Transactions on Materials, Biotechnology and Life Sciences
ISSN: 2960-1932, eISSN: 2960-2319 | Volume 7
MISBP 2024

Applications of Semaglutide for Various Diseases

Jiayun Pan *

WillowWood School, Toronto, Canada

* Corresponding Author Email: yunap@willowwoodschool.ca

Abstract. Semaglutide is a gluten-like peptide 1 (GLP-1) agonist which is responsible for improving blood sugar control and losing weight. It is clinically approved by the FDA for treatment of type 2 diabetes mellitus and is designed in subcutaneous or oral dosage form. Some other diseases share common conditions with obesity and diabetes such as a high blood sugar level and insulin resistance. These factors along with some neuron issues are responsible for neurodegenerative diseases. Obesity and diabetes are two common worldwide health issues. A number of trials have been conducted to estimate the prevalence and drug effects. Scientists also study related diseases such as Non-alcoholic fatty liver disease to verify the usefulness of treatments. Semaglutide is one of the drugs being measured whether has a potential effect on these diseases. Some pre-clinical studies have indicated its therapeutic potential in non-alcoholic steatohepatitis and neurodegenerative disorders. Semaglutide has proved to be effective in treating lots of disorders, especially diabetes and obesity. However, for other diseases, it still remains uncertain even if there are some studies already tested the effectiveness. Much more detailed and considerate studies should be conducted to verify the impact. Semaglutide, the GLP-1 receptor agonist, has shown a positive impact in treating different diseases. Researchers have tested hepatoprotective and neuroprotective activity in animal and human trials to get more reliable data. It turns out that semaglutide improves insulin resistance and reduces blood sugar levels. It also protects dopaminergic neurons and reduces aggregated α-synuclein which improves Parkinson's disease and Alzheimer's disease conditions.

Keywords: GLP-1 receptor agonist, semaglutide, obesity, diabetes, neurodegenerative diseases.

1. Introduction

Diabetes and obesity have raised more and more global concerns due to the rising number of patients. Diabetes is a chronic and metabolic disease. Generally, it leads to elevated levels of blood glucose(blood sugar) and harmful damage to various organs. Type 2 diabetes is the most common one. Usually, adults are the most susceptible to it. The disease develops as the body can no longer produce enough insulin or does not respond to it effectively. Type 1 diabetes is a chronic condition in which the pancreas itself can only secret a little or even no insulin. In general, diabetes occurs when high amounts of consumed fat and sugar cannot be burned off and will be stored in the body. According to the WHO, about 422 million people worldwide suffer from diabetes, which showcases the tense situation for the disease [1]. People worldwide diagnosed with obesity have nearly tripled the prevalence since 1975 (defined by body mass index ≥30 kg m−2) [2] .

The tense world situation accelerates the invention of new drugs. Semaglutide is the most well-known one(presented in **Figure1.**), which was originally developed to deal with diabetes but was found to be effective in addressing obesity and various other diseases later. Semaglutide is a kind of gluten-like peptide 1 (GLP-1) agonist. GLP-1 agonists are a class of drugs that are responsible for improving blood sugar control and losing weight. These drugs prevent β-cell loss, which stimulates the body to produce more insulin [3]. The provided insulin helps lower blood sugar levels. GLP-1 agonists also boost weight loss by slowing the passage of food from the stomach to the small intestine. Patients may eat less as they feel full faster and longer [4]. Semaglutide, the newly developed agonist binds to GLP-1 Receptors in the gastrointestinal tract, pancreas, and brain. It enhances the secretion of glucose-dependent insulin and slows gastric emptying, which leads to a decrease in blood glucose levels and curbs hunger (presented in **Figure2.**) [5] .

