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REVIEW PAPER

Harnessing the gut-brain axis in the treatment of type 2 diabetes mellitus and obesity

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ABSTRACT

Introduction and aim. The most common metabolic disorders include type 2 diabetes (T2DM) and obesity. Their prevalence has increased in recent years. Due to their widespread prevalence and the fact that they increase the risk of cardiovascular disease, morbidity, and mortality, they pose a significant economic burden to the healthcare system. In this review, we will focus primarily on the role of gut hormone signaling produced by enteroendocrine cells (EECs), which are part of the gut-brain axis. Furthermore we will summarize applications of these mechanisms in novel therapies for T2DM and obesity.

Material and method. Literature data analysis was performed using the following databases: PubMed (MEDLINE), Scopus, Web of Science and Google Scholar. The review included articles in Polish and English published between 2000 and 2024.

Analysis of the literature. EECs are specialized transepithelial cells present throughout the intestine. The best-studied EEC subtype is the L cell, which secretes glucagon-like peptide-1 (GLP-1). GLP-1 regulates insulin secretion and contributes to satiety by increasing insulin secretion and inhibiting glucagon secretion. Significant progress in the use of intestinal hormones in the treatment of T2DM and obesity has led to the development of effective therapies for both of these conditions, such as GLP-1 analogs.

Conclusion. The growing understanding of biochemical processes, hormonal signaling, and the development of new technologies contribute to the continuation of research on new, more effective therapies that use mechanisms of action of the gut-brain axis. Despite these achievements, the need for new and more effective treatments is constantly growing, and requires innovative strategies and their potential combination with existing therapies.

Keywords. diabetes, gut-brain axis, obesity

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Introduction

Metabolic disorders include type 2 diabetes (T2DM) and obesity. These conditions frequently coexist. Their prevalence varies widely across the globe.[1,2] According to the International Diabetes Federation, 463 million people worldwide had diabetes in 2019,[3] while, according to the World Health Organization, more than 650 million adults worldwide were obese in 2016.[4] Due to their widespread prevalence and the fact that both T2DM and obesity increase the risk of developing cardiovascular disease, morbidity, and mortality, these conditions impose a significant economic burden on healthcare systems.[1]

One of the available therapies and treatment strategies for these conditions is glucagon-like peptide-1 (GLP-1) therapy. Their mechanism of action is based on the regulation of food intake, hunger and satiety, metabolism, and glucose homeostasis via the gut-brain axis.[5] The gastrointestinal tract responds to a variety of stimuli, such as mechanical factors, pathogens, nutrients contained in food, and toxins.[5] The gut-brain axis mediates bidirectional communication between the gastrointestinal tract and the central nervous system, utilizing specific signaling pathways.[5,6] These pathways include the nervous system, the immune system, the hypothalamic-pituitary-adrenal axis, and enteroendocrine cells (EECs).[6]

Aim

In this review, we will focus primarily on the role of gut hormone signaling produced by EECs, which are part of the gut-brain axis and are involved in the regulation of appetite and glucose homeostasis. Furthermore, we will summarize applications of these mechanisms in novel therapies for T2DM and obesity.

Material and methods

Literature data analysis was conducted between 2020 and 2024 using the following databases: PubMed (MEDLINE), Scopus, Web of Science, and Google Scholar. The review included articles in Polish and English published between 2000 and 2024. Key terms used to identify relevant studies included: "glucagon-like peptide-1," "enteroendocrine cells," "GLP-1 analogues," "incretin effect in type 2 diabetes," "lixisenatide," "liraglutide," "semaglutide," and "tirzepatide." The review included scientific articles, reviews, and clinical trial descriptions in pediatric and adult patients. The review addressed the role of the gut-brain axis in appetite regulation and glucose homeostasis, the role of GLP-1 analogues in the context of the incretin effect, the treatment of T2DM, the treatment of obesity, cardiovascular disease, and other beneficial and adverse effects. Articles published before 2000, articles written in languages other than English or Polish, conference proceedings, and articles with access only to the abstract were excluded. A literature review was conducted by five reviewers using a standard data extraction form. Ninety-two publications were included in the review. The analysis focused primarily on the role of gut hormonal signaling, generated by EEC, as a component of the gut-brain axis, and on the characteristics and effects of GLP-1 analogues, including tirzepatide.

