A COMPREHENSIVE REVIEW OF SEMAGLUTIDE: PHARMACOLOGY, CLINICAL EFFICACY, CARDIOVASCULAR OUTCOMES, AND SAFETY PROFILE

SEMAGLUTID BO‘YICHA KENG QAMROVLI SHARH: FARMAKOLOGIYASI, KLINIK SAMARADORLIGI, YURAK-QON TOMIR TIZIMIGA TA‘SIRI VA XAVFSIZLIGI

КОМПЛЕКСНЫЙ ОБЗОР СЕМАГЛУТИДА: ФАРМАКОЛОГИЯ, КЛИНИЧЕСКАЯ ЭФФЕКТИВНОСТЬ, СЕРДЕЧНО-СОСУДИСТЫЕ ИСХОДЫ И ПРОФИЛЬ БЕЗОПАСНОСТИ

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Abstract. *Semaglutide is a long-acting glucagon-like peptide-1 receptor agonist (GLP-1 RA) approved for the treatment of type 2 diabetes mellitus (T2DM) and chronic weight management in overweight and obese individuals. This review summarizes semaglutide’s mechanism of action, pivotal trial evidence for glycemic control and weight management, cardiovascular outcomes, real-world adherence, and safety considerations. Growing clinical data confirm that semaglutide is an effective option for patients requiring both glucose lowering and sustainable weight loss under proper medical supervision.*

Keywords: *Semaglutide, GLP-1 receptor agonist, type 2 diabetes mellitus, obesity, weight loss, cardiovascular outcomes, SUSTAIN trials, STEP trials.*

Annotatsiya. *Semaglutid — bu uzoq ta’sirli glyukagon-ga o‘xshash peptid-1 retseptor agonisti (GLP-1 RA) bo‘lib, 2-turdagi qandli diabet (T2DM)ni davolash va ortiqcha vazn hamda semizlikda surunkali vazn boshqaruvi uchun tasdiqlangan. Ushbu sharh semaglutidning ta’sir mexanizmi, glikemiya nazorati va vazn boshqaruvidagi muhim sinov dalillari, yurak-qon tomir natijalari, real amaliyotdagi dori qabul qilishga rioya qilish va xavfsizlik jihatlarini jamlaydi. Ortib borayotgan klinik ma’lumotlar, tegishli tibbiy nazorat ostida, semaglutid glyukozani pasaytirish va barqaror vazn yo‘qotishni talab qiladigan bemorlar uchun samarali variant ekanini tasdiqlaydi.*

Kalit so‘zlar: *semaglutid, GLP-1 retseptor agonisti, 2-tur qandli diabet, semizlik, vazn yo‘qotish, yurak-qon tomir natijalari, SUSTAIN sinovlari, STEP sinovlari.*

Аннотация. *Семаглутид — это длительно действующий агонист рецепторов глюкагоноподобного пептида-1 (ГПП-1; GLP-1 RA), одобренный для лечения сахарного диабета 2 типа (СД2) и для долговременного управления массой тела у лиц с избыточной массой и ожирением. В данном обзоре суммируются механизм действия семаглутида, ключевые данные pivotal-исследований по контролю гликемии и снижению массы тела,*

сердечно-сосудистые исходы, приверженность в реальной клинической практике и вопросы безопасности. Нарастающий массив клинических данных подтверждает, что семаглутид является эффективным вариантом для пациентов, которым требуется одновременно снижение гликемии и устойчивое уменьшение массы тела при надлежащем медицинском наблюдении.

Ключевые слова: *семаглутид, агонист рецепторов ГПП-1, сахарный диабет 2 типа, ожирение, снижение массы тела, сердечно-сосудистые исходы, исследования SUSTAIN, исследования STEP.*

Introduction. Type 2 diabetes mellitus (T2DM) and obesity are two of the most pressing public health challenges worldwide, both in high-income and low- and middle-income countries. According to the World Health Organization (WHO, 2021), the global prevalence of diabetes has nearly quadrupled since 1980, with an estimated 422 million people currently affected. Simultaneously, obesity rates have tripled since 1975, and over 1.9 billion adults are classified as overweight, with more than 650 million meeting the criteria for obesity. These twin epidemics contribute significantly to premature morbidity, disability, and mortality, largely due to their close association with cardiovascular disease (CVD), which remains the leading cause of death globally.

