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The Relevance of Semaglutide in Obesity and Diabetes

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Abstract

In spite of strides made in the field of medicine in relation to diabetes, there still remains a prominent percentage of people in the world who suffer from either Obesity or Type 2 Diabetes. Presently, there is no cure for these diseases, and the need for change is clear; therefore, medicine that can help curb the numbers of both diseases is crucial. Fortunately, Semaglutide is a new breakthrough in weight loss medication and has potential to treat Type 2 Diabetes patients as well. This paper aims to explain in depth the history of weight loss treatments, diabetes treatments, and the mechanisms of insulin and Semaglutide. Furthermore, to put this treatment in context, this paper dives deeply into the subtopics of continuous glucose monitoring, glucose management, current insulin research, and present treatment and preventative measures for diabetes today. Drawing from an array of studies, statistics, and scholarly articles, this paper shows the relevance of Semaglutide in a world with rising Obesity and Type 2 Diabetes, and the possible contributions it could have to these widespread diseases. Further research studies and analysis are being conducted daily in hopes of solidifying these first steps towards a cure and prevention.

Keywords:Diabetes, Glucose monitoring, Insulin research, Treatment

1. Introduction

America is one of the most overweight countries in the world, with 33% of American adults classified as obese (IBIS World, 2022). Many studies have shown the negative impacts of elevated BMI (Body Mass Index), such as an increased risk of mortality and morbidity (Padwal et al., 2011). According to one comprehensive study, “each five-unit increment in BMI above 25 kg/m2 is associated with increases of 29% for overall mortality, 41% for vascular mortality and 210% for diabetes-related mortality” (Prospective Studies Collaboration, 2009). There are many complications that come with obesity, one of the many includes type two diabetes. Type two diabetes is caused by obesity because of the increase in fatty acids and inflammation in the body (Boden, 2006). As fatty acids and inflammation go up, insulin resistance also goes up, so the body rejects its own insulin, leading to type two diabetes. More than 37 million Americans have diabetes (about 1 in 10), and approximately 90-95% of them have type 2 (the non-inherited form of) diabetes (CDC, 2022). Diabetes is also comorbid with a number of diseases such as neuropathy, heart diseases, renal failures, and vascular complications (Klimek et al., 2015).

Despite the current "pandemic" of diabetes and obesity in the US, current treatments are not efficient nor long-lasting. This paper aims to compare the pros and cons of past and current treatments for diabetes. Since one of the first steps often recommended to prevent or treat this disease is for an individual to lose weight, methods of weight loss are also explored. Lastly, the new drug semaglutide as a

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potential treatment for Obesity and Type 2 Diabetes is analyzed here.

1.1 Obesity and Weight Loss Treatment

Obesity can have many negative health complications, such as high blood pressure, high cholesterol, coronary heart disease, and most prominently, diabetes. Frequently, people have adopted what could be considered unhealthy habits to control weight. These include, but are not limited to, meal-skipping, fasting, smoking for appetite reduction, intense exercise, as well as consuming stimulants such as caffeine, ephedrine, prescription drugs, and energy drinks (NIDDK, 2022). It has been reported that roughly 12% of adolescent women and 8% of men engage in extreme weight control behaviors including taking diet pills, laxatives, diuretics, or purging (Ferraro et al., 2015).

Many businesses have advertised a magic solution to cure weight problems. Some prominent companies include Sensa, HCG Platinum, Double Shot, and “Get High School Skinny”. These companies seem enticing to customers who do not want to exercise and those who are impatient to see their results. For example, a weight loss company called Sensa advertised the loss of 30 pounds in only six months by sprinkling food with sweet and savory crystals that were meant to keep people full (Smith, 2014). Although these promises sound enticing, there is no solid evidence for the validity of this product, nor any specific diet and fitness guidelines for this product, and the few clinical studies available are not published in reliable medical journals. Other companies boast of dermal products that claim to reduce belly fat by just applying the product to the skin. For instance, slimming patches such as those produced by Myntlife and Isumi are growing in popularity but are not backed with any scientific evidence of drastic weight loss (Wright, 2022). These products are not approved by the FDA, and do not have the proper studies to fortify their claims. Lawsuits against companies such as “Get High School Skinny" have led to charges of deceptive advertising (Federal Trade Commission, 2014), but many companies (and marketing teams) continue to thrive.