Analysis of the literature

The role of the gut-brain axis in appetite regulation and glucose homeostasis

EECs are specialized transepithelial cells present throughout the intestine.[7] Several unique subtypes of EECs have been described, distinguished by their location along the intestine, and the hormones and neurotransmitters they secrete. The nomenclature used to distinguish between the subtypes is based on the detection of specific hormones.[8,9] EEC cells in the stomach produce hormones that, through feedback, regulate their own levels. These include ghrelin, histamine, and gastrin. In the distal intestine, they secrete anorexic hormones, and to support gastric motility, motilin and serotonin, as well as gastric inhibitory polypeptide (GIP).[5] The best-studied EEC subtype is the L cell, which secretes GLP-1.[10] GLP-1 regulates insulin secretion and contributes to satiety by increasing insulin secretion and inhibiting glucagon secretion, thereby suppressing endogenous glucose production and reducing postprandial glycemia. GLP-1 also delays gastric emptying[11] and increases pyloric contractions, thereby slowing the flow of food into the small intestine.[5]

EECs secrete hormones that influence neighbouring receptors, organs, and nerves (including the intestinal and vagus nerves). Therefore, their mechanism of action operates on multiple levels. The primary mechanism of action is through paracrine signaling, characterized by a short half-life.[12-15] Another mode of action is endocrine due to the presence of pancreatic β-cells, which influence the process of food regulation.[14] The third signaling pathway utilizes synaptic connections between EECs and intestinal afferent nerves; these are unable to directly detect chemical signals in the intestinal lumen. Therefore, synaptic connections with EEC cells enable the transmission of sensory stimuli from the intestinal lumen via neurotransmitters such as glutamate.[16]

Prior to food ingestion, gastric EECs produce ghrelin, which modulates orexigenic signaling to the brain. This hormone is detected at high concentrations before meals, suggesting that circulating ghrelin directly engages the hindbrain and the arcuate nucleus to promote appetite.[17] The entry of nutrients into the small intestine inhibits ghrelin secretion[18] and their absorption by the duodenal epithelium stimulates EECs to secrete cholecystokinin (CCK), GIP, and Secretin.[10] CCK

receptors act on sensory nerves located in the region of the vagus nerve and its terminals. In this way, they influence not only satiety but also pyloric contractions, inhibiting gastric emptying.[19,20] GIPs, in turn, activate insulin secretion. They regulate the activity of specific receptors on β-cells and influence the hypothalamus, which leads to fat storage in adipocytes.[21,22] EECs are most strongly activated when nutrients and bile acids pass from the duodenum into the jejunum.[19,23,24,25]

GLP-1 analogs

GLP-1 analogues, or GLP-1 receptor agonists (GLP-1RAs), are incretin-based drugs that are increasingly used in the treatment of patients with T2DM. These drugs are administered via subcutaneous injection (the exception being the oral formulation of semaglutide). Their primary role is to control and regulate blood glucose levels, which occurs through the process of insulin secretion and biosynthesis in a glucose-dependent manner. Additionally, these drugs inhibit glucagon secretion, delay gastric emptying, and promote satiety, which supports glycemic control and weight management in patients. GLP-1 analogues mimic the action of endogenous GLP-1.[26] Theoretically, pancreatic β cells should respond in the same way to glucose, regardless of whether it was administered orally or directly into the bloodstream. In practice, however, the body's response is different - after oral glucose intake, the level of insulin secreted is higher than after intravenous administration, despite similar blood glucose concentrations. This phenomenon is called the incretin effect. This effect is caused by gut hormones, the so-called incretins, which include GIP and GLP-1. GLP-1 is secreted by cells of the duodenal mucosa, while GLP-1 is produced in the cells of the small intestine. Through synthesis with appropriate receptors on the surface of pancreatic β-cells, they stimulate them to increase insulin secretion. The action of GIP and GLP-1 depends on the current glucose concentration – the higher the concentration, the greater the stimulation of insulin secretion and the simultaneous inhibition of glucagon production. When glucose levels drop to baseline, the activity of these hormones ceases. Importantly, incretins do not increase insulin secretion or inhibit glucagon when glucose levels are low – so they do not cause hypoglycemia. Additionally, GLP-1 slows down stomach emptying, which leads to slower digestion and absorption of glucose. This reduces the rapidity of the postprandial increase in blood sugar levels. Slower stomach emptying also promotes a faster feeling of satiety, which may contribute to a reduction in the amount of food consumed. In turn, GIP also affects at the cellular level – it stimulates the expression of the gene responsible for the production of proinsulin, a precursor of insulin.[27]

