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(REVIEW ARTICLE)

Beyond glycemic control: semaglutide's multifaceted impact on metabolic health

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Abstract

Achieving ideal glycemic control is essential for those with Type 2 Diabetes Mellitus (T2DM), as is avoiding hypoglycemia, controlling body weight, and lowering cardiovascular risk. A prospective treatment strategy that meets these demands is provided by agonists of the Glucagon-Like Peptide-1 receptor. These drugs block glucagon secretion, slow stomach emptying, decrease appetite, and increase glucose-dependent insulin secretion, all of which help control weight and minimize the risk of hypoglycemic episodes. Furthermore, a number of GLP-1 receptor agonists have shown promising increase in renal and cardiovascular health. Patients might have a more convenient treatment regimen because they are accessible as weekly or daily injections. Furthermore, a lower risk of cardiovascular disease has been associated with some GLP-1 receptor agonists. According to recent studies, these substances may also have a number of neuroprotective advantages, such as increasing neurogenesis, lowering cell death, shielding neurons from oxidative stress, and lowering neuroinflammation in a range of neurological disorders. These substances are therefore being investigated as potential therapies for neurodegenerative illnesses like Parkinson's and Alzheimer's.

Keywords: Semaglutide; Weight Loss; GLP-1 Receptor Agonist; Type 2 Diabetes(T2DM); Parkinson's Disease; Alzheimer's Disease

1. Introduction

The National Diabetes Statistics Report (2017) indicated that 30.3 million Americans are suffering from diabetes, with an estimated annual incidence of 1.5 million cases. Type 2 diabetes mellitus comprises 90 to 95 percent of the 30.3 million afflicted individuals. T2DM is a complicated condition marked by Insulin resistance and a progressive deterioration in the ability of pancreatic β-cells to store insulin, which results in fluctuating blood glucose levels (3). One well-known and effective therapeutic option for Type 2 Diabetes Mellitus is glucagon-like peptide-1 receptor agonists, or GLP-1RAs. These drugs are based on peptide composition designed for triggering the receptor for the gut-derived hormone GLP-1, which is essential for glucose homeostasis. Within this class of medications, GLP-1RAs differ in their origins and molecular characteristics. Exenatide and lixisenatide are derived from the peptide exendin (a hormone found in Gila monster saliva), which resembles GLP-1 and maintains its activity. In contrast, albiglutide, dulaglutide, semaglutide, and liraglutide are analogs of GLP-1, representing modified versions of its native structure. (4). Lower utilization rates may have resulted from the fact that glucagon-like peptide 1 receptor agonists were first only accessible for subcutaneous injection due to the challenges linked to oral peptide delivery. In order to counteract this, sodium N-8-2-hydroxybenzoyl amino caprylate was used to create an oral Semaglutide formulation that would encourage the stomach to absorb the drug. It is protected from stomach enzymes by this mechanism. In 2019, the first GLP-1RA, oral Semaglutide, that can be taken by mouth, received approval for treating type 2 diabetes. The PIONEER clinical trial investigated formerly-diurnal Semaglutide at doses of 3, 7, and 14 mg taken orally in the morning on an empty stomach, as a monotherapy, in combination with other oral glucose-lowering medications, and when added to insulin regimens. The results showed clinically significant reductions in hemoglobin A1c (HbA1c) levels and weight of the body among individuals with Type 2 Diabetes. The initial oral GLP-1-based treatment for T2DM was approved as a

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result of the PIONEER program's findings, increasing treatment choices and perhaps promoting the earlier and more frequent use of GLP-1RAs for improved glycemic control (5). Considering the beneficial effects of GLP-1RAs on neuropathological characteristics, a connection between T2D and neurodegenerative disorders for example, Parkinson's and Alzheimer's may exist. Affected individuals, as well as their families, careers, and society in general, are significantly impacted by neurodegenerative disorders on a physical, cerebral, social, and provident level (6). Semaglutide influences various organ systems, as illustrated in Fig.1. Enhancing insulin sensitivity, slowing gastric emptying, and diminishing calorie intake and fat absorption. It also boosts feelings of fullness, protects the nervous system, and decreases fat accumulation, which makes it useful for regulating metabolism.

