



Rise of GLP-1 use for the treatment of obesity and their accessibility across various socioeconomic groups

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ABSTRACT: The increasing prevalence of obesity has prompted the exploration of novel therapeutic options, with glucagon-like peptide-1 (GLP-1) receptor agonists (GLP1RA) emerging as a promising therapeutic option. These agents were initially developed for type 2 diabetes management and have demonstrated significant efficacy in reducing body weight and improving metabolic parameters in several clinical trials conducted worldwide. However, the accessibility of GLP1RA treatments varies across different socioeconomic groups, with disparities in uptake observed among individuals from lower-income backgrounds, racial/ethnic minorities, and those with limited health literacy. Factors contributing to these disparities include financial constraints, suboptimal health insurance coverage, and systemic barriers within healthcare systems. Addressing these inequities requires a multifaceted strategy involving policy changes, price reductions, and targeted educational initiatives to ensure equitable access to GLP1RA therapies. By implementing these measures, healthcare systems can enhance the societal benefits of GLP1RA treatments and improve outcomes for diverse patient populations.

Keywords: Obesity, GLP-1 receptor agonists, weight loss therapy, healthcare disparities, drug accessibility, health equity, public health policy

I. INTRODUCTION

Obesity is a major health concern worldwide and has a negative impact on overall health and quality of life. It brings with it several health problems and comorbidities that are difficult to treat and put a financial burden on people. Obesity treatment comprises several options such as medication, exercise, lifestyle changes, and bariatric surgery. A category of drugs known as Glucagon-like Protein -1 (GLP-1) receptor agonists used previously to treat type-2 diabetes, have shown a promising role in weight reduction and can be used in the treatment of obesity. The major challenge is the accessibility of these drugs to various socioeconomic groups. This review explores the increase in GLP-1 use for obesity treatment and examines their accessibility across different socioeconomic groups. The initial sections provide a comprehensive overview of the pharmacological mechanisms of GLP1RAs, clinical trial outcomes, and their role in obesity management. Subsequent sections delve into the socioeconomic disparities in the accessibility of GLP1RA therapies, highlighting the impact of high costs, insurance coverage variability, and geographical differences in availability.

II. OBESITY AND ITS PREVALENCE

2.1 Obesity

Obesity is a condition characterized by excess fat accumulation that is related to a high rate of disability, morbidity, and mortality that results in increased healthcare expenses. It is a disease that contributes majorly to the global disease burden. Associated with severe other health conditions that typically occur due to obesity, treating the condition and losing weight becomes challenging. A sedentary lifestyle and unhealthy food choices are the major reasons for obesity but several factors such as genetic, environmental, and behavioural contribute to the disease. It typically is carried from childhood to adolescence and adulthood along with the health problems that arise due to it and may put the individual at a greater risk of some chronic condition. Hence it is necessary to constantly monitor weight and make efforts to reduce weight to treat obesity.¹

According to the World Health Organization (WHO) statement issued in March 2024, one in eight persons had obesity in the year 2022. Since the year 1990, obesity in adults has doubled, while in adolescents it appears to have multiplied four times.² The diagnosis of obesity is made by body mass index which is calculated by dividing the body weight in kilogram by the square of height in meters. In adults, a person having a BMI of 30 kg/m² is considered obese. However, only BMI cannot be an accurate and sufficient parameter for determining obesity, hence the use of other parameters such as the waist circumference and waist-to-hip ratio is also taken into consideration while determining obesity.³

2.2 Prevalence of Obesity

Obesity is increasing around the world in an alarming rate and is a major health concern on the global level. Several nationwide studies by researchers have published their findings on the incidence of obesity in different age groups in their respective countries and on the global level.^{1,3} A recently published study that included 154 different nations, showed the prevalence of obesity to be 8.5% in children and adolescents as noted in the year 2020. The projected values of obesity in children and adolescents point to 254 million in the year 2030 from 158 million in 2020.¹ According to the WHO reports in the year 2020, 890 million adults were suffering from the health problem of obesity.² The United States (US) contributes largely towards the world obesity prevalence. According to the Centres for Disease Prevention and Control (CDC), 40.8% of the US adult population had obesity from August 2021 to August 2023.⁴

Such an exponential rate of increase in obesity needs to be addressed immediately as it increases the risk of different health conditions and puts a heavy burden on the health system and accessibility of people to treatment options. Currently in the U.S., the novel treatment option for obesity is using the GLP-1 receptor agonists.

