

## **Safety and efficacy of glucagon-like peptide-1 receptor agonists and their effect on weight loss**

Pharmacist/ Abdulaziz Abdullah Alanazi  
aal-onazi@moh.gov.sa

Pharmacist/ Ziyad Mohammad Alnasr  
zalnars@moh.gov.sa

Pharmacist/ Dalya Fayez Alenazi  
dfalenazi@moh.gov.sa

Pharmacist/ Abdulaziz Manea Alanazi  
aalanazi42@moh.gov.sa

Dental Assist / Shoaee Abdullah Alanazi  
shaalenzi@moh.gov.sa

**Abstract:**

Obesity can substantially harm human health, increasing the risk of diabetes mellitus (DM) and other negative effects. To lose weight, successful therapy methods and drugs have been developed. Glucagonlike peptide-1 receptor agonists (GLP-1Ras) are indicated for weight loss in obese persons with or without type 2 diabetes (T2DM). The aim of this research to provide an overview of the safety and efficacy of glucagonlike peptide-1 receptor agonists and to determine whether treatment with a glucagon-like peptide-1 receptor leads to weight loss in overweight or obese patients with or without type 2 diabetes. The current research offers evidence that GLP-1R agonist medication results in weight loss in overweight or obese people with or without type 2 diabetes mellitus. Given its potential benefits in lowering weight in addition to glycemic management, GLP-1 agonists may soon be used to treat obesity in both diabetic and non-diabetic persons. However, further research investigations, namely big clinical trials, are necessary to extend and fully explain the beneficial effects and potential negative effects of GLP-1 agonists. Obesity therapies based on glucagon-like peptide-1 (GLP-1) agonism are now being used and further developed. GLP-1 RA as an addition to LSI is effective and safe in adolescents with obesity who do not react well to lifestyle interventions. Since of the scarcity of data, a general advice is to favor long acting GLP-1 RA over short acting GLP-1 RA since they are licensed for the treatment of obesity and have greater tolerability, safety, and therapeutic response impact.

**Keywords:** Safety, Efficacy, Glucagon-like peptide-1 receptor agonists; Obesity; Weight Loss

**المخلص:**

يمكن أن تضر السمنة بصحة الإنسان بشكل كبير، مما يزيد من خطر الإصابة بداء السكري (DM) والآثار السلبية الأخرى. ولإنقاص الوزن، تم تطوير طرق العلاج والأدوية الناجحة. يشار إلى منبهات مستقبلات الببتيد-1 الشبيهة بالجلوكاجون (GLP-1Ras) لفقدان الوزن لدى الأشخاص الذين يعانون من السمنة المفرطة والمصابين أو غير المصابين بداء السكري من النوع 2 (T2DM). الهدف من هذا البحث هو تقديم لمحة عامة عن سلامة وفعالية منبهات مستقبلات الببتيد-1 الشبيهة بالجلوكاجون وتحديد ما إذا كان العلاج بمستقبلات الببتيد-1 الشبيهة بالجلوكاجون يؤدي إلى فقدان الوزن لدى المرضى الذين يعانون من زيادة الوزن أو السمنة مع أو بدون مرض السكري من النوع 2. يقدم البحث الحالي دليلاً على أن دواء ناهض GLP-1 يؤدي إلى فقدان الوزن لدى الأشخاص الذين يعانون من زيادة الوزن أو السمنة مع أو بدون داء السكري من النوع 2. ونظرًا لفوائدها المحتملة في خفض الوزن بالإضافة إلى إدارة نسبة السكر في الدم، فقد يتم استخدام منبهات GLP-1 قريباً لعلاج السمنة لدى الأشخاص المصابين بالسكري وغير المصابين به. ومع ذلك، فإن إجراء المزيد من التحقيقات البحثية، وتحديدًا التجارب السريرية الكبيرة، ضروري لتوسيع وشرح التأثيرات المفيدة والآثار السلبية المحتملة لمنبهات GLP-1 بشكل كامل. يتم الآن استخدام علاجات السمنة المبنية على ناهضة الببتيد الشبيه بالجلوكاجون -1 (GLP-1) وتطويرها. يعد GLP-1 RA كإضافة إلى LSI فعالاً وآمناً لدى المراهقين الذين يعانون من السمنة والذين لا يتفاعلون بشكل جيد مع تدخلات نمط الحياة. نظرًا لندرة البيانات، فإن النصيحة العامة هي تفضيل GLP-1 RA طويل المفعول على GLP-1 RA قصير المفعول نظرًا لأنها مرخصة لعلاج السمنة ولها قدر أكبر من التحمل والسلامة وتأثير الاستجابة العلاجية.

