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Effect of glucagon-like peptide-1 (GLP-1) agonists on the example of semaglutide on the cardiovascular system and their role in the treatment of obesity

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Abstract.

Obesity nowadays affects an increasing number of people. We can talk about it when the patient's BMI is ≥ 30.0 kg/m² (BMI 25.0-29.9 kg/m² - overweight). While obesity in itself may not be a problem for people suffering from it, its complications can be global and sometimes pose a serious threat to health or even life. Its main complications in the cardiovascular system include: hypercholesterolaemia, arterial hypertension, left ventricular hypertrophy, early atherosclerotic changes, heart and cerebral infarction. Treatment of obesity is based mainly on changing the patient's lifestyle - diet and physical activity, which can sometimes be problematic and difficult to apply.

However, there is a new group of hypoglycaemic drugs - glucagon-like peptide-1 (GLP-1) agonists, which can make obesity treatment easier. These drugs use the incretin effect in the body to increase insulin secretion in response to a meal containing carbohydrates and prevent postprandial hyperglycemia. In this article, we will analyze the latest studies on the effects of GLP-1 receptor agonists, using semaglutide as an example, on the cardiovascular system and on weight loss in patients.

Key words: obesity, weight loss, GLP-1 agonists, cardiovascular risk

Introduction and purpose.

Cardiovascular risk is an estimate of the likelihood of a patient developing cardiovascular complications such as a stroke or heart attack over the next 10 years. In Poland, currently the best tool to assess this risk in adults is the SCORE (Systematic Coronary Risk Evaluation) scale. It allows the estimation of the 10-year risk of a fatal cardiovascular event, taking into account factors such as gender, age, systolic blood pressure, total cholesterol in the blood and nicotine use [12]. The coexistence of diabetes and obesity has a significant impact on the cardiovascular system. Diabetes mellitus is a disease that accelerates the formation of atherosclerotic processes - it intensifies inflammatory processes that have a significant impact on the growth of atherosclerotic plaque. These, in turn, narrow the diameter of the coronary vessels, which hinders blood flow and the supply of nutrients necessary for the proper functioning of the heart muscle, leading to the development of ischemic heart disease.

According to the World Health Organization (WHO), about 1.9 billion people suffer from excess kilograms. About 650 million people are affected by the problem of obesity ($BMI \geq 30.0 \text{ kg / m}^2$) (data for 2016). [1] We can often hear that obesity is taking epidemic proportions. This is because nowadays obesity affects increasingly younger people. In the past, obesity mainly concerned adults, but nowadays it is also more common in children. Less and less movement, more and more time spent at the computer or smartphone, and dietary mistakes, most often resulting from rush, comfort or modern trends, have a huge impact on our body weight. Such bad habits learned from childhood are fixed in adulthood, and this causes an increase in the number of people struggling with the problem of obesity.

While obesity in itself is for many (or sometimes it is not - feeders) an aesthetic problem, its complications for the body are multidirectional and serious.

Early complications of obesity:

- Hypertension,
- Insulin resistance,
- Type 2 diabetes,
- Dyslipidemia,
- Metabolic syndrome,
- NAFLD (non-alcoholic fatty liver disease),
- Hypertransaminasemia (mainly ALT)
- Follicular calculi,
- Glazing of the glomeruli,
- Obstructive sleep apnea,
- bronchial asthma,
- Diseases of the skeletal system,
- Emotional disturbances (low self-esteem),
- Early puberty,
- hyperandrogenism,
- PCOS (polycystic ovary syndrome)

Complications of obesity in adulthood:

- Presence of cardiovascular risk factors (hypercholesterolaemia, hypertension, type 2 diabetes),
- The occurrence of cardiovascular events,
- Left ventricular hypertrophy,
- Shortening the life expectancy. [2]

Treating obesity is difficult. It mainly consists in changing the lifestyle by the patient and using a diet to ensure a caloric deficit. In order to achieve a long-term treatment effect, it is important to slowly and steadily lose weight and to stabilize it. During conservative treatment, lasting 6 months, it is recommended that the maximum weight loss be approx. 5-10% in relation to the initial body weight. A decrease of more than 10% in 6 months may result in a defensive reaction of the body, the effect of which is a slower metabolism and a rebound effect (the so-called yo-yo effect). In patients with a BMI > 35 kg / m², the reduction in body weight may be greater, up to 20%. Then the patient learns new eating and behavioral habits, which allows you to maintain the achieved body weight as long as possible. [3] [4]

In the case of grade II obesity (BMI 35-39.9 kg / m²) and the presence of comorbidities and grade III obesity (BMI ≥40 kg / m²), surgery (bariatric surgery) may be considered.

State of knowledge.

GLP-1 Agonists - Semaglutide (and Liraglutide)

Semaglutide and liraglutide are analogs of glucagon-like peptide-1 (GLP-1). Semaglutide is characterized by the presence of 94% sequences homologous to human GLP-1 and, as its analog, selectively binds and activates it, similar to human GLP-1.

Glucagon-like peptide-1 (GLP-1) is a hormone produced by the human body that has a multidirectional effect in the regulation of appetite and glucose concentration, and also has a significant effect on the function of the cardiovascular system. Through GLP-1 receptors, which are present in the pancreas and brain, it affects the appetite and causes a decrease in blood glucose levels by stimulating insulin secretion and reducing glucagon secretion. The reduction in blood glucose is also caused by delaying gastric emptying after eating. In hypoglycaemia, semaglutide reduces insulin secretion without affecting glucagon secretion. It also inhibits the desire to reach for foods high in fat. Due to the inhibition of appetite, and thus reduced caloric supply, semaglutide reduces body fat and lowers body weight.