GLP-1 and the incretin Effect

A greater and more effective insulin response is induced by an oral glucose load than by an intravenous load.[28,29] This enhanced response is referred to as the incretin effect. GLP-1 is an incretin peptide hormone. It is secreted by L cells in the distal small intestine and colon within minutes of nutrient ingestion. It acts on pancreatic β-cells via GLP-1 receptors. It is estimated that approximately 50–70% of total insulin secretion after an oral glucose load is a consequence of incretin release from the gastrointestinal tract.[29,30,31] GLP-1 suppresses appetite, and sustained activation of the GLP-1 receptor is associated with weight loss.[29,30] The pancreas is not the only site where the GLP-1 receptor is found. It also appears in the stomach, intestines, kidneys, pituitary gland, and central nervous system. Therefore, its influence and role are extensive and multifaceted.[29,30]

Studies on the secretion and action of incretins indicate significantly reduced incretin action in individuals with T2DM.[31] The reasons for this reduced incretin action are not fully understood.[29] Secondary to the development of T2DM, pancreatic resistance to GLP-1 develops, and GLP-1 secretion by L cells decreases.[29,32] Because the attenuation of GLP-1-related incretin action occurs early in the natural history of T2DM, GLP-1 replacement therapy seems a logical choice to restore normal insulin response in patients.[29] Administration of pharmacological doses of GLP-1 has been shown to be an effective way to restore the insulin response to glucose in patients with T2DM. GLP-1 infusion not only increases insulin secretion but also normalizes its secretory pattern, restoring the first phase of the insulin response, which is characterized by a sudden and rapid increase in insulin levels.[29,33] Nauck et al. and Choe et al. demonstrated that continuous intravenous infusion of GLP-1 in patients with poorly controlled T2DM increased insulin secretion, resulting in better glycemic control, particularly of fasting glucose levels.[34,35] The antidiabetic efficacy of GLP-1 administered by continuous subcutaneous infusion was confirmed by Zander, who demonstrated normalization of daily glycemia and a reduction in glycated hemoglobin (HbA1c) levels within 6 weeks of treatment.[36,37] However, continuous administration of native GLP-1 via the intravenous or subcutaneous route is not convenient for long-term use in patients due to its very short half-life of approximately 2 minutes. Therefore, it has been important to develop GLP-1 agonists that are resistant to degradation by the dipeptidyl peptidase-4 (DPP-4) enzyme.[37]

Meta-analyses of clinical trials have shown that the use of GLP-1RAs in patients with obesity and T2DM is not associated with an increased risk of breast cancer, acute pancreatitis, pancreatic cancer, or overall cancer incidence. Furthermore, evidence suggests that GLP-1RAs therapy does not increase the risk of new thyroid nodules in patients with T2DM. Preclinical studies have

also shown potential anti-cancer activity of GLP-1RAs, including by inhibiting the growth of prostate and pancreatic cancer cells. Similarly, growth-inhibiting effects on breast and cervical cancer cells have been observed, suggesting potential future applications of GLP-1RAs in cancer therapy. In particular, liraglutide has shown antiproliferative and proapoptotic properties against pancreatic cancer cells resistant to gemcitabine and other cytotoxic drugs. Despite these promising results, some concerns have been raised about the long-term safety of GLP-1RAs. A population-based matched-case study suggested that exenatide use may increase the risk of hospitalization for acute pancreatitis. Additionally, some data suggest that incretin drugs may be associated with an approximately 1.7-fold increased risk of developing pancreatic cancer. However, due to limited statistical power, short follow-up, and uncertainties in assessing disease severity, a direct causal relationship cannot be unequivocally confirmed. In contrast, systematic reviews of studies assessing mortality and the effects of GLP-1RAs on cardiovascular and renal function in patients with T2DM have not shown an increased incidence of severe hypoglycemia, pancreatitis, or pancreatic cancer. There is currently no clear clinical evidence indicating a carcinogenic effect of GLP-1RAs. On the contrary, a growing body of research suggests that they may have anticancer effects on various types of cancer, including ovarian, breast, prostate, and pancreatic.[38,39,40]

