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Analysis of the therapeutic effect of semaglutide

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Abstract. Obesity and diabetes are diseases with a particularly high prevalence today, and their presence deeply affects people's daily lives and health. Currently available medications for the meciacal treatment and health care for patients with obesity and diabetes, although helpful and therapeutic, have serious side effects and are not suitable for all populations. Semaglutide has attracted a lot of attention from researchers for its all-round efficacy. This research summaries the mechanisms and efficacy of semaglutide in diabetic and obese patients and draws positive conclusions. Afterwards, it will outline the various treatment modalities of semaglutide and its safety profile, oral and injectable, which gives patients a choice and comfort. This research summaries the therapeutic and clinical effects of semaglutide taken by patients with different conditions and in different groups of them, which provides a broad picture of the therapeutic mechanism of semaglutide, with the hope that it will be useful for doctors and patients.

Keywords: Semaglutide, Obesity, Diabetes, Safety, Medicine Taken.

1. Introduction

Obesity is an extremely prevalent disease in the world today. In 2018, Chinese adults with overweight or obesity accounted for 51.2% of the entire population, and researchers predict a 70.5% probability of developing the disease in 2030. Not just in China, the number of obese patients is growing rapidly worldwide. Between 1980 and 2013, the prevalence of obesity increased by 28% in adults and by an even greater 47% in children. Obese patients also face many serious symptoms such as high blood pressure and cholesterol, and some patients even get heart-related diseases, which have a greatly negative impact on their lives [1]. Diabetes is also an extremely serious disease that is cumbersome and costly to treat and is as likely to occur as obesity. Finding solutions to these two diseases, which have a great impact on people's lives, would be of great help to people all over the world and to society as a whole.

Sibutramine is a common diet pill that is known to be widely used until 2020 due to its ability to help people lose weight quickly. However, it can also cause significant side effects in obese patients including headaches, irregular heartbeat, nervousness and anxiety, and when used in high doses. Sibutramine can put their lives at risk, which has led governments to classify it as a banned substance [2]. Metformin is a common medication popularly available in the market for the treatment of diabetes, and it is often given to patients in an oral form. As it works well in lowering the blood sugar of diabetics and suppresses the appetite of diabetics, it has a weight loss effect. Taking metformin for a long period of time has the probability of causing serious side effects in patients, such as lactic acidosis or the teratogenicity and instability that people have when treated with metformin during pregnancy [3]. The emergence of

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semaglutide has attracted the attention of many researchers, and its medical effects on obese and diabetic patients are gradually being explored and gaining widespread attention.

Semaglutide is a peptide consisting of 31 amino acids and its chemical equation is $C_{187}H_{291}N_{45}O_{59}$, which chemical structure is shown on Figure 1. The molecular weight of semsglutide is 4114 g/mol. It is a glucagon-like peptide-1 receptor agonist used in the treatment of type 2 diabetes mellitus, and it could help patients to lower their blood glucose and may also act as an anti-obesity agent, neuroprotective agent and appetite suppressant. It is also a lipopeptide [4].

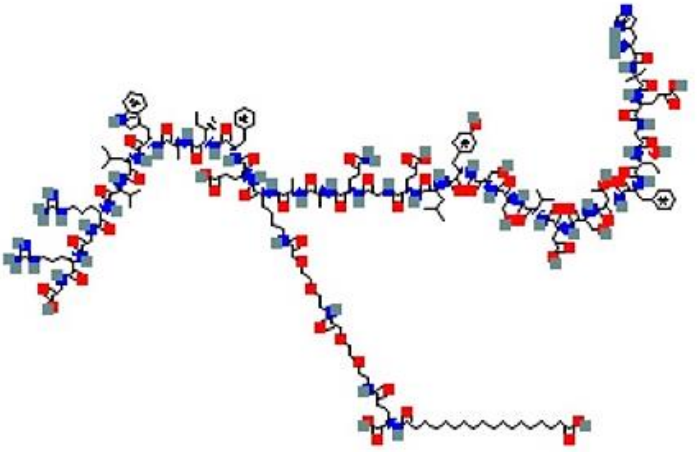

Figure 1. Chemical structure of 1emaglutide [4].

