Are GLP-1 agonists the first group of pharmaceutical agents with a promising future as anti-obesity drug?

A literature review comparing GLP-1 agonists against the current weight loss treatments.

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Date
22th of April, 2022

Abstract

Obesity is a growing problem to society; obesity has a detrimental effect on the health and quality of life of patients by increasing the risk for comorbidities such as T2D, cardiovascular disease and certain forms of cancer. Weight loss in obese individuals can occur through various ways: exercise, a healthier diet, bariatric surgery and pharmacotherapy. Losing weight and maintaining weight loss is difficult due to changes in biological mechanisms as a result of weight loss. Pharmaceutical companies have capitalized on creating a drug which is easy to use and effective. A group of these drugs are GLP-1 agonists. GLP-1 agonists are able to decrease food intake and increase satiety; binding to GLP-1Rs in the brainstem of the hindbrain and the hypothalamus seem to be especially vital for the regulation of food intake and weight loss. The efficacy of two GLP-1 agonists were compared against diet and exercise lifestyle intervention trials and bariatric surgery. One commonality between all the compared strategies was that they all induced weight loss percentages of at least (5%) in most of the subjects, no matter whether short-term or long-term. A weight loss percentage reduction of (5%) can reduce the risk for T2D diabetes, cardiovascular disease, reduce NASH, improve mobility, quality of life and more. Contrastingly, administration of a GLP-1 agonist often comes with gastrointestinal symptoms as side effects such as nausea, vomiting. GLP-1 agonists not only show a significant ability to decrease weight loss, they can also improve obesity-related comorbidities. If pharmaceutical companies upgrade the efficacy more as well as user friendliness of GLP-1 agonists, the future of them being first upcoming mainstream pharmaceutical treatment for obesity might be within reach.

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Introduction

From 1980 onwards, the prevalence of obesity has nearly three-folded and it is estimated that approximately 13% of the adult population worldwide is currently obese; that amounts to about 650 million adults (*Obesity and Overweight*, 2021). Someone is diagnosed with obesity when having a body-mass index (BMI) of at least 30 or higher (Nimptsch et al., 2019). Moreover, while child obesity was uncommon in the 1970s it has become more of a commonality over the years (Lobstein et al., 2015). The increase in obesity prevalence is very alarming, because obesity is a risk factor for a number of non-communicable diseases (NCDs) including cardiovascular diseases (CS), type II diabetes (T2D) as well as several forms of cancer (Fruh, 2017). Taken all together, this has led to obesity being one of the leading risk factors for an early death (Ritchie, 2017).

On top of that, the surge of obesity cases over the last decades has put a heavy burden on society directly and indirectly. Direct consequences of obesity are the increasing medical costs caused by obesity related-diseases, while indirect costs are often related to losses of productivity witnessed in obese workers (Goettler et al., 2017). Although estimates of the total costs differ per study the burden it puts on the society's economy is hard to deny. To give an impression of the economic costs, a recent study estimates that economic costs related to obesity can amount to a total of 79 billion euros in the Netherlands annually (Hecker et al., 2022).

There are a multitude of drivers that have played a part in the augmentation of obesity rates. On a biological level, obesity can simply be viewed as an imbalance in energy intake versus energy output of the body. If the intake of energy is higher than the output, excess energy will be stored in the form of fat in adipocytes, this process is also known as weight gain. Evolutionary theorists have hypothesized that the body has been conditioned over time to be able to store a large amount of excess energy as fat. This was a necessary and effective strategy in pre-agrarian times when food security was low, but in current times of food abundance it has become an obstacle (Neel, 1962). Nowadays, the production and access of food far outweighs the need for it in the wealthier countries. In that light it is not surprising that overall intake of food has on average risen in these countries and the dietary composition has shifted more towards a diet which is higher in refined carbohydrates, added sugars, fats, and animal-source foods than it was before (Popkin et al., 2012)

Besides an overall increased food and thus energy intake, a trend in decreasing energy output has also taken place. A study on energy output of workers in the United States (US) calculated that between the 1960's and the beginning of the new millennium occupational energy expenditure has fallen by more than 100 calories, as occupations have become less physically demanding (Church et al., 2011). As long-term frequent engagement in physical activity in leisure-time can prevent weight gain, it is unsurprising that a decrease in physical inactivity outside of work additionally assisted in the obesity epidemic (Waller et al., 2007). Finally, socio-economic factors such as poverty, inherent biological factors such as faulty genetics and even environmental obesogens also contributed to the obesity epidemic (Gray et al., 2018). Although the current food system certainly has been conducive for this outcome, in detail coverage of the role it played is beyond this review.

Nevertheless, it has been shown that the associated comorbidities in patients with obesity can improve drastically when appropriate weight loss programs are applied. The benefits of losing weight under these circumstances can range from a lower blood pressure to the complete prevention of T2D, and a weight loss percentage of 5% can already be enough to see improvements in these obesity-related comorbidities (Ryan & Yockey, 2017). Loss of

weight does not only result in healthier human beings, but it can also significantly reduce health care costs (Fallah-Fini et al., 2017).

The most non-invasive and cheapest approach has been to increase physical activity frequency and steer towards a healthier diet. Despite the fact that both of these activities in synergy lead to weight loss in some patients, this strategy does not seem to result in long-significant long-term weight loss for a large share (Christian et al, 2019). Even in the majority of cases when weight loss is notable, maintaining the weight loss tends to be extremely complicated eventuating in weight regain in many patients over time (Hall,2018).