Short-acting and long-acting GLP-1 analogs

The first GLP-1 receptor agonist approved for the treatment of T2DM was exenatide, a synthetic exendin-4 peptide isolated from the venom of the Gila monster (Heloderma suspectum).[34] Exenatide is a peptide resistant to DPP-4 and is not inactivated by it. This drug has an affinity for the GLP-1 receptor similar to native GLP-1 and stimulates pancreatic β-cells in a glucagon-like manner. After subcutaneous injection, exenatide has a half-life of about 4 hours, reaching peak concentration between 2 and 3 hours, with a total duration of action up to 5-7 hours. Two-times and three-times daily regimens have been tested. The regimen of exenatide was approved for subcutaneous injection twice daily, before breakfast and dinner.[34] The long-acting-release LAR preparation of exenatide molecule enables weekly administration while maintaining the desired therapeutic effect.[34,41] Although exenatide shares 53% sequence homology with GLP-1, it induces an immune response leading to the formation of antibodies formation, which, however, does not significantly affect its therapeutic efficacy.[34,42]

Lixisenatide is a structural analog of exendin-4, modified by adding six lysine residues at the C-terminal end, while removing a proline residue. This modification makes it resistant to DPP-4 degradation.[43,44] It is administered via subcutaneous injection once daily.[45]

Liraglutide, developed as another GLP-1 receptor agonist, shares 97% sequence homology with native GLP-1. By attaching a fatty acid chain to its structure via a linker molecule, it provides a long-acting drug. Furthermore, it promotes albumin binding in extracellular fluid and plasma.[34,46] Approximately 2% of liraglutide is unbound to albumin. However, the majority of liraglutide is a reservoir from which it can be released into specific and targeted tissues and cells with GLP-1 receptors. The estimated half-life is 13 hours.[34,47] It is approved for once-daily subcutaneous administration.[34] Dulaglutide and albiglutide represent a novel approach in which larger proteins, such as immunoglobulin fragments in the case of dulaglutide[34,48] and albumin in the case of albiglutide[34,49], are linked to two modified (DPP-4-resistant) GLP-1 molecules. Due to their slow systemic elimination, these drugs have a half-life of approximately one week, allowing for once-weekly administration.[34,50,51] The relatively rapid absorption of these drugs results in an earlier response and, consequently, a more rapid onset of clinically noticeable effects.[34,52]

Semaglutide has a molecular structure similar to liraglutide. It has been modified by replacing alanine at position 2 with α-aminoisobutyric acid, which makes it completely resistant to DPP-4 degradation. Due to the stronger binding of the fatty chain, semaglutide has an even longer elimination time, which allows it to be administered once a week.[34,53]

In summary, we distinguish short-acting and long-acting GLP-1RAs. Short-acting GLP-1RAs include exenatide and lixisenatide, administered once or twice daily via subcutaneous injection. Long-acting GLP-1RAs include liraglutide administered as subcutaneous injections once daily, and exenatide, dulaglutide, albiglutide, and semaglutide administered once weekly.[34,45]

An oral form of semaglutide has also been developed, containing the same active molecule as the injectable form, combined with an absorption enhancer, sodium N-[8-(2-hydroxybenzoyl)amino]caprylate (SNAC). SNAC locally increases pH, facilitating semaglutide absorption. However, oral semaglutide has low bioavailability. To achieve similar efficacy as subcutaneous injection (1 mg/week), significantly higher doses (up to 14 mg/day) are required.[34,54] It is recommended to take oral semaglutide once daily in the morning on an empty stomach with a small amount of water, at least 30 minutes before breakfast.[8,54]

GLP-1 analogs in T2DM treatment

The role of GLP-1RAs is to stimulate insulin secretion in a blood glucose-dependent manner – the higher the blood glucose concentration, the greater the insulin secretion.[29] Furthermore, by increasing insulin biosynthesis at the

translational level, they help maintain insulin reserves in β-cells and their secretory capacity.[29,30] Due to their direct effect on pancreatic α-cells, which become more sensitive to glucose, they secrete less glucagon, thus reducing endogenous glucose production. Glucagon stimulates hepatic glucose production, so reducing its secretion leads to reduced hepatic glucose production, which reduces insulin requirements and improves glycemic control.[29,55] Furthermore, GLP-1RAs can influence peripheral glucose metabolism via GLP-1 receptors located in the central nervous system.[29,55] GLP-1RAs reduce gastric acid secretion and slow gastric emptying, both in response to pentagastrin and after a meal. These effects are mediated by the vagus nerve and GLP-1 receptors located in the central nervous system or on afferent vagal fibers, which transmit sensory signals to the brainstem.[29,30] Slowing gastric emptying reduces the rate of glucose absorption, resulting in lower postprandial blood glucose levels. Short-acting GLP-1RAs, administered around meals, have a stronger effect on gastric motility and are more effective in reducing postprandial glycemia than long-acting forms.[29,57]

