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GLP-1 analogs: a comparison of new anti diabetic medications - presenting benefits and risks

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Abstract

Introduction and purpose: Diabetes has emerged as a global lifestyle disease, with an alarming rise in cases, particularly of type 2 diabetes. In Poland, over 3 million people are diagnosed, and an estimated 4 million cases are expected by 2030. Effective treatment involves a multifaceted approach, including dietary intervention, physical activity, and pharmacological options. Incretins, such as glucagon-like peptide-1 (GLP-1), play a pivotal role in carbohydrate metabolism regulation, and GLP-1 analogs have become essential in managing type 2 diabetes. This paper explores the development and mechanisms of GLP-1 analogs, detailing their impact on insulin secretion, gastric emptying, and weight reduction.

Description of the state knowledge: Various GLP-1 receptor agonists, including exenatide, liraglutide, dulaglutide, semaglutide, and the novel tirzepatide, are discussed. These drugs exhibit diverse pharmacokinetics, modes of administration, and effects on glucose metabolism and weight. Despite their efficacy, there is a concerning trend of off-label use, particularly for obesity treatment, leading to shortages for patients with valid prescriptions. This misuse is fueled by para-advertising on social media platforms, contributing to a surge in prescriptions and reimbursement costs. To address this, guidelines for GLP-1 analog use in obesity treatment are proposed, emphasizing the need for a stable drug supply and normalizing drug availability.

Summary: In 2023, concerns intensified with reports of counterfeit GLP-1 analogs, prompting regulatory interventions. The paper concludes by underscoring the critical role GLP-1 analogs play in diabetes and obesity treatment, while emphasizing the importance of responsible prescription practices, guidelines adherence, and regulatory vigilance to ensure patient safety and mitigate the risks associated with misuse and counterfeit drugs.

Keywords: GLP-1 analogs, diabetes, obesity, pharmacology

Introduction and purpose:

Diabetes has become a 21st-century lifestyle disease. Between 1980 and 2014, the global number of diabetes cases doubled, reaching 8.5% of the world's population. By 2045, it is estimated that over 700 million people worldwide will be affected [1]. In Poland, the number of diagnosed diabetes cases exceeds 3 million, constituting 8% of the population [2]. A

significantly larger number of individuals may still be undiagnosed or, due to unhealthy behaviors, are on the path to diabetes [3]. The estimated number of people with type 2 diabetes in Poland will exceed 4 million by 2030 [4]. The average age of diabetes detection is between 63 and 64 years, when the disease's severity requires pharmacological treatment. Across the European continent, the number of individuals with type 2 diabetes surpasses 61 million [5]. Diabetes is a risk factor for premature death and increases the risk of complications, including heart attacks, strokes, kidney diseases, and lower limb amputations [6]. Pharmacological treatment of type 2 diabetes is a derivative of its development mechanism. Impaired insulin secretion with a concomitant decrease in tissue sensitivity to insulin leads to insulin resistance [7]. Increased insulin secretion in the compensation mechanism for hyperglycemia only temporarily maintains a fragile balance [8]. Hyperglycemic states significantly accelerate degenerative processes in tissues [9]. Obesity, affecting over a billion people, including 20% of women and 14% of men, is a significant factor favoring the development of diabetes [10]. Effective diabetes treatment requires a combination of dietary intervention, physical activity, and pharmacological treatment [11]. The following groups of drugs are used in this treatment: biguanides, sulfonylurea derivatives, DPP-4 inhibitors, GLP-1 receptor agonists, PPAR-gamma agonists, SGLT-2 inhibitors, and insulin preparations [12, 13, 14]. This paper explores the development and mechanisms of GLP-1 analogs, detailing their impact on insulin secretion, gastric emptying, and weight reduction.