Figure 1. Outer packaging of semaglutide

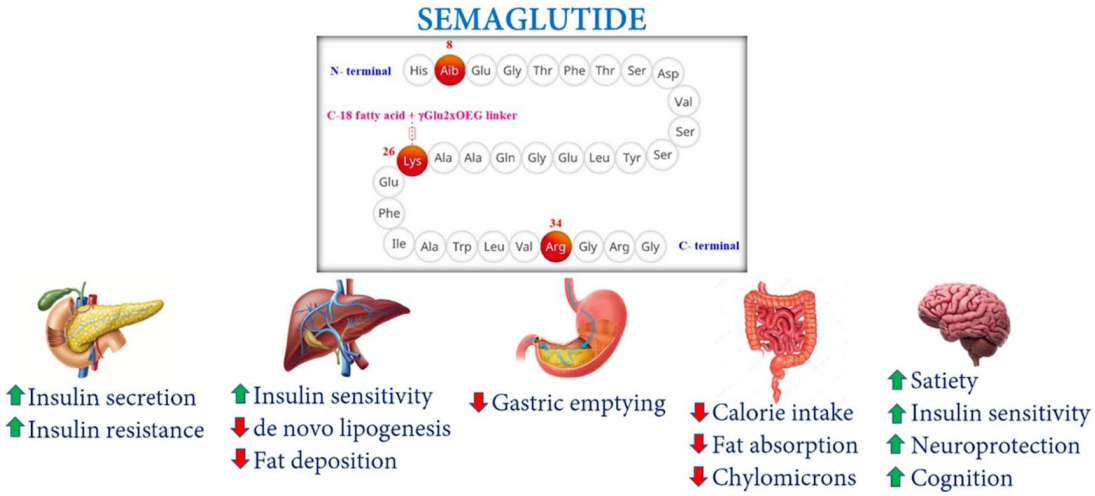

Figure 2. Mechanism of semaglutide for management of obesity, NASH, and neurodegenerative diseases [3].

2. Diabetes-related diseases

Semaglutide causes more hormones to be produced which results in lower blood sugar levels and positively affected diabetes.

2.1. Type 2 diabetes

Diabetes is a worldwide disease which occurs either when the pancreas fails to produce enough insulin or when the body cannot use the insulin effectively. The WHO indicates that diabetes was the direct cause of 1.5 million deaths in 2019 and 48% of the dead were younger than 70 years old [2].

To deal with the global disease, scientists developed a new drug called semaglutide. The drug acts as the hormone: gluten-like 1 which stimulates insulin secretion and showcases its potential effect on reducing the prevalence of diabetes.

The designed study compared semaglutide with placebo and other pharmacologic therapy for diabetes (PTD). The 7-month SUSTAIN 1 trial included adults with Type 2 diabetes mellitus(T2DM). It resulted in significantly lowered HbA1c(glycated hemoglobin) and body weight, compared with diet and exercise alone [6]. The lower HbA1c means the patient has less sugar in the blood than before. The outcomes indicate that semaglutide can significantly treat type 2 diabetes.

2.2. Chronic kidney disease with type 2 diabetes

Patients with chronic kidney disease and type 2 diabetes are likely to be diagnosed with kidney failure and even death. The potential serious health issue causes more researchers to explore the field. Since chronic kidney disease is kidney filter damage caused by high blood sugar levels, semaglutide is an ideal treatment. Its ability to lower the amount of sugar in patient's vessels exactly meets the demand.

To better understand the drug's effectiveness, scientists conducted trials for validation [7]. The study randomly assigned 3533 patients to receive either semaglutide at a dose of 1.0mg weekly or placebo, with 1767 in the semaglutide group and 1766 in the placebo group. Compared with the placebo group, the risk of primary outcome event was 24% lower in the semaglutide group. The risk of death from any cause was 20% lower than others. It was also reported that semaglutide causes less serious adverse events.

In conclusion, semaglutide reduces serious kidney outcomes and death in patients with type 2 diabetes and chronic kidney disease.

3. Obesity-related diseases

Semaglutide treats obesity by influencing the patient's passage of food. The slow-down process makes the patient feel full longer than usual so that the intake amount of sugar and fat can be better controlled.

