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GLP-1 AGONISTS AND WEIGHT MANAGEMENT IN DIABETES: A CRITICAL REVIEW

Mehrab Manteghian*

22318 Lougheed Hwy, Maple Ridge, British Columbia, Canada.

***Corresponding Author: Mehrab Manteghian**
22318 Lougheed Hwy, Maple Ridge, British Columbia, Canada.

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ABSTRACT
Obesity is on the rise globally and is one of the most significant risk factors for non-communicable diseases. It is one of the primary causes of diabetes. Controlling body weight and managing diabetes may help prevent chronic ailments and even lead to their remission. Obesity is caused by specific lifestyle choices and, hence, best managed through lifestyle interventions. However, some obese individuals may benefit from pharmaceutical interventions. In recent years, anti-obesity pills have become quite popular, particularly GLP-1 agonists like liraglutide, semaglutide (Wegovy, Ozempic), and other GLP-1 agonists. Many people are now using these drugs as a primary way to fight obesity. However, it is vital to understand that lifestyle interventions like exercise and dietary measures must remain the prime way to counter obesity, and drug therapy must be used as an adjuvant. GLP-1 agonists are claimed to help lose 10-15% body weight in a year, or even more. However, the literature review shows that the real-life efficacy of these drugs is significantly lower than that claimed in clinical trials sponsored by drug manufacturers. Additionally, these medications commonly cause side effects. Though gastrointestinal distress remains the primary concern, there is increasing evidence that these drugs may cause more severe side effects. Studies suggest that they can significantly increase the risk of thyroid cancer. EMA is now even investigating these drugs for causing suicidal thoughts. Hence, medical practitioners must realize the health threat posed by excessive use of these drugs. This review advocates a paradigm shift towards promoting healthier lifestyles as the primary means of preventing and managing obesity and diabetes, ultimately reducing the burden of this growing global health crisis and considering GLP-1 agonists only in specific cases.

KEYWORDS: GLP-1 Agonists, obesity, diabetes, liraglutide, semaglutide.

1. INTRODUCTION
Diabetes is an ongoing pandemic. It is one of the most common chronic ailments and among the top ten causes of mortality globally. Diabetes also causes significant morbidity and disability. It is among the major causes of kidney failure, blindness, stroke, heart attack, and lower limb amputation. What has been worrisome is the continuous rise of diabetes. Since 1980, the number of people living with diabetes has risen more than four-fold by 2014, from 108 million to 422 million. Moreover, the number of people living with diabetes is projected to keep rising in the foreseeable future. Though diabetes incidence is high in developed nations, but due to the higher population, its burden is exceptionally high in emerging economies.[1]

Diabetes is a preventable lifestyle disorder. That is why it is essential to understand diabetes risk factors. It also means that for preventing diabetes, introducing lifestyle interventions must remain the focus of healthcare providers, and drug therapy must be reserved for cases when lifestyle interventions fail.[2] Diabetes is a multi-dimensional health issue. There are a few factors associated with higher diabetes risk, like ethnicity, genetics, wrong dietary choices, sedentary lifestyle, sleep disorders, stress, and obesity.[3] A significant rise in diabetes in the last few decades indicates that preventable risk factors like wrong dietary choices, sedentary lifestyle, and obesity are the primary causes of its increase globally.

Though there are many risk factors for diabetes, but it appears that obesity is one of the most significant reasons for the risk of diabetes and other non-communicable diseases. Obesity, hyperlipidemia, hyperinsulinemia, hypertension, and hyperglycemia, together forming the metabolic syndrome, significantly increase the risk of diabetes. Metabolic syndrome also contributes to the worsening of the diabetes.[4] Thus, it is vital to realize that the central to the diabetes epidemic is increasing rates of obesity.

Global obesity statistics clearly show that the prevalence of diabetes has increased proportionally to obesity rates.