DESCRIPTION OF THE STATE KNOWLEDGE:

Incretins are a type of peptide hormones produced by the cells lining the small intestine, playing a significant role in regulating carbohydrate metabolism [15]. These incretins are responsible for nearly two-thirds of the insulin response to ingested food. The mediator in this case is the glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) [16]. In individuals with diabetes, the secretion of the latter is reduced [17]. It is suggested that the insulinotropic action of GLP-1 is relatively less impaired compared to GIP, secreted by K cells located in the duodenum, mucosa of the jejunum, and proximal part of the ileum [18]. Therefore, externally administered GLP-1 analogs can stimulate insulin secretion while simultaneously inhibiting glucagon release, leading to a reduction in fasting and postprandial glucose levels [19]. An essential aspect of the action of GLP-1 analogs is the observation of the occurrence of the so-called incretin effect in type 2 diabetes [19]. This term refers to the fact that there is a greater stimulation of insulin secretion when external glucose is given orally than when glucose is administered directly intravenously [20]. In the case of

isoglycemic glucose infusion intravenously, the peak insulin response is similar to that of healthy individuals after oral intake. The difference in insulin secretory response between orally administered glucose and isoglycemic intravenous glucose stimulation is the incretin effect, typically expressed as a percentage of the insulin secretory response after oral glucose administration [21]. The first studies on the insulinotropic effect of GLP-1 were presented as early as 1987, based on research on pancreatic L cells in rodents [22]. The effects of exogenous GLP-1 (7-36) amide in individuals with type 2 diabetes were first published in 1993 [23].

Interestingly, GLP-1 slows down stomach emptying in individuals with type 2 diabetes as well as in healthy individuals. Even low doses exert this effect, contributing to a reduction in postprandial glycemia [24]. Despite the partially preserved insulinotropic activity of GLP-1, the incretin effect is reduced or absent in type 2 diabetes, and in healthy individuals, the action of GLP-1 is also relatively limited [25]. However, this situation changes in the case of bariatric surgery, which results in gastric bypass. The stomach becomes relatively small, undergoes rapid emptying, and nutrients quickly reach the lower sections of the small intestine [26]. It is precisely there, in the human body, where L cells are located, producing GLP-1 [27]. The identification of glucagon-like peptide-1 (GLP-1) originating from the intestines initiated the development of GLP-1 receptor agonists (GLP-1 RAs) [28]. Collaborative efforts by scientists working with J. Holst and J. Habener led to the identification of the amidated 7-36 form, known as short GLP-1, and a longer form of GLP-1 with 6 additional N-terminal amino acid residues, the latter characterized by greater insulinotropic activity [29]. Interestingly, the shorter GLP-1 proved to be significantly more insulinotropic [30]. It was also demonstrated that both forms of GLP-1 (the molecule and the DPP-4 metabolite) are degraded and inactivated by the DPP-4 protease, being eliminated from circulation in just two minutes [31]. The research focused on seeking GLP-1 analogs that would be resistant to DPP-4 while simultaneously avoiding immediate degradation. Serendipitously, the peptide exendin-4 from the saliva of the Gila monster lizard (Heloderma suspectum) was found to be homologous to mammalian GLP-1 and capable of binding to and activating GLP-1 receptors. This discovery led to the development of a medication named exenatide [32, 33].

Under natural conditions, GIP and GLP-1 levels increase within fifteen minutes after food intake, reaching their maximum value between 30 to 45 minutes, gradually returning to baseline values within 2 to 3 hours [34]. By binding to specific receptors on the surface of pancreatic beta cells, they induce insulin secretion. These hormones only act during

hyperglycemia [35]. In normoglycemia, they cease to affect beta cells. As GLP-1 slows gastric emptying, it delays the absorption of glucose, counteracting a sudden postprandial increase in glycemia [36]. The secondary slowing of gastric emptying leads to increased feelings of satiety, thereby reducing carbohydrate intake [37].

Among drugs classified as GLP-1 receptor agonists, those registered in 2010 include exenatide and liraglutide. Other medications in this class are albiglutide, lixisenatide, and taspoglutide, as well as dulaglutide, semaglutide, and tirzepatide [38]. Tirzepatide is a novel molecule capable of controlling blood glucose levels through dual agonism of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors [39]. Incretin hormone receptors are located not only on pancreatic beta cells but also in blood vessel cells, adipose tissue, the heart, and the adrenal cortex [40]. Stimulation of these hormones on beta cells leads to an increase in intracellular calcium and cyclic AMP levels [41]. Exceeding blood glucose concentrations above 5 mmol/L triggers insulin release, accompanied by a decrease in glucagon secretion [42].