**الكلمات المفتاحية:** السلامة، الفعالية، منبهات مستقبلات الببتيد-1 الشبيهة بالجلوكاجون؛ بدانة؛ فقدان الوزن

## 1. Introduction:

Obesity is a rapidly increasing global issue that has significant health and economic implications, making interventions that promote weight loss highly important. Obesity is often characterized by a body mass index (BMI) of 30 kg/m<sup>2</sup> or higher, or 27.5 kg/m<sup>2</sup> or higher in Asian populations. According to the health survey for England 2019, the prevalence of obesity among adults in England is 28%. The rise in obesity rates is not exclusive to the United Kingdom. In fact, it has become a global phenomenon over the last five decades, affecting every country. This growth can be attributed mostly to changes in the global food system and the adoption of more sedentary lifestyles. (Blüher, M, 2019; Swinburn, B. A., et al., 2011).

Between 1999–2000 and 2017–2018, the prevalence of obesity in the United States rose from 30.5% to 42.4%. In 2016, the World Health Organization (WHO) discovered that 1.9 billion individuals over the age of 18 were classified as overweight, accounting for 39% of the global population. Out of these adults, a staggering 650 million individuals were classified as obese, accounting for around 13% of the total population. The discrepancy in obesity prevalence between the UK, USA, and WHO could be attributed to the relatively low occurrence of obesity in low-income countries. Although obesity is a preventable condition with well-documented economic and health consequences, it remains a concern for future generations. In 2019, a staggering 38 million children under the age of were already overweight or obese. Both treatment and prevention will remain crucial interventions.

According to Wu and Ballantyne's research from 2020, obesity and overweight can do significant damage to human health. These conditions can raise the likelihood of developing type 2 diabetes mellitus (T2DM) as well as other adverse impacts, including insulin resistance at the cellular level, hyperlipidemia, and cardiovascular disease. The World Health Organization estimates that around 1.5 billion people were classed as overweight in the year 2011, and that roughly 2.8 million deaths among adults are attributed to being overweight or obese each year (WHO, 2011).

According to Eeg-Olofsson et al. (2009), more than eighty percent of people with type 2 diabetes are obese or overweight. Furthermore, around three-quarters of people with diabetes may acquire complications connected to their condition as a result of obesity, including vascular illnesses and other diabetes-related issues. The goal of many patients and their physicians is to either lose or gain weight while simultaneously maintaining control of their glucose levels. Controlling blood glucose levels and losing weight are goals that are shared by both patients and their physicians (Shin, 2012). Losing weight can help mitigate the adverse effects of type 2 diabetes.

There have been successful therapy options and pharmaceuticals developed to reduce weight, mainly among people with diabetes, in order to minimize the risk of a variety of problems (Bailey et al, 2020). These drugs and therapies include both pharmacological and non-pharmacological means of inducing weight loss. However, it has been demonstrated that medications that are used to manage diabetes, such as insulin, thiazolidinediones, and sulphonylureas, can lead to an increase in food consumption.

Metformin, dipeptidyl peptidase 4 inhibitors (DPP4is), sodium-glucose cotransporter-2 (SGLT-2) inhibitors, and glucagon-like peptide receptor agonists (GLP-1RAs) are medications that reduce body weight while also regulating blood sugar levels. Consequently, there is a tendency to choose solutions that keep glycemic control while not growing weight. This is because of the aforementioned tendency. Glucagon-like peptide-1 receptor agonists, often known as GLP1Ras, are one of these possibilities.

These medications are administered to obese individuals, whether or not they have type 2 diabetes, in order to assist them in losing weight. After a meal, the stomach (intestine) secretes a hormone known as GLP-1RAs, which ultimately stimulates the production of insulin and inhibits the release of glucagon (Maula et al, 2020). This hormone is responsible for the regulation of blood sugar levels. This hormone is responsible for suppressing hunger, slowing the emptying of the stomach, and stimulating satiety. As a result, it plays a significant role in the regulation of blood glucose levels and the reduction of weight in obese individuals.

According to Kanoski et al. (2012), GLP-1RAs has the ability to induce satiety and decrease calorie consumption by delaying the emptying of the stomach. This is accomplished by binding to its receptor on neurons in the hypothalamus at the same time.

There is evidence that GLP-1RAs have the ability to reduce weight in individuals, regardless of whether or not they have diabetes, through the activities that have been outlined above. However, in order to gain a better understanding of the role that GLP-1RAs play in weight loss and the extent to which these GLP-1RAs may be responsible for emptying, it is necessary to conduct an analysis and incorporate the data obtained from both experimental and observational investigations (Moher et al, 2010). Therefore, the purpose of this study is to investigate the safety and effectiveness of glucagon-like peptide-1 receptor agonists, as well as to ascertain whether or not treatment with a glucagon-like peptide-1 receptor results in weight reduction in individuals who are overweight or obese and either have or do not have type 2 diabetes (Aldahash et al., 2021).

