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Current Status of Semaglutide Injection and

Development Prospects in China

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Abstract:

Obesity is a global issue that closely affects public health, and China's obesity rate is among the highest in the world. Recently, Semaglutide injection was approved for marketing in China as the first weekly formulation for long-term weight control. This review consolidates and analyzes various types of research related to Semaglutide regarding weight loss, to comprehensively describe the different aspects of the drug. As a glucagon-like peptide 1 receptor agonists (GLP-1RA), Semaglutide works by mimicking the action of innate hormone to enhance the cell signaling activity and corresponding outcome. It has been approved to effectively reduce weight and improve weight-related factors in overweight or obese patients with a guaranteed safety profile. Comparing to traditional methods of losing weight, this medication is time and effort-saving, which makes it highly competitive in this field. Although there are still unsolved issues and challenges faced by the drug, such as high price and acceptance among doctors and patients, it is highly likely to become a new and anticipated method of weight management in China

Keywords: Semaglutide injection; obese; weight management.

1. Introduction

Obesity has been a global concern due to its detrimental impact on health. It is well known to be the cause of a number of chronic illnesses, such as Type 2 Diabetes Mellitus (T2DM), cardiovascular disease (CVD), respiratory conditions, and even a variety of potentially fatal tumors [1]. As the second most populous country in the world, China also faces a significant challenge with obesity. The National Health Commission (NHC) released a report on adult obesity, which states that the rates of obesity and overweight among residents who are 18 years of age and older are 16.4% and 34.3%, respectively. These rates exceed half of the population and are still rising [1]. However, there are few weight loss medications in China, instead, people are often attracted by the exaggerated or even false propaganda of some weight loss product, the mild outcome shows slight or no weight reduction after use, while the severe outcome may adversely affects health, such as affecting blood pressure and heart rate, interrupting the endocrine system, repeatedly stimulating the intestinal tracts to increase risk of rectal cancer [2].

Recently, National Medical Products Administration (NMPA) has approved Semaglutide injection (Wegovy) for marketing in China to manage weight over the long term [3]. Semeglutide injection, a medication originally prescribed for long-term glycemic control in patients of T2DM, is also recognized for other health-promoting effects such as weight loss, reducing both blood pressure and total cholesterol. Semaglutide injection has two formulations, Ozempic and Wegovy, the latter one is specifically developed for long-term weight management. The drug is a member of the glucagon-like peptide 1 receptor agonist (GLP-1 RA) class of incretin mimetics that enhances insulin secretion to reduce blood sugar levels. The primary cause of the weight loss effect is its capacity to postpone stomach emptying and promote satiety, which lowers overall caloric intake [4]. As the first and only approved weekly formulation of GLP-1RA for long-term weight management, Semaglutide injection significantly contribute to addressing overweight and obesity among populations in a safe and efficient way in China [3]. Nevertheless, subsequent research and data are required to confirm the effectiveness of this drug in Chinese residents, since most studies are conducted in ethnically distinct populations.

This review consolidates findings from a comprehensive search of relevant literature, including cohort studies, retrospective analysis, clinical trials, and meta-analysis. By analyzing these studies, this review seeks to give a thorough understanding of Semaglutide's mechanisms of action, its comparative effectiveness against other weight management interventions and among populations with different health status, and its safety profile and potential

side effects.

2. Mechanism of Action as a GLP-1RA

GLP-1RA is a type of medication that mimics the the way the endogenous hormone GLP-1 works, thus stimulating the signaling of the pathway and improving the outcomes, including glycemic control and weight reduction [5]. When GLP-1R is activated by its ligand GLP-1, it stimulates the pancreas to release insulin from the β-cells while inhibiting the release of glucagon into the circulation, to prevent conditions of high blood glucose [6]. Meanwhile, GLP-1R is also located in the gastrointestinal (GI) tract and is produced by the PPG neurons in the central nervous systems (CNS). When activated, it decreases gut motility and appetite, therefore limiting total food intake and consequently leading to weight loss, as shown in Figure 1 [7,8].

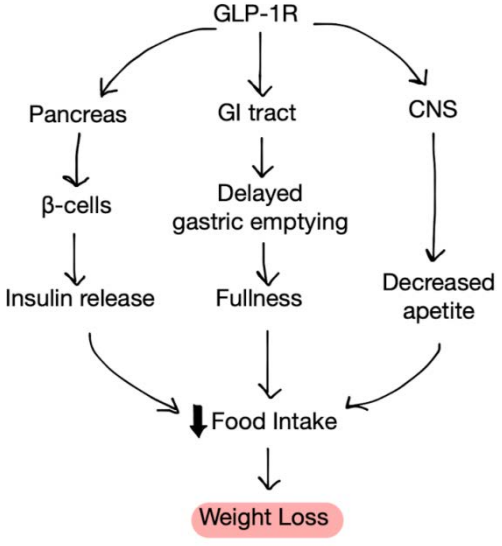

Figure.1 Mechanism of action of Semaglutide on weight loss

Although GLP-1R is located broadly in human body, innate activity of it may not be potent enough to induce weight loss, since the ligand GLP-1 has a half-life of only 2 min and is easily broken down by the dipeptidyl peptidase 4 (DPP-4) protease [9]. However, in the contrast, GLP-1RA has a considerably longer half-life that enables it to extend and intensify the therapeutic action. For instance, Semaglutide has a half-life of about one week, which allows the medication to sustain the effect in human body with a subcutaneous injection of once a week [7].