The degradation of GLP-1 involves the truncation of the GLP-1 9-36 form under the influence of the aforementioned DPP-4 [43]. Central to the significance of GLP-1 is the fact that 60% of postprandial insulin secretion is a result of the incretin effect, and this hormone is part of the so-called entero-insular axis. As GLP-1 and GIP secretion occurs throughout the length of the small intestine, in individuals with gastric resection after meal consumption, secretion is heightened, leading to relative hypoglycemia [44]. Mechanisms influencing GLP-1 secretion include the inhibitory action of sympathetic innervation of the small intestine and the stimulating action of D cells, which produce somatostatin [45]. Another inducer of GLP-1 secretion is the neuropeptide gastrin-releasing peptide (GrP), along with lipids from food and the activation of the GPR120 receptor by fatty acids [46]. The proglucagon gene is located on the long arm of chromosome 2 in humans. It consists of six exons and five introns, with the entire sequence responsible for encoding GLP-1 located on the fourth exon [47]. Regardless of the site of GLP-1 expression in the human body, transcription and translation processes are the same, with differences occurring at the level of post-translational processes in different tissues [48]. While proglucagon expression in the pancreas is a result of hypoglycemia and inhibits insulin secretion, glucagon-like peptide GLP-1 and GLP-2 are formed in L cells and neurons from proglucagon. The role of the latter is to activate proliferation and inhibit apoptosis of cells in the small intestine glands, increase glucose transport in the intestine, and inhibit gastric acid secretion. 80% of the GLP-1 fraction is (7-36), while other forms include (7-37) and (1-36) produced by the pancreas, as well as (1-37) [49]. The aforementioned DPP-

4, also known as CD26, is a serine protease that inhibits proteins and oligopeptides containing alanine or proline [50]. This enzyme is expressed in, among other places, the kidneys, liver, pancreas, spleen, and adipose tissue. Because DPP-4 is also located on endothelial cells in the blood vessels of the small intestine, only 10 to 15% of GLP-1 ultimately reaches systemic circulation. The fasting level of GLP-1 in human serum ranges from 5 to 10 pmol/L [51]. The Yanaihara Institute Inc immunoenzymatic method is among those used to measure GLP-1 levels, employing a microplate reader [52]. GLP-1 has many more properties, depending on the body system. It increases the insulin sensitivity of muscle cells, reduces cell proliferation in inflammation, and increases surfactant production. GLP-1 also increases diuresis, positively influences bone formation processes, reduces degenerative processes in liver cells, has a beneficial effect on the functioning of heart cells, and plays a cardioprotective role by improving the function of the left ventricle [53]. After the approval of exenatide for the treatment of type 2 diabetes, several pharmaceutical companies initiated diverse efforts to stimulate the GLP-1 receptor more effectively and with a longer duration of action [54]. Exenatide must be injected at least twice daily, primarily ensuring active circulating concentrations covering two main meals each day, with low levels between two injections [55]. Liraglutide, approved in 2009, was designed to provide an almost unchanged amino acid sequence compared to mammalian GLP-1. A free side chain of a fatty acid was attached to the peptide, favoring binding to albumins in the serum and interstitial fluid. Only a small portion (approximately 1-2%) of liraglutide circulates in the free form (unbound to albumin), ready to diffuse into tissues and bind to receptors [56]. Other approaches were based on the strategy of combining (modified) GLP-1 with large proteins, such as the Fc fragment of immunoglobulin (dulaglutide or efpeglenatide) or albumin (albiglutide) [57]. These compounds seem to undergo slow degradation, with a half-life of approximately one week. After subcutaneous injection, they reach effective concentrations in circulation relatively early, starting to reduce serum glucose levels soon after the initiation of such treatment [58]. Semaglutide is another compound with a structure generally similar to liraglutide (GLP-1 with a free side chain of a fatty acid) but with a significantly longer half-life, seemingly mediated by even tighter coupling with albumin [59]. As the parent GLP-1 compound has a very short elimination half-life, modifications were made to differentiate analogs into long-acting and short-acting. In the second case, exenatide must be administered twice daily, similar to lixisenatide. The peak concentration of the drug occurs after administration [61]. Long-acting analogs maintain an elevated level of GLP-1. For liraglutide, this is a period of 24 hours, while for semaglutide, it is up to a week [27]. In the case of long-acting analogs, the reduction in postprandial glucose