III. SIGNIFICANCE OF GLP-1 RECEPTOR AGONISTS (GLP1RAS)

GLP-1 receptor agonists liraglutide, semaglutide, tirzepatide, lixisenatide, exenatide and a few others originally used as antidiabetic agents to treat type 2 diabetes, have been explored for weight loss activity, to treat obesity. While most GLP-1 receptor agonists are injectable formulations, some oral options such as semaglutide are available now. An oral drug Orforglipron is under study and has shown good results in clinical trials.^{5,6}

3.1 The GLP-1 Receptor

GLP-1 receptors are in the gut, brain, and pancreas and are primarily responsible for maintaining the energy balance in our body. The receptor is responsible for increased energy expenditure and control of food intake that results in weight loss. The various actions of GLP-1 on different tissues in the body are shown in Figure 1.

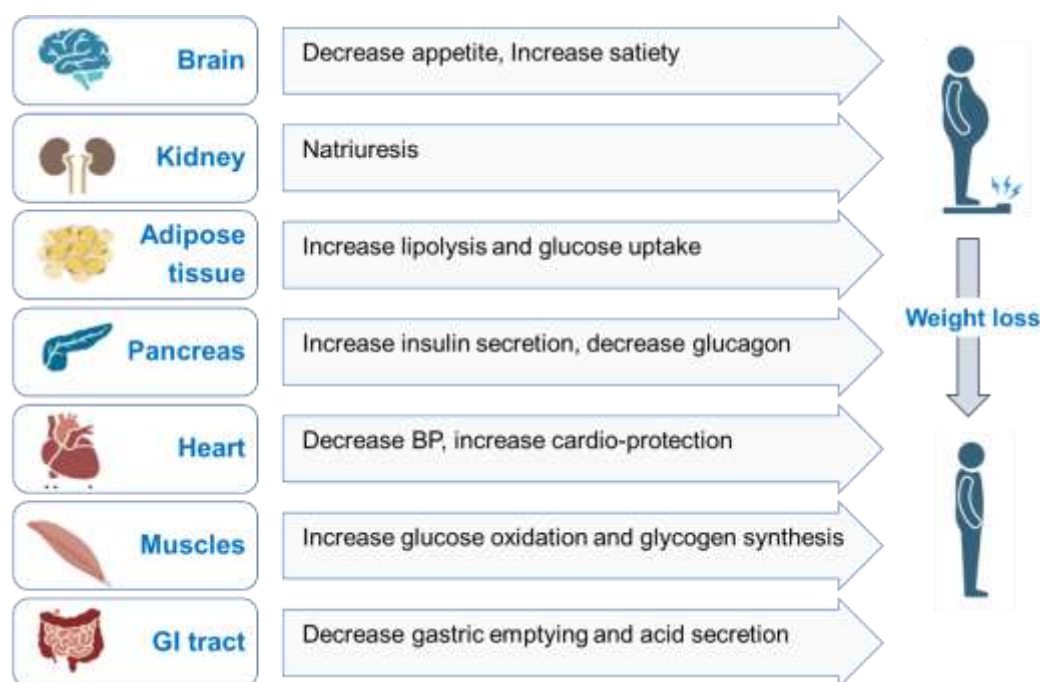


Figure 1. Pharmacological effect observed from the actions of GLP-1 on various tissues in the human body that contribute to weight loss.⁷

A few decades back, drugs known as GLP1RA were used to treat people with type-2 diabetes, and it was noted that these drugs activated the GLP-1 receptors and resulted in weight loss. The weight loss action of GLP-1 RA prompted the exploration of these agents in treating obesity. Since then, several studies have been designed and trials have been carried to investigate their mechanism and prove their role in the treatment of obesity.^{8,9}

The GLP-1 receptor has a complex relationship with obesity and several researchers have tried to explain the significance of GLP-1 in weight reduction. The findings of a study suggest that there is a reduction

of GLP-1 secretion in obese people that may be due to an increase in plasma non-esterified fatty acids (NEFA). In an animal study, administration of GLP-1 to mice resulted in reduced food intake leading to weight loss. Additionally, the receptor plays a role in reducing gastric emptying which also causes weight loss.¹⁰ The above-proposed mechanisms are collectively responsible for reducing the excess weight in obese people.

3.2 Emerging Role of GLP-1 Receptor Agonists

The GLP-1 receptor agonists can be classified as short-acting and long-acting injections. Beinaglutide and exenatide injected two to three times a day are short-acting agonists while Lixisenatide is injected once a day. Long-acting drug preparations are given as an injection with a frequency of one injection per week. Examples of such drugs are semaglutide, dulaglutide, exenatide, and polyethylene glycol loxenate.¹⁰ Refer to Figure 2 for examples of GLP1RA examples. The commonly used GLP1RAs are discussed below:

