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Mechanism of Action and Clinical Analysis of Semaglutide in Weight Loss

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Abstract:

Semaglutide is a long-acting Glucagon-Like Peptide-1 Receptor Agonist (GLP-1RA). It was initially applied in the treatment of type 2 diabetes mellitus, and later widely used in obesity management due to its prominent weight-loss effect. As a novel long-acting GLP-1RA weight-loss drug, compared with traditional GLP-1RAs, it undergoes molecular structural modification to achieve reversible albumin binding, which reduces renal clearance and degradation by dipeptidyl peptidase IV. Meanwhile, it maintains high affinity to GLP-1 receptors, extending its half-life to 156 hours. The long half-life supports once-weekly injection, greatly improving patients' treatment compliance. Its structure is highly similar to natural human GLP-1, with an amino acid sequence homology of 94%. For the above reasons, it has attracted increasing attention. Accordingly, there is a growing demand for comparing the efficacy of semaglutide with that of other weight-loss drugs. This article systematically summarizes the core weight-loss mechanism of semaglutide, efficacy data from large-scale clinical trials, characteristics of adverse reactions and clinical safety, and compares semaglutide with several other weight-loss drugs to clarify their differences and efficacy gaps. It aims to provide objective scientific evidence for the rational clinical application of relevant drugs and scientific weight loss for the public.

Keywords: Semaglutide; weight loss; type 2 diabetes mellitus.

1. Introduction

Obesity has become a major global public health challenge. It is closely associated with type 2 diabetes mellitus (T2DM), cardiovascular diseases, non-alcoholic fatty liver disease, multiple malignant tumors and other chronic complications, which seriously threaten human health and quality of life. According to data released by the World Health Organization, the number of obese people worldwide has exceeded one billion at present. The disease burden caused by overweight and obesity keeps rising, placing a heavy burden on the medical system. The situation of obesity prevention and control in China is also severe.

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The Report on Nutrition and Chronic Disease Status of Chinese Residents (2020) indicated that the overweight rate of Chinese adults reached 34.3% and the obesity rate was 16.4%. The total number of overweight and obese people has exceeded 500 million, and the detection rate of obesity among children and adolescents continues to increase. Obesity has become a key problem affecting national health [1].

Lifestyle intervention including dietary control, regular physical exercise and behavioral correction serves as the foundation of obesity intervention. However, long-term follow-up studies have confirmed that less than 5% of people can achieve sustained weight loss merely relying on lifestyle intervention. Most individuals experience significant weight rebound after the intervention is terminated, making it difficult to achieve the goal of long-term weight management [2]. In this context, safe, effective and tolerable pharmacological treatment has become an important research direction in obesity management, and a variety of weight-loss drugs have entered clinical research and application successively.

As a second-generation long-acting Glucagon-Like Peptide-1 Receptor Agonist (GLP-1RA), semaglutide was initially approved for glycemic control in T2DM. It has gradually become a core drug in the field of obesity treatment owing to its remarkable weight-loss effect observed in clinical trials. In June 2021, the U.S. Food and Drug Administration (FDA) officially approved semaglutide for the chronic weight management of obese or overweight adults, ushering in a new era of the application of GLP-1RAs in weight loss [3]. In June 2024, the National Medical Products Administration (NMPA) of China also approved its indication for weight loss, providing a new treatment option with sufficient evidence-based medical evidence for overweight and obese patients in China [4].

Based on the above background, this paper systematically sorts out the core weight-loss mechanism of semaglutide, efficacy data of large-scale clinical trials, adverse reaction characteristics and clinical safety, and conducts analysis combined with the latest research progress, so as to provide theoretical support and practical reference for standardized clinical application and scientific weight loss of patients.

Unlike previous reviews that mainly focused on the weight-loss efficacy of semaglutide, this review comprehensively discusses its multi-target mechanisms, long-term clinical outcomes, safety profile, and emerging evidence from real-world practice. In addition, recent advances in obesity pharmacotherapy are integrated to critically evaluate the clinical position of semaglutide and its future development. This work may provide updated theoretical support for individualized obesity management and guide the optimization of GLP-1 receptor agonist-based therapeutic strategies.