3. Efficacy

One cohort study provides mportant information about how Semaglutide injection affects weight loss in patients who are overweight or obese. The study included patients with a BMI of 27 kg/m^2 or higher who were prescribed weekly subcutaneous injections of Semaglutide for weight loss and had a 3 to 6-month follow-up. Key findings revealed that at 3 months, the average weight loss among the 175 included patients was 6.7 kg, representing an average weight reduction of 5.9%. This progress was even more significant at 6 months, with an average weight loss of 12.3 kg and an average reduction of 10.9%. The percentage of patients achieving meaningful weight loss was also notable. 53.7% of patients lost at least 5% of their body weight after three months, and 14.9% lost 10% or more. By 6 months, these figures improved to 87.3% and 54.9% respectively. When considering factors such as diabetes status and dose, it was found that patients with type 2 diabetes had lower average weight loss percentages at both 3 and 6 months compared to those without. Furthermore, at three and six months, patients on the higher doses (1.7 and 2.4 mg) lost more weight than those on the lower doses (0.25, 0.5, and 1 mg) [10].

Fat metabolism is closely related to weight control. A retrospective analysis conducted in China analyzed the medical records of patients with T2DM and abdominal obesity. 48 patients were given oral metformin of 0.5 g, three times a day, and subcutaneous injection of Semaglutide of 0.25 mg initially, once a week, with the dose adjusted to 0.5 mg after 2 weeks and maintained at this dose. After 3 months of treatment, the levels of patients' serum irisin showed a significant rise from 3.05 to 4.56 ng·L-1, the spexin (SPX) level also markedly increased (0.44 to 0.71), while sprosin (ASP) level considerably dropped from 2.04 to 1.22 μg·L-1. These changes in fat factors indicate that Semaglutide has a positive effect on regulating fat metabolism. The waist circumference (WC) also showed a reduction of 10.06 cm, indicating that Semaglutide may contribute to a decrease in abdominal obesity [11].

4. Semaglutide vs. Liraglutide

In China, Semaglutide and Liraglutide are two of the few weight loss medications that have been approved for marketing [3,12]. Given their availability and significance in the field, it becomes crucial to compare their efficacy and characteristics. A clinical trial involved only Chinese patients provided comparison of these two medications. Of the 100 patients, 50 were assigned to the observational group and was treated Semaglutide, starting at a dose of 0.25 mg/week, increasing to 0.5 mg/week after 4 weeks, and further increasing to a maximum dose of 1 mg/week after another 4 weeks. The other 50 patients were divided into the control group and was treated with Liraglutide, starting at a dose of 0.6 mg per day and increasing to 1.2 mg after at least 1 week, with a maximum dose of 1.8 mg/

d. The study found that both the two medications showed positive effects in improving blood glucose, lipid, and weight indicators in patients with diabetes and obesity, and both had comparable safety profiles. However, Semaglutide group demonstrated better results in these aspects, especially the BMI index (-5.64 vs. -3.05 kg/m^2) and abdominal circumference (-14.93 vs. -11.1 cm) [13].

A randomized, open-label 3b-phase clinical trial aimed to assess the weight management effects in overweight or obese adults without diabetes was conducted to compared the efficacy of the two drugs. 338 Participants were randomly assigned into four groups, receiving either weekly subcutaneous Semaglutide injection or daily Liraglutide injection of 2.4 mg and 3.0 mg, respectively. The two groups left were given the corresponding placebo. At week 68, the weight change has a substantial difference of -9.4 percentage points (-15.8% vs. -6.4) between the two groups, which clearly indicates the superior weight loss effect of Semaglutide. In terms of achieving specific weight loss percentages, the proportions of weight loss were much higher with Semaglutide compared to Liraglutide. Furthermore, Semaglutide demonstrated better results in various significant indicators, including reduction in waist circumference, lipid profiles, glycemic indicators, and inflammatory indicators. The two groups had similar incidence of side effects (95.2% with Semaglutide and 96.1% with Liraglutide). However, the rate of permanent drug cessation due to adverse events was higher with Liraglutide than with Semaglutide [14].