GLP-1 receptors are also present in the heart, circulatory system, kidneys and the immune system. In clinical trials, semaglutide reduced inflammation, had a beneficial effect on plasma lipids, and also lowered systolic blood pressure. In animal studies, it inhibited the development of atherosclerosis in the process of reducing inflammation, which prevented the development of atherosclerotic plaque. [5]

Ping Zhong and colleagues conducted four studies with 3,447 patients, during which patients were given a weekly subcutaneous injection of semaglutide and their body weight was monitored. Taking into account the percentage and absolute weight loss, drug administration significantly exceeded placebo. It also showed a greater effect in reducing waist circumference and BMI compared to placebo. The use of the drug also had a significant effect on the improvement of cardiac and metabolic risk factors related to health. [6]

Glucagon-like peptide-1 (GLP-1) receptor analogs promote weight reduction in people with diabetes and were originally used to control the disease. This effect sparked the interest of scientists and explored their effects at higher doses in the treatment of obesity. For people with obesity, weight loss and improved glycemia aren't the only potential benefits. It has been established in clinical trials that long-acting GLP-1 is cardioprotective by lowering blood

pressure and cholesterol levels. Therefore, the use of GLP-1 receptor agonists in people at increased risk of cardiovascular events may bring significant benefits.

The first drug to be approved by the FDA for the treatment of obesity was liraglutide, manufactured by Novo Nordisk under the name Saxenda. Based on the results of efficacy and safety studies, on June 4, 2021. Semaglutide has also been approved by the FDA for long-term weight management in people with at least one obesity-related medical condition, such as high blood pressure, diabetes, and hypercholesterolaemia. [7]

In a study that compared the effects of semaglutide to liraglutide, the reduction in caloric intake compared to placebo was greater with semaglutide (35%) than with liraglutide (approximately 16%). Semaglutide also has a greater reduction in appetite, which is less apparent with liraglutide. This may suggest various mechanisms of caloric intake regulation, however, in order to understand the wider effects of these mechanisms, further research is needed. [8]

In the pre-registration phase III trial SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes), 3,297 patients with type 2 diabetes, additionally at high cardiovascular risk, were examined. They were randomly matched to the study group that took either 0.5 mg or 1 mg semaglutide / week. or to the placebo group. After a 2-year follow-up period, it was found that semaglutide significantly (by 26%) reduced the risk of cardiovascular deaths [10].

Another pre-approval phase III study - PIONEER-6 (Peptide Innovation for Early Diabetes Treatment) in patients with type 2 diabetes at high cardiovascular risk investigated the effect of oral semaglutide 14 mg / day on cardiovascular events compared to placebo . After a follow-up period of 16 months, the benefits of semaglutide over placebo were confirmed. Semaglutide reduced the risk of cardiovascular death and all-cause death [11].

The half-life of liraglutide is approximately 13 hours, so it must be used daily in order to maintain the therapeutic dose. The half-life of semaglutide is approximately 1 week, which means that its use is limited to one dose per week. This feature of semaglutide has a significant influence on the control of drug administration by patients. Less frequent dosing is more comfortable for the patient, which translates into an increase in the effectiveness of the treatment - the patient does not have to remember to take the drug every day and is less likely to miss a dose.

Conclusions.

Obesity - is a disease that takes the hallmarks of an epidemic, having a multidirectional impact on human health, causing not only organic but also psychological disorders - lack of acceptance, lowered self-esteem, it is also so difficult to cure. It requires a lot of determination, dedication and hard work to achieve any results. Until recently, there were no effective drugs on the market to help fight obesity. Various companies advertised preparations, most often herbal, of unconfirmed effectiveness, which were supposed to miraculously make the problem of excess kilos disappear. They work mainly through a diuretic or laxative effect, which allows you to notice a slight loss of body weight, but it is associated with the loss of water from the body, but does not reduce the amount of body fat.

Recently, there is a new group of hypoglycemic drugs on the market - glucagon-like peptide-1 (GLP-1) agonists, thanks to which the treatment of obesity may be easier. They take advantage of the incretin effect in the body, increase insulin secretion in response to a meal containing carbohydrates, and prevent postprandial hyperglycemia. Additionally, they inhibit glucagon secretion by pancreatic β cells, reduce hepatic glucose production and delay gastric

emptying. In the hypothalamic mechanism, they also reduce appetite. Their primary use in the treatment of diabetes may be extended to support the treatment of obesity. In addition, according to the research, apart from the effect on weight loss, they have a positive effect on the cardiovascular system and metabolism. They lower blood pressure and cholesterol, reduce the risk of cardiovascular events by preventing the development of atherosclerotic plaque and inflammation.

According to the researchers, a healthy, negative-calorie diet in obese people has a greater impact on weight loss than increased physical activity. [9] The reduction of appetite by GLP-1 agonists and their effect on reducing the desire to reach for high-fat products may significantly contribute to maintaining a caloric deficit and effective slimming therapy.

It should not be forgotten that healthy and effective weight loss is about changing your lifestyle and previous habits. The most beneficial is a combination of a balanced diet and exercise, which allows you to achieve a caloric deficit, and at the same time increase the condition of the body and physical fitness. The drugs in question can be used as an effective supplement, not as an alternative to weight loss therapy. Due to their multidirectional effect on the body's metabolism, these products should only be used under medical supervision.

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