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Therapeutic Roles of Semaglutide in Type 2 Diabetes and Its Complications

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Abstract. Semaglutide is a long-acting GLP-1 receptor agonist and has been widely used in the treatment of type 2 diabetes. This review simply recalls the process of developing the formulation of semaglutide from injection to the oral route. Also, this review summarizes key findings from experimental and clinical studies. In most studies, the oral formulation achieved similar glucose-lowering effects to the injection, and many patients found it easier to take in daily life. Experimental findings suggest that semaglutide can relieve diabetic pain by reducing inflammation, oxidative stress, and neural hypersensitivity. Clinical trials indicate that it can slow down the progression of diabetic kidney disease. Experimental data also showed improvements in retinal vascular structure and inflammatory markers, suggesting a role in preventing diabetic retinopathy. Cardiovascular trials further support its safety and risk-reducing effect in high-risk individuals. Overall, semaglutide is useful for blood glucose control. It also appears to help manage diabetes and its complications.

Keywords: semaglutide, type 2 diabetes, diabetic complications

1. Introduction

Recently, chronic diseases have become the leading causes of mortality and morbidity worldwide. As life expectancy increases, many chronic conditions gradually worsen and require long-term management to maintain quality of life [1]. Diabetes mellitus is a prime example. It is a lifelong metabolic disorder caused by impaired insulin production or use. Type 1 diabetes (T1D) mainly happens because the immune system attacks and destroys the pancreatic beta-cells, leaving the body with little to no natural insulin. T2D, on the other hand, develops when long-term insulin resistance is paired with a gradual loss of beta-cell function, so the pancreas can no longer produce enough insulin to keep up [2].

Poor blood glucose control in T2D is associated with a wide range of complications, including both microvascular and macrovascular diseases. Chronic hyperglycemia in T2D progressively injures blood vessels in multiple organs. Damage to small vessels underlies microvascular complications such as diabetic kidney disease, retinopathy, and neuropathy, whereas involvement of larger arteries contributes to coronary, cerebrovascular, and peripheral arterial disease. These complications can be fatal and may lead to several health deterioration and premature mortality [3].

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The treatment of T2D aims to keep blood glucose under control. More importantly, it aim to lower the risk of long-term microvascular and macrovascular complications. Treatment includes both non-drug and drug approaches. Lifestyle advice, including a balanced diet and regular physical exercise, serves as the first approach to improving insulin sensitivity and overall metabolism. When lifestyle control is not enough, medication should be started. After metformin, several options can be chosen depending on the patients' condition, medical history, and risk of low blood sugar [3].

Among these second-line drugs, glucagon-like peptide-1 receptor agonists (GLP-1Ras) have gained attention because they are effective in controlling blood glucose levels. Moreover, they can help maintain heart and kidney health. Semaglutide, a long-acting GLP-1RA, works by mimicking the natural GLP-1 hormone. It helps the body release insulin when blood sugar is high, lowers glucagon, slows down stomach emptying, and reduces appetite, which can also lead to weight loss. Through these combined actions, semaglutide helps maintain stable blood sugar levels and offers additional cardiovascular and renal benefits for patients with T2D [4].

In the past, basically the only route for semaglutide administration was subcutaneous injection because it is easily destroyed in the gastrointestinal environment. But for lots of patients who have diabetes, it is quite inconvenient to receive injections all the time, and that also makes people less likely to stick with the treatment. Later on, the appearance of oral semaglutide partly addressed this problem. Clinical trials also proved its effectiveness, and it is usually easy for people to tolerate [5].

2. The pharmacology of semaglutide

Semaglutide is a synthetic analog of human glucagon-like peptide-1 (GLP-1) composed of 31 amino acids. Although it is based on the native GLP-1 sequence, several deliberate structural modifications have been introduced, enhancing its stability against enzymatic degradation and reducing renal clearance, so that semaglutide remains in the circulation for a prolonged period and can exert sustained GLP-1 receptor agonism [4].

Earlier research showed that native GLP-1 can be given orally when it is combined with an absorption enhancer called SNAC (sodium N-[8-(2-hydroxybenzoyl)amino] caprylate). SNAC is a small hydrophobic molecule that transiently binds to this peptide drug and modulates the local gastric microenvironment, thereby promoting drug absorption across gastric mucosal cells. Once absorbed into the bloodstream, SNAC separates from semaglutide, which then works in the body as an active GLP-1 receptor agonist.

3. Comparison between oral and injectable semaglutide

Following the development of an oral formulation of semaglutide, it became necessary to compare its efficacy and safety against placebo and against the existing injectable formulation. To do this, Davies and colleagues ran a 26-week randomized phase II trial in adults with T2D. The study used a parallel-group design and tested different oral doses to see the dose-response pattern. They also compared the glucose-lowering effects of the oral form with once-weekly subcutaneous semaglutide and with placebo [5].