The FDA has approved five weight loss drugs — orlistat (Xenical, Alli), phentermine- topiramate (Qsymia), naltrexone-bupropion (Contrave), liraglutide (Saxenda), and semaglutide (Wegovy) — for long-term use. A deeper dive into the mechanisms of these drugs can help those interested in pharmaceutical options. All of these drugs fall under the GLP-1 receptor agonist class, which encourages the interaction of GLP-1 and GLP-1R. This reaction activates the cyclic adenosine monophosphate (cAMP) signaling pathway which activates protein kinase A (PKA) and Rap guanine nucleotide exchange factor 4 (RAPGEF4, also known as EPAC2). PKA activation then leads to an increase in the intracellular calcium concentration, thereby promoting the mitochondrial synthesis of ATP, and the release of insulin particles into the blood through exocytosis (when a cell transports molecules out of the cell)(Zhao et al 2021). Outside of their GLP-1 agonist characteristics, they each also have some specific mechanisms that are worth comparing. Orliastat covalently binds to the serine residues of active sites of lipases and inactivates them (Bansal, 2022). The inactivation of lipases prevents the hydrolysis of triglycerides, and therefore free fatty acids are not absorbed (Bansal, 2022). Phentermine-Topiramate is actually a anticonvulsant that lowers the seizure threshold by acting on high-voltage-activated calcium channels and voltage-gated sodium channels and has an augmenting effect on GABA-A receptors, which have a side-effect of suppressing appetite (Johnson, 2022). Naltrexone-bupropion is a chemical combination that is theorized to work synergistically in the hypothalamus and the mesolimbic dopamine circuit to promote satiety, reduce food intake, and enhance energy expenditure (Sherman et al., 2016). Liraglutide increases intracellular cyclic AMP (cAMP) leading to insulin release in the presence of elevated glucose concentrations (WCG CenterWatch, 2022). As a result, it decreases glucagon secretion in a glucose-dependent manner. Unfortunately, Liraglutide has also been associated with an increased risk of side-effects including inflammation of the pancreas, kidney and gallbladder problems (Victoza, 2022). Finally, Semaglutide works similarly to this last drug, in that it reduces blood glucose

through a mechanism where it stimulates insulin secretion and lowers glucagon secretion, both in a glucose-dependent manner (WCG CenterWatch, 2022). It is worth noting, that all agents in the GLP-1 receptor agonist class (Glucagon like peptide-1 receptor), are associated with gastrointestinal adverse reactions such as nausea, abdominal pain, and vomiting (Hughes, S & Neumiller, J.J., 2020). Subcutaneous Semaglutide is most commonly associated with GI side-effects, however, more rare side effects have also been reported which should be noted carefully by any patients taking the drug (Mayo Clinic).

Semaglutide, also known by its brand name as "Wegovy", is the first approved drug for chronic weight management in adults with general obesity or overweight since 2014 (USFDA, 2021). Semaglutide is an interesting weight loss candidate because while it boasts improvements in weight loss management it has also been studied to help manage symptoms of Type 2 Diabetes. FDA approved in 2021, Semaglutide comes as a solution (liquid) in a prefilled dosing pen to inject subcutaneously (under the skin). Semaglutide is in a class of medications called incretin mimetics. These work by allowing the pancreas to release an adequate amount of insulin depending on the circumstances (Medline Plus, 2022). Importantly, insulin allows sugar to move from blood into other body tissues where it is stored and used for energy. Semaglutide injections also work by slowing the movement of food through the stomach and may decrease appetite to result in weight loss, as well as reducing the amount of insulin needed (Medline Plus, 2022). Remarkably, Semaglutide has been shown to be effective with only weekly injections without regard to meals (USFDA, 202). Further, a study that was published in 2022 concluded that once-weekly subcutaneous Semaglutide compared with once-daily subcutaneous liraglutide (another incretin mimetic), resulted in significantly greater weight loss at 68 weeks (Monaco, 2022). This drug was targeted at those with a body mass index (BMI) of 27 kg/m2 or greater who have at least one weight-related ailment or in patients with a BMI of 30 kg/m2 or greater. It has been proposed that this drug could also be useful to those with both type one and type two diabetes, by managing insulin and glucose levels, and is currently undergoing clinical trials (Tsoukas, 2022).

