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Ozempic: the gold standard for weight normalisation or a "lifeboat"

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Abstract: obesity, type 2 diabetes mellitus (T2DM), and metabolic syndrome remain prevalent global health challenges requiring comprehensive management strategies. Semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1RA), has emerged as a significant pharmacological intervention. The study aims to analyze current scientific data to critically assess the clinical efficacy and safety of semaglutide (Ozempic) in treating T2DM and obesity, determining its position in modern therapeutic protocols. A descriptive review of the literature was conducted, analyzing key phase III clinical trials, including the SUSTAIN, PIONEER, STEP, and SELECT programmes. The review focuses on pharmacokinetic properties, glycaemic control, weight loss outcomes, and cardiovascular safety profiles of both subcutaneous and oral semaglutide formulations. Clinical trials demonstrate that semaglutide significantly reduces glycated haemoglobin (HbA1c) by -1.0% to -1.8% and induces substantial weight loss (averaging ~15%), surpassing earlier GLP-1RAs. The drug exhibits pleiotropic effects, including improved endothelial function and reduced inflammation, contributing to cardiovascular protection, with a relative reduction of major adverse cardiovascular events (MACE) by ~20%. However, rapid weight regains upon discontinuation and potential adverse effects such as gastrointestinal disturbances remain significant concerns. Semaglutide represents a highly effective pharmacological option for managing metabolic disorders, offering benefits beyond glycaemic control. While it sets a high standard for efficacy, issues regarding cost, accessibility, and the necessity for long-term adherence categorize it as a specialized resource requiring strategic implementation rather than a universally accessible cure.

Keywords: Semaglutide, Ozempic, Obesity, Metabolic Syndrome, Type 2 Diabetes Mellitus

Introduction

Ozempic is the trade name for an injectable medication containing semaglutide as its active ingredient. This drug is part of the glucagon-like peptide-1 receptor agonist (GLP-1RA) class, a widely utilized group of medications in medical practice [1]. Initially developed and approved for the treatment of type 2 diabetes, Ozempic has gained notable international popularity due to its remarkable effectiveness in weight management and obesity treatment. Semaglutide, the latest addition to the GLP-1RA family, stands out as the only drug in this class available in both subcutaneous and oral forms. GLP-1RAs are known for their strong efficacy in improving glycaemic control and aiding weight loss, though concerns regarding their safety have emerged in recent years [2]. For semaglutide specifically, these issues have been carefully examined through extensive phase III registration trials, which included studies focused on cardiovascular outcomes.

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Subcutaneous semaglutide was evaluated within the SUSTAIN (Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes) programme, while oral semaglutide underwent evaluation in the PIONEER (Peptide Innovation for Early Diabetes Treatment) programme. Additionally, the drug's safety and effectiveness continue to be investigated through further studies and real-world data registries [3].

Aim

The goal is to perform a thorough analysis and synthesis of current scientific research to critically assess semaglutide (Ozempic) as a treatment option for type 2 diabetes mellitus and obesity. The evaluation will determine whether it qualifies as a 'gold standard' therapy or if its utility is better described as a 'lifeline' tailored to specific patient populations.

Review and discussion

Experimental data showed that, at equivalent exposure levels, comparable responses to glycaemic parameters and weight were observed with both oral and subcutaneous administration of semaglutide. Both forms of semaglutide – subcutaneous and oral – have undergone large-scale clinical trials in phase3 (confirmation of efficacy and dosage, identification of side effects). For the subcutaneous form, administered once a week, the SUSTAIN one was developed, which included 13 randomised phase 3a and 3b clinical trials. The SUSTAIN 1–10 studies were international in nature, while three additional studies were conducted specifically in China and Japan. In four of these, semaglutide was compared with placebo in different patient groups. The SUSTAIN-6 study was designed to evaluate the cardiovascular effects of subcutaneous semaglutide [3,4].

Semaglutide, as a GLP-1RA, has two main mechanisms of action in the endocrine system. First, it enhances glucose-dependent insulin secretion from pancreatic β-cells, providing a physiological response to elevated postprandial glucose levels, which significantly reduces the risk of hypoglycaemia. Second, it simultaneously inhibits the release of glucagon, which further contributes to lowering blood sugar levels [5]. In addition, the drug slows down gastric emptying. This has a dual significance: it improves postprandial glycaemic control and promotes rapid satiety, which is critical for reducing overall calorie intake[5].