Generally, obesity precedes diabetes. Thus, by 2016, global obesity rates have tripled since 1975. Obesity is classified as a BMI above 30, whereas a BMI above 25 to 30 is overweight. Understanding the prevalence of overweight is vital, as it not only precedes obesity and diabetes but is also an opportunity to counter metabolic disorders. Thus, in 2016, 1.9 billion adults were overweight, constituting close to 40% of the global population. Furthermore, 13% of the global population was obese.[5]

Both obesity and diabetes are increasing at an alarming rate. Thus, obesity rates are particularly high in specific parts of the world. Hence, more than 70% of the US population is either overweight or obese. It also means that the US has become one of the first nations to consider obesity as a disease and not merely a risk factor.[6] The picture is equally grim in the EU, with more than 50% of the population either overweight or obese.[7] Further, studies show that the gap between developed nations and emerging economies is fast closing. Thus, the rate of obesity is fast increasing in nations like India, China, Nigeria, Guatemala, Brazil, and others where traditionally obesity rates have been low.[8,9] Hence, it is vital to understand that obesity is not just a problem in prosperous nations. Further, due to the high population in developing nations, most people living with diabetes live in developing nations. BMI and diabetes risk have a strong association. It leads to insulin resistance, dyslipidemia, higher glycerol, hormonal changes, and chronic inflammation, predisposing one to diabetes.

2. MATERIALS AND METHODS

The objective of this article is to explore how countering obesity in different ways may help reduce diabetes risk and help manage diabetes. However, more importantly, this study aims to examine the role of GLP-1 agonists in managing obesity. In recent years, a number of pharmacological drugs have been introduced to address obesity. This is particularly true for GLP-1 agonists like liraglutide, semaglutide, and many others.[10] These drugs are quite good for countering obesity. However, their widespread use is shifting the discourse regarding countering obesity through lifestyle interventions towards managing obesity with drug therapy, which is an unhealthy and alarming trend. This article explores the present trend in the usage of these drugs, explores their real-life efficacy and health risks of these drugs, and looks at the vitality of lifestyle interventions for preventing and managing obesity and, consequently, diabetes. This article tries to reaffirm that lifestyle interventions are the best way to weight loss, and they must remain the primary way to counter obesity. In contrast, drug therapy must have a supportive role and need to be reserved for specific cases.

For the purpose of the study, we primarily searched the PUBMED database. We searched the data regarding the safety and efficacy of various GLP-1 agonists and the database for the efficacy of lifestyle interventions. We also searched the US FDA and European Medical Agency's (EMA's) database to find safety data related to GLP-1 agonists. The study aims to identify the right place for these popular weight loss drugs in obesity management, identify real-life efficacy, and explore real-life safety data.

3. GLP-1 and Weight Management in Diabetes

There is a reason for the popularity of weight loss pills. Many people find it easier to use pills than carry out lifestyle interventions. Additionally, in many instances, doctors find it to be the only non-invasive way to achieve weight loss when lifestyle interventions fail. Few pharmacological drugs are known to promote considerable weight loss or drugs safe for prolonged use. Thus, for example, topiramate and phentermine combination may help achieve some weight loss, but these centrally acting drugs are only approved for short-term use due to safety concerns.[11] In the last few decades, orlistat (Xenical) has also become popular, a drug that inhibits gastrointestinal lipases, thus reducing dietary fat absorption. However, over the years, it has fallen out of favor due to its poor safety profile, severe toxicity in some instances, and many drug interactions.[12]

However, the search for an ideal anti-obesity drug continues. In recent years, GLP-1 receptor agonists have gained much popularity. They have been touted as the most effective drugs, a breakthrough therapy that can help with fast weight loss. They are also generally accepted to be safe for prolonged use. Some of the drugs belonging to this class, like liraglutide and semaglutide, are now approved for use for weight loss, even by those not living with diabetes.[10]

These drugs do have some distinct benefits. They have a unique mechanism of action. Unlike earlier drugs that primarily acted on the central nervous system or disrupted digestive processes, these new classes of drugs have a novel mechanism of action. GLP-1 agonists revive insulin secretion, delay gastric emptying, boost satiety, reduce glucagon production by pancreatic alpha cells, they even reduce apoptosis of pancreatic beta-cells. Thus, they can help with weight loss and positively impact metabolic profile, enhance cardiac output and endothelial function, reduce glucose production in the liver, and exert neuroprotective action. They are quite helpful for weight loss and reducing HbA1C.[10]