1.2 Diabetes and Diabetes Treatment/Glycemic Control

Diabetes and Glycemic Control

Diabetes is characterized by unhealthy levels of glucose in the blood due to poor insulin production or release. Injectable insulin is the most common solution to high glucose levels or poor glycemic control. Glycemic control refers to one's blood glucose levels. Blood glucose levels drop when we are hungry, or have gone a long time since our last meal, and increase after we consume food. Under normal conditions, a person's blood glucose levels are not expected to fluctuate too much since as blood glucose increases, so does our insulin level which helps allow glucose to enter cells and leave the bloodstream (Medical News Today, 2022)(Figure 1).

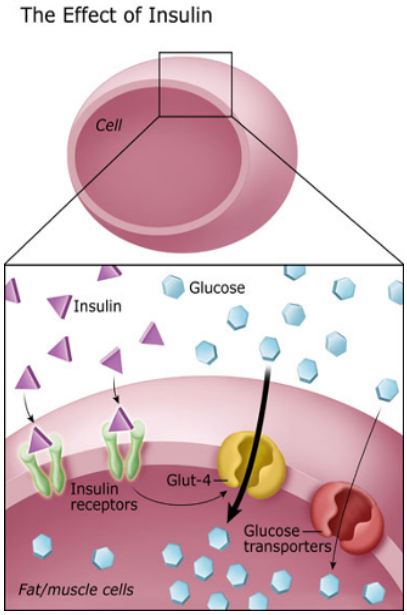

Figure 1. Diagram of insulin and how it reacts with glucose. After food is digested, glucose is released into the bloodstream. In response, the pancreas secretes insulin, which directs the muscle and fat cells to take in glucose. Cells obtain energy from glucose or convert it to fat for long-term storage.(Image source: Diabetes Teaching Center).

Your liver and muscles can take up glucose either for immediate energy or to be stored as glycogen

until it's needed. If the pancreas cannot produce the right amount of insulin to break down the glucose, it will lead to hyperglycemia which is high blood sugar. We also utilize a hormone called Glucagon which is released when our blood sugar is too low and signals to cells to allow sugar (and other fuel) to be released back into the bloodstream (Medical News Today, 2022; Diabetes Teaching Center).

Diabetics deal with two different types of complications of their disease in terms of blood sugar levels: Hypoglycemia and Hyperglycemia, more often known as low and high blood sugar, which can cause serious long term effects if not treated. Hypoglycemia (low blood sugar) has few direct links to critical long-term effects, but they can increase a person's vulnerability to other conditions, such as heart disease, eye disease, kidney disease, and nerve damage (Millar, 2021). Hyperglycemia (high blood sugar) may cause a range of health problems to develop, including skin complications, eye complications, nerve damage, and diabetic ketoacidosis (Felman, 2021). Even though there is no cure for Diabetes, patients can still take measures to treat and prevent their blood sugar from fluctuating.

For most people, blood sugar is an aspect of our diet/biology that is neglected or below our radar, because it is commonly said that if a person does not have diabetes, their sugars will stay level, but this is not always the case. A study in 2018 showed that people without diabetes still had blood sugar spikes (Lily, 2019). In this study, researchers recruited 57 people without diabetes to wear a CGM (Continuous Glucose Monitor) for a "few" weeks where the wearer's blood sugar was monitored every five minutes. The results of this study showed that even non-diabetic people often have blood sugar spikes, some more severe than others, leading to neglected glycemic control. Additionally, the figure below shows an experiment where blood glucose levels were measured after a meal in diabetic and non-diabetic rats (Figure 2). Results showed that after meals, both the diabetic and non-diabetic rats' blood sugars spiked to roughly 300 mg/dl, however non-diabetic and insulin-treated diabetic rats recovered from high blood sugar faster than those without diabetes (Figure 2).

While insulin plays a big role in regulating healthy glucose levels, it cannot fully prevent blood sugar spikes. Blood sugar spikes happen when the body cannot utilize and absorb the insulin fast enough after the body has ingested food, especially carbohydrates. This little gap in the insulin activation process leads to blood sugar spiking during that short amount of time. Even short blood sugar spikes can have negative effects. In the short term, they can cause lethargy and hunger. Over time, the body may not be able to lower blood sugar effectively, which can lead to type 2 diabetes (Smith, 2022). Frequent blood sugar spikes for diabetics can cause diabetic ketoacidosis (DKA), a potentially deadly condition that causes the blood to become too acidic (Cleveland Clinic).