Due to the difficulty of losing weight, pharmaceutical companies have tried to capitalize on the opportunity to create the most effective weight loss type of weight loss medication. Semaglutide, a glucagon-like-peptide 1 (GLP-1) agonist has recently been approved by the FDA and was shown to be an effective weight loss stimulator. Captivated by the discovery of this GLP-1 agonist, this literature review will delve deeper into whether GLP-1 agonists such as semaglutide could be the future of weight loss treatment in combating obesity. To underline the necessity for a weight loss drug, the difficulty of losing weight will be explained and underlying biological mechanisms will be elucidated in chapter 1. To understand the workings and effects of GLP-1 agonists in the body, the physiology of GLP-1 will be untangled in chapter 2. Once the basic understanding for the need for a weight loss drug in the form of GLP-1 agonists and the physiology of GLP-1 has been formulated, the efficacy of GLP-1 agonist treatment will be compared against two different forms of weight loss treatment in chapter 3: lifestyle intervention with a change in diet and physical exercise regimens and bariatric surgery.

Chapter 1: The difficulty of losing weight and why weight regain often takes place

Why is losing weight so difficult?

Obesity is a disease characterized by severe gain in weight. Added weight mostly takes the form of fat stored in adipose tissue, which is the aftermath of excess energy intake relatively to expenditure. Although a simple advice to lose weight would be to “eat healthier and exercise more” (Soelimanet al., 2014), inherent biological mechanisms in some ways can work against the drive to lose weight effectively. Weight loss in obese individuals can occur through various ways: exercise, a healthier diet, bariatric surgery and pharmacotherapy. Often multiple strategies are combined so that energy intake as well as energy expenditure are modified (Collins, 2011). Although weight loss is overall perceived as good, it does have some ramifications for the energy balance; the human body responds strongly when energy balance is negative and is biased towards preservation of weight (Dulloo et al., 1998) In simple terms this means that losing weight itself ironically makes it more difficult to lose weight as the body tries to conserve its energy.

Weight loss reduces the basal metabolic rate (BMR), which is defined as the number of calories that are required to keep your body functioning at rest continually. BMR is lower when weight is lost, as less energy is needed than before to achieve the same standard of bodily functioning, also known as metabolic adaptation (Fothergill et al., 2016). This adaptation has been witnessed in multiple weight loss studies. A study by (Wolfe et al., 2018), showed that BMR was reduced by an average of 300 kilocalories (Kcal) six months after obese patients underwent bariatric surgery. Another study showed that when weight loss was induced by caloric restriction in overweight men, BMR significantly decreased (Frey-Hewitt.,1990). Surprisingly, the BMR rate did not decrease in the group of men who lost weight by exercise only, meaning that the manner in which weight loss is achieved can determine whether BMR will decrease or not. To conclude, weight loss reduction can prime

activate the body's energy preservation mode making it difficult to lose more weight over time.

Why is weight regaining likely to happen?

In spite of the fact that reaching a weight loss target is already an accomplishment on its own, post-maintenance of that weight target can be just as challenging. This is because there are physiological mechanisms counteracting the inner desire to lose weight, even stimulating food intake behavior and eventually weight regain after induction of weight loss.

Gut hormones and adiposity signaling hormones are predominantly important for homeostatic regulation of energy intake versus expenditure (Strader & Woods, 2005). Hormones related to food intake come in two forms: there are those that stimulate hunger while suppressing satiety and those that stimulate satiety while suppressing hunger. Depending on the type of weight loss strategy used, weight loss can result in temporary changes in food intake-related hormones, thereby dysregulating the physiological mechanism for food intake. The dysregulation can generate a predisposition towards increasing food intake, eventually contributing to weight regain. One study underpinning this notion enrolled 50 obese participants who were screened for hormonal levels before and after one year of a period in which weight was reduced. Levels of hunger-suppressing hormones leptin, cholecystokinin, amylin, insulin and peptide YY had decreased, yet hunger stimulating hormone ghrelin had increased in comparison with baseline levels at least one year after weight loss (Sumithran et al., 2011). The findings also applied in cases where weight regain had taken place. Besides, the subjective hunger levels of participants also increased significantly. The latter finding does not mean that concentrations of appetite-related hormones reflect and predict actual hunger; disengagement between the subjective rating of appetite and concentrations of hormones related to appetite have been proven to be possible (Fatima et al., 2015). It does however suggest a possible relationship between changes in hormonal levels as a result of weight loss and the regain of weight as a result of these changes.

A different study found an association with weight regain and lowered GLP-1 concentrations (Thom et al., 2020). However, this is merely an association and it does not fully determine if changes in GLP-1 are the cause of weight regain, or merely an effect of weight loss. Declines of circulating leptin concentrations following weight loss have also been linked to weight regain (Strohacker et al., 2013). Interestingly, low concentrations of leptin have been correlated with higher activation of brain areas related to reward, when obese individuals on a calorie-restricted diet were presented food cues. Injection with leptin was able to reverse activation (Strohacker et al., 2013). Together with complementary results of other studies (Iepsen et al., 2016) (DeBenedictis et al., 2020), they point out that changes of hormonal levels as a reaction to weight loss can predispose the body to increase energy intake. The predisposition to increase food intake can be an enormous obstacle in obese patients that are attempting to lose weight.

In summary, what makes both weight loss and weight loss maintenance difficult can be explained by biological mechanisms including the basal metabolic rate and food intake hormones. Due to their mind-boggling complexity, these processes and mechanisms are not yet fully comprehended. To ease the process of weight loss and its maintenance, the idea to pharmacologically treat obese patients using weight inducing drugs has become progressively popular. GLP-1 agonists are one of the potential medications that have proven to be effectively leading to weight loss as well as to relieve comorbidities related to obesity. To understand how these GLP-1 agonists work, the physiology of GLP-1 should be highlighted. The following chapter will elucidate the function of GLP-1 throughout the body.

