MAKOWSKA, Karolina, BILLEWICZ, Marta, MARCZYK, Aleksandra and LIS, Laura. Is physical activity still the key to treating obesity? - semaglutide, a new position among therapies. Quality in Sport. 2024;20:54194. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.20.54194
https://apcz.umk.pl/QS/article/view/54194

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 10.08.2024. Revised: 22.08.2024. Accepted: 24.08.2024. Published: 28.08.2024.

Is physical activity still the key to treating obesity? - semaglutide, a new position among therapies

Czy aktywność fizyczna to wciąż klucz w walce z otyłością? Semaglutyd - nowa pozycja wśród terapii

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Abstract

Introduction: Obesity is a condition characterized by excessive and abnormal accumulation of fat tissue. It disrupts energy homeostasis, leading to severe health problems. Physical activity is a significant part of reducing obesity. If sport activities are not enough, pharmacological management may be needed. One of pharmacological approaches to obesity treatment is a use of semaglutide. It is a glucagon-like peptide 1 receptor agonists (GLP-1RAs) approved for the treatment of type 2 diabetes. Semaglutide presents many pleiotropic effects and has an impact on several organ systems, such as cardiovascular, digestive, or nervous systems. Clinicals should remember about semaglutide's complex mechanisms of actions and different adverse effects.

Materials and methods: Analysis of the studies available on open access sources at PubMed, Google Scholar, National Library of Medicine and Coachrane. The research was conducted through word analysis keywords, such as: semaglutide, GLP-1RA, GLR-1 or obesity. Selection criteria for articles included consideration of their title, abstract, and publication date, with a focus on English-language publications.

State of knowledge: Semaglutide has recently gained popularity due to the treatment of obesity. Although many mechanisms of actions, impacts on organ systems and side effects have been discovered, there are still many gaps of knowledge that remain.

Conclusion: Future research is needed to understand the compound mechanism of semaglutide and discover its adverse effects in order to develop optimed approaches to management.

Keywords: semaglutide, GLP-1, GLP-1RA, obesity, sport, activities, diabetes mellitus

Abbreviations: BMI - Body Mass Index, OAO - Overweight and Obesity, GDP - Gross Domestic Product, PPP - Purchasing Power Parity, GLP-1 - Glucagon-Like Peptide 1, GLP-1RA - Glucagon-Like Peptide-1 Receptor Agonists, AE - Adverse Effects, DM - Diabetes Mellitus, T2DM - Type 2 Diabetes Mellitus, PPR - Proportional Reporting Ratio, AP - Acute Pancreatitis, PI3K - Phosphatidylinositol-3 Kinase, cAMP - Cyclic AMP, PKA - Protein Kinase A, EGF - Epidermal Growth Factor, CNS - Central Nervous System, MDA - Malonaldehyde, SOD - Superoxide Dismutase, HFpEF - Heart Failure with Preserved Ejection Fraction, HR - Heart Rate, HbA1c - Hemoglobin A1c, CKD - Chronic Kidney Disease, eGFR - Estimated Glomerular Filtration Rate, UACR - Urinary Albumin-to-Creatinine Ratio, CV - Cardiovascular, CVD - Cardiovascular Disease, KCCQ-CSS - Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score, 6MWD - 6-Minute Walk Distance, CRP - C-reactive Protein, NYHA - The New York Heart Association Classification, SCH - subclinical hypothyroidism, TSH - thyroid-stimulating hormone, T4 - Thyroxine, T3 – triiodothyronine,