This trial included adults aged 18 or older with T2D and insufficient blood glucose control, which means an HbA1c level between 7.0% to 9.5%. Eligible participants were treated with diet or exercise alone or with a stable dose of metformin. The additional inclusion criteria required a body mass index (BMI) between 25 and 40 [5].

The study used a stepwise dose-escalation design. Patients received either semaglutide or placebo orally once daily, with doses progressively increased over time to several maintenance levels. An

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open-label control group concurrently received weekly subcutaneous injections of 1 mg semaglutide. The researchers also tested faster and slower dose increases to find the best balance between blood sugar control and side effects [5].

In this trial, the main efficacy measure was the change in HbA1c over the 26-week treatment period compared with baseline. Other prespecified measure included the proportion of participants who achieved HbA1c less than 7.0%, fasting glucose and body weight changes, and weight loss categorized into predefined groups from the baseline measurement [5].

After 26 weeks, about 44% to 90% of people taking oral semaglutide brought their HbA1c below 7.0%. Up to 71% lost at least 5% of their body weight. The 20 mg and 40 mg oral doses worked just as well as the 1 mg injectable version, with very few cases of hypoglycemia and mostly mild gastrointestinal side effects. Overall, oral semaglutide proved to be both effective and safe for treating patients with T2D [5].

4. Semaglutide and diabetic neuropathy

Neuropathic pain (NP) refers to pain caused by injury or dysfunction of the somatosensory system. Among its many causes, diabetes is one of the most common. Diabetic neuropathic pain (DNP) results from long-term poor blood glucose control that damages peripheral nerves, especially those in the legs and feet. Many patients feel pain even from light touches that would not normally hurt. They may also have a stronger reaction to painful stimuli than usual, known as hyperalgesia. DNP greatly affects patients' quality of life, interfering with sleep, mood, and daily activities [6].

Treatment for neuropathic pain mainly includes antidepressants, SNRIs (serotonin-noradrenaline reuptake inhibitors), along with anticonvulsants and opioids [6]. However, these drugs often lead to tolerance, side effects, and limited long-term effectiveness, making chronic pain difficult to manage. Therefore, new therapeutic GLP-1 receptor agonists that can both manage T2D and reduce neuropathic pain are urgently needed [7].

Previous studies showed that GLP-1 receptor agonists can relieve diabetic neuropathic pain by activating GLP-1 receptors in the spinal cord, thereby reducing oxidative stress. They may also improve nerve function and even sleep [8]. Based on these findings, Lee and colleagues examined whether semaglutide could reduce diabetic neuropathic pain in STZ-induced diabetic rats (Figure 1) [7]. The rats were split into four groups: normal control, diabetic neuropathic pain (DNP), DNP with low-dose semaglutide (1.44 mg/kg) oral administration, and DNP with high-dose semaglutide (2.88 mg/kg) oral administration. Semaglutide was administered orally once daily for four weeks. Pain-related behaviour was then assessed using standard assays of mechanical and thermal sensitivity.

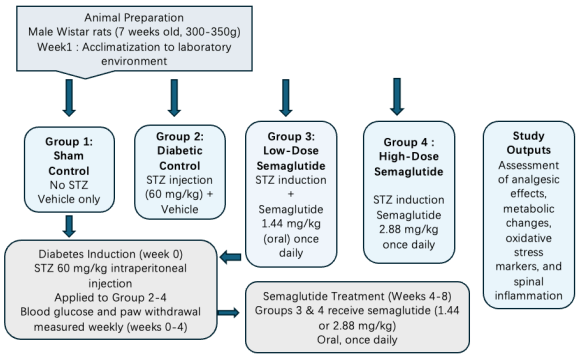

Figure 1. Experimental design of the STZ-induced diabetic neuropathic pain rat model

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After treatment, oral semaglutide significantly increased pain thresholds and reduced hypersensitivity in diabetic rats, indicating clear relief of neuropathic pain. Compared with untreated DNP rats, those receiving semaglutide showed a marked decrease in HbA1c levels, together with reduced accumulation of advanced glycation end products (AGEs), which are harmful molecules formed by chronic hyperglycemia that can damage the nerves and blood vessels. In addition, semaglutide lowered the spinal expression of pro-inflammatory cytokines such as IL-6, TNF-α and IL-1β, and attenuated oxidative stress. This was shown by lower levels of MDA, a sign of cell damage, and better antioxidant activity. These key findings indicate that oral semaglutide effectively relieves diabetic neuropathic pain and supports better neural health and quality of life in patients [7].

