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Review

Current Status of Glucagon-like Peptide-1

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ABSTRACT

Glucagon-like peptide 1 (GLP-1)-based therapies, including GLP-1 receptor agonists, dual-acting GLP-1, and glucose-dependent insulinotropic polypeptide [GIP] receptor agonists, have the capacity to affect glycemia through a variety of mechanisms. These mechanisms encompass a decrease in food ingestion and postprandial glucagon secretion, a delay in gastric emptying, and an increase in glucose-dependent insulin secretion. The utilization of GLP-1-based therapy for the purpose of weight loss in adults who do not have diabetes is covered separately. The inhibition of dipeptidyl peptidase 4 (DPP-4) by dipeptidyl peptidase inhibitors leads to an increase in endogenous GLP-1.

Since it was discovered, GLP-1 has been shown to be a pleiotropic hormone that is responsible for a wide variety of metabolic functions. These functions extend far beyond its traditional classification as an incretin hormone. Because of its many positive effects, GLP-1 is an intriguing possibility for the creation of pharmacotherapies that could be used to treat conditions such as obesity, diabetes, and neurodegenerative illnesses.

KEYWORDS: GLP-1, Incretin, Pleotropic hormone, Semaglutide

INTRODUCTION

A complex hormone with a wide range of pharmacological potential is glucagon-like peptide-1 (GLP-1). GLP-1 has several metabolic effects, including glucose-dependent insulin secretion stimulation, gastric emptying reduction, appetite suppression, enhanced natriuresis and diuresis, and regulation of β-cell proliferation in rodents. Furthermore, GLP-1 diminishes inflammation and apoptosis, safeguards the heart and brain, and influences learning and memory, reward behavior, and palatability. GLP-1 receptor agonists, which have been biochemically altered for increased potency and prolonged activity, are effectively used in clinical settings to treat type-2 diabetes, and a number of GLP-1-based medications are being tested in clinical settings to treat obesity[1].

In 1923, Charles Kimball and John Murlin precipitated a pancreatic fraction that, upon evaporation and reconstitution in water, exhibited a potent hyperglycemic effect when administered to rabbits and canines. The objective was to create a rapid and cost-effective method for commercial insulin purification.. Kimball and Murlin postulated that the hyperglycaemic impact was caused by a secreted factor that

counteracts the hypoglycaemic effect of insulin because the fraction was unable to lower blood glucose. The factor was referred to as "glucagon," or "the glucose agonist"[2]. The molecular foundations of glucose regulation by the two opposing pancreatic hormones became the focus of significant research efforts over the ensuing decades[3].

Different fractions of the intestine glucagon-like material had different molecular sizes and biological activity, making it more heterogeneous than glucagon generated from the pancreas[4,5]. The intestinal glucagon-immunoreactive substance had no glycogenolytic effects in the isolated perfused rat liver and did not cause hyperglycaemia when injected into dogs[4].

TYPES OF GASTRIC PEPTIDES

In order to keep blood sugar levels stable, a complex web of hormones works in tandem. Amylin and insulin are produced by pancreatic beta cells, glucagon by pancreatic alpha cells, and gastrointestinal peptides like GLP-1 and GIP (formerly gastric inhibitory polypeptide). The "incretin" hormones GLP-1 and GIP connect pancreatic hormone release with nutrient absorption from the gastrointestinal system. They serve as one of the physiological links between eating and insulin release and are released during a meal, following the consumption and absorption of glucose, protein, and fat[6] (*Figure 1*). Type 2 diabetes may arise as a result of abnormal control of these peptides.