2. Molecular Mechanism of Semaglutide in Weight Loss

The weight-loss effect of semaglutide is realized through the coordination of central appetite suppression and peripheral metabolic regulation such as improving insulin resistance. In the central nervous system, semaglutide can activate GLP-1 receptors in the hypothalamus, in ways that affect the activity of neural pathways related to food intake, reward, and energy expenditure, both directly and indirectly, by reducing energy intake through regulating appetite and delaying gastric emptying or exerting strong appetite-suppressing effects, ' enhance the transmission of satiety signals, and significantly reduce the body's craving for high-calorie food, cutting daily calorie intake by 15% to 20% and controlling weight gain fundamentally. Recent basic studies have found that Adcyap1+ neurons in the dorsal vagal complex (DVC) of the brain are the key targets mediating the weight-loss effect of the drug [5]. Selective activation of these neurons mainly promotes the decomposition of adipose tissue, exerts little impact on lean body mass (muscle tissue), and causes weak taste aversion, thus realizing the ideal effect of "fat loss while muscle preservation" to a certain extent.

In terms of peripheral metabolism, semaglutide inherits the classic mechanism in the treatment of T2DM, namely improving insulin resistance [5]. This mechanism can not only effectively reduce fat synthesis, but also significantly facilitate the browning of white adipose tissue, raising the basal metabolic rate by approximately 5%-8% [6]. In addition, the drug can also comprehensively optimize the blood lipid profile, and effectively reduce the levels of serum triglycerides and low-density lipoprotein cholesterol [7].

Therefore, semaglutide has therapeutic effects for diseases such as blood sugar reduction and weight loss, with broad clinical application prospects. It holds good application value for both weight management in diabetic patients and overweight/obese non-diabetic patients.

3. Clinical Data Analysis of Semaglutide in Weight Loss Treatment

The STEP (Semaglutide Treatment Effect in People with obesity) program is a large-scale phase IIIb multicenter clinical trial project led by Novo Nordisk, specially designed to evaluate the weight-loss efficacy of semaglutide at the standard dose of 2.4 mg in obese and overweight populations. With rigorous trial design, large sample size

and scientific control setting, it has provided sufficient clinical evidence for the weight-loss indication of the drug [3].

The STEP 1 trial was a controlled study conducted on simple obese people without diabetes. The results showed that the average weight of subjects in the semaglutide intervention group decreased by 14.9%, while that in the placebo group only decreased by 2.4%. More than one third of the medicated subjects achieved a weight loss of over 20%, indicating an outstanding short-term weight-loss effect [8]. The STEP 2 trial focused on obese patients complicated with T2DM. The results verified that semaglutide could still achieve an average weight loss of 10.6% even in people with poor metabolic foundation, bringing dual benefits of hypoglycemia and weight loss [9]. The STEP 3 trial further combined lifestyle behavioral intervention. The results demonstrated that the combined application of the drug with diet and exercise management enabled subjects to achieve an average weight loss of 16%, with an average weight reduction of nearly 17 kilograms, and more than 70% of the subjects reached the weight loss standard. It proved that the drug has a favorable synergistic effect with lifestyle intervention [10]. The long-term follow-up trials STEP 4 and STEP 5 supplemented long-term efficacy data. Continuous medication can steadily maintain the weight-loss outcomes with a low risk of weight rebound under two-year long-term intervention, making it suitable for long-term chronic weight management [11-12].

In addition to the standard therapeutic dose, current clinical research is exploring multiple approaches around different dosages and routes of administration to further improve the clinical application plan of semaglutide. The data from the STEP-UP study of high-dose exploratory trials showed that 7.2mg high-dose semaglutide had a stronger weight loss effect, with an average weight loss of 18.7%, significantly better than the conventional 2.4mg dose. Nearly half of the patients in the high-dose group lost more than 20% weight, providing a more effective treatment option for severely obese individuals [13]. To improve compliance issues caused by injection administration, the development and clinical trials of oral semaglutide are gradually being implemented. The OASIS series of trials is the core clinical study of oral semaglutide. OASIS 1 and OASIS 4 have respectively validated the weight loss effects of two oral doses of 50mg and 25mg. Under long-term oral intervention, subjects can achieve a stable weight loss of over 13% [14]. Subcutaneous injection and oral administration have stable and similar therapeutic effects, which can meet the medication preferences of different patients and further broaden the clinical application scenarios of semaglutide.