5. Semaglutide and diabetic nephropathy

T2D is strongly associated with diabetic nephropathy (DN), also known as diabetic kidney disease (DKD). This complication causes the kidneys to leak more protein into urine, damages the filtering units in the kidneys, and slowly lowers kidney function. Nearly half of patients who need dialysis have diabetes, showing how important it is to find treatments that protect the kidneys in T2D [8,9].

Earlier research have indicated that GLP-1 RAs and dipeptidyl peptidase-4 (DPP-4) inhibitors may help protect the kidneys. They seem to reduce diabetes-related inflammation and oxidative stress, which can help slow the worsening of diabetic kidney disease [9]. Large cardiovascular outcome trials have provided further support for a kidney benefit of GLP-1 RAs. In the LEADER trial, liraglutide treatment reduced a composite renal endpoint that included new-onset persistent albuminuria, sustained increases in serum creatinine, and a decline in estimated glomerular filtration rate (eGFR), corresponding to an approximately 22% lower risk of such events compared with placebo [10]. Similarly, in SUSTAIN-6, once-weekly injectable semaglutide not only improved HbA1c and bodyweight but also reduced major adverse cardiovascular events by about 26% and new or worsening nephropathy by 36% [11]. Together, these observations suggest that semaglutide may have a meaningful role in modifying the course of DKD.

To prove the efficacy and safety in patients with DKD, Mima and colleagues designed a short-term clinical study using oral semaglutide [12]. Six patients (four men and two women; ages ranged from 61.3 to 77.1 years with T2D and DKD received oral semaglutide at a dose of 3 mg daily for an average of nine months. Other glucose-lowering and antihypertensive agents, including SGLT2 inhibitors and angiotensin II receptor blockers, were kept unchanged during the study period. After the treatment, fasting blood glucose and HbA1c tended to decrease(P-value >0.05), although the changes were not statistically significant. The estimated eGFR improved after treatment with oral semaglutide. However, proteinuria symptoms in these participants remained unchanged. Importantly, no adverse events, such as hypoglycemia, diarrhea, or worsening of retinopathy, were reported. These findings show that oral semaglutide is safe and may help stabilize renal function in patients with diabetic kidney disease [12].

6. Semaglutide and diabetic retinopathy

In the SUSTAIN-6 trial, semaglutide showed beneficial effects on microvascular outcomes, including a reduction in nephropathy risk [11]. However, a higher rate of diabetic retinopathy complications (DRC) was observed in the semaglutide group compared with placebo. Poor glycemic control, longer duration of diabetes, and uncontrolled blood pressure are known as the key risk factors for retinopathy development. Although good control of blood glucose can delay the onset and progression of DR, a rapid improvement in blood glucose may cause transient worsening. But

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Vilsbøll and colleagues discovered that patients who developed DRC shared several common features [13]. Most had pre-existing diabetic retinopathy, a long duration of diabetes, a higher baseline HbA1c level, and more frequent insulin use. Therefore, the increased risk was concentrated among participants who already had retinal disease at the start of treatment. Also, DDC events mainly occurred in participants whose HbA1c dropped by more than 1.5% during the first 16 weeks. When this rapid decline was controlled for, the hazard ratio (HR) for DRC decreased from 1.76 to 1.22 and lost statistical significance. All in all, semaglutide did not directly cause an increase in the risk of DRC, as most cases were associated with rapid glycemic improvement and baseline retinopathy [13].

While semaglutide does not appear to directly increase the risk of retinopathy, its potential to improve retinal outcomes has drawn growing attention. Cheng and colleagues examined whether semaglutide could help prevent DR from worsening by protecting retinal blood vessels and reducing oxidative stress [14]. During the experiments, thirty male SD rats were randomly assigned into three cohorts: a control arm, a diabetic model arm and a semaglutide treatment arm. The model arm and semaglutide arm were induced by a single injection of streptozotocin (60mg/kg), and the control arm was induced by the same volume of sodium citrate buffer intraperitoneally. Blood glucose was measured three days later, and rats with a glucose level ≥13.9 mmol/L were considered successfully modeled. From the fourth week, the semaglutide group received subcutaneous injections of semaglutide (100 μg/kg once a week) for four weeks, while the control and model groups were given saline solution [14].

After treatment, semaglutide markedly improved retinal vascular morphology, reducing vessel tortuosity and restoring a more regular vascular network. It enhanced the expression of the tight-junction protein ZO-1 and decreased VEGFA overexpression, suggesting better vascular stability and reduced abnormal angiogenesis. Inflammatory cytokines IL-6 and TNF-α were also lowered, indicating relief of retinal inflammation. Overall, semaglutide may slow the onset and worsening of diabetic retinopathy [14].

7. Cardiovascular safety and protective effects of semaglutide

T2D is strongly associated with an increased risk of cardiovascular disease. Early clinical trials evaluating outcomes in patients with T2D have shown that some GLP-1Ras and SGLT2 inhibitors can lower the risk of major adverse cardiovascular events.