3.1. Obesity

Obesity is now a worldwide disease which receives increasing attention. Over one billion people around the world are living with obesity according to the WHO's study in 2022. Obesity is bad for human health as it is at a high risk of having other complications such as bearing joints and even diabetes [8].

Obesity is a medical condition when people consume too much energy but fail to burn it off. Most of the excess energy components are sugar. The accumulated substances will then be stored as fats and lead to obesity.

The mechanism behind this is that semaglutide plays the role of gluten-like 1 but influences the passage of food in the human body instead. The action leads to decreased appetite and less food will be consumed. These will end up with a lower intake of sugar and fat. Obesity will then be controlled [3].

Researchers conducted a study to learn semaglutide impact on treating obesity. During the trial, researchers found out that the drug could positively affect the treatment of obesity. Semaglutide is associated with a mean reduction in weight, waist circumference and waist-to-height ratio, around 10.25, 7.7cm and 6.9% respectively. The placebo groups only showed -1.5%, −1.3 cm and −1.0%, respectively for each measurement [2].

Overall, semaglutide is suggested to treat obesity.

3.2. Non-alcoholic steatohepatitis and Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease, also known as NAFLD, is a liver problem that occurs in people who hardly drink alcohol. In this case, too much fat is built up in the liver, making it hard to function properly. This showcases that the disease is associated with obesity. Steatohepatitis is an advanced stage of fatty liver disease, which leads to more serious conditions such as inflammation and even liver damage. NAFLD is becoming more and more common as obesity rates rise [9] . It is considered to be the most common chronic liver disease worldwide, with increasing global prevalence from 25.3% in 1990-2006 to 38.0% in 2016-2019.

Semaglutide affects the disease by reducing the intake of sugar and fat, which helps the liver itself recover from the damage. In conclusion, the drug could treat these two diseases [10].

Due to the study design, it is reported that semaglutide does treat the disease. Researchers included eight studies with 2413 patients involved. Semaglutide treatment showed a reduction in serum alanine transaminase(mean difference: 14.07 U/L (95% CI: 19.39 to -8.75);) and a significant improvement in the mean difference in liver fat content(4.97% (95% CI: 6.65 to -3.29)), compared to the placebo groups [11] .

3.3. Cardiovascular disease in obesity without diabetes

Cardiovascular disease(CVD) is a serious disease that affects vital organs: hearts and vessels. According to WHO, approximately 17.9 million people died from CVDs in 2019, which took up 32% of global deaths that year. Theoretically, semaglutide causes a decreasing amount of fat and sugar which lowers the risk of making cardiovascular disease worse.

To verify the drug's effectiveness in this aspect, researchers conducted a study to verify whether the famous drug, semaglutide, can deal with cardiovascular disease in obesity without diabetes [12].

The double-blind study randomized 17604 patients into two different groups. 8801 of them were assigned to the placebo group, while the others were in the semaglutide group. After 34.2 ± 13.7 months of exposure to semaglutide or placebo, 569 patients in the semaglutide group faced a primary cardiovascular end-point event, while 701 cases were in the other group. The difference between the percentages was around 1.5%.

Based on the data provided above, semaglutide can be used to treat cardiovascular disease in obesity without diabetes.

4. Neurodegenerative disorders

The drug manages to control the patient’s blood sugar levels and makes neuronal repair. Therefore, the chances of getting Alzheimer’s are decreased. It also turns out that semaglutide can prevent dopaminergic neurons from damaging and reduce aggregated α-synuclein, which shows a great potential effect on treating Parkinson’s disease.

4.1. Alzheimer's disease

Alzheimer's disease is a common neurodegenerative disorder that happens to the elderly. Most of the clinical manifestations are cognitive impairment and memory loss. In 2023, around 6.7 million Americans over age 65 were diagnosed with Alzheimer’s dementia. Death due to the disease in 2000 has more than doubled comparing the data in 2019, with an increase of 145% [13] . Scientists also found that people with diabetes were more likely to get Alzheimer’s [14].