The SUSTAIN clinical trial programme has clearly confirmed the high efficacy of semaglutide in patients with T2DM. The drug significantly reduced glycated haemoglobin (HbA1c) levels by an average -1.0% to -1.8%compared to placebo. It should be noted that the effect on glycaemia was more pronounced in patients with poorer baseline control: those with HbA1c≥8% showed a more significant reduction in levels compared to patients with HbA1c<8% [4]. Furthermore, semaglutide contributed to a significant reduction in body weight, reaching several kilograms. This effect was observed in all subgroups of the, regardless of baseline glycaemia[6]. The independence of the drug's effect on weight from blood sugar levels emphasises the role of central appetite regulation as the main mechanism of action of semaglutide. International guidelines, including those of the European Society of Cardiology (ESC), identify semaglutide as a priority drug for patients with T2DM and diagnosed atherosclerotic cardiovascular disease. Semaglutide is recommended to reduce the risk of cardiovascular events regardless of baseline glycaemic status or concomitant antidiabetic therapy [6, 7].

Metabolic syndrome dramatically increases the risk of developing coronary heart disease (CHD), as it is a disease caused by impaired blood flow in the heart vessels (mainly in the coronary arteries), leading to insufficient oxygen supply to the myocardium. The cardiovascular benefits of semaglutide are secondary effects of weight loss and improved glycaemic control and include direct or independent pleiotropic effects. Semaglutide improves endothelial function and restores protective immune responses in visceral adipose tissue, as well as improving heart structure and function. This indicates a systemic anti-inflammatory and antioxidant effect that provides a beneficial cardiometabolic effect beyond that achieved by physical reduction of adipose tissue alone [7]. This is particularly important in obesity associated with heart failure with preserved ejection fraction (HfpEF). While preclinical models (such as in mice) have demonstrated significant structural cardioprotective effects, clinical translation makes this drug an important new therapeutic option for patients [7]. In addition, the STEP (Semaglutide Treatment Effect in People with Obesity) has established a new standard in the medical management of obesity. Administering semaglutide at a dose of 2.4 mg once weekly resulted in significant and clinically meaningful weight loss, averaging approximately 15% of body weight over a 68-week period. This level of efficacy surpasses that of earlier medications like liraglutide when comparing average weight loss outcomes [8]. Such substantial weight reduction is particularly important due to its association with improved metabolic health and a lowered risk of organ fat accumulation [7]. The weight loss induced by semaglutide also brings notable systemic improvements in the metabolic profile. The STEP trials demonstrated wide-ranging benefits on cardiometabolic parameters, including

Table 1. Comparison of semaglutide formulations [1, 5]

Feature	Subcutaneous (Ozempic/Wegovy)	Oral (Rybelsus)
Administration frequency	Once weekly	Once daily
Maximal dose	1.0 mg (T2DM) / 2.4 mg (Obesity)	14 mg
Plasma concentration	~45 nM (at 1 mg)	~25 nM (at 20 mg)
Site of administration	Subcutaneous tissue	Gastrointestinal tract
Specific side effect risks	Injection site reactions	Higher GI issues due to portal vein concentration

marked decreases in blood pressure and waist circumference – a key indicator of reduced visceral fat.

Furthermore, semaglutide contributed to positive lipid profile changes, such as reduced levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides (TG), alongside an increase in high-density lipoprotein (HDL) cholesterol. These improvements were consistent regardless of a patient's diabetes status, highlighting semaglutide's ability to address various facets of metabolic syndrome effectively [7].

Additionally, the treatment led to reductions in inflammatory markers such as CRP and provided significant improvements in liver enzyme levels, indicating its potential role in managing fatty liver disease [1].

The target effects of GLP-1RAs are those that contribute to lowering blood glucose levels. The remaining effects can be interpreted as pleiotropic, side effects, or off-target effects, including undesirable ones. Many side effects of this class are characteristic of various GLP-1RAs, although certain differences can be observed [1]. In the case of semaglutide, a different side effect profile is expected depending on the form of administration – oral or subcutaneous (Table 1). For example, tablets do not cause reactions at the injection site, but may lead to more frequent gastrointestinal problems due to higher concentrations in the portal vein. At the same time, the maximum oral dose provides lower plasma levels of semaglutide compared to the maximum subcutaneous dose (an oral dose of 20 mg reaches approximately 25 nM in plasma, while a subcutaneous dose of 1 mg reaches approximately 45 nM). It should be noted that while pharmacokinetic data exist for both forms, direct head-to-head clinical studies comparing their pharmacokinetic profiles remain limited. Also noted are the risks of hypoglycaemia, gastrointestinal side effects, including a potential link to pancreatitis, pancreatic or thyroid cancer, it is essential to clarify that there is currently no conclusive clinical evidence of carcinogenicity in humans; these warnings are predominantly based on preclinical animal experiments [1].