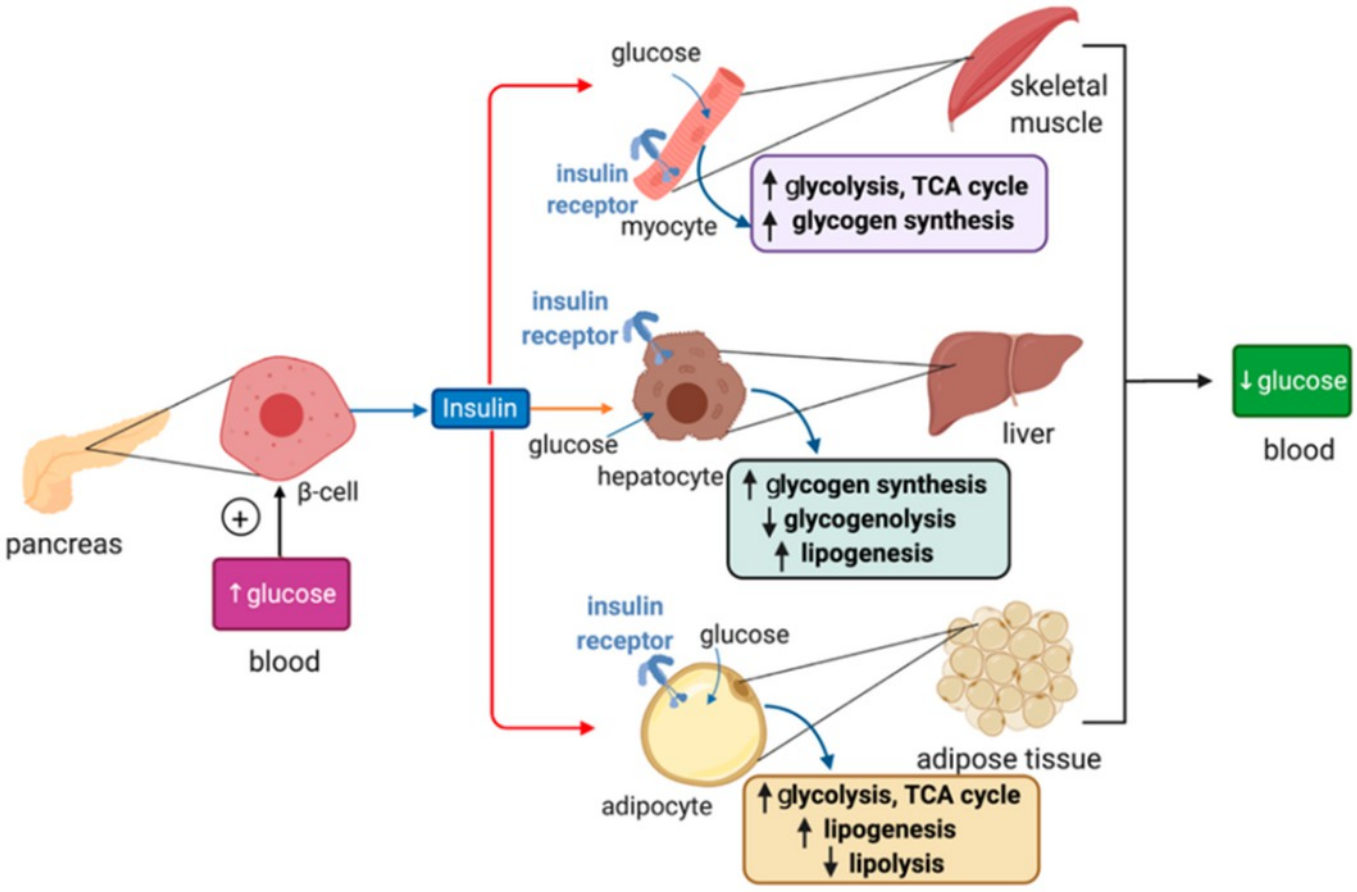

Figure 1: Hormonal Regulation of Glucose Metabolism by Insulin[7]

Glucose-dependent insulinotropic polypeptide (GIP)

The small intestine's K cells make GIP. It attaches itself to a particular GIP receptor that is expressed in many different organs, such as the heart, bone, subcutaneous and visceral adipose tissue, pancreatic beta cells, and pancreatic alpha cells. GIP and GLP-1 are co-secreted during the postprandial phase, and they may work together to enhance glucose-induced insulin secretion [Figure 1]. Nevertheless, GIP and GLP-1 have distinct effects on glucagon secretion. GIP increases glucagon activity in both euglycemic and hypoglycaemia conditions[8,9].