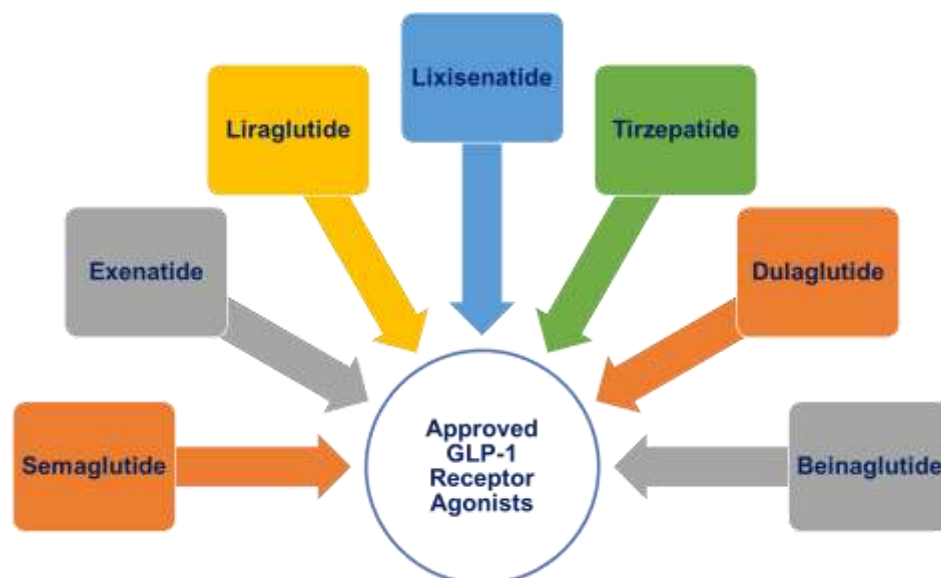


Figure 2. Examples of GLP1RA

Exenatide: It is a man-made version of a natural substance called exendin-4. This natural substance is found in the saliva of a lizard called the Gila monster, native to the southwestern United States. Having a longer half-life and excellent biological activity this drug has been clinically proven to reduce weight. A clinical trial conducted in 100 adolescents both men and women showed that extended-release preparation of exenatide showed initial weight loss.^{11,12} A pilot clinical study in children and adolescents showed a reduction in BMI and weight loss on using exenatide.¹³

Liraglutide: Initially developed to treat Type-2 Diabetes, liraglutide is an excellent candidate to treat obesity. With a long half-life, this drug can be used as once a day injection. It was evaluated in a randomized double-blind trial in obese adolescents. Liraglutide therapy when combined with lifestyle changes, resulted in the reduction of BMI.^{14,15} A clinical study that examined the safety and efficacy of liraglutide in obesity treatment showed positive results for the use of liraglutide 3.0 mg in adults with obesity for weight management.¹⁶

Semaglutide: Used initially as a long-acting, once-a-week, antidiabetic drug, semaglutide also shows weight loss activity. In a clinical trial that compared semaglutidesubcutaneously given once a week with a daily dose of Liraglutide showed that semaglutide was highly effective in weight loss in 68 weeks.¹⁷ Similarly, a double-blind trial with 1961 adults with obesity showed significant weight reduction with the dose of 2.4 mg of semaglutide once weekly.¹⁸ Oral semaglutide has shown significant weight reduction in adults with obesity who took 50mg once a day daily dose as indicated in a clinical trial.¹⁹

Lixisenatide: It is also an injectable GLP-1 agonist which has shown that weight reduction occurred in people who were administered this drug. In these people, the brain was shown to respond in a different way to the food, after the injection of Lixisenatide.²⁰

Beinaglutide: It is the first drug to be approved for its use in obesity in China. Beinaglutide has shown to suppress appetite, delay gastric emptying and reduce weight. Having a short half-life, one needs three injections per day of this drug to get the desired effects. A trial in non-diabetic obese Chinese individuals showed that this drug showed clinically significant weight reduction and good tolerability.²¹

The clinical trial data and latest research in the pharmacological actions of GLP-1 receptor agonists emphasize the emerging role of these agents to treat people with obesity through different molecular mechanisms.

IV. ACCESSIBILITY OF GLP1RA

GLP1RA medications were once obscure but have recently become very important for treating diabetes. Additionally, these medications have shown benefits in other disease conditions too, like heart failure, Parkinson's disease, and more.^{22,23} This has made scientists and common people very excited about their potential application in treating other diseases too. However, making sure these medications are accessible to everyone fairly and sustainably still remains a big public health challenge. Because diabetes and obesity are chronic conditions, it's unlikely that everyone will have access to these treatments, especially in places where healthcare resources are limited. Even if access was possible, these medications alone can't fix the deeper issues that cause obesity and diabetes, such as socioeconomic inequities, unhealthy food environments, and lack of preventive healthcare.

