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Liraglutide - A Promising Approach Against Obesity

Nabila Rafi, Muhammad Sajid Abbas Jaffri, Kamran Yousuf

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Back ground

Obesity has emerged as a global chronic condition that poses a significant public health issue. The World Health Organisation (WHO) has reported a significant increase in obesity rates, which have nearly quadrupled since 1975.[1] Thus, it is crucial to consider the significant health risks associated with this issue, including the potential for developing type 2 diabetes, cardiovascular diseases, endocrinal malignancies, and musculoskeletal difficulties. Furthermore, obesity incurs substantial expenses for healthcare systems and populations at large.[2]

Traditional weight loss methods such as dieting and exercise, while successful in addressing obesity, have shown limited effectiveness in the long-term.[3] Although lifestyle modifications are the primary strategies in treating obesity, most individuals struggle to achieve and sustain significant weight loss with these treatments alone. Several crucial elements that influence weight reduction include gene predisposition, metabolic adaption, environmental conditions, and psychological state.[4]

Liraglutide; As antidiabetic drug

Liraglutide is a GLP-1 receptor agonist and is derived from diabetes type 2 medication . It was initially developed for this purpose, but its unusual action, namely suppressing hunger and facilitating weight loss, has resulted in its approval by the FDA for the treatment of obesity.[5] Liraglutide functions by mimicking the effects of naturally occurring GLP-1, which plays a role in controlling glucose metabolism, insulin release, and feelings of fullness. Moreover, as Nadkarni et al. claim, it reduces the intake of calories, slows down stomach emptying, and speeds up the passage of food through the intestines, which also results in the activation of the central nervous system and peripheral tissues.[6]

Gastric emptying

Gastric emptying is the process by which food is expelled from the stomach and enters the small intestine.[7] The decrease in the jejunum's functionality is due to the reduced rate of absorption of nutrients from the digestive tract into the bloodstream. Consequently, the duration of the feeling of fullness is extended and the quantity of consumed food is diminished. During this time frame, liraglutide was found to slow down the process of stomach emptying.[8]

Insulin Secretion

Liraglutide exerts various effects on insulin production. Additionally, it helps regulate hunger and accelerates the process of emptying the stomach, while also promoting the secretion of insulin from pancreatic beta cells in response to elevated blood sugar level.[9] Type 2 diabetes mellitus (T2DM) patients will have enhanced regulation of blood sugar levels through the insulinotropic property. Liraglutide affects glucagon release from pancreatic alpha cells by acting as a full agonist of the glucagon-like peptide-1 receptor. Moreover, it exerts a hypoglycemic impact by reducing hepatic glyconeogenesis, hence enhancing glucose tolerance. Liraglutide aids in achieving positive outcomes in situations of overweight and insulin resistance by enhancing metabolism.[10]

Central and Peripheral Mechanisms of Action:

Liraglutide demonstrates a particular action through its overlapping impact on both central and peripheral pathways, which, in combination, facilitates fat loss.[11] It is directed on the hypothalamus and other brain regions related to appetite regulation, which leads to decreasing hunger and increasing the feeling of satiety. Furthermore, it also has an indirect impact on the emptying of stomach, the secretion of insulin and the metabolism of glucose, thereby bringing about reduction of calorie absorption and partaking in the metabolic processes successfully.[12]

Clinical Trial

Previous SCALE study has revealed that subjects assigned to the liraglutide 3.0 mg group for 56 weeks did achieve greater weight loss than those in the placebo group in overweight/obese patients with the prediabetes. Another example is the SCALE Diabetes program released liraglutide

Nabila Rafi *(Corresponding Author)*
M.Phil Student in Pharmacology
Bahria University Health Sciences, Campus Karachi
Email: nabz_27@hotmail.com

Muhammad Sajid Abbas Jaffri
Senior professor, Department of medicine
Bahria University Health Sciences, Campus Karachi
Email: drsajid.jaffry@live.com

Kamran Yousuf
Assistant professor, Department of Pharmacology,
Bahria University Health Sciences, Campus Karachi
Email: kamran.bumdc@bahria.edu.pk

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1.8 mg administration superior in weight loss and better blood sugar control in type 2 diabetic patients (T2DM) over 56 weeks compared to placebo.

The SCALE Maintenance trial was conducted to detect the lasting effect of liraglutide 3.0 mg on weight management and to see if liraglutide was as safe for continuous use as it was for weight management. Although 56 weeks of liraglutide medicine had already showed its effectiveness, the benefits of the therapy remained steady, which resulted in longer term weight loss and a lower risk of weight regain than the placebo group.