A significant burden on cardio metabolic health, oncological health, mental health, and financial health will continue to grow as a direct consequence of the rise in obesity population (Di Cesare, M., et al., 2019). In children and adolescents, obesity leads to the increased risk of developing early puberty (De Leonibus, C., et al., 2012), menstrual irregularities in adolescent girls, obstructive sleep apnea, and cardiovascular risk factors including prediabetes, type 2 diabetes mellitus, high cholesterol levels, hypertension, nonalcoholic fatty liver disease, and metabolic syndrome (Sahoo, K., et al., 2015). In addition, children and adolescents who are obese are more likely to suffer from psychological concerns such as social anxiety, depression, low self-esteem, negative body image, and difficulties in relationships with their peers, as well as eating disorders.

## **Lifestyle Interventions, Bariatric Surgery, and Historical Pharmacologic:**

Clinical practice recommendations advise individuals with overweight or obesity to make lifestyle changes, such as adopting a nutritious diet and increasing physical activity, in order to lose weight and lower the likelihood of future cardiovascular disease occurrences (Jensen, M. D., et al., 2014).

This technique is corroborated by data obtained from a secondary analysis of the Look AHEAD (Action for Health in Diabetes) project, which encompassed people who were overweight or obese and had type 2 diabetes (T2D). The study included adults who were involved in a rigorous weight reduction intervention program with the goal of achieving long-term weight loss and improved physical activity levels. Attaining a 10% reduction in body weight or a significant improvement in fitness (measured in terms of metabolic equivalents) within the first year resulted in an approximate 20% decrease in the risk of cardiovascular disease (AHEAD Research Group., 2016).

Nevertheless, sustaining weight loss is one of the most difficult parts of managing obesity. The reason for this is because weight is closely controlled by hormonal, metabolic, and neurological factors. When weight loss occurs, the body undergoes hormonal adaptations that lead to weight return. These adaptations persist for at least one year after the original weight decrease (Evert, A. B., & Franz, M. J., 2017)

Weight loss leads to compensatory mechanisms that involve a decrease in resting energy expenditure and an increase in obsession with food. Additionally, neurological factors contribute to an increase in hunger (Heymsfield, S. B., & Wadden, T. A. 2017).

## **2. Glucagon-like peptide-1 receptor and Obesity:**

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are a medication class principally created for the treatment of individuals with type 2 diabetes (T2DM), and they are the cornerstone therapy method for this condition today (Vilsbøll et al., 2012). GLP-1 (glucagon-like peptide-1) is a gut hormone that is produced from the intestine in response to meal consumption and promotes insulin production while inhibiting glucagon release in a dose-dependent manner (van Valkenhoef et al., 2012). GLP-1 can reduce food intake and appetite, as well as slow stomach emptying and produce satiety, and hence plays a significant role in blood glucose homeostasis. However, the quick inactivation of GLP-1 in vivo, as well as the resulting short half-life, precludes its therapeutic application. Longacting GLP-1 receptor agonists (GLP-1 RAs) that may be given once or twice a day, or even once a week, have been created. Exenatide, liraglutide, albiglutide, taspoglutide, lixisenatide, and LY218926 are examples of GLP-1 RAs. GLP-1 RA treatment improves insulin resistance and glucose homeostasis in Type 2 DM patients (Lu & Ades, 2004). Because of their manner of action, they also have a minimal risk of hypoglycemia. Exenatide and liraglutide are now being used effectively in the treatment of Type 2 diabetes (Salanti et al., 2011).

Overweight or obesity may raise the risk of cardiovascular problems while also causing significant psychological anguish in the majority of Type 2 DM patients (Chaimani et al., 2013). Effective weight-loss therapies are an important aspect of Type 2 DM cares to avoid the development of microvascular and macrovascular problems. However, several diabetes medications (insulin, thiazolidinedione's, and sulfonylureas) because weight gain as a side effect. By attaching to its receptor on hypothalamic neurons, GLP-1 can increase satiety and reduce calorie intake by delaying stomach emptying (Sun et al., 2015).

Obesity has been linked to an increased risk of diabetes and its consequences, such as insulin resistance, dyslipidemia, and cardiovascular disease (Buse et al., 2013). Overweight or obese people account for more than 80% of Type 2 diabetics. It is appealing to both doctors and patients to avoid Type 2 DM weight gain during glycemic control medication. GLP-1 RAs are a novel family of glucose-lowering medications that have been found in clinical investigations of Type 2 DM patients to enhance glycemic control and increase weight reduction. The first long acting stable GLP-1 RA was licensed by the US Food and Drug Administration in 2005. The drugs exenatide (Byetta; EliLilly) and liraglutide (Victoza; NovoNordisk) are now accessible. Both treatments can be used in conjunction with oral diabetes medications such as metformin, thiazolidinedione's, or sulfonylureas. The medicines are approved for Type 2 diabetes patients who have not achieved acceptable glycemic control after therapy with standard diabetes medications (Seino et al., 2015).