Chapter 2: The physiology of GLP-1 and GLP-1 agonists

2.1 What is the physiological role of GLP-1?

GLP-1 is a gastrointestinal hormone which is produced and secreted by intestinal L-cells in the small intestine in response to consumption of a meal including at least carbohydrates or fats (Orskov et al., 1996) as well as in the preproglucagon (PPG) neurons in the nucleus tractus solitarius (NTS) of the brain stem (Holt et al., 2018). After postprandial GLP-1 secretion takes place, a proteolytic enzyme called dipeptidyl peptidase IV (DPP-4) breaks down a vast share of the secreted hormone; only 10 to 15% of the newly produced hormones ends up in the systemic blood circulation (Holst et al., 2007).

Once in the blood circulation, GLP-1 travels to a variety of organs within the human body, where it binds to GLP-1 receptors (GLP1R) to exert its physiological function (**Figure 1**). GLP1Rs can be found in the kidneys, muscles, brain, heart, adipose tissue, and gastrointestinal tract, but the initial function was thought to be related to the pancreas.

It was shown that once GLP-1 bound to its receptors on β-cells of the pancreas, insulin was released from these cells (**Figure 1**) (Doyle., 2007). The spike of blood insulin levels after consumption of a glucose-containing meal as opposed to glucose which is injected intravenously is called the incretin effect and GLP-1 thus belongs to the incretin hormone family (Nauck & Meier, 2016). GLP-1 has also been known to inhibit glucagon secretion of the α-cells pancreas (**Figure 1**), but whether this secretion is inhibited through direct binding to GLP1R's on the cells or through a paracrine effect of increased insulin and somatostatin in neighboring cells S and B cells, is still debated (Ramracheya.,2018). After the glucose-lowering properties of GLP-1 were discovered, soon pharmaceutical drug therapies started to create analogues of GLP-1 that would increase the insulin secretion in T2D patients. GLP-1 agonists therefore were and are initially prescribed as drug treatments for T2D patients. Besides the notable improvements in glucose levels (**Figure 1**), T2D patients also seemed to lose weight when GLP-1 receptor agonists were trialed (Potts et al., 2015). Once the weight-loss inducing property of the GLP-1 agonist had been discovered, clinical trials studying their effect on obese patients started to leap.

To further understand the effects that GLP-1 agonists have on the body when prescribed to obese patients, the physiological function of GLP-1 in a variety of organs will be delineated in this chapter. The discussed physiological functions are based on experiments in which the effects of GLP-1, GLP-1 analog or GLP1R antagonist administration were determined in rodents or humans.

2.2 The central and peripheral nervous system

An important physiological function of GLP-1 in relation to obesity, is its ability to decrease food intake and increase satiety by binding to its receptors in the brain (**Figure 1**) (Turton et al., 1996). After its release by L-cells, speculations are that GLP-1 binds to the nodose ganglion, which is the inferior ganglion of the vagus nerve which has innervating neurons in the connective tissue underneath the intestinal mucosa, after which signals are relayed to the central nervous system (CNS) (Ronveaux et al., 2014). However, GLP1R signaling in the vagus nerve of rats seems to be disposable and not necessarily required for weight loss and food intake; administration of GLP-1 agonists still evokes reduction of food intake and weight loss after deafferentation of the vagus nerve (Secher et al., 2014). Conversely, a study on human subjects in which parts of the vagus nerve was surgically removed to treat

pyloroplasty, did not respond to the GLP-1 effects on their food intake (Plamboeck et al., 2013). These seemingly opposing findings bring up the question whether it is not peripheral GLP-1 activation of the vagus nerve, but either peripheral or central GLP-1 which activates brain regions in the CNS which reduces food intake as well as weight loss.

However, another study shows that approximately five minutes after rats were given a standard meal, GLP-1 plasma levels were elevated in the hepatoportal vein but not in the vena cava, which is probably the result of the rapid enzymatic breakdown of GLP-1 by DPP-4 (Punjabi et al., 2014). So, under normal physiological conditions, GLP-1 receptors in the CNS of rats are likely to be reached exclusively by brain-derived GLP-1, highlighting the importance of GLP-1 production by brainstem PPG neurons in the reduction of food intake.

There are a multitude of rat-studies displaying that GLP-1R induced signaling in the central nervous system (CNS) lowers the food intake and that antagonists of this receptor reverse it (Williams et al., 2008). The physiological mechanism by which food intake is suppressed by GLP1R binding is not fully known, but the mapping of a wide range of involved brain regions has been achieved.

Binding to GLP-1Rs in the brainstem of the hindbrain and the hypothalamus seem to be especially vital for the regulation of food intake and weight loss. GLP-1 receptor blockers in the hindbrain of rats have shown to reduce the motivation to perform tasks in exchange for pleasant-tasting foods as well as to decrease their ingestion (Alhadeff et al., 2014). In addition, the mesolimbic pathway, a key player in the regulation of motivated behaviors and different types of reward in rats as well as humans, also exhibit GLP1R in the ventral tegmental area (VTA) and the Nucleus accumbens (NAc) and is in direct connection with GLP-1 producing PPG neurons of the NTS (Alcaro et al., 2007). These findings mean that GLP-1 might play a role in the suppression of the hedonic drive for eating and motivational behavior towards eating.

Furthermore, central injection of GLP-1 and binding with GLP-1 analogs in the hypothalamus has clearly been linked to anorexic effects. Especially the arcuate nucleus (ARC) of the hypothalamus is known to be the major control center for the regulation of feeding (Timper & Brüning, 2017). GLP1R activation in the proopiomelanocortin (POMC) neurons of the ARC are thought to be partly responsible for GLP-1's observed anorexic effects (Péterfi et al., 2020).

Finally, GLP-1 binds to receptors in the hippocampus in rats. As the hippocampus is well-known for its function related to learning and memory, researchers were dazzled when they found that increasing the GLP1R activity in the ventral hippocampal area reduced food intake (Hsu et al., 2014). A possible route through which GLP-1 can reach the hippocampus is through the cerebrospinal fluid after secretion by the PPG neurons in the NTS (Hsu et al., 2014).