Off-label use for cosmetic weight loss

The unprecedented efficacy of semaglutide in weight reduction has led to a widespread surge in its off-label use for purely cosmetic purposes among individuals without clinical obesity or T2DM. This phenomenon has created substantial ethical and medical challenges, notably precipitating global supply shortages that limit access for patients with legitimate, severe metabolic conditions. Furthermore, using GLP-1RAs without proper medical indication exposes healthy individuals to potential gastrointestinal and systemic side effects without justifiable clinical benefit [1, 2].

Conclusions

The clinical efficacy of semaglutide, confirmed by large-scale research programmes SUSTAIN, STEP and SELECT, has been proven in key areas: significant weight loss, deep glycaemic control and, most importantly, proven cardiovascular protection in patients with T2DM and other metabolic disorders. Notably, the SELECT trial recently demonstrated that semaglutide reduces the risk of major adverse cardiovascular events (MACE) by approximately 20% in overweight or obese patients without diabetes, further validating its cardiometabolic benefits [9]. The multifaceted therapeutic effect elevates this drug to a leading position in the treatment of T2DM, obesity, and metabolic syndrome. However, the success of semaglutide also raises important ethical and medical issues. There is a growing awareness that obesity should be considered a chronic neuroendocrine disease requiring ongoing pharmacological intervention. At the same time, rapid weight regain after discontinuation of treatment is confirmed by extension studies [8]. The need for lifelong use of the drug, combined with its high cost, logistical difficulties, and significant inequality of access to therapy, defines semaglutide as an essential but resource-intensive intervention. It represents a vital therapeutic tool that, while highly effective, requires sustainable access strategies to be available to all patients who need its clinical benefits.

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Оземпік: золотий стандарт нормалізації ваги чи «рятувальний човен»

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Анотація: ожиріння, цукровий діабет 2-го типу (ЦД2) та метаболічний синдром залишаються поширеними глобальними проблемами охорони здоров'я, що потребують комплексних стратегій лікування. Семаглутид, агоніст рецепторів глюкагоноподібного пептиду-1 (ГПП-1), став важливим засобом фармакологічного втручання. Метою дослідження є аналіз сучасних наукових даних для критичної оцінки клінічної ефективності та безпеки семаглутиду (Оземпік) у лікуванні ЦД2 та ожиріння, а також визначення його місця в сучасних терапевтичних протоколах. Проведено описовий огляд літератури з аналізом ключових клінічних випробувань III фази, включаючи програми SUSTAIN, PIONEER, STEP та SELECT. Огляд зосереджено на фармакокінетичних властивостях, глікемічному контролі, результатах зниження ваги та профілях серцево-судинної безпеки як підшкірної, так і пероральної форм семаглутиду. Клінічні випробування демонструють, що семаглутид значно знижує рівень глікованого гемоглобіну (HbA1c) на -1.0%-1.8% та сприяє суттєвій втраті ваги (у середньому ~15%), перевершуючи попередні агоністи рецепторів ГПП-1. Препарат виявляє плейотропні ефекти, включаючи покращення ендотеліальної функції та зменшення запалення, що сприяє серцево-судинному захисту, зі зниженням ризику MACE на ~20%. Однак швидкий набір ваги після припинення лікування та потенційні побічні ефекти, такі як шлунково-кишкові розлади, залишаються значними проблемами. Семаглутид є високоефективним фармакологічним варіантом для лікування метаболічних розладів, пропонуючи переваги, що виходять за межі глікемічного контролю. Хоча він встановлює високий стандарт ефективності, питання вартості, доступності та необхідності тривалого дотримання терапії класифікують його як спеціалізований ресурс, що вимагає стратегічного впровадження, а не як універсально доступну панацею.

Ключові слова: семаглутид, оземпік, ожиріння, метаболічний синдром, цукровий діабет 2-го типу