Introduction

Obesity is a multifactorial condition characterized by excessive and abnormal accumulation of fat tissue. It is typically identified using the Body Mass Index (BMI) which is the ratio of body weight in kilograms to height in meters squared. The BMI scale classifies obesity into three categories: first-degree obesity (BMI 30-34.9), second-degree obesity (BMI 35-39.9), and third-degree or extreme obesity (BMI 40 and above) [1]. A staggering 90% of obesity cases are primary, stemming from an energy imbalance. This is often due to poor eating habits, psychological factors, lack of exercise, and sleep disorders. The remaining 10% is secondary

to other health issues, such as endocrine disorders (like Cushing's disease), neurological conditions (such as hypothalamic tumours) or medication side effects (including steroids, antidepressants, and insulin) [2] . Obesity disrupts energy homeostasis, leading to severe health problems like metabolic and cardiovascular diseases, and even cancer. One of the most alarming consequences is the heightened risk of premature death [3] . Global statistics from 2022 paint a concerning picture: 43% of adults over 18 were overweight and 16% were obese, meaning one in eight people are battling obesity. Among children and teenagers aged five to 19, over 390 million were overweight, with 160 million classified as obese [4] . These numbers highlight the worldwide obesity crisis and the outlook is grim. Projections suggest that by 2030, 51% of the global population will be obese, with 42% moderately obese and 11% extremely obese [5] . The financial burden is immense, covering not only the direct treatment of obesity but also related comorbidities, disabilities, reduced productivity, and premature deaths. Individuals also face substantial costs for medications and care. According to the Milken Institute, in 2016 obesity and related chronic diseases accounted for $480 billion in direct healthcare costs and $1.24 trillion in indirect job loss costs in the U.S. alone [6]. In 2019, the global economic impact of overweight and obesity (OAO) was 2.19% of the global gross domestic product (GDP) with the U.S. contributing $126 billion in purchasing power parity (PPP) values [7] . If current trends persist, obesity-related expenditures could reach 3.29% of global GDP, by 2060 [8]. This escalating issue poses a significant challenge to global public health, necessitating urgent preventive, and therapeutic actions.

Physical activity is one of the most effective methods for managing and treating excess body weight. It not only aids in weight loss but also enhances overall fitness and well-being. A key way to combat the obesity pandemic is to incorporate an adequate amount of physical activity into daily life [9].

If physical activity is not sufficient while reducing obesity, pharmacological treatment might be required. Glucagon-like peptide-1 receptor analogs (GLP-1 RAs) comprise drugs, such as liraglutide and semaglutide have been an innovative drug class in the management of both obesity and type 2 diabetes. Researchers showed that semaglutide modulated food preference, reduced food intake, and caused weight loss without decreasing energy expenses [9][10].

Semaglutide - mechanism of action

Glucagon-like peptide (GLP)-1 is an incretin hormone secreted from the L-cells in the small intestine, α-cells in the pancreas and central nervous system. It stimulates insulin and inhibits glucagon secretions from the pancreatic islets in a glucose-dependent fashion, causing a fall of blood glucose levels. Glucagon-like peptide 1 receptor agonists (GLP-1RAs) mimic natural hormone GLP-1 and are approved for the treatment of type 2 diabetes. Semaglutide is a fatty acid acylated analogue of human GLP-1 and has 94% structural homology with native human GLP-1 [10][11].

Semaglutide works in multiple different ways. One of them is binding to the G protein-coupled GLP-1 receptor (GLP-1R) and activating important intracellular metabolic pathways. The GLP-1 hormone can activate the adenylate cyclase (AC) metabolic pathway, causing elevated levels of intracellular cyclic AMP (cAMP), afterwards activating the protein kinase A (PKA). PKA contributes to exocytosis of insulin-containing vesicles from pancreatic β-cells and increases glucose-dependent insulin secretion [12] . Inversely, GLP-1 can inhibit glucagon release from pancreatic α-cells, decreasing liver production of glucose [13].