GLP-1 is a creatinine hormone secreted from nutrient-responsive enteroendocrine cells and has glucose-regulatory effects on the body. It could improve glucose tolerance as well as inhibits glucagon secretion. GLP-1 shows an irreplaceable role in insulin resistance, which could strengthen and improve of it through intrinsic enterohepatic signalling pathways. Also, it can help to suppress appetite by inhibiting the appetite centre in the hypothalamus, contributing to weight loss. The potential of GLP-1 agonists is huge, as they can be used in the treatment of diabetes, obesity, and even neurological disorders. Semaglutide as a kind of famous agonist of GLP-1 receptor, which equips high medical potential for diabetic and obese patients. Semaglutide is a well-known GLP-1 receptor agonist that has a high medical potential for diabetic and obese patients that is waiting to be explored, thus gaining an inaccessible position in the treatment of such conditions. Somatostatin's structure and function is almost same to human GLP-1 and selectively activates the GLP-1 receptor, since they have 94% sequence homology same [5]. Since the molecular weight of semaglutide is relatively high, its compounds cannot be accessed by traditional liquid-phase synthetic routes, and researchers can now synthesise semaglutide by biofermentation methods, such as the *E. coli* expression system, which is effective.

2. The therapeutic effect of semaglutide

2.1. Mechanism and pharmacology

Semaglutide is produced by yeast fermentation of the peptide chain, and its long-lasting mechanism is based on a structural modification of somatostatin to α-aminoisobutyric acid at position 8 to increase stabilisation and prevent degradation by DPP-4 enzyme. It has been structurally modified to attach an 18-carboxyalipatic acid side chain, which is to the position of lysine, binding to albumin and increasing its molecular weight. Semaglutide is structurally modified by attaching an 18-carbon lipoic acid side chain to the 26th position of the peptide chain, which binds to albumin and increases the molecular weight of the drug. It could also replace the lysine at position 34 with arginine to ensure the stability of the C18 side chain at position 26. Semaglutide activates the GLP-1 receptor, playing a role of agonist and helping to stimulate insulin secretion and reduce the secretion glucagon [6].

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Semaglutide could lower blood glucose in people and has a weight loss effect. In a 12-week pharmacodynamic evaluation of semaglutide, it (only 1 mg dosage) significantly decreases glucose levels in patients with T2D. The researchers found that the use of semaglutide lowered glucose by 29 mg/dL, 74 mg/dL in people 2 h after a meal, and an average 24 h glucose concentration of 30 mg/dL. Similarly, the administration of semaglutide also reduced postprandial glucagon levels in T2D patients. Semaglutide also cause the decreasing of fasting and postprandial glucagon levels in patients with T2D. The fasting glucagon secretion is 8% less the origin, postprandial glucagon response decreases about 14%-15%, and 24 hours glucagon concentration is lower than an average about 12% [5]. 0.5 mg dose of Subcutaneous could achieve maximum concentrations within twenty-four hours to fifty-six hours in normal adult's body. The intake dose escalation study of semaglutide used a 4-times weekly 0.5 dose of kojic acid. This was followed by injections of semaglutide 0.5 mg doses four times, followed by five doses of 1.0 mg of semaglutide. The final result is shown to be similar Gto the Cmax 33-36 hours after the final dosage. The plasma concentration tendency as the time passed is similar as the concentration after a single 0.5 mg dose semaglutide was administered to adults, and similarly after the final dose (1 mg) of the strategy of dose escalation. The subcutaneous bioavailability of semaglutide was approximately 94%. And semaglutide has highest bioavailability among all the GLP-1 agonists.

Semaglutide is metabolized by proteolytic cleavage of the peptide main chain and β-oxidation of the fatty acid-side chain, and the metabolites declined and pass the half-life as the time passes. The researchers finding the semgalutide in the plasma of only the adults who had been administered the drug by 28 days after administration [7]. Most semaglutide circulates in plasma, and the results of experiments in adult humans on semaglutide metabolism indicate that semaglutide can be slowly metabolized by proteolytic cleavage of the peptide backbone and sequential β-oxidation of the lipoic acid side chain due to its long half-life. The degradation is excreted through urine and excrement, but the product, urine, contains very little semaglutide compared to the other degradation products, accounting for only 3% of the total semaglutide content [8].

2.2. Medical treatment for the patient with obesity

Semaglutide can lead to considerable weight loss. It is different from other weight loss substances in that it does not affect energy expenditure. The main feature of semaglutide is that it increases satiety in people, which reduces cravings and leads to a reduction in eating thus to achieve weight loss. The mechanism of semaglutide causing people lose weight is unclear, but researchers have explained that it involves a peripheral mechanism, which is similar to natural GLP-1, leading to a delay in gastric motility and activation of gastric mechanoreceptors, as well as the transmission of signals through the vagus nerve to inhibit areas of the brainstem that can inhibit appetite, which leads to a decrease in appetite and weight loss in people who take semaglutide.