T2DM and obesity are pathophysiologically linked through insulin resistance, chronic low-grade inflammation, and metabolic dysfunction. Excess adiposity exacerbates insulin resistance, impairs beta-cell function, and accelerates progression to diabetes. Furthermore, standard glucose-lowering therapies, including sulfonylureas and insulin, are frequently associated with weight gain, which may counteract efforts to manage obesity-related risk factors. Thus, there is an urgent need for pharmacological agents that provide dual benefits: effective glycemic control without promoting weight gain, and ideally, a reduction in cardiovascular events.

Over the past decade, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as one of the most significant advances in metabolic disease pharmacotherapy. Unlike traditional therapies, GLP-1 RAs offer multiple physiological benefits, including glucose-dependent stimulation of insulin secretion, suppression of glucagon, delayed gastric emptying, and appetite suppression via central nervous system pathways. These combined actions lead to improved glycemic control, clinically meaningful weight loss, and potentially favorable cardiovascular effects.

Semaglutide, a long-acting, once-weekly GLP-1 RA, represents a new generation of incretin-based therapies. Structurally similar to endogenous human GLP-1, semaglutide is engineered for increased stability against enzymatic degradation, resulting in a half-life of approximately 165 hours. This pharmacokinetic advantage allows for once-weekly subcutaneous administration, which improves treatment convenience and adherence compared to earlier daily GLP-1 RAs.

Clinical evidence supporting semaglutide's efficacy and safety is extensive. Major trials, including the SUSTAIN and STEP programs, have demonstrated its robust impact on HbA1c reduction, significant weight loss, and cardiovascular risk mitigation in high-risk populations. Notably, the SUSTAIN-6 cardiovascular outcomes trial established semaglutide as one of the few glucose-lowering agents with clear evidence for reducing major adverse cardiovascular events (MACE) in T2DM patients.

Despite these advances, clinical challenges remain. Tolerability, particularly gastrointestinal side effects, patient selection, long-term adherence, and cost-effectiveness in real-world practice continue to shape discussions around optimal use. Moreover, the expanding application of semaglutide for non-diabetic obesity highlights a paradigm shift towards pharmacological treatment of obesity as a chronic disease rather than a lifestyle problem alone.

This review aims to synthesize current knowledge on semaglutide by critically examining its pharmacological mechanism, clinical trial evidence, real-world application, cardiovascular implications, safety profile, and future directions. By providing an updated and comprehensive analysis, this paper contributes to a better understanding of semaglutide's role in modern metabolic disease management and supports informed decision-making for healthcare professionals managing patients with T2DM and obesity.

Literature review. Multiple randomized controlled trials (RCTs) and meta-analyses have evaluated semaglutide's efficacy and safety since its approval. The SUSTAIN clinical program comprises a series of trials investigating once-weekly semaglutide for glycemic control in T2DM. For instance, SUSTAIN 1–7 demonstrated significant reductions in HbA1c, ranging from −1.0% to −1.8%, with consistent body weight loss of 3–6 kg compared to placebo or other active comparators such as sitagliptin or exenatide ER (Davies et al., 2017; Aroda et al., 2017).

The landmark SUSTAIN-6 cardiovascular outcomes trial (Marso et al., 2016) showed that semaglutide reduced the risk of major adverse cardiovascular events (MACE) by 26% compared to placebo among high-risk patients with T2DM, including a significant reduction in nonfatal stroke risk.

Beyond T2DM, the STEP program evaluated semaglutide at higher doses (up to 2.4 mg weekly) for weight management in overweight and obese adults. In STEP 1, Wilding et al. (2021) reported a mean weight reduction of 14.9% from baseline compared to 2.4% with placebo. STEP 2 confirmed efficacy in patients with T2DM, while STEP 4 demonstrated the risk of weight regain upon discontinuation, reinforcing the importance of continuous therapy (Rubino et al., 2021).