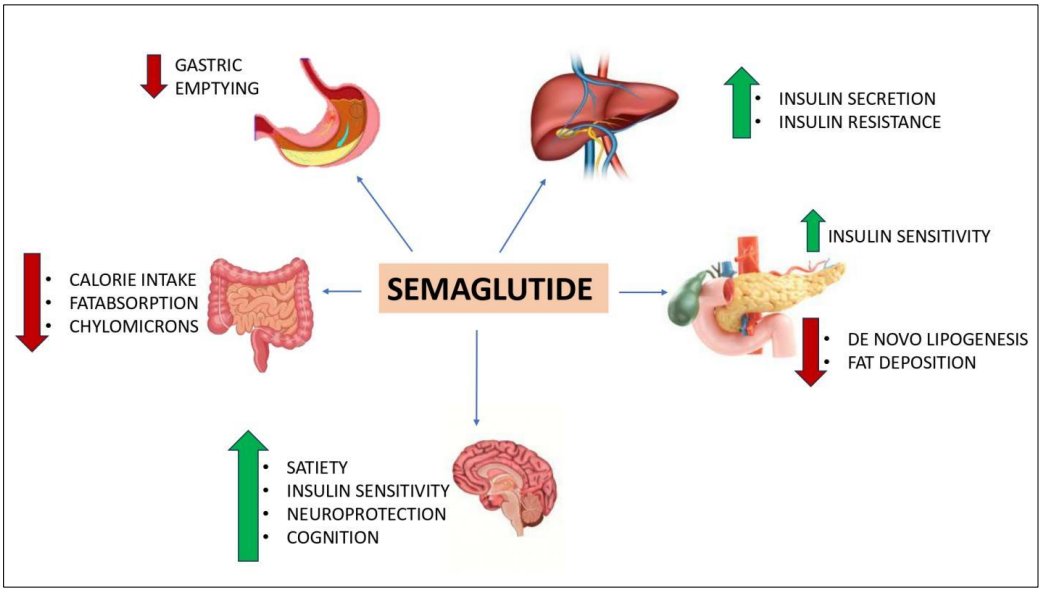

Figure 1 Mechanism of action of semaglutide on various organ systems

1.1. Semaglutide as Therapeutic Option for Treatment Type 2 Diabetes Mellitus

Type 2 diabetes mellitus is treated by using the pharmaceutical active ingredient semaglutide. It is an agonist of the glucagon-analogous peptide-1 (GLP-1) receptor. This indicates that it functions by imitating the effects of GLP-1, a naturally occurring hormone that aids in blood sugar regulation (1)(7). GLP-1 receptor binding and activation is the mechanism of action of semaglutide. Due to its degradation by the enzymes DPP-4 and neutral endopeptidase, native GLP-1 has a short half-life of approximately one to two minutes (8). Semaglutide, however, varies from natural GLP-1 in two amino acid positions due to structural changes. The substitution of α-aminoisobutyric acid for alanine at position 8 increases semaglutide's resistance to degradation mediated by DPP-4. At position 34, arginine is used in place of lysine. Furthermore, the acylated lysine at position 26 enhances semaglutide's affinity for albumin. A once-weekly dosage schedule is made possible by the much-extended half-life of around one week (165 hours) that these structural alterations produce (9). Endogenous GLP-1 and other class of comparators attach to the GLP-1 receptor, resulting in insulin secretion from β-cells and inhibition of glucagon secretion from α-cells in the pancreas. Apart from its high expression in pancreatic β-cells, GLP-1 receptor is also present in the stomach and duodenum, which might be connected to an earlier feeling of fullness and delayed gastric emptying (10). The receptor is also found in the heart's myocytes, the sinoatrial node, and the smooth muscle cells of blood vessels (arterioles or arteries) (7).

2. Therapeutic effectiveness

2.1. Dose-Finding Investigation and Additional Phase II Investigations

12-week phase II research was carried out to ascertain the ideal dosage schedule for the phase III clinical trial program (11). 415 patients with type 2 diabetes were randomly given semaglutide subcutaneous injections at stable dosages of 0.1, 0.2, 0.4, and 0.8 mg or escalated from 0.4 mg to 1.6 mg once weekly. This was contrasted among a placebo group and liraglutide (given at daily dosages of 1.2 or 1.8 mg). The results showed a dose-dependent and clinically meaningful decrease in weight and HbA1c levels following a 12-week course of semaglutide medication. In the second Japanese research, 308 type 2 diabetic patients were randomly assigned to receive 100 mg of sitagliptin once a day or 0.5 or 1.0 mg of semaglutide once a week. After 30 weeks of therapy, semaglutide significantly reduced HbA1c levels (20.8

mmol/mol for the 0.5 mg dosage and 24.1 mmol/mol for the 1.0 milligram dose), but sitagliptin only demonstrated a reduction of 7.7 mmol/mol (12).