The researchers conducted trials of the effects of semaglutide treatment in obese patients, and in all trials net energy expenditure was judged by estimating basal metabolic rate x physical activity level values. The researchers conducted 10 trials of semaglutide's therapeutic efficacy in different populations including adolescents with obesity, different measures of semaglutide intake, and different durations to determine semaglutide's effectiveness in weight loss [5]. The data are shown in Table 1. The results show that semaglutide can be in clinical studies can help obese patients very effective weight loss results. Semaglutide has been proved by the FDA and EMA as a very effective weight loss drug. The results of these trials, which lasted 68 weeks or even 108 weeks, show that semaglutide is effective over the long term, and that in trials with young people and minors, the efficacy of semaglutide was not compromised and did not harm their bodies.

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Table 1. The weight loss effects of semaglutide in different step trials [5].

Step	Objective	Exclusive criteria	Popolation	Duration (weeks)	Trail Dose (mg)	Lossinhg Weight
1	Random normal obese patients	Type 2 diabetic patients	1961	68	2.4 Placebo	-14.9 -2.4
2	Random fat patients with type 2 diabetic	Patients with insulin	1210	68	2.4 Placebo	-9.6 -3.4
3	Patients with intensive lifestyle in a specific program	Patients hba1c⩾ 6.5%	611	68	2.4 Placebo	-16.0 -5.7
4	Random normal obese patients	Patients hba1c⩾ 6.5%	902	68	2.4 Placebo (switch-on)	-7.9 +6.9
5	Random normal obese patients	Patients with hba1c⩾ 6.5%	304	104	2.4	-
6	Random normal obese patients with 1.7 mg and 2.4 mg semaglutide	Type 2 diabetic patients with renal impairment	401	68	2.4 1.7 Placebo	-13.2 -9.6 -2.1
7	Random normal obese patients	Type 2 diabetic patients with renal impairment	375	44	2.4	-
8	Efficacy of semaglutide compared toliraglutide in obese patients	Obese patients with type 2 diabetic	338	68	3.0	-15.8 -6.4
Teens	Random adolescents with obesity	Type 2 diabetic patients: obesity of secondary origin (hypothalamic or endocrinal)	163	68	1.0	-

2.3. Medical treatment for the diabetes patient

Type 2 diabetes is a serious disease, which is very common in the world and due to its progressive nature. Many people who receive basal insulin are treated additionally so that they can be more insured and better able to keep their blood sugar down. Currently, semaglutide is a well-discovered method of doing this. A 30-week random experiment with methods of double-blind, placebo, multinational multicenter research evaluating the efficacy of semaglutide as an add-on to basal insulin was conducted by Rodbard

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et al. at 90 sites in five countries, including the United States, Japan, and Germany. For this trial researchers organized 397 patients that took either semaglutide or placebo randomly, and 380 patients successfully adhered to the trial. Only 23 patients required rescue medication during, with three subjects taking 0.5 mg of semaglutide, one taking 1.0 mg of somalutide, and 19 in the placebo group during the trial, which is shown in Table 2. And at the end of the trial, the mean reductions in HbA1c were about 15.8 mmol/mol and 20.2 mmol/mol for patients using semaglutide 0.5 mg and 1.0 mg, compared to the reduction of 0.1% for those on placebo, which could show that semaglutide has a good hypoglycaemic effect and is very helpful for diabetic patients [9].

Table 2. The hypoglycemic efficacy of semaglutide in patients of different races and regions [9].