(Ard et al., 2021) indicated that obesity is a chronic disease associated with many complications. Weight loss of 5-15% can improve many obesity-related complications. Despite the benefits of losing weight, there are many challenges with losing

weight and maintaining weight loss over the long term. In a study by Baden et al., (2023), glucagon-like peptide-1 receptor agonists showed potential for treating obesity and reducing the risk of developing type 2 diabetes, but there is a lack of studies comparing adverse events across different populations, and compare indirect adverse events of pharmaceutical preparations agonists of glucagon-like peptide-1 receptors for the treatment of overweight or obesity in adults, adolescents, and children.

### 3. Safety and efficacy of glucagon-like peptide-1 receptor in the Management of Obesity:

Obesity is a chronic and progressive condition; hence weight control must be maintained throughout one's life (Hope et al., 2018). Obesity treatment is accomplished in three stages: (1) LSI with behavioral therapy, physical activity, and food modification; (2) medication; and (3) bariatric surgery. The intervention is decided based on the BMI, waist circumference, comorbidities, and response to previous anti-obesity therapy (Davies et al., 2021). LSI alone has been linked to mild weight reduction that is eventually restored. It produces a large number of poor responders in both the adult and pediatric populations (Wadden et al., 2021). Although bariatric surgery is regarded as the most successful treatment, it comes at the expense of irreversibility, surgery-related problems, and significant late complications. Although pharmacotherapy can supplement lifestyle treatment and bariatric surgery, the duration of such intervention is unknown (Jepsen et al., 2021).

Maintaining weight reduction achieved with any treatment method is particularly difficult due to adaptation, which is defined by changes in appetite-regulating hormone levels and a drop in resting metabolic rate. Some research suggests that even momentary weight loss may have longterm advantages, although the evidence is inadequate to justify short-term anti-obesity therapies (Nauck et al., 2021).

#### 3.1 GLP-1 RA for the Treatment of Obesity

GLP-1 agonism in combination with existing GLP-1 RA and novel anti-obesity drugs would probably serve as a model for future pharmacological anti-obesity therapy. GLP-1 receptors of functional significance can be found in the pancreas, gut, and hypothalamus. The activation of neuronal pathways producing decreases in appetite regulating areas of the hypothalamus causing reductions in hunger and food intake and so promoting weight loss is most significant for the weight-reducing capabilities (Lau et al., 2015).

Liraglutide was the first long-acting GLP-1 RA licensed for the treatment of obesity by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). It was found to be effective in lowering body weight in people with and without diabetes, as well as in youngsters. Following then, further work focuses on boosting efficacy and extending benefits through several critical structural alterations. With these characteristics in mind, semaglutide, a novel long acting GLP-1 RA, has been created (Pi-Sunyer et al., 2015). Liraglutide is a polypeptide with 97% similarity to human GLP-1 with a fatty acid side chain connected through a linker molecule. Semaglutide is structurally similar to liraglutide, but with slight differences in the GLP-1 moiety, with 94% homology to human GLP-1 and another fatty acid side chain (Wadden et al., 2013). The improved pharmacokinetic characteristics of semaglutide allow for once-weekly dosage rather than once-daily delivery of liraglutide (Le Roux et al., 2017).

The alteration leads to increased effectiveness, which was initially seen in a phase 2 study in people with obesity, where patients achieved a mean weight reduction from baseline of 13.8% compared to 7.8% for liraglutide at week (wk) 52 (Blackman et al., 2016). The FDA authorized injectable semaglutide as the newest anti-obesity medicine in the United States in June 2021. The recommended dosages for both medications for weight reduction are higher than those for glycemic control: 3.0 mg against 1.8 mg for liraglutide and 2.4 mg versus 1.0 mg for semaglutide. The difficulties in losing weight in persons with type 2 diabetes mellitus compared to people without diabetes are well established. Smaller weight reductions with both GLP-1 RA have been confirmed in treating individuals with type 2 diabetes mellitus vs those without (Garvey et al., 2020).

#### 3.2 GLP-1 RA for Pediatric Obesity:

At the moment, the only two GLP-1 RA drugs with pediatric evidence are the short acting GLP-1 RAs exenatide and liraglutide. From 2016 to 2019, a randomized, double-blind, placebo-controlled phase 3 study was conducted to assess the effectiveness and safety of subcutaneous liraglutide 3.0 mg as an addition to lifestyle treatment for weight management in adolescents with obesity (Tamborlane et al., 2019). The experiment included a 12-week run-in period, a 56-week treatment period, and a 26-week no-treatment follow-up period. They enrolled people aged 12 to 18 with obesity and a poor response to lifestyle changes alone. There were 125 individuals in the liraglutide group and 126 in the placebo group (O'Connor et al., 2017). Liraglutide outperformed placebo in terms of change from baseline in the BMI standard deviation score at week 56, with an estimated difference of 0.22 points. A 5% reduction in BMI was reported in 43.3% of individuals in the liraglutide group and 18.5% of people in the placebo group; a 10% reduction in BMI was recorded in 33% and 9% of participants, respectively. Liraglutide was shown to be more effective than placebo in terms of BMI, with an estimated difference of 4.64



percentage points, and body weight, with an estimated difference of 4.5 kg for absolute change and 5.01% for relative change. After cessation, liraglutide caused a larger rise in the BMI standard deviation score than placebo (Tamborlane et al., 2019).