levels occurs through the mechanism of increasing insulin levels and simultaneously inhibiting glucagon [62]. Weight reduction with the use of GLP-1 results from the fact that GLP-1 promotes satiety, thus reducing food intake. More interestingly, the use of the exenatide analogue has been found to inhibit brain activation in processes induced by eating. Administration of high doses of this drug via infusion led to an increase in metabolism in the central nervous system, including areas responsible for the functioning of the food reward system. Various classes of GLP-1 receptors, called GLP-1R, have been shown to exist in the central and autonomic nervous systems, and their activation also affects neural pathways responsible for controlling the body's energy expenditure [63]. GLP-1 analogs have the ability to cross the blood-brain barrier, interacting with the nervous system via humoral pathways and also affecting GLP-1R receptors in the periventricular areas of the brain [64]. Studies with patients using semaglutide have demonstrated that weight reduction was caused by decreased energy intake [65]. In this regard, a greater effect was achieved than with liraglutide, which additionally has the disadvantage of requiring daily administration. In the second case, a reduction in body weight above 5% was achieved two to three times less frequently [66].

Eksenatide is indicated for the treatment of type 2 diabetes from the age of 10, either in combination with other drugs or insulin. In its extended-release form, it is administered once a week. The steady state is achieved after administration over the course of 6-7 weeks. Despite a weekly interval between doses, the drug maintains therapeutic levels. Elimination occurs through glomerular filtration and proteolytic breakdown. Adverse effects include hypoglycemia when used with sulfonylurea derivatives, nausea (which tends to resolve during treatment), and diarrhea. Common side effects encompass headaches, dizziness, decreased appetite, indigestion, abdominal pain, constipation, itching, and redness at the injection site. The drug is contraindicated during pregnancy, breastfeeding, or when planning pregnancy. The therapeutic dose is 2 mg per week. It is available as a powder and solvent for preparing an extended-release suspension [57]. In the Bhavsar study, controlled phase 3 clinical trials lasting from 12 to 52 weeks showed that exenatide at a dose of 10 mg twice daily reduced the average HbA1c level by -0.8% to -1.7% in monotherapy or in combination with metformin, sulfonylurea derivatives, or thiazolidinediones, with an average weight loss of -1.2 kg to -8.0 kg. In controlled phase 3 trials lasting 24 to 30 weeks, exenatide at a dose of 2 mg once a week reduced the average HbA1c level by -1.3% to -1.9%, with an average weight loss of -2.3 kg to -3.7 kg. Exenatide was generally well-tolerated [27,67]. In the long-term Holman study and others, no significant impact of exenatide on vascular events in people with diabetes

compared to placebo was found. In the Ye studies, exenatide was found to be superior to metformin in the treatment of women with polycystic ovary syndrome, and this treatment affected an increase in fertility [68,69,70].

Lixisenatide is another GLP-1 receptor agonist, which binds to plasma proteins in 55% of cases. It is excreted through glomerular filtration, undergoes secondary absorption in the renal tubules, and is metabolized. Treatment with this compound carries the risk of acute pancreatitis. When used in combination with sulfonylurea derivatives and basal insulin, it causes hypoglycemia and may also lead to upper respiratory tract infections, viral infections, tachycardia, and digestive disorders. Treatment starts with a dose of 10 mcg for two weeks, followed by a doubling of the dose. It is administered daily, before the same meal. The preparation is available in doses of 10 or 20 mcg [71, 72]. This drug has a half-life of 2.8 hours compared to 2.4 hours for exenatide in both forms. In the Ratner study and others, on a sample of 542 patients over a period of 13 weeks treated with metformin, administration of this drug at doses from 5 to 30 mcg resulted in a reduction in HbA1c levels of 0.47% for 5 mcg and 0.75 to 20 mcg [73]. The Becker study and others showed that at a dose of 20 mcg, this drug restores the first and second phase of insulin response. When used in monotherapy, this drug caused a decrease in serum glucose levels by 1 mmol/L [74].

Taspoglutide is another drug in the GLP-1 agonist class, and studies have shown that when administered to patients with type 1 diabetes along with metformin once a week, it reduces fasting glucose levels and causes weight loss [76]. In the Raz studies, taspoglutide was administered at doses of 10 or 20 mg to 373 patients. Over the course of a 12-week experiment, the doses caused a reduction in HbA1C below 6.5% in 60% of patients for the 10 mg dose and 66% for the 20 mg dose. The main side effects included nausea and vomiting [77].