5. Safety

Semaglutide primarily induces mild and transient gastrointestinal disturbances, such as nausea (incidence of 14.4 to 20%), vomiting (4 to 11.5%), and diarrhea (4.5 to 11.3%), which are generally self-limiting and can be managed through dose escalation and dietary adjustments [15]. According to a meta-analysis conducted by Bi, et al., the incidence of diarrhea in the Semaglutide group was higher to that in the placebo group. In terms of other adverse reactions such as abdominal pain, headache, acute pancreatitis, acute renal failures, there were no significant differences between the two groups [16]. However, conditions could become complex when these symptoms intensify or lasts longer, or when patients suffer from more severe side effects such as spread pain, limb edema, confusion or unconsciousness etc. Moreover, when Semaglutide is used along with sulfonylurea and/or insulin therapy, the risk of hypoglycemia increases [4,15]. Patients should be aware of the signs and symptoms of low blood sugar and monitor their blood sugar levels before and during treatment [17].

The thyroid cancer risk associated with Semaglutide is primarily based on rodent studies, and the evidence in humans is less clear. Notwithstanding the minor variations in GLP-1 receptor expression between human thyroids, regulatory authorities have mandated supplementary pharmacovigilance measures as a result of the apprehension [15]. It is crucial that individuals with a history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia syndrome type 2 avoid using Semaglutide injection [17].

In terms of cardiovascular safety, Semaglutide increases heart rate, but this has not been associated with an increase in cardiovascular outcomes. In fact, the beneficial effects of the drug on cardiovascular risk factors and physiology outweigh the possible risk of the associated heart rate increase [15].

6. Future Outlooks

6.1 The Competitiveness of Semaglutide Injection

When it comes to weight control measures, medication such as Semaglutide is not the only option, but other methods such as diet, metabolic surgery, and exercise intervention have not yet been well-developed. A large number of Chinese residents have not grasp nutrition knowledge such as Acceptable Macronutrient Distribution Range (AMDR) and the concept of food calories. Besides, young generations tend to be unwilling to spend time and energy on cooking, thus increasing the proportion of having unhealthy fast foods and takeouts. According to the data collected from 1990 to 2017, the proportion of fat contributing to total energy had increased from 22.0% to 34.6%, which had exceeded the recommended fat intake (20%~30%) [18]. The development of China's obesity metabolic surgery also faces some problems. Although the annual surgery volume has reached the global forefront, the proportion of surgeries among eligible obese patients is still one of the lowest in the world. The rapid growth in the number of obese populations also brings burdens and challenges to medical facilities [19]. In terms of exercise intervention in China, there is still room for improvement in the diversity and individualization of intervention methods. Currently, the main intervention methods still focus on aerobic exercise, and the combination of various exercise methods and other interventions needs to be further explored and optimized [20]. Additionally, most people cannot persist in exercise due to limited free time or feeling of exhaustion. Given the current situation that other weight management methods are still underdeveloped in China, Semaglutide injection, a convenient and fast medication that does not require lots of time and effort, is likely to play a crucial role in this field.

6.2 Potential Challenges faced by Semaglutide Injection

Although Semaglutide Injection is highly competitive in the field of weight control, there are also potential challenges that need to be addressed. For instance, the relatively high price may be a limiting factor. Although the cost may have come down due to health insurance negotiations, it is still relatively expensive compared to other weight loss methods or medications, which may limit its accessibility for some patients. The coverage and reimbursement policies for this drug may vary, which could also affect its widespread use. Additionally, the perception and acceptance of new medications by both doctors and patients may pose a challenge. Some doctors and patients may be hesitant to use a relatively new drug or may have concerns about its side effects or long-term effects. To overcome these challenges, technological innovation and large-scale production may be a way to reduce the price of the drug. In terms of medical insurance coverage, continuous improvement and adjustment of relevant policies are needed to promote the wide application of the drug. At the same time, efforts should be made to increase the awareness and acceptance of the drug among doctors and patients through education and training.

7. Conclusion

As a newly approved weight-control medication in China, Semaglutide injection has been verified through a series of rigorous clinical studies and practical applications to effectively improve multiple indicators related to weight-control, such as BMI, waist circumferences, and weight loss percentages. It also simultaneously exerts positive effect on other health-affecting factors, such as glycemic indicators and lipid profiles. Comparing to other weight-control methods, it saves more time and effort, and the safety is guaranteed. However, there are still some unresolved problems. Its relatively high prices may bring a certain economic burden to many patients with weight loss needs. The uncertainty of medical insurance coverage is also likely to hinder the widespread use of this drug. But comprehensively weighing various factors, including its excellent weight loss effect, positive impact on health, and possible adjustments in the future market and policies, it still has huge potential and development space, and is expected to become a rising star in the field of obesity treatment in China, bringing new hope and effective treatment options to numerous obese patients.

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