GLP-1 analogs significantly reduce the level of HbA1c. Studies show that GLP-1RAs used in monotherapy lower HbA1c level by 0.5–1.0% more than placebo. In combination with metformin, the reduction of HbA1c was 0.5–1.1%, with sulfonylureas 0.6–1.4%, and with thiazolidinediones 0.8–1.1%.[29] Direct comparisons have shown that the reduction of HbA1c achieved with GLP-1RAs is greater than in the case of DPP-4 inhibitors, due to their higher receptor binding affinity.[29,58] The reduction of HbA1c levels with the use of GLP-1RAs is comparable to that achieved with the use of insulin (including basal insulin analogs, mixed formulations, and NPH insulin), but without the risk of hypoglycemia or weight gain that are associated with insulin therapy.[29,59,60] In clinical practice, the degree of HbA1c reduction depends on the patient's initial hemoglobin level.[5]

GLP-1 analogs in obesity treatment

GLP-1 plays an important role in multiple areas of physiology. The most important in terms of obesity treatment is reducing appetite and food intake. This effect promotes long-term weight loss. Studies indicate that GLP-1 secretion from the gastrointestinal tract is impaired in obese individuals, suggesting its involvement in the pathophysiology of obesity.[61,62]

GLP-1RAs mechanism of action includes both central and peripheral processes that together promote satiety, reduce hunger, and consequently lead to decreased food intake.[61] Central effects involve the activation of GLP-1 receptors present in brain regions involved in the regulation of food intake and energy balance. Indirect mechanisms include the activation of vagal afferents originating from the intestines and portal circulation.[61,63] Slowed gastric emptying and transient nausea induced by GLP-1 analogs may contribute to weight loss, but their role is thought to be minor and short-lived.[61,64]

Weight loss was consistently observed in all pivotal clinical trials of GLP-1RAs. Studies have shown that albiglutide[45,59] and dulaglutide[32] were less effective in reducing body weight compared with liraglutide and semaglutide. The larger molecular structures of albiglutide and dulaglutide limit the ability of GLP-1RAs to penetrate the brain and affect the satiety center.[65,66,67] Food and Drug Administration -approved injectable GLP-1 analogues for the treatment of obesity include liraglutide and semaglutide.[65,68]

GLP-1 analogs and cardiovascular diseases

Cardiovascular diseases remain the most common cause of death in Poland. Cardiovascular risk is defined as the probability of developing cardiovascular disease or dying from it within a specified time period. Numerous studies confirm that people with T2DM are exposed to higher cardiovascular risk compared to the general population. The level of this risk is influenced by many factors, which can be divided into classic (e.g. hypertension, hypercholesterolemia, smoking) and non-classic (e.g. inflammation, oxidative stress, metabolic disorders). T2DM is often accompanied by hyperglycemia and other metabolic disorders, which significantly increase the risk of developing both cardiovascular diseases and microvascular complications. Randomized clinical trials have shown that maintaining proper glycemic control reduces the risk of microvascular complications. However, its effect on preventing macrovascular complications, such as atherosclerosis, is moderate. Despite this, it has been shown that more effective treatment of hyperglycemia can lead to a reduction in the number of serious cardiovascular events. GLP-1 analogues, in addition to their hypoglycemic effect, also have a beneficial effect on cardiovascular risk factors. It is suspected that drugs from this group affect them indirectly, mainly by reducing body weight. Therapy with GLP-1 analogues often also leads to an improvement in the lipid profile – a reduction in the level of total cholesterol, low-density lipoprotein (LDL) fraction and triglycerides – as well as a decrease in systolic blood pressure. Additionally, preclinical and clinical studies suggest that stimulation of GLP-1 receptors affects the functioning of endothelial cells, the immune system and platelets, which are involved in the process of atherogenesis. It has also been shown that drugs such as exenatide, liraglutide or semaglutide reduce oxidative stress and the expression of adhesion molecules in blood vessels, which may slow down the development