Firstly, there are differences between semaglutide and Tirzepatide. Tirzepatide is a glucose dependent insulinotropic polypeptide. It can not only promote insulin release and inhibit glucagon, but also accelerate fat breakdown by acting on GIP receptors to improve lipid metabolism. In theory, it should be more effective than semaglutide in improving metabolic related diseases and weight control. Comparison of Tirzepatide and Semaglutide after treatment. The study found that the decrease in BMI value of patients treated with tilboptide was 0.84 more than that of the semaglutide group, and the difference was not statistically significant (MD=-0.84, 95% CI: -1.81~0.14). The combination of semaglutide with other hypoglycemic, lipid-lowering, or weight-loss drugs can further enhance weight control effectiveness and comprehensively improve metabolic disorders. Combination therapy is more suitable for patients with severe obesity or multiple metabolic abnormalities, but the long-term safety, optimal compatibility, and dosage regimen of the combination therapy still need to be validated by more high-quality clinical studies.

The overall safety of semaglutide is good, with mild to moderate adverse reactions, most of which can be gradually tolerated with prolonged medication time. During clinical use, potential risks such as acute pancreatitis and gallbladder disease should be monitored. It is strictly prohibited to use it for individuals with a personal or family history of medullary thyroid cancer. During medication, medical advice should be strictly followed and relevant indicators should be regularly monitored

4. Adverse Reactions and Safety of Semaglutide

Although semaglutide has shown remarkable efficacy in weight loss, its potential adverse reactions cannot be ignored. Firstly, gastrointestinal reactions are the most common adverse events, mainly manifested as nausea, vomiting, diarrhea, constipation Hypoglycemia, decreased appetite, cholelithiasis, fatigue, elevated lipase, elevated amylase, and other symptoms; occasional allergic reactions, taste perversion, increased heart rate, acute pancreatitis, and injection site reactions have also been reported.. This type of reaction is mostly mild to moderate, with an incidence rate of about 30% to 50%, and can gradually be tolerated with prolonged medication time [3,8]. In addition, clinical data shows that the use of GLP-1 receptor agonists may increase the risk of acute pancreatitis and gallbladder diseases such as gallstones [15]. Meanwhile, based on animal experimental results, the drug has a potential risk of triggering thyroid C-cell tumors, therefore it is contraindicated for patients with a personal or family

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history of medullary thyroid cancer [3,5].

Overall, the currently available evidence indicates that the safety profile of semaglutide is generally favorable, with most adverse events being predictable, dose-dependent, and manageable through gradual dose escalation and appropriate supportive care. Although serious adverse events, such as acute pancreatitis and gallbladder disease, occur infrequently, careful patient selection and regular clinical monitoring remain essential, particularly in individuals with pre-existing risk factors or contraindications. Therefore, the substantial benefits of semaglutide in weight reduction and metabolic improvement should be balanced against its potential risks to achieve individualized and safe obesity management.

5. Conclusion

Simeglutide is a clinically proven long-acting GLP-1 receptor agonist that relies on a dual mechanism of central appetite suppression and peripheral metabolism regulation. It has demonstrated outstanding clinical value in weight management for overweight and obese populations. Large scale multicenter clinical trials have fully confirmed that this drug can achieve significant and lasting weight loss effects at conventional therapeutic doses, while simultaneously improving multiple metabolic abnormalities such as blood lipids and insulin resistance. It provides a safe and effective drug intervention plan for obese patients with simple obesity and concomitant metabolic disorders.

At present, there are still certain limitations in the clinical application of semaglutide. Gastrointestinal discomfort is common in the early stages of medication, and there are strict contraindications for special populations. The long-term economic cost of medication is high, and some people may experience weight rebound after discontinuation. These issues limit the widespread use of the drug. By optimizing drug structure, improving administration methods, and perfecting safety monitoring systems, future research aims to further balance weight loss efficacy and medication safety, providing a more comprehensive treatment plan for the long-term management of chronic obesity diseases.

Future studies should focus on optimizing semaglutide-based therapeutic strategies through individualized treatment, combination therapies, and long-term efficacy and safety evaluation. In addition, identifying reliable biomarkers to predict treatment response and prevent weight regain may facilitate precision obesity management and improve long-term clinical outcomes.

Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

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