Although exact delineation of the underlying mechanism remains unknown, it is clear that the weight-losing effect of GLP-1 agonists is a direct function of the reduction of food intake that results from the binding on GLP-1R's in the aforementioned brain regions. Once-daily administration of GLP-1 agonist liraglutide for example, increased postprandial satiety, fullness ratings as well as reduced hunger in obese subjects.

2.3 The gastrointestinal tract (GI tract)

Studies testing the effect of GLP-1 agonist liraglutide have shown that administration significantly delayed gastric emptying and slows down motility in the duodenum and the small intestine of T2D subjects (Nakatani et al., 2017). Slowing of the gastric emptying can impact glucose absorption and thus affect postprandial glycemia (Deane et al., 2010). Delayed gastric emptying has been associated with decreases in postprandial glycemic

excursions, which implies that GLP-1 agonists are helpful for regulation of blood-glucose concentrations in T2D obese patients. Receival of a GLP-1 antagonist on the other hand accelerated the gastric emptying in healthy subjects, further demonstrating the physiological functions of GLP-1 in the GI tract (**Figure 1**).

2.4 The kidneys

Immunohistochemistry with a monoclonal antibody in primate and human targeted organs, localized GLP-1Rs in the smooth muscle cells of the arteries and arterioles of the kidney (Pyke et al., 2014). One current hypothesis about the role of GLP-1 in the kidneys is that it might be responsible for the dilation of vessels which supply the blood-filtering glomeruli. Furthermore, when GLP-1 was intravenously injected in rats, urinary flow rate and excretion of particular waste products was higher in this group than in the placebo group which had undergone the placebo treatment (Crajoinas et al., 2011). Increased natriuresis, glomerular filtration rate (GFR) but not diuresis was also observed in healthy as well as obese subjects (Gutzwiller et al., 2004) (**Figure 1**). Even more intriguing, GLP-1 agonists have been reported to be BP lowering in dependent on the treatment group (**Figure 1**). However, it is unclear whether it is the GLP1R activation in the kidneys that results in the lowering of BP (Ferdinand et al., 2014). If GLP-1 agonists can directly lower blood pressure, the utility of this could have far-reaching beneficial consequences for obese patients; the prevalence of hypertension is often high in patients with obesity (Bramlage et al., 2004).

2.5 Liver

Non-alcoholic fatty liver disease (NAFLD), a disease in which a buildup of fat is found in the liver, is associated with obesity. In a number of cases, NAFLD can advance into an inflammatory disease called non-alcoholic steatohepatitis (NASH) in which liver tissues can be damaged. A study by (Newsome et al., 2021) showed that administration of semaglutide was positively correlated with resolution of NASH in comparison with a placebo. Another study showed that liraglutide had a similar effect when administered to treat NASH (Armstrong et al., 2016) (**Figure 1**). The liver however does not contain any GLP-1R's and again the exact mechanism behind the resolution of NASH by the GLP-1 agonists is still up for debate.

2.6 Heart

Obesity directly can lead to cardiovascular disease as well as contribute to its risk factors. GLP-1Rs have been detected in different cell types of the heart and application of several GLP1 agonists have been linked to cardiovascular benefits in T2D patients as well as obesity patients (Sheahan et al., 2019). The beneficial cardiovascular outcomes emanating from GLP-1 agonist use presumably spring from their ability to lower cardiovascular risk factors such as glycemic variability (GV), high arterial hypertension, dyslipidemia and endothelial dysfunction, which in turn reduce the risk for myocardial infarction, strokes and cardiovascular death (del Olmo-Garcia & Merino-Torres, 2018) (**Figure 1**).

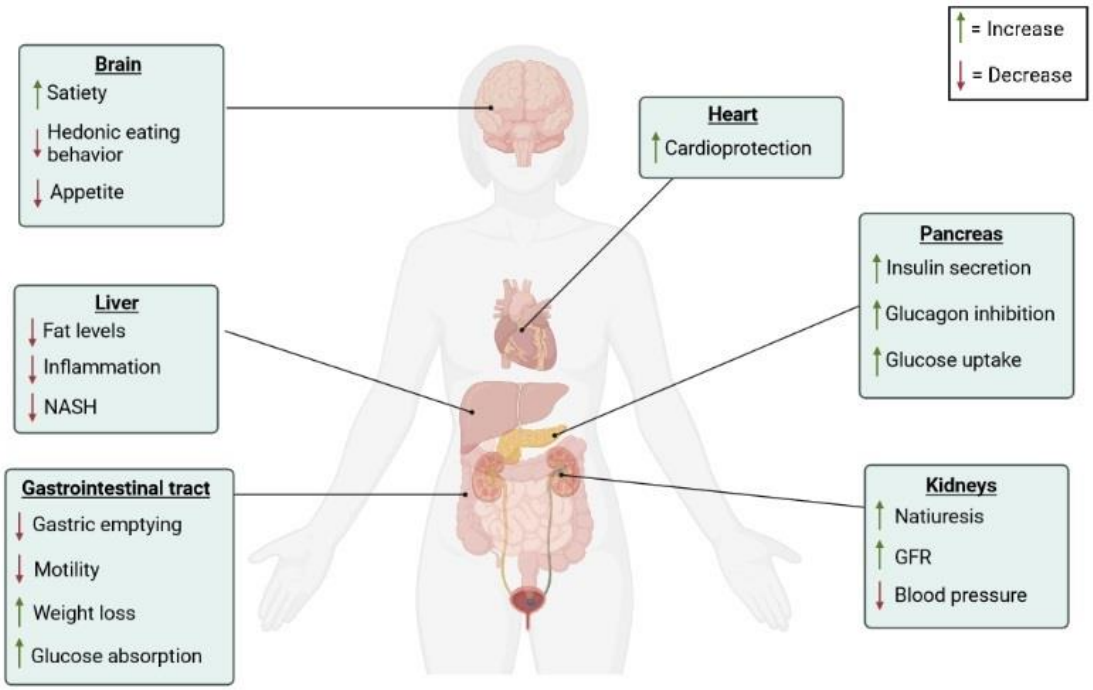

Figure 1 *- The effect of GLP-1 on several organs of the human body. The green arrows indicate an increase while the red arrows indicate a decrease.*