The observed reduction in BMI standard deviation score with liraglutide (0.22) was bigger than differences seen in US Preventive Service Task Force trials of lifestyle treatment (0.17) and a summary of Cochrane reviews (0.13). Despite some changes in the weight loss trajectory, the treatment difference in body weight seen with liraglutide was similar to the treatment effect observed in the analogous study of liraglutide in adults (Kushner et al., 2020). The weight gain seen throughout the 26-week follow-up period was consistent with findings from placebo controlled studies of liraglutide 3.0 mg in adults (Wilding et al., 2021).

The liraglutide group reported more gastrointestinal adverse events (64.8% vs. 36.5%) and adverse events that resulted to trial treatment discontinuation (10.4% vs. 0%). There were few significant adverse events in either group (2.4% vs. 5 [4%]). Additional significant adverse events occurred in 1 person who got liraglutide (1 incident) and 4 individuals who received placebo (5 occurrences) throughout the 26-week follow-up period. Psychiatric illnesses were experienced by 13 participants (10.4%) in the liraglutide group and 18 participants (14.3%) in the placebo group. There were no clinically significant changes between treatment groups in terms of mental health questionnaire scores. However, one suicide occurred in the liraglutide group about 340 days after treatment began, and two patients (1 from each treatment group) reported a suicide attempt during the 26-week follow-up period. These three incidents were assessed unlikely to be connected to the study therapy by the site investigators. Liraglutide caused more hypoglycemia episodes than placebo (26 vs. 18), however none were classified as severe by the American Diabetes Association-International Society for Pediatric and Adolescent Diabetes criteria. There were no discernible variations in growth or pubertal development between treatment groups (Tamborlane et al., 2019).

Adverse events that resulted in trial treatment discontinuation occurred in 13 patients (10.4%) in the liraglutide group and none in the placebo group ( $p < 0.001$ ). Ten competitors dropped out owing to stomach issues. Adherence was  $>80\%$ , which was higher than in many prior studies including obese adolescents (about 70%). However, as the treatment period progressed, the fraction of samples acquired for pharmacokinetics analysis with liraglutide values below the lower limit of quantification rose (Riesenberg, 2019).

In conclusion, liraglutide 3.0 g as an addition to lifestyle treatment resulted in a higher decrease in BMI than placebo in adolescents with obesity. The increased occurrence of gastrointestinal side effects with liraglutide shows that this medication may not be appropriate for all individuals (Tamborlane et al., 2019). From 2012 to 2018, another bigger trial was done in kids with type 2 diabetes to determine if liraglutide 1.8 mg added to metformin with or without basal insulin therapy is safe and effective. The weight loss was reported but not classified as a primary or secondary outcome (Abuzzahab, 2013).

Patients aged 10 to 17 were randomly randomized to receive subcutaneous liraglutide or placebo during a 26-week double-blind period, followed by a 26-week open-label extension term. A BMI more than the 85th percentile and a glycated hemoglobin level between 7.0 and 11.0% if the patients were treated with diet and exercise alone or between 6.5 and 11.0% if they were treated with metformin with or without insulin, were the inclusion criteria. During the experiment, all participants were given metformin. After 26 weeks, the major end point was the change in glycated hemoglobin level. The change in fasting plasma glucose level was a secondary end objective (Schwarzenberg, 2012). The trial's safety was monitored at all times. A total of 135 patients were randomly assigned to receive at least one dosage of liraglutide (66 patients) or placebo (68 patients) (Jensterle & Janež, 2021).

#### 4. The effect of glucagon-like peptide-1 receptor on weight loss

More over two-thirds of the population in the United States is overweight (BMI 25-29.9) or obese (BMI 30). This share is lower in Europe, but it is growing (Finucane, 2011). According to the World Health Organization, 1.5 billion persons worldwide are overweight, with 500 million obese. Every year, about three million Americans die as a result of being overweight or obese. These weight issues are responsible for an estimated 44% of the diabetes burden, as well as 23% and 7-41% of the burdens for ischemic heart disease and certain malignancies, respectively (WHO, 2011).

Weight reduction is difficult to achieve and maintain. Meta-analyses of clinical studies on non-pharmacological weight loss techniques found 1-6 kg weight loss that was difficult to sustain (Pronk, 2007). Meta-analyses of sibutramine and orlistat studies show average weight loss of 3 to 5 kg, but some of the included trials had attrition rates of up to 50%, which might be attributable to adverse events, suggesting that the therapies may be less successful in practical practice (Gourlan et al., 2011). Meta analyses have revealed that bariatric surgery improves long-term mortality in obese patients, but the safety concerns and costs restrict its usage in broad patient groups.