Dose-Response Relationship:

Studies[13-15] have conclusively demonstrated a clear connection between liraglutide and the reduction of body weight. The amount of weight loss achieved is directly influenced by the dosage administered. Greater doses of liraglutide, namely over 3.0 mg, resulted in more significant weight reduction results in comparison to lesser doses or a placebo. While the precise processes behind this dose-response connection are not fully understood, it is likely that it involves increased feelings of fullness, decreased consumption of food, and better metabolic factors.

Side effects

Commonly seen side effects of liraglutide usage include gastrointestinal symptoms such as nausea, vomiting, diarrhoea, and constipation.[16] Usually, these negative effects appear in the first few weeks after starting treatment and may get better over time as individuals adjust to the medication. Higher doses of medication often lead to an increase in gastrointestinal side effects. In severe circumstances, some persons may stop taking the medication because the adverse effects become intolerable.[17]

The primary adverse effects of liraglutide are pancreatitis and hypoglycaemia.[18] Furthermore, pancreatitis is an infrequent negative outcome observed in people who get this medication. Pancreatitis can be identified by attentively observing symptoms such as prolonged abdominal pain.[19] Immediate discontinuation of medication is necessary for suspected cases of pancreatitis. In addition, liraglutide has the potential to cause hypoglycemia, especially when used in combination with insulin or sulfonylureas in persons diagnosed with type 2 diabetes mellitus.[20]

Cardiovascular Safety:

The cardiovascular safety data for liraglutide is obtained from wide-ranging clinical trials and continuous post-marketing observations. Unlike other medications in the market, liraglutide is not only free of those adverse cardiovascular effects but it also reduces cardiovascular risks of individuals with obesity and type 2 diabetes mellitus.

The LEADER (Liraglutide Effect and Action in Diabetes), which dealt with the cardiovascular consequences in high-risk patients with cardiovascular disease and type 2 diabetes. This trial indeed proved a significantly high occurrence of the major cardiovascular adverse events, including the cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke, among the liraglutide participants compared with the placebo group.

Similarly, the SCALE trial demonstrated that liraglutide, as one of the GLP-1 receptor agonists, improves many cardiovascular risk factors like lowering blood pressure, cholesterol, blood sugar, and inflammation markers.

Patient selection:

Liraglutide has received approval as a treatment choice for those with body mass index (BMI) that falls under the 30 kg/m² mark in their adulthood. Besides this, guidelines say it should be suggested for those who have a BMI of over 27 kg/m², provided they have any of the weight-related co-morbid conditions such as hypertension, type 2 diabetes mellitus or abnormal lipid levels. Determining individuals at risk of obesity-related complications should be one goal.

The assessment of patients' conditions should involve the prioritization of and consideration of many issues, such as patients' BMI, their comorbidities already existing, and the treatment history. An individual with a body mass index of 30 kg/m² or higher is considered an appropriate patient for liraglutide therapy because he/she belongs to the group of people vulnerable to obesity-related health problems. Nevertheless, patients with a BMI of 27 kg/m² and suppose that they also suffer from diseases including diabetes, cardiovascular diseases, non-alcoholic fatty liver disease, dyslipidemia, and high blood pressure could also benefit from liraglutide treatment. But in our part of the world it is very costly .The inclusive technique is oriented at working with the problems of weight and metabolic aspects at the same time.

Current scientific research on the GLP-1 associated treatment for obesity centers around creating new formulations and combination treatments in order to enhance weight loss outcomes. Researchers are studying if the long-acting release forms of liraglutide might facilitate patient compliance and the convenience of use. Moreover, the continuous evaluation of the combination of liraglutide with other medications commonly prescribed in weight-loss management is being conducted, for instance, GLP-1 receptor agonists and metabolic modulators. This collaborative approach aims to bring together the two approaches for additive weight loss and potent therapeutic outcomes in obesity treatment.

CONCLUSION:

In conclusion, liraglutide stands out among the group of anti-obesity drugs and there is a possibility that it will fill the gaps in the current treatment of obesity. Meta-analysis of a wide range of clinical studies revealed that it has a significant impact on weight loss, metabolic parameters, as well as reduction of use of medications in the treatment of

obesity-associated comorbidities. The unique feature of its dual-action mechanism that targets both appetite control and metabolism determines it as an innovatively reliable treatment approach. For the future, research should aim at focusing on improving patient selection criteria, examining combo therapies and overcoming the obstacles to the maintenance and success. Additionally, spurring research on new formulations and personalized models is a major step towards extending the clinical utility of liraglutide in dealing with obesity and its related metabolic implications which would in turn improve patient outcomes in this evolving scenario.

Authors Contribution:
Nabila Rafi: Conception of Study
Muhammad Sajid Abbas Jaffri: Critical Review
Kamran Yousuf: Final Proof read

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