Patients with diabetes often have improperly functioned pancreas which leads to disturbed blood glucose levels and severe insulin resistance. Insulin acts as an important growth factor in the brain, therefore, the impairment of its signalling can reduce neuronal repair and develop the chance of getting Alzheimer's.

Due to semaglutide ability to help produce insulin properly, blood sugar levels are being controlled. The risk of getting the neurodegenerative disorder becomes less.

The trial done on the mice illustrates that semaglutide can increase the expression levels of SIRT1 and GLUT4 and improve learning and memory at the same time. The present study also shows that taking semaglutide can promote glucose metabolism in the brain and provide a reliable strategy for effective therapy of Alzheimer’s disease [14].

4.2. Parkinson’s disease

Parkinson’s disease is an unusual brain condition which leads to trouble in movement, problems in mental health and other health issues. According to the WHO, the number of people diagnosed with the disease in 2019 is twice as the data in the past 25 years. It is projected that an increasing number of patients are facing disability and death [10].

The key feature of Parkinson’s disease is uncontrolled movements due to the loss of dopaminergic neurons in the midbrain and the accumulation of aggregated alpha-synuclein (α-syn). However, semaglutide shows potential effectiveness as it protects dopaminergic neurons and reduces aggregated α-synuclein [15].

The study conducted a stereotactic surgery which included 40 adult male Sprague-Dawley (SD) rats . All rats were controlled at 3 months old and weighed around 220-250 grams. They were fed with a standard rat diet and sufficient water. Besides, they were grouped and lived in the animal room to control variables. During the surgery, rats were randomly divided into four groups and received different treatments: a sham + saline group; a 6-OHDA + saline group; a 6-OHDA + semaglutide group; and a 6-OHDA + DA5-CH group, with 10 rats in each group. For the group with 6-OHDA and other drugs, each rat was injected intraperitoneal with 25 nmol/kg drug once every two days for 31 days. The sham group was given the same volume of saline. According to the data provided, semaglutide plays an important role in protecting dopaminergic neurons in the substantia nigra against 6-OHDA. Semaglutide also shows the impact on improving the 6-OHDA-Induced Reductions in striatal dopamine content, with a significant difference from the sham + saline group ($p \leq 0.0002$). The study also measured the effect of the drugs on α-synuclein expression. According to the collected data, the level of monomer and aggregated α-synuclein was reduced by the drug.

It is evident that semaglutide is a potential treatment for Parkinson's disease due to the fact that dopaminergic neurons are protected and accumulation of aggregated alpha-synuclein is decreased.

5. Suggestions

Though there are already a lot of trials that study the effect of semaglutide, they are still not considerate and nuanced. It is suggested that more research and tests such as phase 3 trials should be done on this so that the data will be more realistic and reliable. Besides, post-marketing surveillance is also needed to investigate the worldwide situation so that scientists can deal with the disease better.

6. Conclusion

Semaglutide was approved by the FDA for its effectiveness on type 2 diabetes. It has proved to be effective not only in treating obesity and diabetes but also in non-alcoholic steatohepatitis and neurodegenerative disorders. The efficacy of semaglutide for Parkinson's disease was a pre-clinical phase which tested on adult mice. The drug reveals a potential treatment for different diseases meanwhile more detailed trials should be held.

References

[1] Information on: https://www.who.int/news-room/fact-sheets/detail/diabetes

[2] D.H. Ryan, I. Lingvay, J. Deanfield, S. E. Kahn, E. Barros, B. Burguera, H. M. Colhoun, C. Cercato, D. Dicker, D. B. Horn, G. K. Hovingh, O. K. Jeppeses, A. Kokkinos, A. M. Lincoff, S. M. Meyhöfer, T. K. Oral, J. Plutzky, A. P. V. Beek, J. P. H. Wilding, R. F. Kushner, Long-term weight loss effects of semaglutide in obesity without diabetes in the SELECT trial, Nat Med 30(2024), 2049–2057.