Dulaglutide is another GLP-1 agonist with 90% homology to naturally occurring human GLP-1. It reduces fasting, pre- and post-meal glucose levels. The steady state for this drug is achieved after 2 to 4 weeks, with a half-life of 5 days. It undergoes breakdown into amino acids in the catabolic pathway of proteins. It does not affect the availability of other drugs, including digoxin, atorvastatin, and contraceptives. At a dose of 1.5 mg, when used with insulin, metformin, or glimepiride, it causes hypoglycemia. Common side effects include bloating, indigestion, fatigue, sinus tachycardia, and first-degree atrioventricular block. In monotherapy, the drug is used at a dose of 0.75 mg per week, with a maximum weekly dose of 4.5 mg [78]. The drug is available in injectable form at doses of 0.5 ml, corresponding to 0.75, 1.5, 3, and 4.5 mg/0.5 ml [79]. Unlike the previously mentioned GLP-1 agonists,

dulaglutide is defined as a large molecule, with a dimeric structure in which the amino acid chains are covalently linked to a modified Fc element of human immunoglobulin G4 [81]. In the DURATION-6 and AWARD-6 studies, the use of dulaglutide or liraglutide indicated a superiority of the latter for weight reduction [82]. In the AWARD-3 study with a sample of 800 patients over a period of 26 weeks, the use of this drug resulted in a reduction in HbA1C of 0.78% compared to 0.56% achieved with metformin [83]. Literature presents a case of a 39-year-old woman with type 2 diabetes for 19 years, treated with dulaglutide at a dose of 1.5 mg per week. The drug was discontinued in the 13th week of the newly diagnosed pregnancy, and no complications occurred in the newborn [84].

Semaglutide is another new GLP-1 analog with 94% similarity to natural GLP-1. A beneficial side effect of the drug is the reduction of atherosclerosis development in arteries [85]. Steady state is achieved after 4 to 5 weeks of treatment with doses of 0.5 mg and 1 mg. Administering the drug with meals or fluids slows down its absorption [86]. The drug binds to 99% of plasma proteins, and its metabolism occurs through proteolytic breakdown and beta-oxidation of the side chain of fatty acid [88]. The drug is excreted in urine and partially in feces, with a half-life of one week. An oral dose of 14 mg once a day has similar effects to a subcutaneous dose of 0.5 mg once a week. Administering the drug orally with other medications reduces its absorption. Nausea, diarrhea, and complications from diabetic retinopathy are among the side effects [89]. In the case of oral administration, conditions such as gastroesophageal reflux disease, gallstones, increased lipase and amylase activity may occur. The drug is available as a solution for injections and tablets. The maximum dose for subcutaneous administration is 2 mg per week, while for oral administration, it is 14 mg per day [90, 91]. The oral form of semaglutide was approved by the FDA and EMA in 2019. The SUSTAIN and PIONEER 6 studies confirmed its effectiveness. The oral form is created by combining semaglutide with sodium N-[8-(2-hydroxybenzoyl)aminocaprylate], which prevents the proteolytic breakdown of the drug before absorption by the stomach wall into the bloodstream [92,93]. Both semaglutide preparations received official warnings about medullary thyroid carcinoma in the USA, with an estimated incidence of 0.2 cases per 100,000 patient-years. It is suggested that other specific side effects such as pancreatitis, kidney issues, diabetic retinopathy may be due to pre-existing advanced carbohydrate metabolism disorders rather than the drug [94]. The STEP-1 study among obese patients using semaglutide revealed that within a year after discontinuation of the drug, weight and the risk of cardiovascular complications returned to baseline, indicating that GLP-1 analog therapy must be continuous [95].