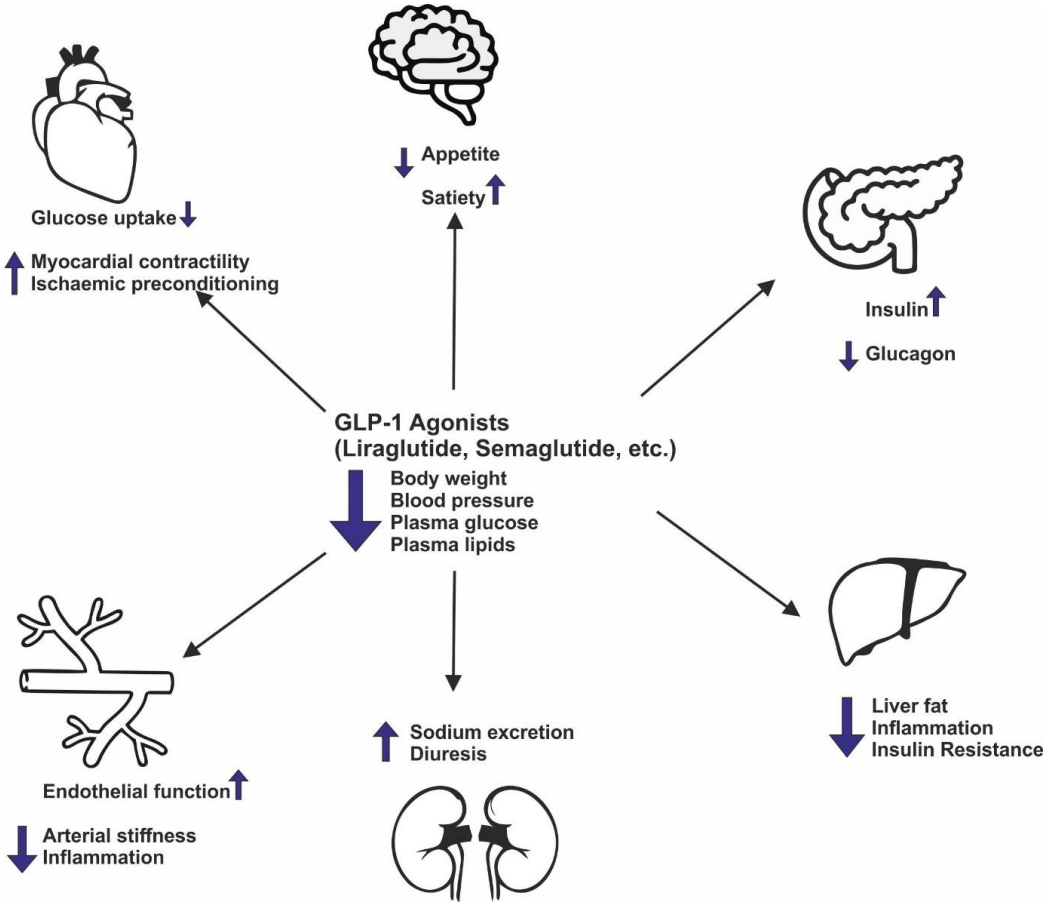

Figure 1: GLP-1 Agonists- Mechanism of Action.

Liraglutide (Saxenda) was among the first GLP-1 agonists from this new class of drugs approved for weight loss. It is vital to understand that despite the widespread misconception, it is only approved for use along with dietary measures and exercise for weight management. The drug was never intended to be used as a sole means for weight loss. Clinical studies show that if this drug is taken regularly for more than one year, it results in weight loss greater than 5% in more than half the cases. Additionally, it also helped achieve more than 10% weight loss in about one-third of cases. Thus, it was proven superior to previous drugs approved for weight loss, including orlistat. Nonetheless, it is vital to understand that all clinical trials showing these excellent results had confounding factors, that is, lifestyle interventions.[13]

However, perhaps even more popular weight loss pill from the class is Wegovy, Ozempic, or Rybelsus, essentially the brand names or trade names for semaglutide. It has been subject to numerous clinical studies, with SUSTAIN clinical trials primarily focusing on its subcutaneous injection form and PIONEER trials on its oral drug form.[14] It has also been subject to extensive studies for weight loss. Thus, one of the most extensive RCTs was in 1961-adults with a BMI greater than 30. This particular trial continued for 68 weeks, and participants were assigned to semaglutide and placebo groups in a 2:1 ratio. At the end of the study, semaglutide 2.4 mg weekly s.c. was significantly superior to placebo, with 86.4% achieving weight loss greater than 5%, whereas in the placebo group, just 31.5%. In fact, in semaglutide groups, 50.5% achieved weight loss greater than 15%, while just 4.9% reported similar weight loss in the placebo group.[15]