Chapter 3: Comparing the effect of GLP-1 agonists on weight loss with other treatments

Now the physiology of GLP-1 is clearer, the efficacy of GLP-1 agonists can be compared to the different treatments and therapies which are applied to increase weight loss in obese patients. The most effective GLP-1 agonists will be used for comparison against two different weight loss strategies: a strategy focusing on improving diet and/or increasing physical activity as well as other lifestyle changes and finally a more invasive strategy involving bariatric surgery to lose weight. For every type of weight loss strategy, two studies were analyzed and key details including the weight loss percentage and side-effects of treatment (e.g the impact on existing comorbidities) have been displayed in (**Figure 2**).

3.1 GLP-1 agonists

The research used for this analysis consists of a study on the weight loss efficacy of GLP-1 agonists liraglutide and semaglutide, which are the latest and most effective GLP-1 agonists related to weight loss. Pharmacotherapy to induce weight loss is not advocated as a substitute for a lifestyle change composed of a healthy diet and regular physical exercise. Research evaluating the efficacy of GLP-1 agonists are therefore usually adding the effect of lifestyle intervention to it.

Liraglutide is a FDA approved pharmaceutical drug already prescribed for weight loss treatment in obesity. In a 56-week double-blind trial 3731 overweight and obese subjects were randomly assigned in a 2:1 ratio for the receival of a single daily subcutaneous injection of 3.0mg liraglutide or a placebo (Pi-Sunyer et al., 2015). Both groups were also provided with lifestyle counseling. The study evaluated the effect of liraglutide on weight change from baseline as other endpoints such as cardiometabolic biomarkers or glycemic control variables. After 56 weeks of treatment, the liraglutide group lost a mean body weight percentage of (8.0%) and the placebo group (2.6%). A larger fraction of participants in the liraglutide group (63.2%) lost at least 5% of initial body weight than the placebo group

(27.2%). Interestingly, about three times more subjects (9.9%) of the liraglutide treated group discontinued treatment due to experience of adverse events than the placebo group (3.8%). The most common reason for discontinuation was related to gastrointestinal occurrences (Pi-Sunyer et al., 2015). Nausea and vomiting were additional common side-effects but were predominantly displayed between the 4th and 8th week after start of the treatment. Observed remission of the symptoms was thought to be a sign of drug-tolerance (Pi-Sunyer et al., 2015). Besides superior weight loss improvements, the liraglutide group also showed improved variables of glycemic control including improved insulin resistance and beta cell function. Liraglutide was found to be associated with a lower prevalence of prediabetes in comparison with the placebo; liraglutide seriously ameliorates glucose-tolerance. Blood pressure, fasting lipid levels, inflammatory markers and other biomarkers of cardiometabolic health also tended to be significantly improved in the liraglutide group (Pi-Sunyer et al., 2015).

Semaglutide is a novel GLP-1 receptor agonist with a significantly longer half time than endogenously produced GLP-1. In combination with lifestyle intervention, its effect on weight loss was studied in 1981 obese adults over a period of 68 weeks in a study by (Wilding et al., 2021). Dosage of semaglutide was 0.4 mg from the first week, and the dose was increased every 4 weeks by 0.4 mg until 2.4 mg. On top of that, counseling sessions were given every 4 weeks for the adherence to the 500-kcal deficit and 150 minutes of weekly physical activity. After 68 weeks of a subcutaneous injection or a placebo (2:1 ratio respectively), the mean percentage of weight loss in comparison with initial body weight was (14.9%) in the semaglutide group and (2.4%) in the placebo group (Wilding et al., 2021). Weight loss percentage thus was 12.4 percentage points higher in the semaglutide treated group. Additionally, (86%) of participants of the semaglutide group lost 5% of the initial body weight, in comparison with (32%) of the placebo group (Wilding et al., 2021). Lastly, approximately one third of the semaglutide population lost a weight percentage of (30%) in comparison to baseline weight. Besides comparably higher weight loss, subjects of the semaglutide group also showed improved markers signifying cardiometabolic health including lower blood pressure, lipid levels as well as lower level of inflammatory marker C-protein (Wilding et al., 2021). Self-reported physical functioning also improved more in subjects administered with semaglutide than those injected with the placebo. The safety and side-effect profile of both groups was also assessed and compared. The semaglutide group showed comparable percentage points of reported adverse events (89.7%) as the placebo group (86.4%). Out of all the adverse events, gastrointestinal disorders were significantly higher in the semaglutide group (74.2%) than the (47.9%). Nausea, diarrhea, vomiting and constipation were adverse events that were at least double more frequent in the semaglutide group than in the placebo group (Wilding et al., 2021).

GLP-1 agonists thus not only show a significant ability to decrease weight loss, they can also lower the risk factors for comorbidities as liraglutide and semaglutide both were able to lower markers related to cardiometabolic health and inflammation and liraglutide alone was able to improve markers related to glycemic control. As obese patients frequently suffer from a comorbidity such as cardiovascular disease or T2D, the utility of GLP-1 agonists can be stretched further than the induction of weight loss alone.

3.2 Diet and exercise and other changes in lifestyle

In the following paragraphs, two separate studies with a similar weight loss strategy have been analyzed. Weight loss intervention programs like those described in the first study often focus on a combination of lifestyle modifications such as shifting towards a healthy and hypocaloric diet, a lifestyle characterized by frequent physical exercise and a change in the mental relationship with food and behavior associated with food intake. The goal of these modifications is to increase energy expenditure while decreasing energy intake, thereby eventuating in weight loss. Specialists such as psychologists, behavioral therapists, dietitians, lifestyle coaches and physicians often take part in these programs to optimize the

reduction and to overcome obstacles during the weight loss journey.

