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GLP-1 and GIP analogues in the treatment of obesity

Analogi GLP-1 i GIP w leczeniu otyłości

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Abstract

Obesity is a chronic disease and a significant public health problem. It is estimated that more than 650 million adults, 340 million adolescents, and 39 million children are obese. Obesity leads to organ complications including type 2 diabetes, hypertension and heart diseases. The management of obesity is based on nutritional therapy combined with lifestyle changes and increased physical activity. Pharmacotherapy is also crucial, and incretin analogues are a relatively new group of drugs. Glucose-independent insulinotropic peptide and glucagon-like peptide-1 are natural incretins. These short half-life hormones are degraded by the enzyme dipeptidyl peptidase-4. Glucose-independent insulinotropic peptide and glucagon-like peptide-1 receptor agonists increase blood glucose-dependent insulin secretion while inhibiting glucagon secretion and delaying gastric emptying, thus enabling the treatment of both type 2 diabetes and obesity. Glucagon-like peptide-1 also exhibits cardioprotective and neuroprotective effects. This study aimed to review the literature on the use of glucagon-like peptide-1 analogues and verify reports on the use of glucose-dependent insulinotropic polypeptide for weight reduction. An analysis of the available literature on the efficacy and safety of liraglutide, semaglutide and tirzepatide was conducted. The potential role of these drugs in weight reduction and possible adverse effects are discussed. Attention was also paid to the pharmacokinetics of the drugs and the mechanism of incretin action in the body.

Keywords: obesity, liraglutide, semaglutide, tirzepatide, GLP-1 analogues

Streszczenie

Otyłość to choroba przewlekła i istotny problem zdrowia publicznego. Szacuje się, że na otyłość choruje ponad 650 mln dorosłych, 340 mln nastolatków i 39 mln dzieci, a sama jednostka chorobowa prowadzi do powikłań narządowych, w tym cukrzycy typu 2, nadciśnienia tętniczego czy chorób serca. Podstawą leczenia otyłości jest terapia żywieniowa połączona ze zmianą stylu życia i zwiększeniem aktywności fizycznej. Kluczowa jest również farmakoterapia, w której analogi inkretyn stanowią stosunkową nową grupę leków. Naturalne inkretyny to glukozozależny peptyd insulinotropowy i glukagonopodobny peptyd-1. Są to hormony o krótkim okresie półtrwania, które ulegają rozkładowi przy udziale enzymu dipeptydylopeptydazy 4. Agoniści receptorów tych hormonów zwiększają zależne od stężenia glukozy we krwi wydzielanie insuliny, hamując jednocześnie wydzielanie glukagonu, i opóźniają opróżnianie żołądka, umożliwiając tym samym leczenie zarówno cukrzycy typu 2, jak i otyłości. Glukagonopodobny peptyd-1 wykazuje również działanie kardio- i neuroprotekcyjne. Celem pracy był przegląd piśmiennictwa dotyczącego zastosowania analogów glukagonopodobnego peptydu-1 oraz weryfikacja doniesień na temat wykorzystania zależnego od glukozy polipeptydu insulinotropowego w redukcji masy ciała. Dokonano analizy dostępnej literatury na temat skuteczności i bezpieczeństwa zastosowania liraglutydu, semaglutydu oraz tirzepatydu. Omówiono potencjalną rolę tych leków w redukcji masy ciała i możliwe działania niepożądane. Zwrócono również uwagę na farmakokinetykę leków i mechanizm działania inkretyn w organizmie.