Moreover, GLP-1 can encourage the epidermal growth factor (EGF), activating the phosphatidylinositol-3 kinase (PI3K), which turns on transcription factors combined with β-cell growth while inhibiting those linked to β-cell apoptosis [14] GLP-1RA, such as semaglutide also influences the central nervous system (CNS) including blood pressure, satiety, neurogenesis, thermogenesis, and inflammation reduction. In addition, studies have shown that GLP-1RAs are present in macrophages, monocytes and lymphocytes which regulate immune cell signalling by suppressing proinflammatory cytokines, such as TNF-α, IL-1β, and IL-6. As obesity has been associated with chronic inflammation, GLP-1RAs can prevent or inhibit these inflammatory processes [15].

What is more, semaglutide is present in different brain regions, such as the thalamus, hypothalamus, cerebral cortex, cerebellum, and substantia nigra. Its interaction with GLP-1 receptors in the hypothalamus may alleviate sensations of hunger, reduce food cravings, and intensify the feelings of satiety [16][17].

Semaglutide has an impact on leptin and hormone YY which are crucial in promoting fullness. Leptine puts an end to the orexigenic (appetite-inducing) pathway and activates the anorexigenic (satiety-inducing) pathway.

In addition, this hormone effects lipid metabolism. The molecular mechanisms involve GLP-1R which stimulates the Wnt/β-catenin signalling pathway. Activation of the Wnt/β-catenin pathway has negative effects on adipogenesis by decreasing in sensitivity of the expression of genes related to de novo lipogenesis [17].

Effects of semaglutide on organ systems

A) Diabetes and Chronic Kidney Disease

Studies have demonstrated the significant benefits of oral semaglutide in managing type 2 diabetes, particularly in reducing HbA1c levels. The PIONEER trials highlighted semaglutide's superiority over other medications, such as empagliflozin and sitagliptin. In PIONEER 2, semaglutide 14 mg achieved a greater reduction in HbA1c than empagliflozin after 26 weeks, with the effect sustained for 52 weeks [18]. Similarly, PIONEER 3 showed semaglutide outperforming sitagliptin at both 26 and 78 weeks [18].

Furthermore, semaglutide's flexible dose-adjustment approach proved more effective than sitagliptin in maintaining lower HbA1c levels over a year. Comparisons with subcutaneous GLP-1RA dulaglutide in Japanese patients (PIONEER 10) revealed that semaglutide at 14 mg significantly reduced HbA1c more than dulaglutide at 26 and 52 weeks [19].

Placebo-controlled trials reinforced these findings. PIONEER 1 indicated that semaglutide monotherapy significantly improved HbA1c levels versus placebo. In patients with more advanced T2D on basal insulin (PIONEER 8), semaglutide addition resulted in substantial HbA1c reductions compared to placebo at both 26 and 52 weeks [20] . Additionally, PIONEER 5 demonstrated that semaglutide effectively lowered HbA1c in patients with moderate renal impairment, indicating its suitability for managing glycemic control in this population [21].

Chronic kidney disease (CKD) is a common complication for people with type 2 diabetes (T2D), affecting around 40% of them. The risk of developing CKD increases as diabetes persists, and having CKD can raise healthcare costs by nearly 50% compared to treating diabetes alone [22] . The exact mechanism by which GLP-1 receptor agonists (GLP-1RAs) benefit the kidneys is not fully understood yet. Studies from major clinical trials like SUSTAIN 6 (semaglutide), REWIND (dulaglutide), and LEADER (liraglutide) suggest that while improvements in blood sugar levels, weight loss, and reduced blood pressure are helpful,

they do not completely explain the kidney-protective effects of these medications [23]. Other factors, such as reduced inflammation, lower oxidative stress, or changes in blood flow, might also be at play. For example, semaglutide has been shown to reduce oxidative stress and inflammation in animal studies, particularly in the kidneys. However, more research is needed to understand these effects fully. The REMODEL trial (NCT04865770) is investigating this further using advanced techniques like MRI to measure kidney oxygenation and inflammation, biopsies for gene analysis, and blood and urine tests for kidney function markers [23].