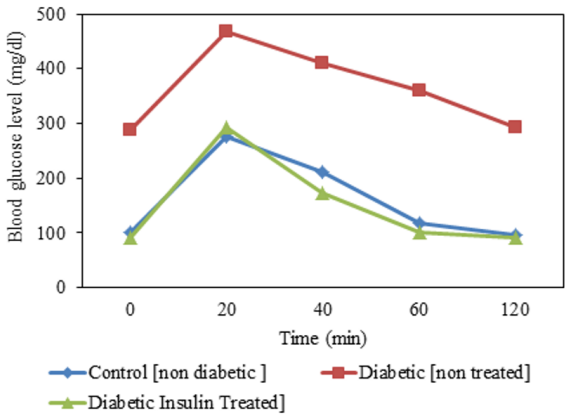

Figure 2. Blood glucose level (mg/dl) using oral Glucose Tolerance Test (OGTT) in Diabetic (red and green) and non-Diabetic (blue) Albino Rats. Time on the Y-axis refers to the time after a meal is given. The Diabetic rats were split into two groups, one treated with Insulin (green) and the other not (red). This graph shows that the diabetic, non-treatment group (red) exhibited much higher blood glucose levels than the other two groups (Figure source: Jato et al., 2018).

Furthermore, consistent blood sugar spikes can lead to insulin resistance, causing longer periods of time the body is in the hyperglycemic state. As a result, patients often suffer from poor glycemic control, although whether or not it is related to obesity is strongly debated amongst the medical community. However, there are multiple studies that prove that poor glycemic control correlates with obesity, as shown in Figure 3 below (Gupta, 2020).

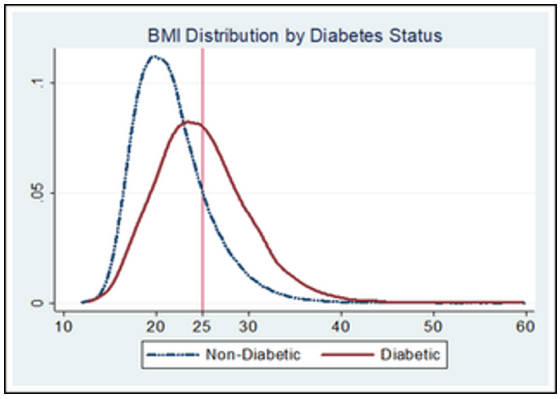

Figure 3. BMI Distribution by Diabetes Status. Figure constructed by author based on NFHS data for year 2015–16. (Gupta, 2020).

Diabetes treatment

Diabetes medicine has varied throughout the years; from injections to pills to even nasal sprays. The major component in all of these medications however is insulin. In both Type 1 (inherited) and Type 2 (developed) diabetes the pancreas (specifically the insulin-producing cells in the body) is negatively affected, limiting the body's ability to produce its own insulin. As a result, scientists came up with an artificial pancreas and injectable insulin. Presently, in order for someone to treat themselves, they must prick their finger throughout the day to check their glucose levels and inject themselves with insulin to make up the difference needed (Figure 4)(Morris, 2021). Insulin can also be administered with an "artificial pancreas", or an insulin pump.

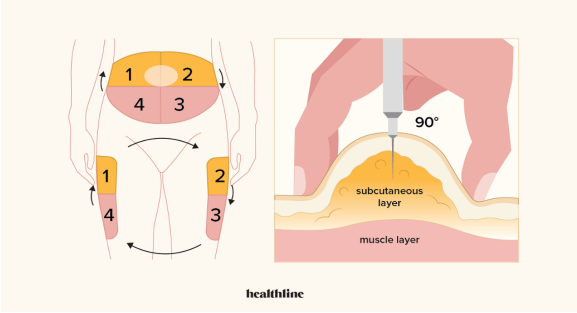

Figure 4. Diagram of Insulin Injection Technique. On the left is a diagram showing sites on the body where insulin injection should be targeted. The areas in yellow are areas high in fat, which better absorbs insulin than muscle (areas in red). On the right-hand side is a cross-section of the layers of skin, subcutaneous layer (fat) and muscle (Morris, 2021).

People with diabetes face many hardships, even with the vast amount of treatments out there. For example, a diabetic person must prick their finger up to eight times a day just to check their blood sugar. CGMs (continuous glucose monitors) were made to get rid of the pricks, however, users have to wear a patch on themselves every day, and still prick their finger to calibrate the machine. The patches are large and painful, and often require a large needle to insert the monitor (Figure 5)(Moses, 2019). We have found in this analysis that semaglutide will have a positive effect on patients, and could specifically help control blood glucose and reduce the risk of obesity. As previously explained, studies find that injection of semaglutide versus none at all promote more efficient weight loss results.