2.2. Phase III Study Program

Six studies were part of the "Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes" (SUSTAIN) clinical research program. The change in HbA1c from baseline to the end of the trial (EOT), which lasted between 30 and 56 weeks, was the main outcome that was assessed. A cardiovascular outcomes study (CVOT) was also carried out (12). 8,416 individuals with type 2 diabetes took part in the research overall. Semaglutide was tested in a number of type 2 diabetes populations, including people who had never taken the medication before, as well as those receiving insulin, metformin, thiazolidinediones, sulfonylureas, and other oral antidiabetic medications (OADs). All the studies had been designed as randomized controlled trials to assess the effectiveness of Semaglutide compared to a placebo, other GLP-1 receptor agonists, DPP-4 inhibitors (DPP4i), and long-acting insulin analogs (12).

2.3. Semaglutide as Therapeutic Option for Treatment Obesity

A major global public health concern, obesity is a chronic illness (13). It is linked to major consequences such Type 2 Diabetes, nonalcoholic fatty liver disease and cardiovascular disease, and can cause insulin resistance, hypertension, and dyslipidemia (14). Obesity also shortens life expectancy. Furthermore, it has recently been linked to an increased risk of mortality among patients suffering from coronavirus disease 2019

(COVID-19), an increase in hospitalizations, and the requirement for mechanical ventilation (15). Although diet and exercise are essential lifestyle strategies for managing weight, it can be challenging to sustain weight loss over the long term (16). Clinical recommendations advocate for adjunctive medication, especially for individuals with a body mass index or BMI above 30, or above 27, for those with accompanying medical conditions. The calculation of BMI involves dividing the person's weight (in kilograms) by the square of their height (in metres). Nonetheless, due to their limited effectiveness, safety concerns, and high expense, the use of drugs that are currently available frequently restricted (17). Research indicates that Semaglutide enhances dysfunctional adiposity associated with obesity by promoting the adipose tissue browning and generation of new adipocytes via GLP-1 (18). The body consists of two main types of adipose tissue: white adipose tissue or WAT, which stores energy, and brown adipose tissue or BAT, which generates heat. In addition, there is beige adipose tissue or BeAT, which has characteristics of both white and brown adipocytes (18).

Seaglutide signaling may induce browning of White adipose tissue or WAT and the differentiation of white adipose tissue into brown adipose tissue or BAT, according to interactions with the transcription factors that have been identified. By increasing fatty acid oxidation capability and improving mitochondrial biogenesis, this procedure may speed up metabolism and prevent weight gain. However, the majority of the evidence for this theory comes from a small number of preclinical models, and further investigation is required to determine the precise mechanisms at play (18).

According to a study, when semaglutide was used in combination with a lifestyle modification, adults who were overweight or obese and had either one or more weight-related medical concerns but had no diabetes lost weight at an average of 14.9% of their baseline weight. When compared to the placebo group that received the identical lifestyle intervention, this weight loss was 12.4 percentage points larger. Compared to 4.0% to 10.9% weight reduction seen with presently licensed anti-obesity drugs, the semaglutide group's average weight loss of 14.9% is noticeably greater (19). Furthermore, compared to just 32% of participants in placebo group, 86% of patients who took semaglutide lost about 5% or even more baseline body weight. The standard for a clinically significant response is generally accepted to be this 5% loss (20). Both direct and indirect effects on the brain are thought to be accountable for the weight reduction observed with semaglutide, which leads to a decrease in energy intake because of decreased appetite (21).

Semaglutide's safety was comparable to that of the phase 2 study, which employed a once-daily dosage schedule for obese people. The safety findings were also in line with studies of people using subcutaneous semaglutide once a week with Type 2 Diabetes, which involved over 8,000 participants that received dosages up to 1 mg. These results are also consistent with the safety profile that has been demonstrated for the whole family of glucagon-like peptide-1 receptor agonists (44).