Current evidence indicates that GLP-1RAs might help slow the progression of CKD in T2D patients who are at high risk for cardiovascular events. However, dedicated studies focusing specifically on kidney outcomes for these patients are still lacking. The FLOW trial is the first to address this, evaluating the impact of semaglutide on kidney health in individuals with T2D who are at high or very high risk for CKD progression. This trial, involving participants with an average eGFR of 47.0 ml/min/1.73 m^2, a median UACR (urinary albumin-to-creatinine ratio) of 568 mg/g, and a mean HbA1c of 7.8%, is expected to complete by late 2024 [23].

B) Effects on the cardiovascular system

In clinical studies, semaglutide exerted beneficial effects on plasma lipid levels, lowered systolic blood pressure, and reduced inflammation. Furthermore, in animal studies, semaglutide decreased the progression of atherosclerosis by preventing the development of atherosclerotic plaques and reducing plaque inflammation [24] [25]. Obesity, a significant cardiovascular risk factor, is contributing to a global increase in the number of patients requiring treatment for cardiovascular diseases [26]. Previous studies have demonstrated that semaglutide significantly reduces the incidence of cardiovascular events in patients with type 2 diabetes [27].

Given the lack of proven therapies to reduce cardiovascular risk in severe obesity, the SELECT study was designed to evaluate the effect of semaglutide compared to a placebo, alongside standard care, on reducing cardiovascular events in overweight or obese individuals with cardiovascular disease but without diabetes (including those with prior myocardial infarction, stroke, or peripheral artery disease) [28].

Analysis of the SELECT study supports the widespread use of semaglutide administered subcutaneously once weekly at a dose of 2.4 mg as an adjunct therapy for reducing

cardiovascular events in overweight or obese individuals without diabetes but with pre-existing cardiovascular disease. The study demonstrated that semaglutide 2.4 mg safely and effectively produced clinically significant weight loss, with a sustained average reduction in body mass of up to 16% across all subgroups based on sex, age, race, glycemia, renal function, and anthropometric categories. Moreover, this weight loss was maintained over a period of 4 years [29].

The STEP-HFpEF trial showed that semaglutide significantly improved symptoms, physical limitations, and exercise function while reducing body weight in patients with the obesity phenotype of HFpEF. This prespecified analysis confirmed these benefits across all obesity categories, demonstrating consistent improvements in the Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-CSS), 6-minute walk distance (6MWD), and C-reactive protein (CRP). The degree of weight loss was directly related to the magnitude of these improvements.

These findings highlight the importance of weight loss as an effective treatment strategy for HFpEF patients with obesity. Semaglutide's benefits were observed across a range of obesity classes, not just in those with severe obesity, indicating its broad applicability. The trial's results support semaglutide-mediated weight loss as a key approach to managing the obesity phenotype of HFpEF, improving overall health and quality of life [30] . An analysis of semaglutide's impact on various NYHA functional classes indicated significant benefits in lower classes, but specific recommendations for class IV patients were not established, highlighting the need for more targeted research in this area [31] A systematic review and meta-analysis indicated that the use of GLP-1 receptor agonists, including semaglutide, can result in an increase in heart rate. In various studies, an average increase of 1 to 6 beats per minute has been reported during clinical trials.

The recently completed ELIXA and LEADER trials suggest that an increase in heart rate (HR), regardless of its extent, does not seem to elevate cardiovascular risk in individuals with type 2 diabetes (T2DM) who have or are at high risk of cardiovascular disease. Nevertheless, a significant rise in HR may be linked to negative clinical outcomes in patients with both T2DM and advanced heart failure [32].