[3] M. K. Mahapatra, M. Karuppasamy, B.M. Sahoo, Therapeutic Potential of Semaglutide, a Newer GLP-1 Receptor Agonist, in Abating Obesity, Non-Alcoholic Steatohepatitis and Neurodegenerative diseases: A Narrative Review, Pharmaceutical Research, 39(2022), 1233–1248.

[4] Information on: https://www.mayoclinic.org/diseases-conditions/type-2-diabetes/expert-answers/byetta/faq-20057955

[5] Information on: https://www.ncbi.nlm.nih.gov/books/NBK603723/#:~:text=Mechanism%20of%20Action&text=The%20mechanisms%20through%20which%20semaglutide,tract%2C%20pancreas%2C%20and%20brain.

[6] K. E. Miles, J. L. Kerr, Semaglutide for the Treatment of Type 2 Diabetes Mellitus, The Journal of pharmacy technology: jPT: official publication of the Association of Pharmacy Technicians, 34(2018), 281–289.

[7] V. Perkovic, K. R. Tuttle, P. Rossing, K. W. Mahaffey, J. F. E. Mann, G. Bakris, F. M. M. Baeres, T. Idorn, H. Bosch-Traberg, N. L. Lausvig, R. Pratley, FLOW Trial Committees and Investigators. Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes, The New England journal of medicine, 391(2024), 109–121.

[8] Information on: https://www.who.int/news/item/01-03-2024-one-in-eight-people-are-now-living-with-obesity#:~:text=New%20study%20released%20by%20the,to%2019%20years%20of%20age

[9] Information on: https://www.mayoclinic.org/diseases-conditions/nonalcoholic-fatty-liver-disease/symptoms-causes/syc-20354567

[10] V. W. Wong, M. Ekstedt, G. L. Wong, H. Hagström, Changing epidemiology, global trends and implications for outcomes of NAFLD, Journal of hepatology, 79(2023), 842–852.

[11] S. Bandyopadhyay, S. Das, S. S. Samajdar, S. R. Joshi, Role of semaglutide in the treatment of nonalcoholic fatty liver disease or non-alcoholic steatohepatitis: A systematic review and meta-analysis, Diabetes & metabolic syndrome, 17(2023), 102849.

[12] A. M. Lincoff, K. Brown-Frandsen, H. M. Colhoun, J. Deanfield, S. S. Emerson, S. Esbjerg, S. Hardt-Lindberg, G. K. Hovingh, S. E. Kahn, R. F. Kushner, I. Lingvay, T. K. Oral, M. M. Michelsen, J. Plutzky, C. W. Tornøe, D. H. Ryan, SELECT Trial Investigators. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes, The New England journal of medicine, 389(2023), 2221–2232.

[13] Information on: https://www.alz.org/media/Documents/Facts-And-Figures-2023-At-A-Glance-Stats-Fact-Sheet.pdf#:~:text=An%20estimated%206.7%20million%20Americans%20over%20age%2065,65%20with%20Alzheimer’s%20dementia%20%284.1%20million%29%20are%20women.

[14] Z. J. Wang, X. R. Li, S. F. Chai, W. R. Li, S. Li, M. Hou, J. L. Li, Y. C. Ye, H. Y. Cai, C. Hölscher, M. N. Wu, Semaglutide ameliorates cognition and glucose metabolism dysfunction in the 3xTg mouse model of Alzheimer's disease via the GLP-1R/SIRT1/GLUT4 pathway, Neuropharmacology, 240(2023), 109716.

[15] L. Zhang, C. Li, Z. Zhang, Z. Zhang, Q. Q. Jin, L. Li, C. Hölscher, DA5-CH and Semaglutide Protect against Neurodegeneration and Reduce α-Synuclein Levels in the 6-OHDA Parkinson's Disease Rat Model, Parkinson's disease, 10(2022), 1428817