of atherosclerosis. In recent years, many studies have been conducted to assess the effect of GLP-1 analogues on the risk of cardiovascular events. For example, the use of liraglutide at a dose of 1.8 mg for 3.5 to 5 years in patients with T2DM led to a significant reduction in the risk of cardiovascular death, heart attack and non-fatal stroke. The effect of individual GLP-1 analogues on the cardiovascular system varies. Studies have shown that lixisenatide and exenatide do not differ in terms of efficacy from placebo in the context of cardiovascular risk. On the other hand, liraglutide, albiglutide and dulaglutide showed a beneficial effect in reducing this risk. Although most studies concerned patients with T2DM, the effect of GLP-1 analogue therapy in people without diagnosed diabetes is increasingly being analyzed. Preliminary results suggest that these drugs may improve glucose metabolism, reduce the amount of perivascular and epicardial adipose tissue, which is important in preventing atherosclerosis. In addition, they are indicated to have a potential role in reducing chronic inflammation and oxidative stress – two important factors increasing cardiovascular risk – which may be indirectly related to weight loss. [69,70]

Studies show that GLP-1 analogues can reduce the risk of cardiovascular events in overweight or obese individuals, regardless of diabetes. They also have potential protective effects on the circulatory system, helping to reduce the risk of cardiovascular complications. Table 1 shows cardiovascular and renal effects in obese individuals caused by GLP-1 drug supplementation.

Table 1. Cardiovascular and renal effects in obese individuals caused by GLP-1 drug supplementation

With diabetes	No diabetes
weight loss	weight loss
lowering systolic blood pressure	lowering systolic blood pressure
lowering the level of total cholesterol, LDL fraction and triglycerides	improving kidney function, reducing the risk of developing or worsening kidney disease
reducing oxidative stress and the expression of adhesion molecules in blood vessels, which may slow down the development of atherosclerosis	reducing oxidative stress and the expression of adhesion molecules in blood vessels, which may slow down the development of atherosclerosis
reducing the incidence of cardiovascular death, heart attack and stroke	reducing the incidence of cardiovascular death, heart attack and stroke

Other positive effects of GLP-1 analogs

GLP-1 analogs may also benefit patients with conditions other than diabetes and obesity, as indicated by subsequent studies.[71] It has been demonstrated that GLP-1 analogs have a protective and therapeutic effects in the central nervous system through the reduction of neuroinflammation, enhancement of signal transduction in cells, and stimulation of neuronal growth and differentiation.[71,72] Particularly beneficial effects have been observed in case of Alzheimer's disease, Parkinson's disease, depression, and in post-stroke conditions. In Alzheimer's disease, GLP-1 analogs improve glucose metabolism in brain, improving glucose transport across the blood-brain barrier.[71,73] They also have a protective effect on dopaminergic neurons in the substantia nigra, which may positively influence motor activity in Parkinson's disease.[71,74] GLP-1RAs have also demonstrated a significant impact on reducing stroke incidence and enhancing neuroprotection in both preclinical and clinical studies.[71,75] Furthermore, GLP-1 analogs may exhibit antidepressant effects by improving cognitive function, promoting neuroprotection, and modulating neurotransmitter release. They may be effective as adjunctive medications not only in neurodegenerative diseases and substance abuse disorders, but also in mood disorders such as depression.[71,76] In addition, GLP-1 analogs appear to be a promising therapeutic option for the treatment of chronic pain, offering analgesic effects without severe adverse effects or addiction risks.[71,77]

These medications show cardioprotective properties by exerting anti-inflammatory effects and reducing myocardial damage induced by ischemia. They also modify the processes of lipid synthesis and secretion, while improving endothelial function. Studies suggest that GLP-1 analogs may be effective in the treatment of hypertension and atherosclerosis.[71,78]

In individuals reporting typical or atypical chest pain, increased circulating GLP-1 levels were correlated with reduced atherosclerotic plaque burden as assessed by coronary computed tomography. In animal models of atherosclerosis, treatment with GLP-1RAs, particularly semaglutide, has been shown to reduce fatty changes in the aortic root, ascending aorta, and iliac bifurcation. On the other hand, one study of type 2 diabetic patients receiving liraglutide reported increased plaque volume. Despite the growing body of evidence, it remains unclear whether GLP-1RAs therapy actually contributes to plaque regression or stabilization of those more likely to rupture.[79]

Atherosclerosis is a chronic inflammatory-degenerative process in which fibrolipid changes occur in the arterial wall. It is the leading cause of death worldwide. Particularly dangerous are cases in which thrombosis overlaps – this leads to the most serious complications, such as myocardial infarction or stroke.