C) Influence on liver and neurodegenerative diseases

Obesity and its related metabolic issues play a key role in the onset of nonalcoholic steatohepatitis (NASH). In a groundbreaking phase 2 clinical trial, researchers explored the

impact of semaglutide on the progression of liver fibrosis to stages F2 and F3 over 72 weeks. Remarkably, the control group saw a significant reduction in NASH severity compared to the placebo group [33]. In another intriguing study on mice, scientists investigated semaglutide's effect on liver mass, proinflammatory cytokine secretion, and glucose levels. The findings were highly promising: after just 12 weeks, there was a notable decrease in blood glucose, lipid parameters (TG, TC, and LDL), and liver enzymes (ALT and AST). Additionally, oxidative stress was mitigated by lowering malonaldehyde (MDA) expression and boosting superoxide dismutase (SOD) levels [34] . Recent research highlights the role of insulin resistance in the development of neurodegenerative diseases [35]. GLP-1 has been shown to enhance insulin signalling in the brain, suggesting that agonists of this receptor play a neuroprotective role and positively influence cognitive functions. Reduced GLP-1 expression has been linked to neurodegenerative processes [36].

In studies using a mouse model of Parkinson's disease, semaglutide demonstrated a positive effect on motor disorders induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and decreased the amount of tyrosine hydroxylase (TH). This led to limited lipid peroxidation, inhibition of the apoptosis pathway, and increased expression of autophagy-related proteins, ultimately protecting dopaminergic neurons in the substantia nigra and striatum [37].

Adverse effects (AF)

The on-target of semaglutide is a reduction of glucose levels. Any other effects might be regarded as off-target, pleiotropic or if they are unwelcome, adverse effects. Adverse effects may depend on the dosage taken.

Maximum subcutaneous dosage plasma levels are higher (1 mg yields plasma levels of +- 45nM) compared with the maximal oral dosage (20mg yields plasma levels of +- 25nM). It is expected there are different side effects for subcutaneous and oral versions [38] . In this section, we will discuss both oral and subcutaneous adverse reactions, such as risk of hypoglycemia, gastrointestinal disorders, acute pancreatitis, risk of cancers, and depression.

Hypoglycemia

GLP-1RAs are believed to link to quite a low risk of hypoglycemia as they stimulate glucose-dependent insulin secretion and glucagon release does not happen under hypoglycemic

conditions. Marso et al. showed that severe hypoglycemic episodes or hypoglycemia as confirmed on plasma glucose testing were noticed in similar rated with semaglutide doses of 0.5 mg (191 [23.1%]) and 1.0 mg (178 [21.7%]) and placebo doses of 0.5 mg (177 [21.5%]) and 1.0 mg (173 [21.0%]) [39] . In SUSTAIN 4 (Semaglutide Unbated Sustainability in Treatment of Type 2 Diabetes) it was presented that severe or confirmed hypoglycemia occurred in 16 (4%) of 0.5 mg semaglutide-treated patients, 20 (6%) 1.0 mg semaglutide-treated patients and 38 (11%) of insulin glargine-treated patients. It was also reported that hypoglycaemia mostly occurs in patients taking sulfonylurea agents [40]. In SUSTAIN-3, the majority of hypoglycaemic advert effects were seen in patients concurrently taking sulfonylureas in both semaglutide 1.0 mg and exenatide ER 2.0 mg groups [41].

Marre et al. showed proportions of hospitalization and fatality resulting from hypoglycemia after various GLP-1RA. Semaglutide was found to have the hospitalization proportion 42.86% (14 reports), while liraglutide had the highest hospitalization proportion 62.50% (96 reports). The research revealed semaglutide may induce hyperglycemia in a very short onset time of 2 days, while liraglutide even after 2 years. The onset time of GLP-1RA-related hypoglycemia needs further investigation. Individualized monitoring should be performed after treatment as differences in the onset time among different GLP-1RA are vast [42].

The risk of hypoglycemia caused by semaglutide by itself is thought to be low but the risk is increased when combined with insulin therapy and/or sulfonylurea. A great number of experts suggest reducing the dose of sulfonylurea and low-, short-acting insulin prior to or during assessment of GLP-1RA to reduce the risk of hypoglycemic events [43].