3. Semaglutide in Patients with Obesity and Heart Failure with Preserved Ejection Fraction

More over half of all heart failure patients in the US are heart failure preserving ejection fraction, and their frequency is rising (22). Most people who suffer from this illness are either fat or overweight. According to mounting data, obesity and excess body fat may not only be coexisting conditions but also have a major impact on the onset and course of heart

failure with preserved ejection fraction (23). Compared to patients with heart failure with preserved ejection fraction who are not obese, those who have both conditions typically have more negative hemodynamic and clinical features, a higher burden of symptoms, a lower functional capacity, and a more significantly reduced quality of life (24). Whether pharmacotherapies that target obesity particularly can enhance exercise performance, lessen physical restrictions, and alleviate discomfort in this unique patient population is yet unknown. A potent GLP-1 receptor agonist that has been authorized for long-term weight control is semaglutide, which is taken subcutaneously once a week at a dose of 2.4 mg. It was shown to reduce body significantly weight in overweight and also obese people and to have a beneficial impact on cardiometabolic risk factors (1)(25). Our goal was to find out if giving 2.4 mg of semaglutide once a week to patients with obesity and heart failure with a preserved ejection fraction may result in outcomes such as weight loss, improvements within exercise function, and a decrease in symptoms and physical limitations. Compared to patients getting a placebo, semaglutide-treated patients had a significantly decreased risk (26%) of the main composite outcome, which includes nonfatal stroke, nonfatal myocardial infarction, and death due to cardiovascular effects. A noteworthy 39% drop in the rate of nonfatal strokes and a nonsignificant 26% drop in the rate of nonfatal myocardial infarctions were the main causes of this decreased risk. The rate of cardiovascular fatalities did not show any discernible variation. Similar risk decreases were observed with dosages of 0.5 milligrams and 1.0 milligrams (25).

3.1. Semaglutide as Therapeutic Option for Treatment Neurodegenerative Disorders

Common types of progressive neurodegeneration that result in mental incapacitation are neurodegenerative disorders such as Parkinson's disease and Alzheimer's disease. According to some studies which were done recently, resistance to insulin has a role in the brain and is directly connected to the pathophysiology of Parkinson's and Alzheimer's illnesses (26). GLP-1, or glucagon-like peptide-1, is crucial for improving insulin transmission in the brain. The brain's GLP-1 receptors are also implicated in cell apoptosis, synaptic transmission in hippocampus neurons, and cognition. While a lack of these receptors can raise the risk of seizures and neurodegeneration, their overexpression is linked to enhanced cognitive performance and neuroprotection (2)(27).

3.2. Alzheimer's Disease (AD)

The hallmark of Alzheimer's disease (AD) is cognitive and memory decline, which impacts speech, behavior, motor function, and visuospatial orientation. AD, which is the most common type of dementia, is associated with progressive neurodegeneration and is frequently accompanied with brain cerebrovascular lesions. The pathophysiology of AD includes cortical atrophy, growth of the frontal and temporal horns withinside the lateral ventricles, and a decreased weight of the brain. Frequent pathological properties of AD are said to be extracellular amyloid plaques, intracellular neurofibrillary complications, brain amyloidopathy, plain body, exposure-positive neuro-filament threads, activated microglia and reactive stellar states(astrocytes). (28). In human neuroblastoma, Chang et al. Semaglutide showed that it has neuroprotection benefits against amyloid-β plaque, a critical feature of Alzheimer's disease. Increased inhibition of apoptosis may be the mechanism behind this effect (29). The progression of 14 mg oral semaglutide in clinical phase-3 studies in patients with Alzheimer's disease is supported by a series of preclinical and phase 2 studies. Two placebo-controlled phase 3 studies, Evoke and Evoke +, were launched to assess the efficacy of 14 mg oral dosage of semaglutide in the early stages in patients with Alzheimer's disease. The changes in Alzheimer's disease, the time required to develop an assessment of dementia and clinical dementia are some of the main findings of these studies (43).

3.3. Parkinson's diseases (PD)

The loss of axons from dopaminergic neurons within the Substantia nigra, that project to the nigrostriatal pathway, due to their degradation, leads to Parkinson's disease. The illness is characterized by a variety of both the motor symptoms and non-motor symptoms, such as psychosis, bradykinesia, stiffness, tremors, ataxia, shuffling gait and sleep disturbances. Two crucial pathogenic features of this illness are the protein deposits of alpha-synuclein (Lewy bodies) and the astrocyte and microglial activation. Parkinson's disease, both familial and idiopathic forms, is associated with mutations in various genes such as PARK7, PINK1, SNCA, and LRRK2 (30). Since 2018, Oslo University Hospital has recorded a phase-2 clinical study aimed at examining the efficacy of Semaglutide as a treatment option for Parkinson's disease. (30).