Glucagon – like peptide 1 (GLP)

Proglucagon [Figure 2], which is found in the L cells of the small intestine, is responsible for the production of GLP-1. The active 30-amino acid polypeptide GLP-1 is produced when proglucagon is transformed into it. This GLP-1 interacts to a particular GLP-1 receptor that is expressed in the kidney, lung, heart, skin, immune cells, pancreatic beta cells, pancreatic ducts, gastric mucosa, and hypothalamus[10]. On the condition when GLP-1 is present, the pancreatic islets secrete insulin in a manner that is dependent on glucose. Moreover, it slows the emptying of the stomach, suppresses the release of erroneous glucagon after meals[11,12,13], and lowers the amount of food that is consumed[11]. Patients who have type 2 diabetes have a decreased insulin sensitivity to GLP-1, which may be the result of a decrease in postprandial GLP-1 production[14] or other mechanisms[15]. Animal studies on diabetes and prediabetes have shown that GLP-1 increases beta cell mass and proliferation; however, this effect has not been reproduced in human subjects.[16].

The enzyme dipeptidyl peptidase 4 (DPP-4) is responsible for the N-terminal degradation of GLP-1, which results in a half-life of only one to two minutes. Synthetic GLP-1 receptor agonists are resistant to degradation by the enzyme DPP-4 in varying degrees. As a result, they have a longer half-life, which makes their clinical application more easily accessible. Antibodies that have a longer duration of action on the GLP-1 receptor can be delivered once daily or once weekly. Synthetic GLP-1 receptor agonists, just like native GLP-1, bind to the GLP-1 receptor and promote glucose-dependent insulin release from the pancreatic islets. This is the principal effect that these agonists have on reducing glucose levels[17].

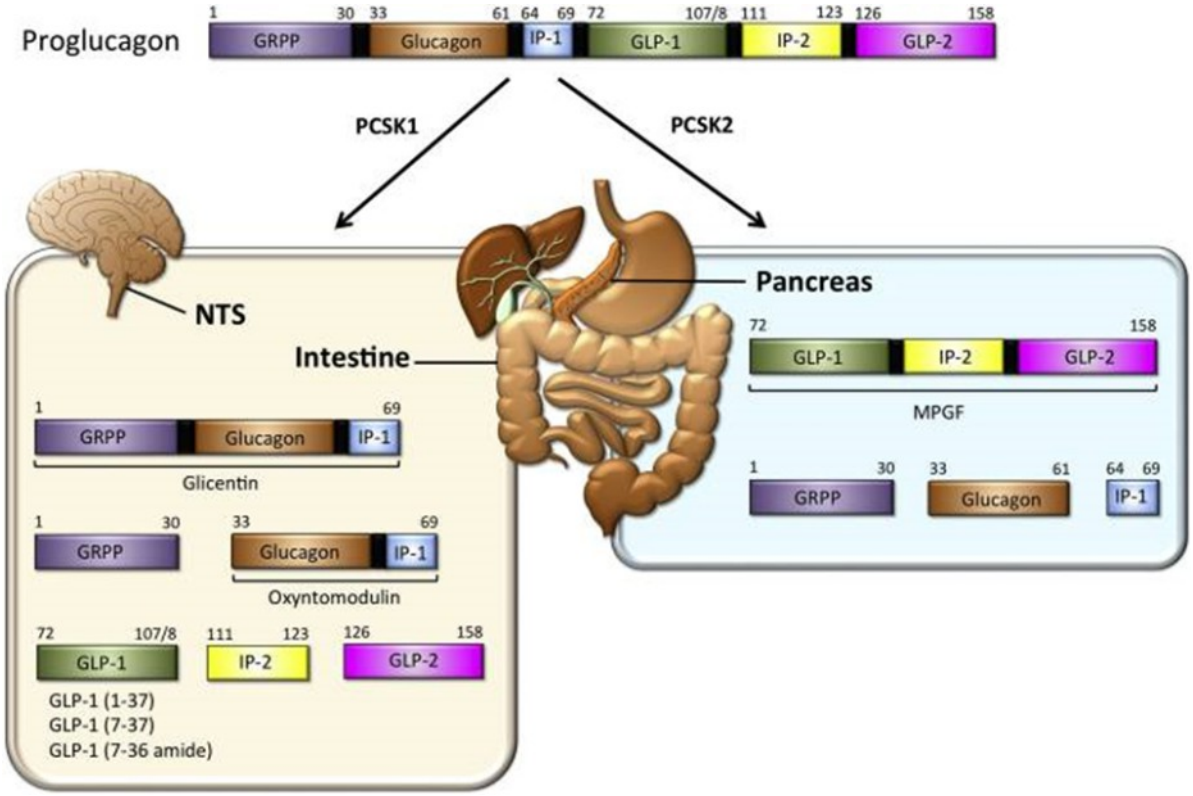

Figure 1: Processing of Proglucagon
(Posted under Open Access – Creative Commons License from *Muller et al.*[1])