In many low- and middle-income countries in the southern part of the world, the cases of diabetes and obesity are increasing.²⁴ This is because cities are growing, people's lifestyles are changing, and the healthcare systems aren't strong enough. In developed and wealthier countries, certain racial and ethnic minorities are also more likely to have diabetes and obesity.²⁵ This happens because of various social factors that affect their health. These groups often face difficulties getting preventive care, early diagnosis, and advanced treatments. Hence, it's crucial to develop strategies focused on fairness in treating diabetes and obesity.

Medicine shortages are a worldwide problem, but they hit low- and middle-income countries the hardest. Since September 2021, the number of different medicines that were in short supply in multiple countries has more than doubled. Unexpected drug shortages of the long-acting GLP1Ras namely dulaglutide and semaglutide emerged in late 2022 and it continued through the early days of the year 2023.²⁶ This was mainly due to the sudden increase in demand for these drugs without an adequate increase in production to fulfill the demand. When medicines are hard to find, it often leads to fake or poor-quality medicines being sold. People might also try to buy medicines from unofficial sources, like the internet, which can be risky. Medicines sold without a valid prescription and without the need for a licensed pharmacist are potential health hazards. The WHO advises people to buy their medicines from approved and regulated suppliers. Getting medicines from unauthorized or informal sellers may lead to serious consequences.²⁷

A recently published letter to the editor of the Journal of Medicine, Surgery, and Public Health highlighted the issue of counterfeit versions of GLP1RA in the market.²⁸ These products may contain harmful ingredients, inadequate dose, or may even lack the active ingredients. Such falsified medicines increase the burden on healthcare expenditure resulting from increased surveillance efforts and hospitalization.²⁸ Therefore, to ensure the safety of patients, integrity is required in adequate and safe supply chain management. To ensure access to safe and good quality medicines, the WHO collaborates with national authorities and supply chain experts in different countries and also shares information and works together to solve local problems, which can help reduce risks of shortages worldwide.²⁷

Another issue regarding GLP1Ras is the cost of therapy. The uptake of these drugs is low in people who live in socioeconomically disadvantaged areas, have low income and education levels, or belong to racial/ethnic minorities.²⁹ A retrospective study analyzed the trends in the use of various anti-diabetic medications in older adults based on their commercial insurance or Medicare Advantage health plans.³⁰ More than 3 lac patients' data was analyzed. It was concluded that lower-income patients are linked to decreased GLP1RA initiation. Also, there were racial disparities in GLP1RA usage in Asian, Black, and Hispanic minorities which were most pronounced in Asian patients. Older age was also linked to lower GLP1RA uptake.³⁰

One more issue that has affected the accessibility of GLP1RA is inappropriate use of GLP1RA drugs.³¹ As GLP1RAs have shown great promise in helping people manage obesity, according to many large studies, some people are using them for the aesthetic purpose of weight loss and not to address actual health problems. A study explored how aesthetic plastic surgeons (doctors who perform cosmetic surgeries) use GLP-1 RAs in ways that are not officially approved (off-label use).³² Approximately 30% of surgeons reported personal use of these drugs, and 70% of the use was for cosmetic weight loss. More than 68% of surgeons found the drugs useful for effective weight loss and also recommended it to others.³² This study emphasizes the need for more substantial ethical guidelines and clear recommendations within the plastic surgery community for the responsible and medically appropriate use of GLP1RAs to prevent any misuse.³³ As GLP1RAs are very effective in treating obesity and diabetes, using them just for cosmetic reasons causes problems for patients and society. It is therefore important to use these drugs correctly, inform people about the dangers of the misuse of these drugs, and also create policies to prevent misuse. This will ensure that the drugs are used safely and effectively for those who need them for health benefits.

V. CONCLUSION

The rising prevalence of obesity has positioned it as a significant public health challenge worldwide. GLP1RAs have emerged as a promising class of therapeutic agents for managing obesity, showing efficacy in

promoting weight loss and improving metabolic health. Limited access can aggravate health disparities, as those who cannot afford or access these medications may experience poorer health outcomes compared to those who can. The cost of managing diabetes and obesity-related complications may be higher for individuals without access to GLP1RAs which may lead to increased healthcare costs. Patients with limited access may have a lower quality of life due to unmanaged symptoms and complications. Unequal access can strain public health systems, as untreated or poorly managed conditions can lead to higher rates of hospitalizations and chronic health issues. The comparisons between high-income and low- to middle-income populations, the inadequate production and supply shortage, and the inappropriate use of these drugs underscore the need for equitable healthcare policies and innovative pricing strategies to ensure broader access to these life-saving medications. There is a need for multidisciplinary approaches involving policymakers, healthcare providers, and pharmaceutical companies to bridge the gap in treatment accessibility and promote health equity in obesity management. To make a real and lasting impact, these medications need to be part of a bigger plan that includes modifications in healthcare policies, lifestyle improvements, priority settings, and systematic efforts to address the root causes of obesity.

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