Gastrointestinal adverse effects

Research showed both oral and subcutaneous semaglutide caused gastrointestinal AF. When compared with placebo, subcutaneous semaglutide for 30 weeks induced nausea in 11.4 - 20% patients (placebo 3.3-8%), vomiting in 4-11.5% (placebo 2-3%) and diarrhoea in 4.5 to 11.3% (placebo 1.5-6%) [43]. In a group of 3297 patients the majority of gastrointestinal AE were mild or moderate during the first 30 weeks. Treatment pause because of gastrointestinal AE was more often in the semaglutide group than placebo group. [39] Shu et al. reported that gastrointestinal AE of semaglutide were more likely to occur in middle-aged patients (18-65 years, 56.73%) than the elderly patients (>65 years, 43.12%). In FAERS database the most common gastrointestinal AE were nausea (n = 2,369), vomiting (n = 1,338), diarrhoea (n =

1,195), constipation (n = 663). There was also abdominal pain, pancreatitis, dyspepsia and more [44].

Acute pancreatitis (AP)

Semaglutide and other GLP-1RAs might be linked to the presence of acute pancreatitis and pancreatic cancer but there are still conflicting outcomes. Patients diagnosed with diabetes mellitus (DM) have a 74% increased risk of acute pancreatitis [45] . Patients with diabetes who are prescribed GLP-1RA especially present more risk factors of pancreatitis, such as obesity, longer diabetes duration and co-medication.

In PIONEER 6 (Peptide Innovation for Early Diabetes Treatment trial) acute pancreatitis occurred in one semaglutide-treated patient and in three placebo-treated patients [41] . In SUSTAIN 6 in nine semaglutide-treated and 12 placebo-treated patients [39] . Meanwhile, a case presentation by Patel et al. showed a 61-years-old female with a history of type 2 DM. She started weekly semaglutide 0.5 mg two months prior and did not present typical factors of AF, such as abdominal trauma, steroid use or ethanol use. Laboratory workup was negative for hypertriglyceridemia, hypercalcemia, leukocytosis and there were no imaging findings. Semaglutide may be the most likely cause of AP [35,37].

Tumours

A study from 2004 to 2021ca based on FAERS (FDA Adverse Event Reporting System) showed a total of 8718 GLP-1RA associated tumours. Important signals were discovered between GLP-1RA and tumours, such as thyroid cancer: medullary (proportional reporting ratio -PRR 27.43) and papillary (PRR 8.68), pancreatic neoplasm malignant (PRR 9.86). Adding dipeptidyl-peptidase IV inhibitors (DPP4i) to GLP-1RA may cause tumour-related adverse effects. [46] Both oral and subcutaneous semaglutide have received an official box warning for thyroid C-cell tumours in the US [43].

Thyroid

Semaglutide has been linked to potential effects on thyroid function, though evidence is still emerging. A documented case suggests that semaglutide may contribute to subclinical hypothyroidism (SCH) by delaying gastric emptying, which could interfere with the

absorption of levothyroxine and lead to increased thyroid-stimulating hormone (TSH) levels. While larger studies have not shown a significant impact of semaglutide on overall thyroid disorders, it is advisable for patients taking both semaglutide and levothyroxine to undergo regular thyroid function testing to ensure early detection of any potential dysfunctions [47]. This is particularly important given the vital roles of thyroid hormones in the body. Thyroxine (T4) is the main hormone produced by the thyroid gland, with an average daily secretion of around 80 μg. In contrast, triiodothyronine (T3) is released in much smaller amounts, approximately 4-6 μg per day, but it is about five times more potent than T4. Maintaining proper levels of these hormones is crucial for regulating metabolism and overall health [48].

Other adverse effects

With GLP-1RA treatment there is an increased risk of cholelithiasis, increased heart rate, acute kidney injury (AKI), diabetic retinopathy or depression [43][49].