One of the causes of atherosclerosis is elevated plasma cholesterol levels, especially in the form of low-density lipoproteins. These are responsible for transporting cholesterol through the bloodstream. Emerging atherosclerotic plaques undergo fibrosis over time, forming fibrous caps and calcium deposits. Numerous studies have shown that semaglutide and liraglutide can positively impact lipid profiles and lower blood pressure, reducing the risk of developing atherosclerosis and car-

diovascular disease. Furthermore, animal models have shown that drugs from this class inhibit the progression of atherosclerosis. The mechanisms of action of GLP-1RAs in atherosclerosis include: reduced inflammation, decreased intima-media thickness, improved lipid profile, and normalized endothelial function. These drugs have also been shown to lower systemic inflammatory markers, which is important because chronic inflammation plays a key role in the pathogenesis of cardiovascular disease. Furthermore, there is evidence that GLP-1RAs may prevent the formation of macrophage foam cells, thereby delaying the progression of atherosclerotic lesions. Although no GLP-1 agonists have been officially approved for the treatment of atherosclerosis, the results of previous studies suggest that these drugs may represent a promising therapeutic option for the prevention and treatment of this disease.

Research results indicate that GLP-1 analogs may also play a beneficial role in the treatment of polycystic ovary syndrome, contributing not only to weight reduction but also beneficially affecting androgen levels.[71,80]

Moreover, these medications seem to be effective in the treatment of non-alcoholic fatty liver disease. GLP-1RAs have been shown to directly influence adipogenesis, lipotoxicity, fatty acid oxidation, and the release of cytokines associated with liver inflammation and fibrosis. They also reduce visceral obesity and hepatic fat deposition.[71,81]

Adverse effects of GLP-1 analogs

When presenting the characteristics of GLP-1 analogues, it is also important to mention their potential side effects. The most common adverse effects include nausea and vomiting. Their incidence is lower with long-acting preparations. These symptoms may be due to delayed gastric emptying or the analogues' effects on the central nervous system. Nausea and vomiting are particularly common at the beginning of therapy, but their severity usually decreases within the first 4–8 weeks of treatment, as observed in studies with exenatide and liraglutide.[29,82] Other adverse effects of GLP-1RAs inhibitors include diarrhea and constipation. Diarrhea occurs in approximately 10–20% of patients, and constipation in approximately 4–10% of those treated with these drugs.[29] Injection-site reactions, such as itching or soft tissue nodules, may also occur in patients taking GLP-1 analogues. These reactions are usually mild and transient. Injection site nodules are observed primarily with exenatide and are the result of an inflammatory reaction to the polymer.[29] Additionally, GLP-1RAs use may slightly increase heart rate.[29] It is worth noting that when GLP-1 analogs are used in monotherapy, the risk of hypoglycemia is low because the analogs stimulate insulin secretion and inhibit glucagon release in a glucose-dependent manner. The risk of hypoglycemia may be a concern when analogs are combined with insulin therapy.[29]

GLP-1RAs for weight loss were associated with an increased risk of pancreatitis, gastroparesis, and intestinal obstruction compared with bupropion/naltrexone therapy, but no increased risk of biliary tract disease. Although these adverse events are relatively rare, given the increasing use of GLP-1 agonists, they should be taken into account by patients considering the use of these drugs for obesity treatment.[83]

Patients taking GLP-1 analogues often experience side effects from the digestive system, such as nausea, vomiting, diarrhea or constipation. These symptoms may result from the drug's effect on the motility of the digestive tract and the mechanisms regulating the feeling of satiety.

In gastroenterology practice, you should be prepared for the following phenomena:

- Nausea, vomiting, diarrhea - these are the most common side effects, which may affect even over 50% of patients.
- Constipation - slowed intestinal peristalsis caused by the drug may lead to constipation, which can be particularly troublesome in patients with existing pelvic floor dysfunction.
- Bloating - may be a consequence of both constipation and a general slowing of intestinal transit.
- Abdominal discomfort - manifested by abdominal pain, a feeling of fullness or tension, may be related to the effect of the drug on the digestive tract.
- Intestinal obstruction – a rare but potentially serious complication that can occur in those with anatomical or functional predispositions.
- Pancreatitis – although rare, some studies suggest a possible association between the use of GLP-1 analogues and an increased risk of pancreatitis.
- Gastroparesis – slowed stomach emptying, known as gastroparesis, can also occur as a side effect of therapy.