Słowa kluczowe: otyłość, liraglutyd, semaglutyd, tirzepatyd, analogi GLP-1

INTRODUCTION

Obesity is a chronic disease and an important public health problem requiring effective prevention and treatment. According to a World Health Organization (WHO), more than 650 million adults, 340 million adolescents, and 39 million children are obese[1]. The significant increase in the prevalence of obesity and the growing social and economic costs of this phenomenon are prompting the search for solutions to help prevent and treat this disorder[2]. Diet combined with increased physical activity is the mainstay of obesity treatment. More severe cases require pharmacological or surgical approaches[2]. Glucagon-like peptide-1 (GLP-1) receptor agonists, also known as incretin mimetics, are agents that lower blood glucose and simultaneously cause weight loss. Glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1) are natural incretins. These hormones directly activate GLP-1 and GIP receptors, resulting in improved glucose tolerance, as well as weight loss[3]. GLP-1 analogues have been developed primarily for the treatment of type 2 diabetes mellitus (T2DM). GLP-1 and GIP are hormones secreted in the small bowel in response to food stimuli. They have a relatively short half-life (18 minutes). The presence of an alanine residue at position 2 of the polypeptide chain makes them substrates for dipeptidyl peptidase-4 (DPP-4), which is responsible for their breakdown[4]. GIP receptors are expressed primarily in pancreatic islet β-cells and are found in smaller numbers in adipose tissue and the central nervous system (CNS). In turn, GLP-1 receptors are expressed in pancreatic islet α and β cells, in the central and peripheral nervous system, heart, lungs, gastrointestinal tract and kidneys. Activation of both receptor types increases cellular levels of cAMP (cyclic adenosine monophosphate) and calcium ions, resulting in the release of insulin. GLP-1, secreted into the portal vein, activates the portal vein glucose sensor, which transmits a signal to the CNS and enhances insulin secretion. Additionally, GLP-1 and GIP bind to specific receptors on the surface of pancreatic islet β-cells, stimulating glucose-dependent (glucose >5 mmol/L) insulin secretion and inhibiting the release of glucagon[4]. They also slow down intestinal peristalsis, reducing digestion. Furthermore, GLP-1 acts on the CNS satiety centre, leading to decreased appetite. Also, a slight drop in blood pressure was observed as a result of inhibition of renal sodium reabsorption[3].

GIP is composed of 42 amino acids (H-Tyr-Ala-Glu-Gly-Thr-Phe-Ile-Ser-Asp-Tyr-Ser-Ile-Ala-Met-Asp-Lys-Ile-His-Gln-Gln-Asp-Phe-Val-Asn-Trp-Leu-Leu-Ala-Gln-Lys-Gly-Lys-Lys-Asn-Asp-Trp-Lys-His-Asn-Ile-Thr-Gln-NH_2) with a molecular weight of 4,984 g/mol and a general molecular formula $C_{226}H_{338}N_{60}O_{66}S$, whereas GLP is a 36- or 37-amino acid peptide (H-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-NH_2) with a molecular weight of 3,298 g/mol and a general molecular formula $C_{149}H_{226}N_{40}O_{45}$.

This paper is a review of clinical data and literature on the role and importance of incretin therapy in weight reduction.

INCRETIN PHYSIOLOGY

Incretins are hormones produced in the small intestine in response to oral food, primarily carbohydrates, due to their direct stimulation of enteroendocrine cells[5]. These include GIP and GLP-1, which increases insulin secretion following food-induced secretion[6]. GLP-1 is a peptide hormone synthesised in endocrine L-cells of the small and large intestinal mucosa, which is also expressed in the CNS. It is the biologically active form of GLP-1(1–37) (proglucan degradation product) found in two equivalent forms, i.e. GLP-1(7–37) and GLP(7–36)amide. GLP(7–36)amide predominates in human plasma. GIP and GLP-1 plasma levels increase after meal ingestion, peaking approximately one hour later, with GIP levels usually higher than those of GLP-1[7]. GIP is produced by K cells of the small intestine, located in the duodenum and proximal jejunum[8]. It is also released in the CNS, where it regulates cellular regeneration processes[4].