Tirzepatide is another drug in the GLP-1 agonist group. At a dose of 15 mg, it increases insulin secretion in the first and second phases by 466% and 302%, respectively. The drug also increases insulin sensitivity by 63%, and at a dose of 15 mg, it reduces glucagon secretion by 28% on an empty stomach. Steady-state of the drug is achieved after 4 weeks, and it binds to albumin in plasma by 99%. The half-life is 5 days, and metabolite excretion occurs with both feces and urine. Side effects include vomiting, indigestion, constipation, and fatigue. The initial dose is 2.5 mg once a week, with a maximum dose of 15 mg [96]. Tirzepatide is the first GLP-1 analog that is simultaneously a GIP agonist, approved in 2022 by EMA and FDA. The synergistic action of both hormones primarily affects pancreatic beta cells and causes weight loss. GIP does not affect glucagon secretion. The long half-life achieved in this way means that normoglycemia lasts longer. The drug is administered subcutaneously, like other GLP-1 analogs, injected into the thigh, abdomen, or arm. The drug's bioavailability is 80%, with a half-life of 5 days, and metabolites are excreted in both urine and feces. The initial dose is 2.5 mg every week, increased to 5 mg after four weeks, with a maximum dose of 15 mg [96]. Since 2023, the drug is registered in the USA and Europe for the treatment of obesity. In numerous clinical studies, a dose of 15 mg resulted in weight loss ranging from 8.8 kg to 12.9 kg in SURPASS and SURMOUNT studies [97]. Side effects occur more frequently with higher doses of the drug [98]. Tirzepatide's mechanism of action, modulating lipid storage in adipose tissue by interacting with GIP receptors, is attributed to its greater effectiveness in reducing fat tissue [39].

The guidelines of the Polish Diabetological Society suggest that in the case of obesity with prediabetes, when non-pharmacological interventions do not yield the desired effect, the use of GLP-1 analogs should be considered. For patients with atherosclerotic cardiovascular disease, heart failure, and chronic kidney disease, drug selection should take into account, first and foremost, their positive cardiovascular and nephroprotective effects. In patients with kidney disease, if there are contraindications to the use of SGLT2 inhibitors, GLP-1 analogs are recommended. For patients with heart disease, combination therapy is recommended, considering GLP-1 analogs. GLP-1 agonists are recommended as a possible first-line treatment for type 2 diabetes, including insulin therapy [11].

Summary:

The dissemination of knowledge regarding a new category of diabetes medications has led to a significant increase in interest in GLP-1 analogs. This interest largely stems from the potential for weight reduction. Consequently, unfavorable phenomena have emerged in Poland from the perspective of patients, including the mass sale of these drugs beyond

medical indications with reimbursement and the circulation of counterfeits. This issue pertains to GLP-1 analogs introduced to the market in recent years, such as Ozempic (semaglutide) and Trulicity (dulaglutide). In cases where patients meet reimbursement criteria, they can obtain these drugs with a discount for indications related to type 2 diabetes. However, there is an increasing trend of selling these drugs without reimbursement indications, specifically for obesity treatment, leading to shortages for patients with valid prescriptions. To combat this phenomenon, actions have been taken, including placing GLP-1 drugs on the export control list to prevent their export from the country, and initiating controls to assess the extent to which these drugs are prescribed to patients actually suffering from diabetes. In the case of reimbursement, patients pay only one-third of the drug's price. The indications for semaglutide and dulaglutide include previous treatment with at least two drugs for type 2 diabetes, a hemoglobin A1c level above 7.5%, and the coexistence of obesity, as well as a high cardiovascular risk. Within just two years from 2020 to 2022, there was a sixfold increase in prescriptions for Ozempic and an eightfold increase for Trulicity. In 2020, 20,439 and 43,926 packages of these drugs were dispensed, respectively, and in 2022, the numbers rose to 129,452 and 340,002, respectively. Simultaneously, the availability of these drugs sharply declined from 2022 onwards. Meanwhile, using these drugs outside their registered indications poses a real risk of unpredictable medical events, including patient death [99]. According to the National Health Fund (NFZ) audits, some doctors issued prescriptions for GLP-1 drugs, especially in private facilities where patients pay for visits, and yet they receive the drug at a discounted rate despite the lack of medical indications. In 2020 alone, NFZ spent over PLN 5 million on reimbursement for Ozempic and Trulicity, and by 2022, this figure had risen to PLN 42 million. The problem is exacerbated mainly due to para-advertising activities. On popular social media platforms like TikTok, many individuals involved in diet and weight loss promote the use of these drugs. Some posts in this regard have garnered hundreds of millions of likes. A straightforward solution to this problem could involve specifying guidelines for the use of GLP-1 drugs in obesity treatment. Due to the positive side effects of semaglutide, such as appetite suppression, prolonged periods of satiety, and reduced calorie intake, the FDA has approved this drug for obesity treatment at a dose of 2.4 mg once a week, marketed as Wagovy [100]. Obesity treatment guidelines in Poland recommend liraglutide at a dose of 0.6 mg daily up to a maximum therapeutic dose of 3.0 mg daily. It is noteworthy that the dosage of GLP-1 drugs for obesity treatment is higher than that for type 2 diabetes. Semaglutide, registered in 2022 by the European Medicines Agency (EMA) for obesity treatment, is administered at an initial dose of 0.25 mg per week, gradually increasing to the