	132 Semaglutide 0.5 Mg	131 Semaglutide 1.0 Mg	133 Placebo	396 Total
Male Sex, N (%)	74 (56.1)	77 (58.8)	71 (53.4)	222(56.1)
People From Different Country, N (%)				
German	25(18.9)	24 (18.3)	21 (15.8)	70 (17.7)
Japanese	17 (12.9)	22(16.5)	22(16.5)	45 (11.4)
Serbian	17 (12.9)	13(9.9)	15 (11.3)	45 (11.4)
Slovak	13(9.8)	13(9.9)	14 (10.5)	40 (10.1)
American	60(45.5)	59 (45.0)	61 (45.9)	180 (45.5)
Race, N (%)				
White	108 (81.8)	98(74.8)	101 (75.9)	307 (77.5)
Asian	19 (14.4)	23 (17.6)	24(18.0)	66 (16.7)
Black Or African American	4(3.0)	9(6.9)	8 (6.0)	21 (5.3)
Other	0(0.0)	1(0.8)	0(0.0)	1 (0.3)
Baseline Hbai. N (%)				
⩽ 8.0% With Metformin	41 (3.1)	41 (31.3)	40 (30.1)	122 (30.8)
⩽8.0% Without Metformin	8 (6.1)	8 (6.1)	9 (6.8)	25 (6.3)
>8.0% With Metformin	69 (52.3)	69 (52.7)	70(52.6)	208(52.5)
>8.0% Without Metformin	14 (10.6)	13 (9.9)	14 (10.5)	41 (10.4)
Hba1, Mean (Min.-Max.), Mmol/Mol	67.9 (53.0 89.1)	67.3(51.9 94.5)	68.6(50.8-97.8)	67.9(50.8-97.8)
Hbaic Mean (Min. Max). %B	8.4(7.0-10.3)	8.3(6.9-10.8)	8.4 (6.8-11.1)	8.4 (6.8-11.1)
Fasting Glucose In Plasma, (Min. Max.) Mmol/L	8.9 (2.9-21.9)	8.5(2.6-17.1)	8.6 (3.9-19.1)	8.6 (2.6-21.9)
Fasting Plasma Glucose, Mean (Min.-Max.), Mg/Dl	161.0 (52.3-394.6)	152.5 (46.9-308.1)	154.1 (70.3-344.2)	155.9 (46.9-394.6)

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3. Safety

3.1. General safety

Semaglutide has advantages in terms of efficacy, cardiovascular benefit and long duration of administration. Semaglutide has also been shown to be effective in the treatment of diabetic nephropathy. Somaglutide did not increase the risk of adverse cardiovascular events. The safety profile of somaglutide was consistent with the known safety profile of GLP-1 analogues, with gastrointestinal adverse events being the most common adverse drug events and did not result in serious harm or effects to patients.

Patients with diabetes should take extra care when using this drug during pregnancy, and they should be aware of the risks to both mother and child. If the patient's blood sugar is not controlled during pregnancy, there is a high probability of spontaneous abortion and premature birth. According to statistics, after diabetic women use this drug before pregnancy, the probability that the foetus will be born with genetic defects or physical defects is 6%~10%, and some studies have shown that as diabetic patients with higher blood glucose during pregnancy, the probability that their children will be born with defects is greater. At present, the risk mechanism of taking semaglutide in pregnant patients is being studied by researchers, but it is undeniable that taking semaglutide can pose certain safety risks to pregnant patients [10]. Both 0.5 mg and 1 mg of semaglutide have been shown to be effective in patients. The structure of semaglutide is 94% homologous to human GLP-1, which is similar to liraglutide, and the structural modification makes it more stable in binding to serum albumin, and it is administered only once a week, which reduces the fluctuation of blood glucose, and thus leads to a smoother recovery of blood glucose in patients.

3.2. Semaglutide by oral administration

One of the major advantages of semaglutide is that it can be taken orally by patients, which is helpful for diabetics who have difficulty with injections of glucose-lowering substances, as well as giving patients who don't like the convenience of syringe injections of their medicines a wider range of options. However, similar to other oral medications, taking semaglutide can still have an effect on the patient's stomach and intestines, and prolonged use of semaglutide can lead to nausea, especially when the patient takes the medication on an empty stomach, but if the patient does not choose to take semaglutide when their stomach is empty, the efficacy of the medicine will be greatly reduced [11].

3.3. Semaglutide by injection

Similarly, semaglutide can be injected into humans for treatment. Injectable semaglutide was approved for use in the U.S. in 2017, and researchers have completed additional clinical trials proving the safety as well as efficacy of semaglutide. The efficacy of semaglutide had already been confirmed in lowering glucose level and body weight without any safety-related hazards. One other notable finding about semaglutide is that it can be used in conjunction with other common hypoglycemic drugs or other hypoglycemic medical treatments, which provides a complementary effect [12].

4. Conclusion

This research summarises the mechanism of action and pharmacology of semaglutide as a novel drug for the treatment of obesity and diabetes, and learns how semaglutide helps patients to lower their sugar levels and lose weight. From the previous experiments, it can initially conclude that semaglutide is very helpful for patients who need to reduce sugar and weight, and that it has the potential to become a widely available drug to the general public. It then outlines the safety concerns regarding semaglutide and give patients two treatment options for semaglutide. Currently, the side effects of taking semaglutide such as dizziness, nausea, and eye lesions need to be studied further until they are resolved.

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