

# New practice in semaglutide on type-2 diabetes and obesity: clinical evidence and expectation

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**Abstract** Obesity is an important risk factor of type 2 diabetes (T2D), which has become an important factor threatening human health. However, no perfect drug choice for obesity exists. Semaglutide is a kind of human glucagon-like peptide-1 (GLP-1) analog that promotes insulin secretion while inhibiting glucagon secretion through a glucose concentration-dependent mechanism. GLP-1 can also delay stomach emptying and suppress appetite to help lose weight. This review summarizes clinical evidence of the semaglutide effect on T2D and obesity and establishes expectations on future clinical trials for obesity treatment.

**Keywords** semaglutide; type 2 diabetes; obesity

## Introduction

With the improvement of people's living standards in recent years, diabetes has become an important factor threatening human health. The International Diabetes Federation statistics in 2019 showed that approximately 463 million adults aged 20–79 years in the world were suffering from diabetes, indicating that 1 in 11 people had diabetes. Another estimate is that the number of diabetic patients will reach 578.4 million by 2030, and the number may reach 700.2 million by 2045 [1]. Diabetes is a kind of metabolic disease characterized by high blood sugar and is often characterized by polydipsia, polyphagia, polyuria, and weight loss. Moreover, long-term hyperglycemia causes chronic damage and dysfunction of various tissues, especially eyes [2], kidneys [3], heart [4], blood vessels [5], and nerves [6]. Meanwhile, obesity is a chronic disease that requires long-term treatment [7,8], and approximately 650 million people suffer from obesity worldwide [9]. Obesity is a recognized risk factor for ischemic heart disease, atherosclerosis, and stroke [10]. Furthermore, it can lead to common chronic diseases such as chronic kidney disease, hypertension, and type-2 diabetes (T2D) [11]. Nowadays, a range of restrictive measures limiting the spread of coronavirus disease 2019 (COVID-19) may

have a negative impact on weight-management practices, and a high body mass index has also been identified as a risk factor for COVID-19 mortality [12–14].

Obesity and T2D are closely correlated. People with abnormal glucose metabolism often have dyslipidemia, hypertension, hyperuricemia, fatty liver, and obesity, and insulin resistance is the common cause of these abnormalities. Obesity is regarded as an important cause of T2D. As the condition progresses, many obese patients are bound to evolve to the stage of clinical T2D, and a series of complications will soon occur. Therefore, the development of efficient weight-loss drugs is imminent. However, no perfect drug choice exists for obesity. Complex medication regimens [15,16] and subsequent adverse events may further affect patient compliance.

Glucagon-like peptide-1 (GLP-1) is an intestinal hormone secreted by the L cells of the small intestine after eating stimulation [17]. GLP-1 receptors are primarily distributed in the pancreas, intestine, and central nervous system. GLP-1 receptor agonists can enhance insulin secretion caused by increased glucose and inhibit glucagon secretion. In detail, glucose plays a major role in regulating insulin secretion. When extracellular glucose levels rise, pancreatic  $\beta$  cells allow glucose entry via glucose transporter-2 [18]. This phenomenon elevates intracellular ATP [19,20], thereby promoting the closure of ATP-sensitive potassium channels [21]. Furthermore, changes in cell-membrane potential and voltage-dependent  $\text{Ca}^{2+}$  channel activation lead to  $\text{Ca}^{2+}$  flowing in from outside the