GLP-1 – Saving Precious Beta cells and more

Not only does the prevalence of type 2 diabetes increase with age, but it also has a correlation with having an excessive amount of body fat[18]. There is a consistent correlation between the evolution of type-2 diabetes and a decrease in the functional β-cell mass[19,20]. It has been observed that the capacity of β-cells to proliferate decreases with age in both rodents and humans[21,22]. The rate of replication of human β-cells is highest during the early stages of childhood and puberty, but it gradually decreases as the age of the individual increases[21,22]. These data, when taken together, provide evidence that suggests that age-related alterations in β-cell neogenesis and replication could potentially have a causal relationship with the development of type 2 diabetes[18,23]. It has also been suggested that β-cell dedifferentiation plays a part in the process[24].

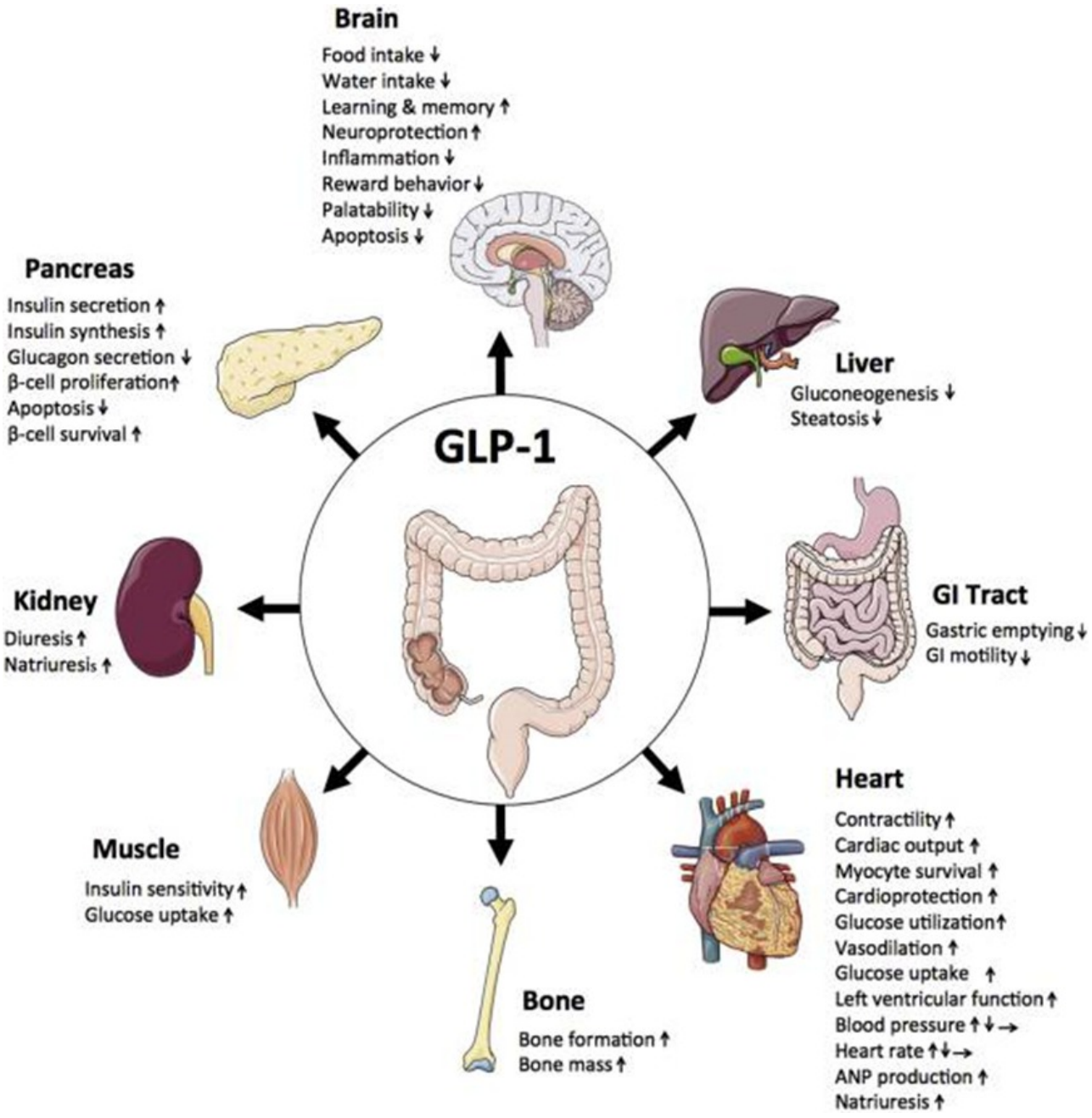

Figure 3: GLP-1 on Metabolism
(Posted under Open Access – Creative Commons License from *Muller et al.*[1])

GLP-1 On Heart and Weight

It has been observed that GLP-1R is predominantly present in the endothelium, coronary arteries, and smooth muscle cells of humans.[5]. In spite of this, there is a lack of consistency between the localization data obtained from immunohistochemistry and the detection of GLP-1R mRNA using in situ hybridization. It is possible that some of the incongruent findings are the consequence of a lack of antisera specificity. This is not surprising when considering the numerous specificity issues that are associated with antibodies that target the GLP-1 receptor. Using antibodies that have been thoroughly described, expression was observed in the sinoatrial node of both human and non-human primates[26]. This finding would be compatible with the influence that GLP-1 has on the rate of heart muscle contraction. In a recent study, it was also reported that the GLP-1 receptor mRNA was expressed in human cardiac ventricles[27]. Nevertheless, the precise location of the GLP-1R protein was not determined. This discovery was somewhat unexpected.

GLP-1R agonism is most commonly recognized for its insulinotropic and weight-reducing effects; however, it also has a number of beneficial effects on the cardiovascular system in rodents. The following are included in this category: an increase in the survival of cardiomyocytes by inhibiting apoptosis[28], an amelioration of endothelial dysfunction[29,30], and an improvement in regional and global