Within minutes after their release, the active forms of GIP(1–42), GLP-1(7–37) and GLP(7–36)amide are inactivated by DPP-4 to form GIP(3–42), GLP-1(9–37) and GLP-1 (9–36)amide, respectively. It is noteworthy that GLP-1 degrades much faster than GIP. For this reason, the level of the active form of this incretin is lower than that of the insulinotropic polypeptide. In contrast, both hormones are present as a mixture of active and inactive forms during physiological metabolism. GIP and GLP-1 are rapidly eliminated via the kidneys[4].

THE MECHANISMS OF ACTION OF GLP-1 AND GIP

An integrated network of neuronal and endocrine signals coordinates postprandial glucose and lipid metabolism by regulating gastric transit, stimulating insulin secretion and activating satiety pathways. Once secreted in the bowels, GLP-1 and GIP activate their G-protein-coupled receptors on the surface of pancreatic β-cells. Factors that accompany GLP-1 and GIP receptor activation include an increase in intracellular Ca^{2+} ions, inhibition of voltage-gated potassium (*Kv*) pumps (in the case of GLP-1), release of arachidonic acid (in the case of GIP) and activation of immediate early gene expression through effects on protein kinase C and phosphoinositide 3-kinase (PI3K)[4]. Stimulation of incretin receptors increases intracellular cAMP in pancreatic β-cells, and activates kinase A-mediated metabolic pathways[4]. This initiates the so-called incretin effect, i.e. stimulation of glucose-dependent insulin secretion and regulation of glucose and lipid levels[9]. Furthermore, GLP-1 inhibits glucagon secretion by stimulating GLP-1 receptors located on the surface of pancreatic islet α cells or by triggering somatostatin release, which also contributes

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to lowering blood glucose. Glucose absorbed by the intestinal epithelium is taken up by peripheral tissues[4]. GLP-1 infusion has been shown to increase satiety, reduce hunger and potential food intake, and even reduce *ad libitum* meal energy intake[10].

In the pancreas, GIP and GLP-1 stimulate β-cell proliferation and inhibit apoptosis, thereby increasing the mass of these cells[11]. It is worth noting that GLP-1 slows apoptosis by blocking caspase-3 expression and nuclear fragmentation of pancreatic β-cells. In turn, GIP increases pancreatic cell vitality through p38 MAPK (p38 mitogen-activated protein kinases) pathway-dependent inhibition of caspase-3 secretion[4]. GIP was found to increase postprandial glucagon response, which is inhibited by GLP-1[11]. GIP also promotes energy storage by acting directly on adipose tissue, and enhances bone formation by stimulating osteoblast proliferation and inhibiting apoptosis. Intravenous infusion of GIP has been shown to rapidly reduce plasma CTX (collagen type I crosslinked C-telopeptide) responsible for bone resorption[8,12].

Intestinal hormones, including glucagon-like peptide 1 and insulinotropic polypeptide, reach the brain (afferent pathway) and produce central signals that transmit impulses to peripheral organs via the efferent pathway, producing an effect. GLP-1 has anorexigenic and hypoglycaemic effects[13]. For this reason, excessive incretin release after bariatric surgery contributes to favourable outcomes: weight loss and blood glucose control, which is associated with improved metabolic function and receptor sensitivity to intestinal peptides[5,7,14].

GLP-1 AND GIP ANALOGUES IN THE TREATMENT OF OBESITY

Glucagon-like peptide-1 receptor agonists are a class of agents that exhibit incretin effects. They facilitate weight loss by promoting satiety and delaying gastric emptying, as well as are used in the treatment of T2DM[15,16]. GLP-1 also has cardio- and neuroprotective effects, reduces inflammation and apoptosis, as well as has been shown to influence learning and memory processes[17]. GIP stimulates insulin secretion and increases the feeling of gastric fullness[18]. Although GIP is less organ-specific than GLP-1, it can beneficially regulate lipid storage in adipose tissue by increasing lipogenesis and regulating lipoprotein lipase, showing direct effects in the CNS[3,19].