4. Adverse drug reactions

Although Semaglutide provides considerable therapeutic advantages, it is linked to a range of possible adverse effects, as shown in Fig. 2. This includes gastrointestinal events, increased heart rate, pancreatitis, gallbladder disorders, thyroid cancer, and renal effects, all of which require careful monitoring during treatment.

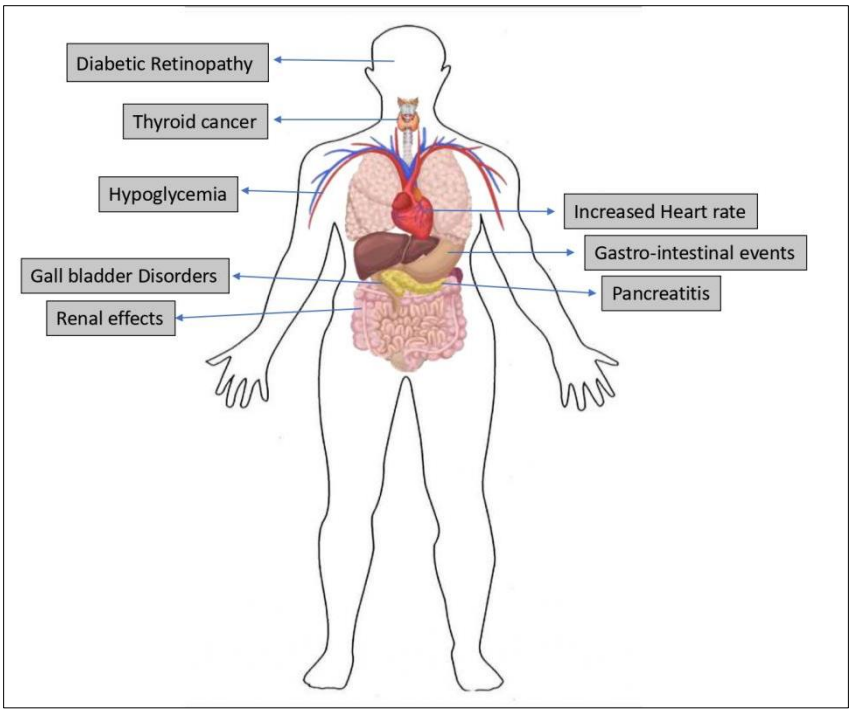

Figure 2 Potential adverse effects of semaglutide on different organ systems.

- **Hypoglycemia:** GLP-1 agonists have the potential to induce hypoglycemia through the mechanism of reducing blood glucose levels. The likelihood of hypoglycemia increases significantly with higher doses of semaglutide and when it is used together with other anti-hyperglycemic medications such as insulin, metformin, or sulfonylureas. (31).
- **Gastrointestinal (GI) Adverse Effects**: In the phase 3 studies, both oral and subcutaneous semaglutide was linked to gastrointestinal issues, including diarrhea, nausea & vomiting. This medication class is familiar with these consequences. Subcutaneous semaglutide induced nausea in 11.40% to 20.00% of individuals (as opposed to placebo which was 3.30% to 8.00%), vomiting in 4.00% to 11.50% (as opposed to placebo which was 2.00% to 3.00%), and diarrhea in 4.50% to 11.30% (as opposed to placebo which was 1.50% to 6.00%) among patients administered with the drug over a period of 30 weeks.(31).In phase-3 studies, gastrointestinal problems account for up to 12% of medication discontinuations. These conclusions are also supported by empirical data. 9.5% of 189 Type 2 Diabetes Mellitus patients, who began subcutaneous semaglutide stopped treatment because of gastrointestinal (GI) issues, and 5.8% had side symptoms that prevented them from increasing the dose, according to one retrospective research (32). 10.4% of 164 T2DM patients who were switched from a different glucagon-like peptide-1 receptor agonist to Semaglutide stopped taking it due to negative gastrointestinal side effects (33).
- **Acute kidney damage:** It can result with semaglutide, especially in individuals who suffer from nausea, vomiting, diarrhea, or dehydration while receiving medication. Volume depletion brought on by these symptoms may be the reason of the elevated risk of kidney damage. Instead of just addressing the symptoms of volume depletion, it is advised to stop taking semaglutide or lower the dosage (42).
- **Gallbladder Disorders:** Cholelithiasis (gallstones) and cholecystitis (gallbladder inflammation) are two gallbladder and biliary system problems that semaglutide has been linked to (34). The precise processes that underlie these negative consequences are yet not entirely understood. Nevertheless, current in vitro and animal research indicates that GLP-1 (glucagon-like peptide-1) may enhance the functional activity and proliferation of cholangiocytes, the cells lining the bile ducts. The development of gallbladder problems may be facilitated by this improvement (35). Additionally, some studies have theorized that semaglutide may decrease gallbladder emptying and lengthen gallbladder refill periods by inhibiting the release of cholecystokinin, a hormone that stimulates gallbladder contraction. These elements taken together could contribute to the development of gallbladder problems (36).
- **Pancreatitis:** Although semaglutide treatment has been linked to some documented incidences of acute pancreatitis, results from the SUSTAIN 6 trial indicate that the incidence rate of pancreatitis is similar for the semaglutide and placebo groups (37). It is still unknown if semaglutide and acute pancreatitis are causally related. Semaglutide and other GLP-1 receptor agonists work by directly activating GLP-1 receptors found in