The PIONEER program assessed the efficacy and safety of oral semaglutide across different stages of T2D, from early monotherapy to insulin add-on therapy, using 3, 7, and 14 mg doses with 4-week escalation. Cardiovascular safety was specifically evaluated in PIONEER 6, which included 3183 patients with high cardiovascular risk-those aged ≥50 years with established CVD or CKD, or ≥60 years with CV risk factors during the observation period, major heart events happened in 3.8% of people taking oral semaglutide and 4.8% of those on a placebo, showing that semaglutide is just as safe for the heart. Deaths related to cardiovascular problems and overall deaths were also lower in the semaglutide group, confirming that it is safe for the heart in people with T2D [15].

Similar to the PIONEER trial, the SOUL trial used the same once-daily oral dose treatment of semaglutide starting at 3 mg and gradually increased to 14mg. This trial also includes patients with T2D and either atherosclerotic cardiovascular disease or chronic kidney disease. The SOUL enrolled nearly 10,000 patients with T2D at high cardiovascular risk and followed them for nearly four years. Once-daily oral semaglutide led to a modest but clinically relevant reduction in MACE compared with placebo, with the main difference driven by fewer nonfatal myocardial infarctions. Notably, this pattern of results differs from those observed in the SUSTAIN-6 trial, where the injectable

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formulation demonstrated greater efficacy in reducing the risk of cardiovascular death. The reasons for this discrepancy are not fully understood at present, potentially relating to patient characteristics, background medication use, and the longer follow-up duration in the SOUL study. Overall, existing evidence supports that both injectable and oral formulations of semaglutide provide cardiovascular benefits in high-risk populations [16].

Beyond its use in patients with diabetes, semaglutide has also been shown to lower cardiovascular risk in people with obesity but without diabetes. Lincoff and colleagues conducted the SELECT trial (Semaglutide Effects on Heart Disease and Stroke in Patients with Overweight or Obesity), a large phase 3 randomized controlled study. This trial demonstrated that weekly semaglutide treatment improved cardiovascular outcomes and reduced the overall risk of heart disease in individuals with obesity but not diabetes. These benefits appeared to result from improvements in body weight, inflammation, and vascular health rather than glucose control alone [17].

8. Semaglutide in combination therapy

Studies have found that semaglutide shows enhanced efficacy when used in combination therapy for diabetic retinopathy (DR) [18]. Rosiglitazone (RSG) is an antidiabetic drug of the thiazolidinedione class. It can decrease blood glucose level by activating peroxisome proliferator-activated receptor gamma (PPAR-γ) to enhance insulin sensitivity [18]. Both semaglutide and rosiglitazone are effective and safe for treating diabetes and slowing the DR development, which led to the exploration of their combination use for DR. Based on this finding, Yang and colleagues used a streptozotocin-induced diabetic rodent model and a high-glucose cell model to explore whether adding semaglutide to rosiglitazone could provide additional protective effects. Compared with either drug alone, the combination therapy improved metabolic control, reduced markers of oxidative stress and inflammation, and led to a more favourable retinal vascular morphology. Although these results are limited to animal and cell studies, they suggest that semaglutide-based combination therapy may enhance retinal protection [18].

Combination therapies with semaglutide are also being explored in DKD. Right now, DKD is usually treated with four main types of medicine: renin–angiotensin system inhibitors (ACEI/ARB), SGLT2 inhibitors, mineralocorticoid receptor antagonists (MRAs), and GLP-1 receptor agonists like semaglutide. In the FLOW study, semaglutide resulted in a similar degree of reduction in renal outcome events in patients with or without background MAR therapy. Furthermore, regarding albuminuria and cardiovascular outcomes, the benefits conferred by semaglutide appeared to be additive rather than merely duplicating existing effects. These findings are consistent with earlier studies of SGLT2 inhibitors combined with finerenone, in which drugs targeting different pathways produced complementary reductions in albuminuria. Overall, these findings support the idea that semaglutide can be safely combined with other kidney-protective drugs [19].

9. Conclusion

Overall, semaglutide has become a key therapeutic option for managing T2D. It lowers glucose and supports weight loss, but in daily practice it is usually used together with other medicines. Adding semaglutide to metformin, SGLT2 inhibitors, insulin or RAS inhibitors can further improve metabolic control and may also reduce the risk of renal, ocular, and cardiovascular complications. At the same time, in some regions, high drug prices counite to affect patient's long-term medication adherence and accessibility. Further work is needed to determine the most appropriate combination

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regimens for different patient populations and to explore cost reduction strategies, thereby enabling more patients to driven tangible benefit from routine clinical care.

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