Diabetes risk increases with excess body weight, increasing thrice with a body mass index of 25.0 to 29.9, and 20-fold with an index of 35 or above compared to a healthy value of 18.5-24.9. The low number (50%) of patients treated to treatment

objectives reflects the challenges faced in the management of type 2 diabetes (Padwal et al., 2011). Bodyweight gain (thiazolidinedione's, sulphonylureas, and insulin), hypoglycemia (sulphonylureas, repaglinides, and insulin), and gastrointestinal side effects (metformin and alpha glucosidase inhibitors) are some of the problems with current treatment management (Pontiroli & Morabito, 2011).

GLP-1 (glucagon-like peptide-1) is a gut hormone produced from the intestine in response to meal consumption. GLP-1-based therapy was recently announced as a new therapeutic option for people with type 2 diabetes. GLP-1 treatment increases endogenous insulin release caused by meal intake while inhibiting glucagon secretion, promoting glucose homeostasis. Notably, it reduces food intake and appetite. Trials in type 2 diabetes patients reveal that agonists of the GLP-1 receptor (GLP-1R) have favorable effects on metabolic control and may result in weight reduction (Bolen et al., 2007).

The rapid rise in obesity rates poses a serious danger to public health. In European Union nations, 30-70% of adults are overweight, while 10-30% is obese. Since 1980, the incidence has increased in several European regions. Furthermore, the prevalence of overweight and obesity among children and adolescents has increased drastically from 4% in 1975 to slightly more than 18% in 2016. In 2016, nearly 340 million children and adolescents aged 5 to 19 were overweight or obese. In 2019, 38.2 million children under the age of five were expected to be overweight or obese (Styne et al., 2017). The estimated percentage of obese adolescents who become overweight/obesity adults ranged from 24% to 90% (Singh et al., 2008).

At the age of two, extremely obese children have a 20% chance of not becoming fat by the age of 35, and by the age of five, the likelihood has reduced to 10%. The permanence of heightened risk is striking: a fat 2-year-old is more likely to be obese at 35 than an overweight 19-year-old (Ward et al., 2017). If present trends continue, more than 1.1 billion people will be obese by 2030, which is about 2.5 times the number of adults currently living with diabetes (Jepsen et al., 2021).

As a result of the obesity epidemic, a significant cardio metabolic, oncological, psychological, and economical burden will continue to grow (Di Cesare et al., 2017). Obesity increases the risk of developing early puberty in children and adolescents (De Leonibus et al., 2012), menstrual irregularities in adolescent girls [67, 68], obstructive sleep apnea [69], and cardiovascular risk factors such as prediabetes, type 2 diabetes mellitus, high cholesterol levels, hypertension, nonalcoholic fatty liver disease, and metabolic syndrome. Furthermore, obese children and adolescents have psychological problems such as sadness, anxiety, low self-esteem, body image and peer interactions, and eating disorders. Obesity, with its increased all-cause morbidity and death, reduced quality of life, and decreased national production, should be characterized as one of the key initiatives to battle the growing non-communicable disease epidemic across the lifespan beginning in infancy (Rankin et al., 2016).

Recognizing obesity as a chronic progressive disease by relevant organizations is a critical first step in advocating for effective obesity healthcare management and treatment. The primary aims of adult obesity treatment are to prevent problems by keeping the patient metabolically fit, to prevent or cure comorbidities if they already exist, to combat stigma, and to restore well-being, positive body image, and self-esteem. Body weight reduction is not seen as a top concern. Treatment objectives should be adjusted to the complications. Adults should always be offered predicted weight loss as a signal of what may be accomplished to reduce cardio metabolic risks (Frühbeck et al., 2016).

It is more difficult to identify such immediate therapy goals customized to the difficulties in the juvenile population. A change in the standard deviation score of the body mass index (BMI) of at least 0.2 has been indicated to be clinically relevant in children and adolescents, but the data are sparse and ambiguous (Grossman et al., 2017). The US Preventive Services Task Force reported that complete intensive lifestyle treatment that resulted in a 0.17 change in the mean BMI standard deviation score did not result in concomitant improvements in cardio metabolic indicators (Ells et al., 2017). Exenatide, on the other hand, resulted in improvements in glucose and cholesterol levels despite a minor reduction in the BMI standard deviation score difference of 0.09 (Wiegand et al., 2015). To further establish clinically relevant treatment goals in the juvenile population, the particular relevance of different weight management techniques and long-term follow-up regarding risk reduction for obesity related comorbidities should be examined.