This is a fast-expanding group of drugs with new molecules being added every few years. Moreover, over the years, the focus has shifted from primarily using these drugs for diabetes management to obesity management. Hence, in 2022, the US FDA approved tirzepatide (Mounjaro). It is worth noticing that it differs from pre-existing drugs as it is both GLP-1 and GIP agonists, making it a more potent weight loss drug.[16] It is now regarded as one of the most potent weight loss drugs that can help reduce body weight by as much as 20%.[17]

4. GLP-1 Agonists Safety and Efficacy Concerns

However, despite so many clinical studies, some questions remain. Are these medications as good in real life as found in clinical studies? Quite often, drugs are not as efficacious in the real world as in clinical studies. Clinical studies sponsored by manufacturers tend to be biased. This is especially true, particularly when confounding factors are present.[18] It means there is a need for further studies to fully understand the safety and efficacy of these weight-loss drugs. Though systemic

reviews and meta-analyses confirm the superiority of GLP-1 agents over placebo for weight loss, nevertheless, a study by Vosoughi et al. also confirms a significant risk of bias in these clinical studies due to unclear random sequence generation, allocation concealment, and incomplete outcome data.[19]

Even clinical studies sponsored by drug producers show that these new classes of drugs cause adverse effects in a large number of patients. One of the most common side effects of these drugs is gastrointestinal issues like nausea, vomiting, diarrhea, and dyspepsia. Other frequent side effects include headaches, nasopharyngitis, UTIs, increased pancreatic enzymes, and occasional pancreatitis. Among infrequent side effects are changes in pulse rate, cholelithiasis, and cholecystitis.[14,15] Gastrointestinal symptoms are quite common, affecting close to 40% of users and resulting in therapy discontinuation in about 10% of the cases.[13]

Although gastrointestinal adverse events were primary findings in early trials, but now even more worrisome data is emerging from post-marketing studies and studies done by different researchers. These studies suggest that GLP-1 agonists might have some adverse effects on long-term use. A French study shows that these drugs significantly **increase the risk of thyroid cancer**. The French study found that those exposed to GLP-1 agonists for 1-3 years had a 1.58 times higher risk of thyroid cancer and 1.78 times higher risk of medullary thyroid cancer.[20] Similarly, the European Medical Agency's (EMA) safety committee is investigating an increase in the risk of suicidal thoughts or self-harm related to prolonged use of GLP-1 Agonists on prolonged use.[21]

Not only are there concerns regarding side effects, there are also worries that these drugs are not as effective in the long term. Thus, for example, follow-up studies show that on discontinuation of drug therapy, there are significant chances of weight regain. Hence, in the extension analysis of the STEP 1 trial that randomized 1961 adults for weight loss using semaglutide, the extended study for another 68 weeks found that significant numbers of those who discontinued drug therapy regained body weight and a net loss of body weight at 120 weeks was just about 5.6%. These are still relevant indicators but much below those shown in clinical studies. Not only that, the study found that most cardiometabolic improvements returned to baseline at 120 weeks. These findings just show that obesity is a chronic health issue requiring lifelong efforts and also underline the importance of lifestyle interventions over drug therapies.[22]

Further, real-world studies are emerging, questioning the claimed efficacy of GLP-1 agents. It appears that in the real world, their efficacy is much lower than that in clinical studies. Thus, in the retrospective cohort study in the UK of 589 patients, the study found that at 12 months, 33.4% reported weight loss greater than 5%, and these numbers were 43.5% at 24 months. These results are much lower, and weight loss is less significant than reported in clinical trials.[23] In yet another retrospective study by White et al. that included 2405 patients with a baseline BMI of 37, researchers found that just one-third of patients lost body weight greater than 5% at 72 weeks.[24] Findings are similar for other benefits for GPL-1 agonists. Similarly, studies confirm that all the cardiovascular benefits of these agents are reversed upon their discontinuation.[25]

It is regretful that, at present, there are no head-to-head clinical trials comparing GLP-1 agonists alone with intensive lifestyle interventions done under medical supervision. This is despite the fact that early diabetes prevention studies have shown that lifestyle interventions are better than drugs in preventing diabetes, as they result in better body weight control. Moreover, weight control through lifestyle interventions is more sustainable. Thus, for example, early diabetes prevention studies showed that lifestyle intervention reduced diabetes risk by 58%, compared to 31% in the metformin group. This higher benefit of lifestyle interventions has been due to greater weight loss through lifestyle interventions.[26]