It should be taken into account during GLP-1 therapy that persistently high GLP-1 levels lead to significant glucose drop and weight loss, but may also induce gastrointestinal symptoms, such as nausea or vomiting[9].

Liraglutide

Liraglutide is a GLP-1 analogue showing 97% structural homology to the parent human GLP-1[20]. It is partially resistant to DPP-4, contains a structural modification at Lys34, and an additional glutamine and palmitic acid residue at Lys26. It is characterised by a prolonged pharmacokinetic profile (half-life of 10–14 hours) due to the formation of a strong non-covalent complex with albumin (only 1–2% of the peptide is found in the bloodstream in free form). Such strong bonds are formed by the acyl substituent of liraglutide[4,21]. Liraglutide was the first GLP-1 analogue approved by the US Food and Drug Administration (FDA) for the treatment of obesity[22]. Its health benefits include weight reduction through appetite suppression by direct stimulation of anorexigenic pathways in the hypothalamic arcuate nucleus via the GLP-1 receptor. Fasting and postprandial glucose, as well as glycated haemoglobin are then reduced by up to 1.75%, which either inhibits weight gain or causes weight loss[21].

In a randomised trial, 251 adolescents aged 12 to <18 years (126 on placebo and 125 on liraglutide) with obesity and poor response to lifestyle changes were allocated into two groups: subcutaneous (SC) liraglutide (3.0 mg) or placebo once daily. At least 5% reduction in body mass index (BMI) was observed in 51/113 participants receiving liraglutide and in 20/105 participants in the placebo group. Serious adverse reactions occurred in very few patients in both groups. Most participants reported gastrointestinal symptoms[23].

Another randomised trial involving non-diabetic adults with a BMI of 32–43 kg/m^2 showed that combined strategies (physical activity, pharmacotherapy and diet) led to greater weight loss compared to placebo after one year. Weight loss was 4.1 kg in the physical activity group, 6.8 kg in the liraglutide group and 9.5 kg in the group using both strategies. The combined strategy (physical activity and liraglutide) produced the greatest expected changes in body weight and a 3.9% reduction in body fat vs. controls[24].

A study on the efficacy of liraglutide 3.0 mg in reducing body weight in patients on antipsychotics showed significant body weight reduction, with the mean body weight before vs. at 16 weeks of treatment estimated at 93.2 kg and 88.9 kg, respectively ($p < 0.05$)[25].

Mild and transient nausea, vomiting and diarrhoea are the most common adverse effects of liraglutide[21].

Semaglutide

Semaglutide is a liraglutide analogue with a long half-life elimination (165 hours)[26]. The structure of the peptide shows 94% homology to the endogenous hormone GLP-1. The high stability of semaglutide is due to the conversion of the DPP-4-specific N-terminal Ala2 residue to 2-aminoisobutyric acid. Furthermore, in the case of semaglutide, the liraglutide-specific palmitic acid is converted to dicarboxylic stearic acid. This structural modification gives rise to a more stable peptide/albumin complex, significantly increasing the drug's half-life[17]. It has been shown that semaglutide can be used orally with an analogous dose-response relationship to that following subcutaneous administration, and that administering the peptide once a week using this route is sufficient for effective sustained therapy[17].

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Semaglutide dose	STEP 1 (obesity) *N* = 1,961	STEP 2 (T2DM, overweight, obesity) *N* = 1,210	STEP 3 (obesity) *N* = 611	STEP 4 (obesity) *N* = 902	STEP 5 (obesity) *N* = 304
2.4 mg	−17.3%	−9.6%	−16.0%	−7.9%	−15.2%
1.0 mg	–	−7.0%	–	–	–
0 mg (placebo)	2.0%	−3.4%	−5.7%	6.9%	−2.6%

Tab. 1. Mean weight loss with semaglutide

Drug	Dose	Mode of administration	Regimen	Escalation	Mean weight loss
Semaglutide	2.4 mg	SC	Once weekly	16 weeks	−15.8%
Liraglutide	3.0 mg	SC	Everyday	4 weeks	−6.4%