The retrospective study by (Christiansen et al., 2007), evaluated long-term weight loss maintenance over a period of 2 to 4 years in severely obese subjects after a lifestyle intervention of 21 weeks in a weight loss camp. Lifestyle intervention included a low-calorie diet (LCD) meaning a diet based on approximately 15 kcal/kg of body weight per day) together with a daily intensive physical activity of approximately 2 hours. Furthermore, behavioral modification classes focused on improvement of diet and personal development were given. 21 weeks of intensive lifestyle intervention led to an average body weight reduction of (15%). Unfortunately, the follow-ups 2 to 4 year after the weight loss camp were characterized by prevailing weight regain of most participants and weight maintenance was estimated at (5.3%) of the starting weight pre-treatment (Christiansen et al., 2007). Successful weight loss maintenance is defined as maintaining a weight loss of 10% or higher and was accomplished by between (20 to 28.9%) percent of all participants. Interestingly, the percentage of weight loss was positively correlated with the amount of body weight, which also meant that participants with a lower initial body weight also lost less weight in comparison. It is worth noting that initial body weight of the subjects of this intervention study was relatively high: 142 kg in comparison with most intervention studies, in which initial bodily weight typically ranges between 100 and 110 kg. Splitting the subjects in two groups according to body weight provided a more reliable weight loss outcome. The group of subjects belonging to the highest quartile based on BMI (mean BMI = 59) indeed showed a higher weight loss of (17%), and maintenance of (8%) after 2 to 4 years. Meanwhile the lower quartile BMI subjects (mean BMI =37) showed a weight loss of (11%), but had a weight loss maintenance of (0%). Weight regain therefore was more prevalent in subjects with the lowest BMI and this particular lifestyle intervention trial proved to be only effective for the most obese subjects (Christiansen et al., 2007).

The second study is a randomized controlled trial in which the independent effects of exercise and diet on weight loss and comorbid conditions in 52 obese men were assessed (Ross, 2000). Along the change in weight, the change in cardiovascular fitness, glucose tolerance and insulin sensitivity were measured. An identical weight-maintenance diet comprising of (60% carbohydrates, 20% proteins and 20% fats) was instigated in both groups, but the diet-induced weight loss group was asked to lower caloric intake of the diet by 700kcals for 12 weeks. In contrast, the exercise-induced weight loss group took part in daily exercise consisting of either a brisk walk or a light jog session on the treadmill for the same period of 12 weeks. Length of the exercise session was determined by the time it takes to expend a total of 700 kcal. Additionally, all groups participated in a weekly lecture given by a dietician on how to select the appropriate food stuffs and how to prepare them. Food records were kept and checked. In both the exercise and diet group, weight loss percentage of initial body weight amounted to (8%). Cardiovascular fitness, measured by the peak oxygen uptake, was improved in the exercise-induced, but not the diet group (Ross, 2000). Glucose disposal increased significantly after both diet and exercise treatments (5.6 and 7.2 mg/kg skeletal muscle per minute) in comparison with the control groups (-1.0mg/kg skeletal muscle per minute). Fasting insulin levels were lowered in both diet and exercise groups, but insulin area was significantly reduced in the diet group (Ross, 2000).

By comparison, inducing weight loss through diet, exercise and supplementary lifestyle changes is a laborious, disciplinary and often futile approach for a long-term weight loss in obese patients. While weight loss percentages of the compared studies on average were lower than those of GLP-1 agonist therapies and bariatric surgeries, they did bring about enough weight loss to improve risk factors as well as comorbidities by improving cardiovascular fitness as well as glucose disposal, a marker for T2D. It is intriguing however to see that diet alone was not able to improve cardiovascular fitness in the study by (Ross., 2000), but exercise was.

3.3 Bariatric surgery

Bariatric surgery is generally used as a last resort treatment if all other non-invasive therapies or treatments were unsuccessful. Unsurprisingly, the treatment is usually only feasible and recommended to two specific groups: the group of morbidly obese patients (BMI >40) or a group of obese patients with a BMI between 35 and 40 who have been diagnosed with an obesity-related comorbidity (UCSF Health, 2022).

There are a number of types of bariatric surgery to date, but annual report of the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) stated that between 2014 and 2018, 38.2% of 394.431 international bariatric surgeries were Roux en Y gastric bypasses (RYGB), 46.0% were sleeve gastrectomy operations (SG), 7.6% were anastomosis gastric bypasses (GB) and 5.0% were gastric banding operations (AGB). All bariatric surgeries result in either a reduction of space for food to be taken up or a reduction in the digestive system's ability to absorb nutrients. Ultimately all types are proven to result in long-term weight loss. Moreover, bariatric surgery has been proven to result in the rapid delivery of nutrients to the GI tract where the L-cells are located. Nutrient delivery to the L-cells would eventually augment post-prandial GLP-1 levels, stimulating satiety and weight loss. Furthermore, this postprandial rise in GLP-1 has been associated with the remission of T2D (Hutch & Sandoval, 2017). This is likely to be the result of post-surgery amelioration of insulin sensitivity and its secretion.

The first included study is a retrospective cohort study in which weight loss outcomes of obese patients who underwent RYGB surgery were set side by side to that of group of obese patients who did not undergo any form non-surgical treatment over a period of 5 years (Baheeg et al., 2021). The study included 100 subjects, meaning that each group contained approximately 50 individuals. After a year had passed, weight loss percentage was (30.16%) in the group who underwent RYGB surgery and (1.48%) in the non-surgery group. 5 years down the line however, weight regain had taken place in the RYGB group, while weight loss continued to occur in the non-surgery group. Weight loss in percentage of the initial body weight was (18.88%) in the RYGB surgery group after the five years, while the non-surgery group had a weight loss of (6.36%). Secondary effects of the treatments on the comorbidities hypertension, dyslipidemia, cardiovascular diseases and the incidence of diabetes were also measured. Although an overall lower incidence of all comorbidities was observed in the RYGB group, the difference was not significant (Baheeg et al., 2021). Compellingly, patient satisfaction based on the user-friendliness of procedure, the skill of healthcare professionals and the patient's personal expectations was significantly higher in the former group (90%) than in the latter (4%).