Similarly, new studies are emerging showing significant weight loss and diabetes remission through extensive lifestyle measurements like the short-term introduction of a very low-calorie diet (VLCD). VLCD is generally described as a diet with fewer than 800 kcal/day. In most such studies, people are switched to VLCD for just 8 weeks, followed by 4 weeks of transitionary period. And in most instances, 12 weeks of this intervention is sufficient to cause significant weight loss and diabetes remission that is also sustainable for long with continued lifestyle measures like dietary measures and exercise. Smaller studies show that such interventions may result in diabetes remission in the majority of cases.[27] One of the most extensive studies, the DiRECT trial, found that such an intervention could result in diabetes remission in 46% of adults at 12 months. This also means that such a short intervention along with continued efforts, could result in significant and sustainable weight loss. At the end of one year, at least one-fourth had achieved a weight loss of 15 kg or more.[28,29] The DiRECT trial has been groundbreaking in many ways, as it showed that significant and sustainable weight loss and diabetes remission are possible through lifestyle interventions alone.

Here, it is vital to note that although there are no studies comparing GLP-1 agents directly with intensive lifestyle interventions, nonetheless, there is sound evidence that lifestyle interventions when used methodically, can result in greater benefit that is comparable or even better than drug therapy. Moreover, since obesity is a chronic health issue, lifestyle interventions are sustainable over the long term. Finally, not to mention that lifestyle interventions have a better safety profile.

5. DISCUSSION

People these days are more likely to die from non-communicable diseases. Diabetes is among the most common chronic metabolic disorders that are preventable in most cases through lifestyle interventions. The sudden rise of diabetes in the last few decades has been proportional to the rise of obesity. Though there are many reasons for diabetes, but obesity is the most significant risk factor. This is also proven by the fact that significant weight loss can not only help reduce diabetes risk but even lead to diabetes remission. Moreover, it is worth understanding that obesity increases the risk of a range of other health conditions. It is a risk factor for almost every non-communicable disease.

All this means that if we have to tackle the pandemic of non-communicable diseases, we must counter obesity. Obesity is best managed by lifestyle interventions like dietary measures and exercise. At the same time, drug therapy may have the role of adjuvant. However, recently, the popularity of some anti-obesity drugs like GLP-1 has emerged as a worrisome trend where drugs are more frequently promoted as an alternative to lifestyle interventions. These "The Skinny Shot" or "Quick weight loss pills" have become so popular that even diabetics are having difficulty accessing them. This unusual popularity of these drugs is a worrisome trend.[30]

It is vital to understand that though these drugs promote weight loss, but they are known to work only with lifestyle interventions. Additionally, most studies showing significant weight loss were those studies that were sponsored by drug manufacturers. Emerging real-life data shows that the efficacy of these drugs is much lower than claimed in clinical studies and, at best, is moderate. On the other hand, early diabetes prevention studies and the latest clinical studies aimed at diabetes remission through weight loss confirm that quick and sustainable weight loss is possible through lifestyle interventions alone. Moreover, studies indicate that lifestyle interventions are safer and generally more effective both in the short and long term. Hence, medical practitioners have a duty to raise social awareness of health risks associated with the prolonged use of weight loss pills. Additionally, they need to raise awareness about the benefits and sustainability of non-pharmacological strategies, that is, lifestyle interventions.

6. CONCLUSION

GLP-1 agonists are quite effective for weight loss and are among the most effective drugs. However, it is vital to understand that they should not be used in place of lifestyle interventions. Instead, they must be used to support weight loss through lifestyle efforts. It is also vital to realize that real-life data shows that these drugs are less efficacious than claimed in manufacturer-sponsored clinical studies. Additionally, these drugs frequently cause gastrointestinal side effects and are known to increase the risk of thyroid cancer. Further, there are concerns that weight loss and metabolic health benefits of these drugs are not sustainable, and they tend to return to baseline on discontinuation of the drug therapy. Lifestyle interventions are safe, and an increasing number of studies show that they might be quite effective for weight loss and diabetes remission when implemented methodically.

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