Tab. 2. Mean weight loss by active substance used and the dose based on STEP 8[34]

Semaglutide treatment for over 40 weeks is associated with up to 7% body weight reduction and a 1.8% drop in glycated haemoglobin. Semaglutide also has cardioprotective effects, reducing the incidence of cardiovascular disease, myocardial infarction and stroke in T2DM patients[17]. Semaglutide is slowly metabolised via proteolysis of the peptide backbone and β-oxidation of the fatty acid side chain, with its degradation products eliminated in faeces and urine[27].

The Semaglutide Treatment Effect in People with obesity (STEP) clinical trial programme evaluated the effects of subcutaneous semaglutide 2.4 mg once a week on weight control in overweight or obese patients (Tab. 1). The mean age of study participants ranged from 46.2–55.3 years, the mean BMI was 35.7–38.5 kg/m^2. A 500-kcal/day deficit and ≥150 min/week of physical activity were introduced as an additional criterion for lifestyle change in STEP 1, 2, 4 and 5. In STEP 3, a low-calorie diet (1,000–1,200 kcal/day) was followed for eight weeks, followed by a hypocaloric diet (1,200–1,800 kcal/day). Participants were also recommended 100 minutes of physical activity per week[28–32].

Adverse effects were more common with semaglutide 2.4 mg than with placebo. They mostly included nausea, diarrhoea, vomiting and constipation. Gastrointestinal adverse events were mostly mild to moderate, transient and occurred most frequently during dose escalation[33].

The randomised STEP 8 trial (Tab. 2) assessed the effects of once-weekly subcutaneous semaglutide vs. once-daily liraglutide in non-diabetic overweight or obese adults. The study enrolled 338 participants with a BMI ≥30 kg/m^2 or ≥27 kg/m^2 and at least one weight-related comorbidity[34]. Gastrointestinal disorders, which occurred in 84.1% of those on semaglutide and 82.7% of those taking liraglutide, were the most common adverse reactions. Most of these disorders were mild to moderate and were reported most frequently at dose escalation and shortly thereafter, with mild disorders persisting throughout the study period[34]. The STEP trial did not reveal any new safety signals. The rates of gallstones were consistent with the known metabolic association between rapid weight loss and increased risk of gallstones. There was no significant increase in the incidence of acute pancreatitis after semaglutide 2.4 mg[35].

A double randomised controlled trial in adolescents (aged 12 to <18 years) with obesity (BMI in the 95th percentile or higher) or overweight (BMI in the 85th percentile or higher) assessed subcutaneous semaglutide 2.4 mg once weekly vs. placebo supplemented with lifestyle changes. Semaglutide was found to be associated with a mean 16.1% decrease in BMI compared to 0.6% increase with placebo. Additionally, there was an improvement in cardiometabolic risk factors. The benefit was greater with greater weight loss, with significant superiority of semaglutide over placebo[36].

The SUSTAIN 10 trial (Tab. 3) compared the efficacy and safety of semaglutide and liraglutide. This was a phase IIIa trial involving 577 patients with T2DM. Both drugs showed similar safety profiles with the exception of frequent gastrointestinal disturbances, which led to more frequent discontinuation of semaglutide compared with liraglutide[37].

Semaglutide is contraindicated in pregnancy and a positive personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2, as well as a known hypersensitivity to the drug or any of its components[38].

Tirzepatide

Tirzepatide belongs to a new class of incretin drugs, i.e. the so-called dual agonists. It is a structural modification of GIP showing the same activity towards the GIP receptor and less activity towards the GLP-1 receptor compared to GLP-1[9]. Like liraglutide and semaglutide, it has a fatty acid residue (unsaturated C20 diacid) in its structure, which results in its strong binding to albumin, ensuring its long half-life. Like semaglutide, tirzepatide can be used weekly for effective long-term therapy[9]. It acts by increasing insulin secretion, reducing glucagon levels and decreasing fasting and postprandial glucose[39]. The drug was developed for the treatment of T2DM, obesity and non-alcoholic fatty liver disease (NAFLD)[40].