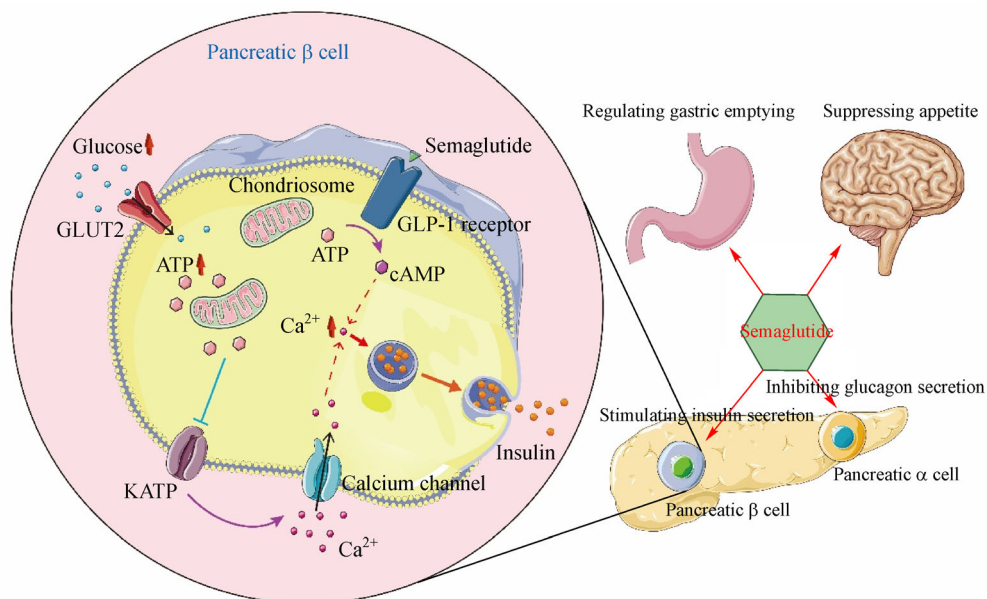
cell, which then promotes exocytosis and insulin secretion. GLP-1-mediated insulin secretion can be observed only at elevated glucose concentration. GLP-1 analogs produce more cAMP by binding to GLP-1 receptor on pancreatic  $\beta$  cells [19] and subsequently enhance glucose activity by further increasing the permeability of  $\text{Ca}^{2+}$  channels, thereby enabling more  $\text{Ca}^{2+}$  influx to increase insulin release [22]. It can also delay stomach emptying [23] and suppress appetite [24] (Fig. 1; created using material in Servier Medical Art under CC BY 3.0 license). Some GLP-1 receptor agonists such as liraglutide, exenatide, and efpeglenatide [25] have been marketed and used to treat obese patients, and their efficacy is shown in Table 1. Furthermore, GLP-1 receptor agonist such as liraglutide provides better and longer glycemic control with a lower risk of hypoglycemia in individualized treatment of T2D patients. It showed as well an advantage in reducing major cardiovascular adverse events and mortality compared with other treatment regimens [26]. In general, GLP-1 receptor agonists are extensively used in the treatment of obesity and T2D. However, their efficacy and usage mode can still be improved. Semaglutide is a kind of human GLP-1 analog that promotes insulin secretion while inhibiting glucagon secretion through a glucose concentration-dependent mechanism. Notably, the risk of hypoglycemia is not high [27].

### Clinical evidence of the effect of subcutaneous semaglutide on T2D

T2D is a complex disease with different factors affecting

blood-sugar control. Many people still cannot reach the recommended blood-glucose concentration [28] despite wide-ranging treatment options [15]. Moreover, complex medication regimens [15,16], subsequent adverse events, medication-induced weight gain, and possible risk of hypoglycemia [29] may affect patient compliance and further hinder the achievement of blood-glucose goals. Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) is a series of phase-3 clinical trials that comprehensively evaluate the efficacy, safety, cardiovascular, and renal adverse events, as well as other outcomes, of subcutaneous semaglutide in the T2D population.

Among them, SUSTAIN 1–5 [30–34] and SUSTAIN 7–10 [35–38] compare semaglutide with placebo and active control drugs in a randomized and double-blind trial population, with the efficacy and safety of semaglutide as the main research endpoints. The results after 30–56 weeks show that semaglutide performs significantly better in reducing  $\text{HbA}_{1c}$  than other controls, including placebo, sitagliptin, insulin glargine, canagliflozin, dulaglutide, liraglutide, and exenatide extended release. The proportion of patients with  $\text{HbA}_{1c} < 7\%$  or  $\leq 6.5\%$  in the semaglutide group is significantly higher than that in the other controls. As high as 80% of patients in the semaglutide 1.0 mg group could achieve the standard rate of  $\text{HbA}_{1c}$  ( $\text{HbA}_{1c} < 7\%$ ), with the highest reaching 1.8%. Additionally, the weight-loss effect of semaglutide is better than those of the others, with the semaglutide 1.0 mg group losing weight up to 6.5 kg. In terms of safety, semaglutide has a similar incidence rate of adverse events to other controls, among which the most common adverse events