The second study compared the effect of several bariatric surgeries (RYGB, SG, and AGB) on the amount of weight loss in obese patients with a BMI of 35 or higher, measured over a period of five years (Arterburn et al., 2018). One year after surgery RYGB, SG and AGB induced an average weight loss percentage of (31.2%), (25.2%) and (13.7%) respectively. At the 5-year mark, relative weight regains had taken place, lowering the weight loss percentages to (25.5%), (18.8%) and (11.7%). It is worth mentioning that weight regain only started taking place about one and a half year after surgery had taken place, indifferently of the type of bariatric surgery. In conclusion, RYGB proved to be the most effective for the induction of weight loss in obese patient, followed by SG and AGB (Arterburn et al., 2018). Based on this research weight loss percentage after one year can range between (13.7 - 31.2%) and between (11.7 - 25.5%) after 5 years, depending on the chosen bariatric surgery (Arterburn et al., 2018). The effect of this weight loss on the existing comorbidities in the subjects was beyond the scope of this particular study.

Of all weight loss treatments, bariatric surgery is one of the most invasive, but also most effective weight loss strategies. Depending on the type of surgery, weight loss percentages over time can be double as high as that of GLP-1 agonists liraglutide or semaglutide. Besides weight loss, improvements in obesity-related comorbidities are also common to occur currently making it the best long-term strategy to induce weight loss and treat comorbidities in obese patients.

Research paper	Type of treatment	Treatment group	Number of subjects	Effects on weight loss change (%?) in treated group	Effects on weight loss (%) in placebo group	Difference (%) between groups	Treatment time	Side effects (+/-)
(Pi-Sunyer et al., 2015)	GLP-1 agonist (Daily subcutaneous Liraglutide, 3.0mg) + Lifestyle counseling	Individuals with a BMI >= 30 or with a BMI > 27 + weight-related coexisting condition	3731 adults	8%	2.6%	5.4%	58 weeks	- Nausea - Vomiting - Lower prediabetes - Improved glucose tolerance -Improved inflammatory markers - Improved cardiometabolic markers
(Wilding et al., 2021)	GLP-1 agonist (Weekly subcutaneous Semaglutide, 2.4mg) + Lifestyle intervention	Individuals with a BMI >= 30 or with a BMI > 27 + weight-related coexisting condition	1961 adults	14.9%	2.4%	12.5%	68 weeks	- Increased gastrointestinal disorders - Nausea - Diarrhea - Vomiting - Constipation - Improved cardiometabolic markers - Improved inflammatory markers
(Christiansen et al., 2007)	Diet restriction and exercise	Severely obese individuals (Mean BMI = 47.5)	249 adults	15%, but 5.3 % after 2-4 years.	N/A	N/A	21 weeks	N/A
(Ross,2000)	Diet restriction and exercise	Obese individuals (Mean BMI = 31.3)	52 male adults	8%	0%	8%	12 weeks	<u>Diet:</u> - Improved glucose disposal - Lowered fasting insulin levels - Reduction of insulin area <u>Exercise:</u> - Increased cardiovascular fitness - Improved glucose disposal - Lowered fasting insulin levels - Reduction of insulin area
(Baheeg et al., 2021)	Bariatric surgery (RYGB)	Obese individuals (Mean BMI = 35)	100 adults	First year: 30.16% Fifth year: 18.9%	First year: 1.48% Fifth year: 6.36%	First year: 28.68% Fifth year: 12.54%	1-5 years	-Lowers incidence of hypertension, dyslipidemia, cardiovascular diseases and the incidence of diabetes
(Arterburn et al., 2018)	Bariatric surgery (3 types)	Severely obese individuals (Mean BMI = 49.1)	<u>46510 adults:</u> N= 24982 RYGBS N= 18961 SG N= 2567 AGB	(13.7 - 31.2%) One year after (11.7 - 25.5%) Two years after	N/A	N/A	1, 3, 5 years	N/A

Figure 2 - A comparison of different weight loss treatments on weight loss and additional end points such as possible side-effects on the comorbidities and risk for comorbidities.

Discussion

Based on sheer weight loss efficacy, bariatric surgery is by far the most effective treatment of obesity out of the analyzed treatments, followed by GLP-1 agonists and then diet and exercise lifestyle intervention studies. Weight loss percentages after one year of bariatric surgery can, depending on the type of surgery, go up to as high as (30.16%), while that of liraglutide treatment after 58 weeks was (8%) and that of semaglutide was (14.9%) after 68 weeks as presented in table 2. However, some weight regains after RYGB, SG, and AGB surgery is likely to take place after 1.5 years, reducing the weight loss percentage to a maximum range of (11.7%-25.5%) five years after surgery (Arterburn et al., 2018). The lifestyle intervention described in (Christiansen et al, 2007) had the ability reduce weight loss by (15%) after 21 weeks, while the 12-week diet and exercise regimen described by (Ross, 2000) was able to reduce weight loss percentage by (8%). However, weight loss through the lifestyle change strategy consisting of improved diet and frequent exercise often seems to be only short-lived and weight regain is bound to occur; between 2-4 years after the weight loss program described in (Christiansen et al, 2007), overall weight loss percentage shrunk from (15.3%) to (5.3%). Long-term weight assessment was beyond the scope of the study by (Ross, 2000), but weight regain is a common reoccurring event amongst obese individuals who have lost significant amounts of weight (Hall, 2018). Weight regains in the studies evaluating the weight loss efficacy of liraglutide and semaglutide were not observed, but has been observed that weight regain takes place when GLP-1 agonist ingestion is discontinued (Le roux et al., 2017). This indicates that continuous GLP-1 agonist is necessary for weight loss as well as weight loss maintenance.