Governments and communities should prioritize public health strategies that optimize lifestyle intervention (LSI) and reduce responsible environmental exposures for the prevention and treatment of childhood obesity (Bergsten et al., 2020). However, LSI is frequently insufficient in the treatment of obesity. There is still a subset of children and adolescents that are resistant to lifestyle interventions. The need for safe and efficient weight-loss medications is obvious for these poor responders. Recognizing that aberrant satiety and eating signals inside the brain contributes to successful treatment methods that target central nervous system processes via glucagon-like peptide-1 (GLP-1) agonism (Cardel et al., 2020). Following the encouraging findings in the adult population with and without type 2 diabetes, evidence on the efficacy and safety of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in juvenile obesity have been accumulating over the last decade (Jensterle et al., 2021).

## 4.1 The Current Position of GLP-1 RA for the Weight Management

GLP-1 RA for overweight and obesity should be used as an addition to lifestyle therapy rather than as a stand-alone treatment, with the goal of producing higher weight reduction and weight loss maintenance as compared to lifestyle therapy alone (Garvey et al., 2016). Pharmacotherapy is appropriate for adult patients with a BMI more than 30 kg/m<sup>2</sup> or a BMI greater than 27 kg/m<sup>2</sup> with comorbidities. Anti-obesity medications have responders and nonresponders. After three months of therapy, nondiabetic individuals should lose 5% of their body weight and diabetic patients should lose more than 3%. If this is not the case, the anti-obesity medication should be discontinued. Weight loss medications should be avoided during pregnancy, breastfeeding, and childhood (Durrer Schutz et al., 2019). Clinicians should consider differences in efficacy, side effects, cautions, and warnings that characterize medications approved for chronic management of obesity, as well as the presence of weight-related complications and medical history, when selecting the optimal weight loss medication for each patient; these factors are the basis for individualized weight loss pharmacotherapy; and a generalizable hierarchical algorithm for medication preferences that would be applicable to all patients (Jensterle et al., 2021).

Obesity prevention and lifestyle weight management therapies, such as instructional exercise and nutritional education, promotion of healthy alternatives, and behavioral counseling, are the cornerstones of obesity management in children. Rather than addressing obesity as an individual problem, it is critical to approach this issue through the lens of the family unit (Kansra et al., 2021).

Although these interventions have the potential to be extremely beneficial in select individuals in the right situation, they have evident limits and may benefit from additional techniques or therapies (Ryan et al., 2021). Adolescents are only offered bariatric surgery if they are severely obese, and it is performed seldom (Bolling et al., 2019). Liraglutide, the first and so far only class of GLP-1 RA, was approved by the FDA in 2020 for use in children aged 12-17 years with obesity (weight >60 kg and BMI >30 kg/m<sup>2</sup> according to international criteria 10/95th percentile). Currently, the EMA has not authorized any pharmacotherapeutic medicines for childhood obesity. A double-blind placebo-controlled phase 3 study is under way to assess the effectiveness and safety of liraglutide 3.0 mg on weight management in children aged 6-12 years (Clinicaltrials.gov ID: NCT04775082). A phase 2 trial evaluating the efficacy of liraglutide in adolescents (12-20 years) with obesity after sleeve gastrectomy is also underway, as is a double-blind placebo-controlled phase 3 trial evaluating the efficacy and safety of semaglutide 2.4 mg once weekly in the treatment of adolescents with overweight and obesity (Jensterle et al., 2021).

Taha et al (2022) conducted a study discussing the role of GLP-1RAs in obesity management. Two subcutaneous GLP-1RAs, liraglutide and semaglutide, have been evaluated in several weight loss clinical trials. Liraglutide achieves an average weight loss of 4-7 kg, and over 50% of treated individuals achieve 5% or greater weight loss. Semaglutide has a greater effect on weight loss, with the average weight loss being 9-16 kg, and over 50% of treated individuals achieving 10-15% or greater weight loss. These results led to regulatory approval of these agents for weight loss in obese individuals, regardless of diabetic status. In addition to weight loss, the benefits of GLP-1RAs extend to other risk factors, such as controlling blood sugar and blood pressure. Gastrointestinal symptoms are the most frequently encountered adverse events with a frequency of between 5 and 30%. Finally, cost remains one of the most important challenges limiting the use of GLP-1RAs. The study showed that GLP-1RAs have powerful benefits in weight loss and are expected to have a critical role in the

management of obesity in the coming years. Upcoming studies will evaluate the durability of weight loss achieved with GLP-1RAs and the effect on cardiovascular outcomes (Taha et al., 2023).

Both GLP-1RAs and SGLT-2is are recommended as medication options in type 2 diabetes mellitus patients with overweight or obesity. Semaglutide 2.4mg showed the greatest effects on losing body weight, controlling glycaemic level and reducing blood pressure while it was associated with high risk of adverse events. In terms of serious adverse events GLP-1RAs were associated with a higher risk of SAEs compared to placebo in a network meta-analysis, but there was no significant difference between SGLT-2RAs and placebo. In obese patients or with no diabetes, major reduction of body weight, HgA1c and FPG has been observed for both GLP-1RAs and SGLT2Is (Ma et al., 2023).