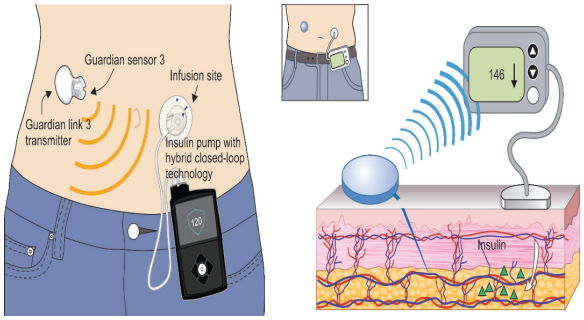

Figure 5. Diagram of a continuous glucose monitor and insertion. On the left is an example of a continuous glucose monitor along with an infusion site and a pump that connects to the glucose monitor. On the right is a diagram of how the glucose monitor communicates with the insulin pump (Moses, 2019).

Over the years, there have been very few drugs approved for the treatment of Diabetes. The most commonly recommended way to keep glucose levels under control is to exercise. Exercise can have a prominent effect on a person's body because when the body uses its muscles, it draws sugar from the blood to obtain energy. Depending on the duration or intensity of exercise, blood sugars can more or less be positively affected through physical activity (Roland, 2020). Exercise can improve peripheral insulin sensitivity as well as enhance insulin binding. Exercise also decreases abdominal fat, reduces free fatty acids, and increases insulin-sensitive skeletal muscle, which may result in improved glycemic

control (Whyte, 2013). Although it's been shown that in people with Type 2 diabetes exercise can improve insulin sensitivity (Whyte, 2013) this isn't always achievable or easily incorporated into regular habits by patients, or other chronic issues/injuries could prevent regular exercise.

Metformin, first approved in 1995 (Whyte, 2013), is another option for those who struggle with glycemic control. Although this drug is meant for those with Type 2 Diabetes, people with Type 1 Diabetes can also take and benefit from this medicine. Metformin works by helping to restore your body's proper response to the insulin you naturally produce. It also decreases the amount of sugar that your liver makes and that your stomach/intestines absorb (WebMD, Metformin).

Semaglutide, alongside weight loss, also treats unregulated glycemic control. Semaglutide can decrease appetite as well as help the pancreas to produce the right amount of insulin needed, thus leading to regulated glycemic control (Meier, 2021). The underlying mechanism for this drug involves targeting glucagon-like peptide-1 receptors. These are a well established class of glucose-lowering drugs that have been proven to help correct multiple issues that type 2 patients experience and can also help regulate glycemic control (Meier, 2021). As obesity decreases and glycemic control increases, this may lead, for example, a pre-diabetic person to become free from the potential risk of diabetes. As for a person with diabetes, this can greatly assist a person in their weight loss journey as well as keep them at healthy blood sugar levels. This could, in turn, mean fewer painful needle sticks throughout the day to monitor blood sugar levels.

2. Discussion

Despite significant progress in medical treatments for diabetes, the prevalence of obesity and type 2 diabetes remains high. This paper has explored the history of weight loss treatments, diabetes treatments, and the mechanisms of insulin and Semaglutide. Semaglutide, a new breakthrough in weight loss medication, has the potential to treat both obesity and type 2 diabetes. By examining current research on continuous glucose monitoring, glucose management, insulin, and current treatment and preventative measures for diabetes, this paper has shown the relevance of Semaglutide in addressing these widespread diseases. These data indicate that semaglutide may promote more efficient weight loss in patients, and could specifically help control blood glucose and reduce the risk of obesity.

As medicine exponentially improves within the next few years, semaglutide may be a major benefactor to the field of diabetes. As a potentially effective weight loss drug, semaglutide can help save many who struggle with obesity and are on the brink of diabetes. Not only will this solve ongoing health issues related to the effects caused by obesity and diabetes, but it will also curb the number of cases of obesity per year by taking measures to help prevent those who are at risk of disease from acquiring it. This is only the first of many to come, and semaglutide will act as a reference to study from for years to come. Ongoing research studies and analysis aim to solidify the potential of Semaglutide as a treatment and prevention measure for obesity and type 2 diabetes. As scientists and researchers make further breakthroughs, the future of weight loss and diabetic control drugs will surely be bright.

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