**Fig. 1** Regulatory mechanism of semaglutide.

**Table 1** Effects of different GLP-1 receptor agonists on losing weight

Trial	Patients ( <i>n</i> )	Intervention	Duration (week)	Main inclusion criteria	Frequency	Supplementary measure	Test result
Astrup [64]	564	Liraglutide; orlistate; placebo	20	Obese adults	Subcutaneously administered once a day	With an energy-deficit diet of 500 kcal per day and increasing physical activity	Liraglutide 1.2, 1.8, 2.4, and 3.0 mg groups lost 4.8, 5.5, 6.3, and 7.2 kg, respectively, whereas the placebo group lost 2.8 kg and the orlistat lost 4.1 kg. The liraglutide 3.0 mg group had 76% of the weight loss more than 5%, the placebo group had 30% and the orlistat group had 44%
Rosenstock [65]	152	Exenatide; placebo	24	Obese adults without T2D	–	With lifestyle intervention	The exenatide group lost 5.1±0.5 kg from the baseline 109.5±2.7 kg, whereas the placebo group lost 1.6±0.5 kg from the baseline 107.6±2.6 kg
Lundkvist [66]	50	Dapagliflozin + exenatide; placebo	24	Obese adults without T2D	Oral dapagliflozin 10 mg once a day + subcutaneous exenatide 2 mg once a week	With a balanced diet and moderate exercise	Dapagliflozin 10 mg once a day + exenatide 2 mg once a week group lost 4.48 kg, whereas the placebo group lost 0.35 kg. The experimental group had 36% of the weight loss more than 5%, the placebo group had 4.2%
Pratley [67]	295	Efglenatide; placebo	20	Obese adults	Once or twice a week	With a hypocaloric diet	Efglenatide (4 mg once a week, 6 mg once a week, 6 mg once every 2 week, and 8 mg once every 2 week) groups lost 6.6, 7.3, 6.4, and 7.1 kg, respectively, whereas the placebo group lost 0.1 kg
Wilding [49]	1961	Semaglutide; placebo	68	Obese adults without T2D	Subcutaneously administered once a week	With lifestyle intervention	In all randomized patients, the semaglutide 2.4 mg treatment group lost 14.9% from the average baseline weight of 105.3 kg, whereas the placebo group lost 2.4%. Meanwhile, 86.4% of the semaglutide 2.4 mg group lost more than 5%, and 31.5% of the placebo group lost more than 5%

are gastrointestinal adverse events. Mild to moderate and transient nausea are the most common gastrointestinal adverse events of semaglutide. In early December 2017, a once-a-week subcutaneous injection of semaglutide was approved by the US FDA and marketed under the brand name Ozempic.

### Clinical evidence of the effect of oral semaglutide on T2D

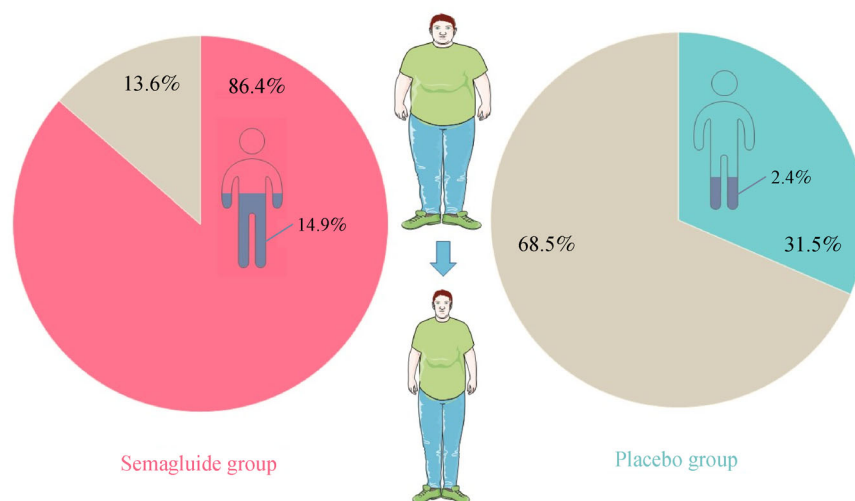
Oral GLP-1 receptor agonist can be used in early-stage T2D and is more acceptable to T2D patients. Oral dosage forms need to overcome various challenges, including extremely low oral bioavailability, limited gastrointestinal epithelial penetration, degradation under proteolytic enzymes, and low pH environment in the stomach. Oral semaglutide is the first GLP-1 receptor agonist for oral administration. To study its efficacy, safety, and adverse reactions, 10 phase-3 clinical trials of Peptide InnOvation for Early DiabEtes TReatment (PIONEER) series have been performed, covering a wide range of people with T2D [39–48]. An analysis of all 9543 patients with T2D who had or had not been treated with insulin has shown that oral semaglutide is effective in improving blood-sugar control across various baseline blood-glucose levels. Compared with all control groups, 7 and 14 mg doses of semaglutide could significantly reduce HbA<sub>1c</sub>. Furthermore, the safety of oral semaglutide is consistent with that of other GLP-1 receptor agonist drugs, similar to that of subcutaneous semaglutide. In the PIONEER 1–5, 7, and 8 studies, the proportion of T2D patients who reach the HbA<sub>1c</sub> < 7% target in the oral semaglutide 7 and 14 mg groups is higher

than that in the control groups. This finding indicates that oral semaglutide may help T2D patients who have uncontrolled blood-sugar levels to improve their condition.