therapeutic dose of 2.4 mg per week. The effectiveness of these drugs is considered achieved if there is a minimum 5% reduction in body weight within three months from the baseline [101] Research by Pasek et al. indicates that liraglutide was registered for obesity treatment by the FDA in 2014 and by the EMA in 2015. Studies demonstrated an average weight loss of 5.9 kg per year, along with additional benefits such as lowering LDL cholesterol, total cholesterol, and triglyceride levels. For semaglutide, the weight reduction for a 1 mg dose was 4.3 kg over a year [102,103]. Orłowski et al. compared the effectiveness of semaglutide and liraglutide in obesity treatment at doses of 0.4 mg and 3 mg, respectively, gradually titrating to the therapeutic dose in a trial involving 957 individuals. After 52 weeks, the average weight reduction for liraglutide was 7.8%, and for semaglutide at the maximum dose of 0.4 mg, it was 13.8%. Researchers also highlight the effects of tirzepatide, approved for diabetes treatment in the USA in 2022. In a trial with 2539 participants, the drug was administered at doses of 5, 10, and 15 mg. For the latter, the average change in body weight was 20.9%, and at 5 mg, it was 19.5% [104].

In summary, GLP-1 drugs indeed provide an excellent approach to treating obesity, given specific criteria and exhaustion of traditional methods. Nevertheless, due to the significant demand for effective obesity treatment in the population, it is essential to incorporate this fact into guidelines and ensure a stable drug supply to normalize the situation over the long term. The availability of medicinal products is verified, among other methods, through the ZSMOPL system (Integrated System for Monitoring the Turnover of Products). For the product Victoza (liraglutide), difficulties in 2022 were caused by the temporary suspension of its turnover by the manufacturing entity. In 2022, to counteract shortages, the Minister of Health issued approvals for emergency imports, allowing wholesalers to temporarily introduce the drug into circulation in foreign-language packaging [105]. On January 30, 2023, the Ombudsman intervened, addressing the deficit in GLP-1 drugs. It was indicated that the energy crisis and limited production capacities of entities producing these drugs, as well as the purported effectiveness of the export control list and intensive efforts of the Team to Counteract Shortages in the Availability of Medicinal Products established for this purpose, were the reasons. According to the Ministry of Health, sufficient measures were taken at that time to address the shortages [106]. However, in 2023, serious warnings began to emerge, including those presented by the Chief Pharmaceutical Inspectorate, regarding the distribution of counterfeit drugs allegedly containing GLP-1 analogs. The situation in this regard did not significantly improve; at the end of the previous year, the Chief Pharmaceutical Inspectorate reported the withdrawal of several batches of Ozempic, which turned out to be counterfeits

containing additional contaminants. In mid-2023, the Chief Pharmaceutical Inspectorate reported initiating 129 proceedings related to the illegal trade of substances, including GLP-1 analog counterfeits. This was connected to the so-called "receptomat" scandal. This activity involved the massive use of the internet to automatically prescribe drugs without verifying the appropriateness of drug use based on patient declarations. Despite these efforts, the trade in GLP-1 analogs, including smuggling, remains a serious problem. In conclusion, considering the aspects of using GLP-1 analogs, it is crucial to emphasize that the development of this class of drugs offers great hope for achieving a lasting elimination [107,108].

Author's contribution:

Conceptualization: M.D.; methodology: M.D, P.S,; software: S.Z., M.S.; formal analysis: J.T., M.D., Ł.S., K.Ż., K.K.; investigation; A.B, O.K., P.S., S.Z., M.S., J.T., M.D., Ł.S.; resources: A.B, O.K., P.S., S.Z., M.S., J.T., M.D., Ł.S., K.Ż., K.K.; data curation: A.B, O.K., P.S., M.D.,K.K.; writing - rough preparation: A.B, O.K., P.S., S.Z., M.S., J.T., M.D., Ł.S., K.Ż., writing – review and editing:M.S., J.T., M.D., Ł.S., K.Ż., K.K.; visualization: A.B., O.K., P.S.,; supervision: Ł.S., K.Ż., K.K.,; project administration: S.Z., M.S., J.T., M.D.

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