PIONEER (Peptide Innovation for Early Diabetes Treatment), and STEP (Semaglutide Treatment Effect in People with Obesity).

In the SUSTAIN 1 study, patients receiving semaglutide 0.5 mg/week had an average decrease in HbA1c levels of 1.45% from baseline to week 30. In the group taking 1.0 mg/week, HbA1c fell by an average of 1.55%. By comparison, the decrease in HbA1c in the placebo group was only 0.02%. Approximately 74% of patients in the 0.5 mg group and 72% in the 1.0 mg group achieved HbA1c levels below 7.0%, while only 25% of patients in the placebo group reached this goal. Patients receiving 0.5 mg of semaglutide experienced an average weight reduction of 3.73 kg, while those receiving 1.0 mg experienced a reduction of 4.53 kg. In the placebo group, weight decreased by an average of 0.98 kg [10].

In the SUSTAIN 2 study, 1231 patients with type 2 diabetes were treated with either semaglutide or sitagliptin for 56 weeks. The results showed that semaglutide significantly reduced HbA1c levels compared to sitagliptin: the average reduction in HbA1c was 1.5% with a dose of 1.0 mg of semaglutide, compared to 0.7% with sitagliptin. Additionally, patients treated with semaglutide experienced greater weight loss, averaging 4.3 kg, compared to 1.9 kg in the sitagliptin group [11].

The results of the SUSTAIN 3 study show that semaglutide at a dose of 1.0 mg caused a greater reduction in HbA1c than exenatide at a dose of 2.0 mg, by 1.5% compared to 0.9% over 56 weeks [12].

In the SUSTAIN 4 study, semaglutide was compared with insulin over a period of 30 weeks of treatment. In the study, patients achieved a significantly greater reduction in HbA1c when using semaglutide compared to insulin [13].

In the SUSTAIN 5 study, it was demonstrated that in individuals with type 2 diabetes who were administered semaglutide (as an addition to insulin therapy or insulin plus metformin treatment), a significantly greater reduction in HbA1c levels in the blood was achieved [14].

The conclusions from the SUSTAIN 6 study suggest that semaglutide not only aids in the control of type 2 diabetes but may also reduce the risk of cardiovascular events in patients with type 2 diabetes and high cardiovascular risk or existing heart diseases. The study revealed a noteworthy 26% decrease in the composite primary endpoint comprising cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. This endpoint was

observed in 6.6% of patients treated with semaglutide and 8.9% of those receiving placebo over a median follow-up period of 2.1 years [15].

In the SUSTAIN 7, 8, and 10 studies, a greater reduction in HbA1c was observed with the use of semaglutide compared to dulaglutide, canagliflozin, and liraglutide [16,17,18].

The PIONEER trials focused on the oral form of semaglutide.

In the PIONEER 1 study, patients were randomly assigned to receive daily oral semaglutide at doses of 3, 7, or 14 mg, or placebo. A reduction in HbA1c ranging from 0.6% to 1.1% was observed. The 14 mg dose also resulted in a significant reduction in body weight compared to placebo [19].

In the PIONEER 2 and 3 trials, orally administered semaglutide proved to be more effective in lowering HbA1c and reducing body weight compared to Empagliflozin and Sitagliptin [20,21].

In the PIONEER 4 study, oral semaglutide was compared with subcutaneously administered liraglutide and placebo. Similar results in lowering HbA1c were achieved with the above-mentioned drugs compared to placebo (after 26 weeks of treatment, a decrease in HbA1c of 1.2% with semaglutide, 1.2% with liraglutide, and 0.2% in patients receiving placebo). In this study, semaglutide showed greater weight loss (average of 4.4 kg) compared to liraglutide (average of 3.1 kg), but both drugs were more effective than placebo (0.5 kg) [22].

In the remaining PIONEER trials, the following observations were made: the effectiveness of the drug in patients with impaired kidney function (PIONEER 5), the possibility of reducing the average daily insulin dose when used together with semaglutide (PIONEER 8), and higher effectiveness in lowering HbA1c with oral semaglutide at a dose of 14mg compared to Dulaglutide at a dose of 0.9 mg (PIONEER 10) [23,24,25].

In the STEP trials, the focus was on assessing the effectiveness of semaglutide in reducing body weight.

In STEP 1 study, 1961 individuals with obesity or overweight, but without concurrent diabetes, participated. Over 68 weeks of treatment with semaglutide at a dose of 2.4mg along with lifestyle modification, an average reduction in body weight of 14.9% was observed compared to individuals receiving placebo along with lifestyle modification (where the weight

reduction was 2.4%). In this study, 86.4% of patients receiving semaglutide lost at least 5% of their body weight [26].

In STEP 2 study, 1210 participants with type 2 diabetes and concurrent overweight or obesity were involved. The reduction in body weight was compared among patients receiving 2.4mg semaglutide, 1.0 mg semaglutide, and placebo. The reductions in body weight were 9.64%, 6.99%, and 3.42%, respectively [27]. In the remaining STEP studies, involving individuals without concurrent diabetes, the results consistently indicated a decrease in body weight in individuals receiving the drug [28,29,30].

To effectively monitor the treatment's effects, patients should undergo regular check-ups under the supervision of their attending physician. The best therapeutic outcomes are achieved by combining medication with physical activity and a healthy diet.

Adverse effects

With the increasing popularity of semaglutide, particularly due to its beneficial impact on weight reduction, many myths and concerns have arisen regarding its negative effects.

The most common adverse reaction of this medication involves gastrointestinal disturbances such as nausea, vomiting, and diarrhea [31]. This is the leading cause of discontinuation of the drug [32]. These disturbances typically have a transient nature and mainly occur with rapid dose escalation [33]. To minimize gastrointestinal side effects, the medication dose should be gradually increased, and the intake of fatty foods should be limited, while the pace of eating should be reduced [34].