Tirzepatide is a new drug approved by the FDA in May 2022 for the treatment of T2DM[41]. It has a half-life of 5 days, which allows dosing once a week. The bioavailability of the drug is approximately 80%, with peak serum levels reached after 8–72 hours[42].

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Drug	Dose	Mode of administration	Regimen	Mean body weight (baseline 96.9 kg)
Semaglutide	1.0 mg	SC	Once weekly	−5.8 kg
Liraglutide	1.2 mg	SC	Everyday	−1.9 kg

Tab. 3. Mean weight loss by substance and dose based on SUSTAIN 10[37]

Tirzepatide used once weekly for obesity was assessed in a randomised, double-blind, placebo-controlled trial (Tab. 4). The study group included 2,539 non-diabetic adults with a BMI ≥30 kg/m^2 or ≥27 kg/m^2 and at least one obesity-related complication. The mean reduction in body weight after 72 weeks of therapy was −15.0%, −19.5% and −20.9% in the groups receiving tirzepatide 5 mg, 10 mg and 15 mg, respectively, compared to −3.1% in the placebo group[43,44].

A 40-week phase III trial randomly allocated 1,879 patients to groups receiving tirzepatide 5 mg, 10 mg or 15 mg or semaglutide 1 mg. The mean body weight of patients was 93.7 kg and the mean age was 56.6 years. All doses of tirzepatide were more effective in reducing body weight than semaglutide (Tab. 5). Additionally, target glycated haemoglobin of <5.7% (normal blood glucose) was achieved in 27–46% of patients receiving tirzepatide (dose-dependent) and in 19% of patients receiving semaglutide[45].

Mild to moderate gastrointestinal disorders were the most common adverse reactions reported with tirzepatide[43]. In the system and organ classification, lack of appetite was a frequently reported adverse effect during the therapy, although it is suggested that this is the potential cause of the intended weight loss[42].

CONCLUSIONS

Liraglutide, semaglutide and tirzepatide are effective incretin drugs used for the treatment of both type 2 diabetes and obesity. The ability of these compounds to form stable complexes with albumin allows for less frequent dosing, which may translate into pharmacotherapeutic efficacy. As new drug classes, GLP-1 and GIP agonists have been shown to be effective in reducing excessive body weight. Pharmacotherapy combined with appropriate diet and physical activity can increase the efficacy of obesity treatment. The analysis of clinical trials has shown that semaglutide has a higher efficacy in weight reduction compared to placebo and other antidiabetics such as liraglutide. Tirzepatide, a GIP analogue selectively modifying signalling pathways, which also translates into a weight reduction significantly higher than the one seen with semaglutide, is a new and at the same time promising drug with proven efficacy.

Tirzepatide dose	Route	Mean percentage change in body weight
5 mg	SC	−15.0%
10 mg	SC	−19.5%
15 mg	SC	−20.9%
Placebo	SC	−3.1%

Tab. 4. Mean percentage change in body weight following tirzepatide (dose-dependent) or placebo[43]

Substance and dose	Mean weight loss
Tirzepatide 5 mg	−7.6 kg
Tirzepatide 10 mg	−9.3 kg
Tirzepatide 15 mg	−11.2 kg
Semaglutide 1 mg	−5.7 kg

Tab. 5. Mean weight loss by substance and dose[45]

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

Author contribution

Original concept of study: RJB. Collection, recording and/or compilation of data: RJB. Analysis and interpretation of data: AJB, RJB, PB, MT, MO, BD. Writing of manuscript: AJB, RJB, PB, NK, MT, KC. Critical review of manuscript: USG. Final approval of manuscript: JL.

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