Tirzepatide (Mounjaro) a new agent in T2DM and obesity treatment

Currently, drugs are also available that can perform dual functions. Tirzepatide is the first dual agonist of the GIP and GLP-1 receptors. Currently, tirzepatide is approved only for the treatment of type 2 diabetes.[84,85] It is a synthetic peptide composed of 39 amino acids and structurally similar to incretins. Its structure contains a fatty acid residue linked to hydrophilic linkers. Additionally, the peptide contains two non-encoded amino acid residues, which are responsible for its extended half-life and strong affinity for albumin. Similar to other drugs, tirzepatide has a mean half-life of approximately five days.[85] Tirzepatide acts through the aforementioned incretin effect. Studies indicate that

it lowers HbA1c levels more effectively than semaglutide and induces weight loss, depending on the dose administered. This effect is primarily mediated by GIP, although the combination of GIP and GLP-1 receptor agonism demonstrates synergistic effects.[86-89] The phase III SURPASS trials demonstrated that tirzepatide, both as monotherapy and as adjunctive therapy, is more effective in lowering blood glucose and insulin levels compared with GLP-1RAs. Furthermore, the risk of hypoglycemia and other adverse cardiovascular events is low with tirzepatide.[84] Currently, tirzepatide is also being evaluated for its use in the treatment of obesity in patients with T2DM. It is also anticipated that this drug could be used in the future to treat nonalcoholic steatohepatitis or obstructive sleep apnea.[90,91,92] Adverse events are rare, usually during dose escalation, and are generally mild to moderate in severity. Five SURPASS clinical trials confirmed the potent glucose-lowering and weight-reducing properties of tirzepatide, with an overall safety profile comparable to that of GLP-1RAs.[84,88] Figure 1 shows the effect of GLP-1 on selected internal organs.

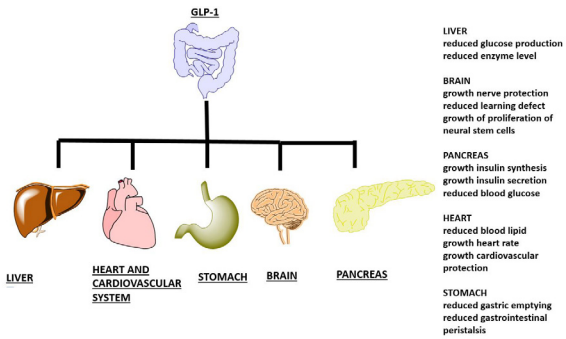

Fig. 1. Effects of GLP-1 on organs

Conclusion

Significant progress in the use of intestinal hormones in the treatment of T2DM and obesity has led to the development of effective therapies for both of these conditions, such as GLP-1 analogs. These drugs are now commonly used to treat T2DM, and recent studies have shown that they are also effective in weight loss. The growing understanding of biochemical processes, hormonal signaling, and the development of new technologies contribute to the continuation of research on new, more effective therapies that use mechanisms of action of the gut-brain axis. Despite these achievements, the need for new and more effective treatments is constantly growing, and requires innovative strategies and their potential combination with existing therapies.

Declarations

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Author contributions

Conceptualization, Ko.K.; Ka.K.; M.M.; J.F-R.; A.P.B.; K.D.; D.A.; R.W. and A.K-K.; Validation, Ko.K.; Ka.K.; M.M.; J.F-R.; A.P.B.; K.D.; D.A.; R.W. and A.K-K.; Formal Analysis, Ko.K.; Ka.K.; M.M.; J.F-R.; A.P.B.; K.D.; D.A.; R.W. and A.K-K.; Resources, Ko.K.; Ka.K.; M.M.; J.F-R.; A.P.B.; K.D.; D.A.; R.W. and A.K-K.; Writing – Original Draft Preparation, Ko.K.; Ka.K.; M.M.; J.F-R.; A.P.B.; K.D.; D.A.; R.W. and A.K-K.; Writing – Review & Editing, Ko.K.; Ka.K.; M.M.; J.F-R.; A.P.B.; K.D.; D.A.; R.W. and A.K-K.; Visualization, Ko.K.; Ka.K.; M.M.; J.F-R.; A.P.B.; K.D.; D.A.; R.W. and A.K-K.; Supervision, A.K.K.

Conflicts of interest

The author(s) declare no competing interests.

Data availability

All data generated or analyzed during this study are included in this published article.

Ethics approval

Not applicable.

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