### Clinical evidence of the effects of subcutaneous semaglutide on obesity and future expectations

In a newly published article, a double-blind randomized controlled trial was conducted by Wilding *et al.* [49], recruiting 1961 obese or overweight adults without diabetes. Accompanied with lifestyle interventions, semaglutide 2.4 mg or placebo was subcutaneously injected once a week. Results showed that among obese or overweight participants, semaglutide 2.4 mg once a week plus lifestyle interventions correlated with sustained, clinically significant weight loss (Fig. 2). In all randomized patients, the semaglutide 2.4 mg treatment group lost 14.9% from the average baseline weight of 105.3 kg, whereas the placebo group lost 2.4%. Additionally, 86.4% of the semaglutide 2.4 mg group lost more than 5%, and 31.5% of the placebo group lost more than 5%. For the trial product estimand, the semaglutide 2.4 mg treatment group lost 16.9% of the body weight, whereas the placebo group lost 2.4%. The semaglutide 2.4 mg group had 92.4% of the weight loss  $\geq$  5%, and the placebo group had 33.1%. Among patients receiving semaglutide, the most common adverse event is gastrointestinal. Most effects are transitory and only mild to moderate.

Semaglutide is a good choice for weight loss, and its once-a-week dosing method greatly improves compliance.



**Fig. 2** In the research of Wilding *et al.* [49], people in the semaglutide 2.4 mg treatment group lost 14.9% weight from the average baseline weight of 105.3 kg, whereas those in the placebo group lost 2.4%. Meanwhile, 86.4% of people in the semaglutide 2.4 mg group lost  $\geq$  5% weight, and 31.5% of those in the placebo group lost more than 5%.

However, compared with oral administration, injection administration still has certain operational difficulties. In that case, the dosage form of semaglutide and the corresponding weight-loss effect can further be explored in the future. Other GLP-1 receptor agonists such as liraglutide also have weight-loss effects [50] (Table 1), but these are not as obvious as those of semaglutide. Among them, liraglutide needs to be subcutaneously administered once a day, and these GLP-1 receptor agonists can lead to weight loss of only up to 7.3 kg, whereas semaglutide 2.4 mg can lead to an average weight loss of 15 kg. However, due to different research objects and different experimental designs, the exact corresponding effects compared with semaglutide are not easy to obtain. Thus, trials can also be designed to compare the weight-loss effects of semaglutide and other weight-losing products.

Lifestyle intervention is not clearly defined in the study of Wilding *et al.* [49], and it has a considerable influence on weight loss [51,52]. From this point of view, whether the results of complementary lifestyle interventions exaggerate the effects of semaglutide remains to be discussed. Furthermore, whether weight rebound occurs after semaglutide withdrawal, resulting in significant weight gain or drug dependence, can also be studied. Notably, the methodology of studies evaluating gastrointestinal symptoms is primarily through self-report rather than the use of available validated gastrointestinal symptom questionnaires.

Obesity is a significant risk factor for cardiovascular disease and related complications that significantly increase the risk of death [53,54]. Individuals with abdominal obesity are at increased risk of angina, heart failure, myocardial infarction, and atrial fibrillation [55]. As an auxiliary means of lifestyle intervention, the use of antiobesity medications can improve the risk factors of cardiovascular disease [56,57] and usually exert a beneficial effect on certain cardiometabolic parameters [58]. Studies have shown that the children of mothers exposed to metformin have lower central hemodynamics and diastolic index than those exposed to placebo. These results suggest that the use of metformin in obese pregnant women may have beneficial cardiovascular effects on their offspring [59]. However, some reports have reflected poor cardiovascular outcomes after the application of weight-loss drugs [60,61]. Aminorex can result in pulmonary hypertension; fenfluramine and dexfenfluramine may result in cardiac valvulopathy; and sibutramine may lead to myocardial infarction. After the withdrawal of sibutramine from the market due to its life-threatening side effects, the FDA sought for cardiovascular safety data on new antiobesity medications [62]. Therefore, continuous monitoring of antiobesity products for any potential safety issue is important [63]. Nevertheless, a once-a-week subcutaneous injection of semaglutide 2.4 mg is still proven to play a crucial role in improving the condition of

obese or overweight people, with only mild to moderate gastrointestinal adverse reactions. Overall, semaglutide has great potential and value in various diseases and may benefit many more patients in the near future through a few more studies in obese or overweight people.

## Conclusions

Obesity is closely correlated with T2D, which brings about many complications. Semaglutide is a kind of human GLP-1 analog that has undergone a series of clinical trials for obesity and T2D treatment. However, its effects on cardiovascular disease when treating obese people require further study.

## Compliance with ethics guidelines

Yalin Liu and Xianghang Luo declare that they have no conflict of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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