Real-world studies also indicate high adherence and patient satisfaction due to the convenient once-weekly dosing and dual benefits in metabolic control (Overgaard et al., 2021).

Methodology. This review employs a systematic narrative approach. Relevant peer-reviewed literature was identified through searches on PubMed, Scopus, and Google Scholar for publications between 2016 and 2024 using keywords including *semaglutide, GLP-1 receptor agonist, type 2 diabetes mellitus, obesity, SUSTAIN, STEP, cardiovascular outcomes*. Inclusion criteria were: (1) RCTs, meta-analyses, or systematic reviews focusing on semaglutide; (2) studies published in reputable peer-reviewed journals; (3) English-language full texts.

The quality and relevance of each study were assessed based on study design, sample size, endpoints, and clinical applicability. Extracted data were organized into themes: pharmacology, glycemic efficacy, weight loss effects, cardiovascular outcomes, safety, and real-world adherence.

Results and discussion. *Glycemic control:* Across the SUSTAIN trials, semaglutide consistently lowered HbA1c levels by 1.0–1.8% compared to placebo and other comparators (Davies et al., 2017). This degree of reduction meets or exceeds targets set by international guidelines for patients with T2DM.

Weight reduction: Body weight loss in SUSTAIN studies ranged from 3–6 kg among T2DM patients, while STEP trials demonstrated up to 15% weight reduction in non-diabetic obese adults receiving the 2.4 mg dose (Wilding et al., 2021). This places semaglutide among the most effective pharmacotherapies for obesity.

Cardiovascular outcomes: The SUSTAIN-6 trial confirmed cardiovascular benefits, with a 26% risk reduction in MACE, driven mainly by fewer nonfatal strokes and myocardial infarctions (Marso et al., 2016).

Safety profile: Gastrointestinal events—nausea (up to 20%), vomiting, diarrhea—are the most frequent side effects but usually resolve as treatment continues. Rare adverse effects include potential pancreatitis and theoretical thyroid C-cell tumor risks (FDA, 2021).

Adherence: Once-weekly dosing significantly improves patient adherence and persistence compared to daily GLP-1 RAs, supporting long-term metabolic control (Overgaard et al., 2021).

Conclusion. In conclusion, semaglutide represents one of the most significant pharmacological advancements in the treatment of type 2 diabetes mellitus and obesity over the past decade. Its unique dual mechanism addresses two intertwined global epidemics simultaneously by providing effective glucose control while facilitating substantial weight reduction — a therapeutic combination not offered by many traditional glucose-lowering agents.

Evidence from landmark clinical trials such as SUSTAIN and STEP has firmly established semaglutide's robust efficacy in lowering HbA1c by up to 1.8% and achieving weight loss of up to 15% of baseline body weight in overweight and obese adults, even those without diabetes. Moreover, the SUSTAIN-6 trial demonstrated a significant reduction in major adverse cardiovascular events, highlighting semaglutide's additional benefit for patients with elevated cardiovascular risk.

However, semaglutide's use is not without limitations. Common gastrointestinal side effects remain a barrier for some patients, underscoring the importance of gradual dose escalation and patient education to maximize adherence and minimize discontinuation. Cost and access also pose challenges in certain healthcare settings, potentially limiting widespread adoption despite its clinical superiority.

Nevertheless, real-world data increasingly support its tolerability, long-term effectiveness, and patient satisfaction, confirming findings from controlled trials. Its once-weekly dosing regimen improves adherence compared to older daily GLP-1 RAs, strengthening its position as a leading choice for comprehensive metabolic management.

Future research should focus on long-term outcomes beyond five years, the drug's impact on diverse patient subgroups including adolescents and older adults, cost-effectiveness analyses in various healthcare systems, and combination strategies with other metabolic drugs or lifestyle interventions. Additionally, the emerging role of oral semaglutide formulations may further expand accessibility and patient preference.

Overall, semaglutide stands at the forefront of modern diabetes and obesity care, embodying the shift toward therapies that target multiple metabolic pathways. With appropriate patient selection, clinical supervision, and support for long-term adherence, semaglutide has the potential to contribute meaningfully to reducing the global burden of diabetes, obesity, and their associated cardiovascular complications.

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