Clinicals should be aware of potential adverse effects of GLP-1RA therapy. No major concerns have arisen to date, as mostly it generates mild, transient gastrointestinal symptoms but tumours especially thyroid cancer or pancreatic cancer should not be drawn. As semaglutide is one of the youngest GLP-1RA, further research is needed to become clear about possible adverse effects and their frequency.

Characters and effectiveness

Semaglutide is available in two primary forms: injectable and oral. The injectable form is administered once weekly and is available in doses of 0.25 mg, 0.5 mg, 1.0 mg and 2.0 mg. Clinical trials, such as the SUSTAIN 1 study, have shown significantly improved glycemic control and result in weight loss for patients with type 2 diabetes compared to placebo. The 0.5 mg and 1.0 mg doses significantly reduced HbA1c and body weight with a safety profile similar to other GLP-1 receptor agonists. Oral semaglutide is taken once daily and has shown efficacy in lowering HbA1c and body weight in patients with type 2 diabetes. Clinical studies have confirmed its effectiveness and highlighted its benefits for patients who prefer non-injectable options [50]. Effective reductions in blood glucose, HbA1c, and body weight can be achieved with semaglutide, available in subcutaneous and oral forms.

Healthcare professionals and patients can select the formulation that most appropriately meets the individual's specific needs. Subcutaneous semaglutide is administered once weekly by

injection. This form may be convenient for patients taking multiple medications or traveling frequently, thanks to the easy-to-use prefilled pen device.

No specific dosing instructions are required, but it needs refrigeration. Adherence might improve with once-weekly dosing compared to more frequent schedules. Cost considerations include comparing the cost-effectiveness with other treatments and assessing formulary and reimbursement factors. Oral semaglutide is administered once daily by tablet. It benefits patients concerned about injectables, such as those fearing needle pain or worried about injecting correctly. Daily dosing instructions must be followed precisely. It does not require refrigeration but should be stored in blister packs. Adherence may be better compared to injectables if daily instructions are manageable. Cost-effectiveness should be considered, along with formulary and reimbursement factors [51].

Conclusion

Physical activity brings a series of beneficial changes to the patients' body, especially while obese. Sometime sport might be not enough and individuals ask for pharmacological help. One of such medication is semaglutide. Semaglutide is a glucagon-like peptide 1 receptor agonist secreted from mostly α-cells in the pancreas. Numerous studies have investigated the molecular mechanism of GLP-1 in energy homeostasis. One of them is activating protein kinase A that contributes to the increase of glucose-dependent insulin secretion and decreasing liver production of glucose what leads to inhibition of glucagon release from pancreatic α-cells. Semaglutide can modulate satiety, neurogenesis, and reduce inflammatory processes by suppressing proinflammatory cytokines. Due to these properties, GLP-1 therapies have been successfully used for the treatment of T2D and obesity.

Semaglutide has demonstrated significant efficacy in reducing HbA1c levels in type 2 diabetes patients, outperforming other medications and showing benefits in those with chronic kidney disease. The exact mechanisms by which GLP-1 receptor agonists protect kidney health are still being studied, but they likely involve reductions in inflammation and oxidative stress.

In the cardiovascular system, semaglutide has shown promise in treating HFpEF, especially in obese patients, by significantly improving symptoms and overall quality of life through weight loss. Ongoing research, such as the FLOW and SELECT trials, is crucial to further

understanding semaglutide's impact on renal and cardiovascular health and improving treatment protocols for diabetic complications.

Semaglutide presents many pleiotropic effects. Patients might be afraid of hypoglycaemia but GLP-1RAs are believed to link to quite a low risk by itself. The majority of adverse effects are gastrointestinal disorders, such as nausea, vomiting, diarrhoea. There might be a higher risk of acute pancreatitis but more scientific data is needed. Important signals were discovered between GLP-1RA and tumours, such as thyroid cancer and increasing heart rate so it is important to pay attention to any abnormalities that may happen in a short or even few years onset time.

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