Why weight regain is more present after lifestyle intervention stimulated weight loss than in bariatric surgery, has all to do with the physiological alteration of gut hormones that are a result of surgery. Satiety hormones including GLP-1 tend to increase after surgery, which staves off weight regain for a period of time (Sinclair et al., 2018). On the other hand, decreases of satiety hormones together with a lower BMR as a result of weight loss can explain the predisposition towards weight regain in the lifestyle intervention studies (Hutch & Sandoval, 2017). Weight regains is not likely to take place in individuals on GLP-1 agonist medication, as they are used exactly for their weight-loss maintaining properties.

One commonality between all three strategies is that they all had weight loss percentages of at least (5%) in most of the subjects, no matter whether short-term or long-term. This is an essential finding since (5%) initial body weight loss in obese individuals can lead to a significant improvement of obesity-related comorbidities (Ryan & Yockey, 2017), the major threat for obese patients. A weight loss percentage reduction of (5%) can reduce the risk for T2D diabetes, cardiovascular disease, reduce NASH, improve mobility, quality of life and more (Ryan & Yockey, 2017). However, the cost of reaching weight loss is different per strategy. Losing weight on a specific diet and exercise regimen takes discipline, perseverance and patience. Bariatric surgery can come with certain risks and complications such as postoperative stenosis, ulcers, internal hernias and bleedings, malnutrition, infections, chronic nausea and vomiting and more (Lim et al., 2018). Another problem with bariatric surgery is that only the most severe obese individuals or those with a comorbidity are eligible for the treatment (UCSF Health, 2022). This makes bariatric surgery not accessible for every obese patient. Although subcutaneous injection with GLP-1 agonists is not yet as effective as bariatric surgery, they are less invasive as opposed to an invasive, permanent procedure such as RYGB or SG. Contrastingly, administration of a GLP-1 agonist often comes with gastrointestinal symptoms as side effects such as nausea, vomiting, diarrhea as has been shown in the studies on liraglutide and semaglutide. In closing, GLP-1 agonists tend to also have additional side-effects that are beneficial for obesity patients. As GLP-1 agonists were first used in T2D patients they can improve and control blood sugar

levels. In the study by (Wilding, et al, 2021), use of semaglutide was also associated with improvement of cardiometabolic risk factors, physical functioning while the study by (Pi-Sunyer et al., 2015) showed improved variables of glycemic control including improved insulin resistance and beta cell function.

Nevertheless, GLP-1 agonist treatment does have some obstacles. Although significant weight loss is induced while taking for example GLP-1 agonist semaglutide, weight loss percentages similar to that of the most effective bariatric surgery are still not likely to occur. Besides, when the proper lifestyle changes are not in place after discontinuation of the treatment, weight regain is very likely to take place (Singh et al., 2021). This means that long-term and maybe even permanent use is possibly called for to ensure weight loss maintenance. Two major problems with this scenario are the way in which GLP-1 agonists are currently administered and their cost. As of now, most effective weight loss is seen when GLP-1 agonists are injected subcutaneously (Singh et al., 2021). This is a problem as distress or discomfort when injected with a needle are common amongst individuals with a chronic disease who are frequently exposed to needles (Duncanson et al., 2021). Even though oral GLP-1 agonists are being produced, they are not as effective as subcutaneously injected agonists. Further development of ingestible agonists is needed to make its usage more practical. A final stumbling block of GLP-1 agonists use is that they are quite expensive as of now. For example, it is estimated that annual use of semaglutide would amount to around $2500. In comparison to the price of bariatric surgery, averaged between $15000 and $23000 this is cheap if used for only a couple of years. But as was said before, long-term or annual use of these drugs would make it likely to be just as, or even more expensive. However, as more pharmaceutical companies will develop effective GLP-1 agonists, it is likely that prices will fall and become more affordable.

As with every study, there are however some limitations to this literature review. First of all, the comparison of GLP-1 agonist treatment versus other weight loss strategies only included a small total of six studies, two per treatment. Analysis of such a small number of studies is prone to observations and conclusions that are not as accurate and reliable as could be. Furthermore, although the treatment group of each study generally consisted of obese patients, fluctuations in BMI were still observed between studies. This could partially have perturbed conclusions regarding the weight loss efficacy of each treatment, as weight loss is often higher in individuals with a high BMI in comparison with a lower BMI (Christiansen et al., 2007). The same goes for the difference in treatment times between the different studies. To confirm the reliability of the comparison made in literature review, a follow-up study is necessary in which parameters such as BMI, treatment time and secondary end points are identical.

Obesity is a complicated disease to treat. While weight loss surgeries are effective, they are invasive and not very inclusive. Diet and exercise regimens in the form of lifestyle intervention programs are more inclusive, but unfortunately not effective in the long-term. GLP-1 agonist usage on the other hand is less invasive than bariatric surgery, but more invasive than a change of diet and exercise regimen. Efficacy-wise, GLP-1 agonists do not yet induce the same weight loss amount of bariatric surgery, but certainly more than diet and exercise regimens would bring about. This does not mean that diet and exercise are pointless, because changes of the sort are still needed for the optimal weight loss and weight loss maintenance when GLP-1 agonists are prescribed. Besides weight loss, GLP-1 agonists can improve a range of obesity-related comorbidities as well as prevent them from occurring. As pharmaceutical companies are continuously upgrade the efficacy as well as user friendliness of the GLP-1 agonist medications, the future of the GLP-1 agonists as the first upcoming mainstream pharmaceutical treatment for obesity might be within reach.

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