Subcutaneous administration of semaglutide over 30 weeks of treatment resulted in nausea in 11.4-20% of patients (placebo 3.3–8%), vomiting in 4-1.5% (placebo 2–3%), and diarrhea in 4.5-11.3% (placebo 1.5–6%) [35,36].

The most common increase in the frequency of adverse effects associated with the use of this medication was related to high doses of the drug. Therefore, it is recommended to initiate treatment with a low dose and gradually increase it [37]. Patients are also advised to limit the intake of fatty foods and reduce the pace of eating [34].

One of the dangerous adverse effects of using semaglutide may be hypoglycemia. Studies have not confirmed an increased frequency of hypoglycemia in patients using semaglutide monotherapy [38].

However, an increased frequency of hypoglycemia has been observed in patients using semaglutide in combination with sulfonylurea derivatives or insulin. Due to the risk of hypoglycemia in patients using insulin or sulfonylurea derivatives along with semaglutide, it may be necessary to reduce the doses of these aforementioned drugs [39]. When combining these medications, it is necessary for the patient to independently monitor their blood glucose levels due to the higher likelihood of hypoglycemia.

Acute pancreatitis and pancreatic cancer are among the most dangerous and controversial adverse effects of using semaglutide. Initial studies upon the drug's introduction indicated a slight increase in the incidence of acute pancreatitis and pancreatic cancer in patients using the medication [40]. However, in subsequent years, research focused on determining the actual likelihood of acute pancreatitis and pancreatic cancer occurring in patients taking the drug.

In animal studies, a slight increase in blood amylase and lipase levels was observed a few hours after administration of the medication [41,42]. Depending on the dose, orally administered semaglutide was found to asymptotically increase lipase levels by 9-55%, while subcutaneously administered drug increased lipase levels by 36% [37].

In the SUSTAIN 6 study, acute pancreatitis occurred in 9 patients receiving the drug and in 12 receiving placebo. Pancreatic cancer in the same study occurred in 1 patient receiving the drug and in 4 receiving placebo [14].

In the subsequent study, PIONEER 6, acute pancreatitis occurred in 1 patient receiving the drug and in 3 patients receiving placebo. Pancreatic cancer was not observed in this study [43]. It is important to note that acute pancreatitis and pancreatic cancer are rare conditions, which is why the studies mentioned above were controversial. Additionally, individuals with diabetes who use semaglutide may have a higher frequency of risk factors for acute pancreatitis and pancreatic cancer compared to the general population.

In one of the latest safety studies regarding the use of semaglutide, from March 2024, a meta-analysis did not confirm an increased frequency of acute pancreatitis. In this study, various treatment regimens with the drug were compared, and none of the regimens showed an increased frequency of acute pancreatitis [44].

Another adverse effect attributed to semaglutide is an increased risk of thyroid tumors. Studies in rodents have shown increased GLP-1 receptor expression, leading to increased calcitonin synthesis and a higher risk of medullary thyroid carcinomas and adenomas. In the SUSTAIN trials, two cases of thyroid malignancy were observed in patients treated with semaglutide, compared to one case in the comparator group. None of the detected tumors were medullary thyroid carcinoma. There was also no observed increase in calcitonin levels in study participants [10-18]. In the PIONEER trials, four cases of thyroid tumors occurred in patients treated with semaglutide and one case in a patient receiving placebo [19-25].

Due to the rarity of medullary thyroid carcinoma, it is difficult to determine its association with semaglutide use. Further research over an extended period is required to clarify this relationship.

The use of semaglutide increases the risk of gallstones and gallbladder symptoms, such as biliary colic [8,32]. In the PIONEER study, gallstones were more common in patients treated with semaglutide compared to those receiving placebo (0.6% vs. 0.1%, respectively). In this study, the risk of cholecystitis was similar between the groups [45]. Although the number of cases was relatively small, it highlights the need to monitor patients for symptoms indicative of gallbladder issues.

Conclusions

It can be concluded that semaglutide therapy is an efficacious treatment option for patients with excess body weight and diabetes. Of significant importance in the treatment of diabetes is the reduction of HbA1c by semaglutide, as demonstrated in clinical trials such as PIONEER 1 and 3. Therapy with an analogue of human glucagon-like peptide-1 facilitates weight loss by slowing down gastric emptying and thus reducing the amount of food consumed. It is important to note that patients must be aware of the potential side effects associated with the drug, including nausea and vomiting. To mitigate these effects, it is recommended that the dose be gradually increased and that fatty products be limited. Additionally, recent studies have demonstrated that patients taking semaglutide have a reduced risk of heart attack and stroke. This suggests that this drug may be an appropriate treatment option for patients at higher risk of cardiovascular events.

Disclosure

Author's contribution

Conceptualization: Rafał Makuch and Adam Kucharski; Methodology: Alicja Wawrzyniak; Software: Alicja Chrościcka; Check: Andrzej Czajka and Kamil Gała; Formal analysis: Konrad Pilarski and Martyna Dewicka; Investigation: Paweł Lenard and Sara Michalska; Resources: Kamil Gała; Data curation: Alicja Chrościcka; Writing - rough preparation: Adam Kucharski and Rafał Makuch; Writing - review and editing: Alicja Wawrzyniak and Konrad Pilarski; Visualization: Martyna Dewicka; Supervision: Sara Michalska; Project administration: Rafał Makuch and Paweł Lenard; Receiving funding - no specific funding.

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Conflict of interest

The authors deny any conflict of interest.

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