Based on the Look AHEAD (Action for health in diabetes; ClinicalTrials.gov Identifier: NCT00017953) trial, which showed that weight loss of more than 5% is associated with improvements in different surrogate markers for cardiovascular disease such as blood pressure and lipids. Look ARG, Wing RR. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: Four-year results of the Look AHEAD trial (Williamset al., 2022).

The results of the network meta-analysis by Alkhezi et al. also showed that tirzepatide produced better weight loss in non-diabetic patients compared with liraglutide and semaglutide, and the safety results were similar with no difference. Alkhezi O.S., et al., Comparative effectiveness of glucagon-like peptide-1 receptor agonists for the management of obesity in adults without diabetes: A network meta-analysis of randomized clinical trials (Lin et al., 2023).



## Current drug therapies for obesity

Individuals with a body mass index (BMI) of 30 kg/m<sup>2</sup> or higher and a condition associated to obesity, such as type 2 diabetes, hypertension, or dyslipidemia, are encouraged by the current European guidelines to undergo medication treatment (Yumuk, V., et al., 2015). The European Medicines Agency (EMA) has approved several drug regimens, such as orlistat, bupropion/naltrexone, and liraglutide, which have been found to effectively promote significant weight loss.

Results from the Look AHEAD (Action for health in diabetes; ClinicalTrials.gov Identifier: NCT00017953) trial showed that improvements in multiple surrogate markers for cardiovascular disease, including lipids and blood pressure, were associated with weight losses of more than 5% of total body weight, which is generally considered a meaningful weight loss.

Drug therapies for obesity typically aim to induce satiety, reduce hunger, and/or decrease fat absorption or breakdown. Orlistat, for example, works by inhibiting pancreatic lipase, which reduces the digestion and absorption of fat in the intestine. This leads to an average weight loss of 2.9-3.4 kg per year. However, orlistat often causes unpleasant gastrointestinal side effects, such as steatorrhea and malabsorption of fat-soluble vitamins, which limits its usage. Additionally, its cost per quality-adjusted life year (QALY) is estimated to be as high as £45,881, which restricts its use in the UK based on the recommendation by the National Institute for Health and Care Excellence (NICE).

Nevertheless, orlistat frequently induces unpleasant gastrointestinal side effects, such as steatorrhea and malabsorption of fat-soluble vitamins, hence restricting its usage. Fourteen The National Institute for Health and Care Excellence (NICE) has recommended limiting the use of the treatment due to its high estimated cost per quality-adjusted life year (QALY), which is up to £45,881 in the UK (Apovian, C. M., et al., 2015)

## 5. Conclusion

GLP-1RAs appear to be an effective therapy option for weight control in persons with antipsychotic-related obesity, improving glycaemia and lipid profile parameters. Given its potential benefits in lowering weight in addition to glycemic management, GLP-1 agonists may soon contribute to the treatment of obesity in both diabetic and non-diabetic persons. However, further research investigations, namely big clinical trials, are necessary to extend and fully explain the beneficial effects and potential negative effects of GLP-1 agonists. Current therapies for type 2 diabetes patients include flaws (weight gain, hypoglycemia, and other side effects) that restrict the number of patients who achieve acceptable therapeutic goals. The current meta-analysis offers solid evidence that GLP-1R agonists have clinically relevant positive effects on body weight when administered to obese people with or without diabetes.

There is considerable interest in the present usage and continuing development of obesity therapies based on GLP-1 agonism, which have been shown to reduce morbidity and mortality in the adult population. Obesity prevention and LSI within the family unit are the cornerstones of anti-obesity treatment in children. Pediatricians now have nothing to give patients who are resistant to lifestyle changes. GLP-1 RA seems to be safe and mildly beneficial in lowering weight and improving cardio metabolic profile in children with obesity who do not respond to LSI alone.

Although this comprehensive analysis discovered that GLP-1 agonists have a good effect on weight loss, physicians must write prescriptions with caution to avoid potential adverse effects of the GLP-1 agonists while providing an opportunity for the general health of obese persons with or without diabetes. Additional benefits to blood pressure and total cholesterol may be obtained. Patients with diabetes who are fat or overweight should consider the intervention. More research is needed to determine the impact of GLP-1R agonists in the treatment of obese persons who do not have diabetes. Since of the scarcity of data, a general advice is to favor long acting GLP-1 RA over short acting GLP-1 RA since they are licensed for the treatment of obesity and have greater tolerability, safety, and therapeutic response impact. New studies are being conducted to collect pediatric data, including long acting GLP-1 RA semaglutide. Future semaglutide studies are being planned in order to offer conclusive answers to this intriguing and demanding therapy topic.

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