exocrine duct cells and pancreatic islet beta cells. According to research, this stimulation can cause the cells lining smaller ducts to proliferate, which might result in hyperplasia, elevated pancreatic weight, duct obstruction, back pressure, and either acute or chronic inflammation later on (38).

- **Thyroid C-cell tumor risk:** Animal research revealed the occurrence of thyroid C-cell tumor`s during the initial phases of semaglutide medication development (39). However, it is yet unknown how semaglutide and thyroid tumors in people are related. Individuals with MEN 2 (multiple endocrine neoplasia type 2) syndrome, or those who have a past history or familial history of MTC (medullary thyroid cancer), might have an increased risk (40). Also, Liraglutide, another glucagon-like peptide-1 receptor agonist, has been linked to documented cases of MTC, according to the manufacturer.
- **Diabetic retinopathy:** Semaglutide medication may increase the chance of developing diabetic retinopathy, especially in individuals who already had retinopathy at baseline. It is yet unclear exactly how semaglutide and the development or course of diabetic retinopathy are related. However, some studies indicate that there could be a connection to quick gains in glycemic control (41).

5. Conclusion

Semaglutide, which is a glucagon-like peptide-1 receptor agonist (GLP-1RA), has surfaced as an innovative treatment choice for type 2 diabetes mellitus (T2DM), obesity, as well as associated complications. Semaglutide mimics GLP-1 effects to enhance insulin secretion, lower glucagon production, delay gastric emptying, and promote weight loss. Due to its structural modifications, including resistance to DPP-4 degradation and an extended half-life, it can be administered conveniently on a weekly or daily basis, thereby enhancing patient adherence. The clinical programs PIONEER and SUSTAIN have reliably shown its effectiveness in lowering HbA1c levels, body weight, and cardiovascular risks when compared to other anti-diabetic agents.

In addition to its known function in T2DM, semaglutide demonstrates encouraging potential for tackling obesity and its metabolic repercussions through the promotion of white adipose tissue browning and enhancement of mitochondrial function. Moreover, its neuroprotective effects observed in preclinical models indicate a potential function in the therapy of neurodegenerative diseases like Parkinson's and Alzheimer's, where insulin resistance may play a part in the disease process. While semaglutide has its advantages, it comes with drawbacks such as gastrointestinal symptoms, gallbladder issues, and possible dangers of hypoglycemia and pancreatitis. To reduce these risks, it is crucial to carefully adjust the dose and monitor the patient. To sum up, semaglutide marks an important progress in the treatment of chronic diseases like diabetes and obesity, as well as possibly neurodegenerative disorders. Its dual effects on glycemic control and weight management, along with its positive cardiovascular profile, highlight its transformative potential. Nonetheless, additional studies are necessary to investigate its long-term safety, mechanisms, and broader therapeutic uses in neurodegenerative and cardiovascular diseases.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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