cardiac output following damage and heart failure[31,32]. It has also been noted that hypertensive persons have a reduction in their blood pressure[33]. Treatment with liraglutide for an extended duration enhances the cardiovascular prognosis of individuals with type 2 diabetes[34]. It is crucial to acknowledge that the improvement of cardiovascular performance by GLP-1 is, at least in part, unrelated to its ability to increase lipid metabolism and reduce body weight. Furthermore, GLP-1 may promote its effects on the heart through direct action at GLP-1R as well as indirect mechanisms that are independent of the action of cardiac GLP-1R[35].

GLP-1 Agents

For the treatment of type 2 diabetes, a number of structurally refined GLP-1 derivatives that have increased bioavailability and prolonged action have been created[36].

These agents are depicted below in Figure 4 according to their timeline.

MAJOR OUTCOMES

In recent trials that compared exenatide administered twice daily with exenatide administered once weekly, liraglutide administered once daily, or dulaglutide administered once weekly, the reduction in A1C was greater with the longer-acting (daily or weekly) treatment. The treatment difference was considerably greater for GLP-1 receptor agonists (-0.3 to -0.7 percent).[37] In contrast to longer-acting GLP-1 receptor agonists, the shorter-acting compounds exhibit a more pronounced effect on postprandial hyperglycaemia and gastric emptying, as well as a less pronounced effect on fasting glucose[38,39].

When used with oral medications for background therapy, GLP-1 receptor agonists lowered A1C by about 0.5 to 1.4 percentage points in meta-analyses[40,41], and they achieved a higher reduction in A1C than either oral drugs or baseline insulin[42]. The two drugs that reduce glucose levels the most effectively, tirzepatide and subcutaneous semaglutide, were left out of several of these studies. However, insulin treatment was not titrated correctly in all trials. Also, many study participants stop using GLP-1-based treatments because of gastrointestinal adverse effects, which is a pretty high rate[43].

The cumulative incidence of A1C ≥7 percent was similar for patients randomly assigned to liraglutide (68 percent) or glargine (67 percent) as add-on treatment in a comparative effectiveness trial (GRADE) with an average follow-up of five years in 5047 patients with type 2 diabetes on metformin monotherapy, but lower than for those who received glimepiride (72 percent) or sitagliptin (77 percent)[45].

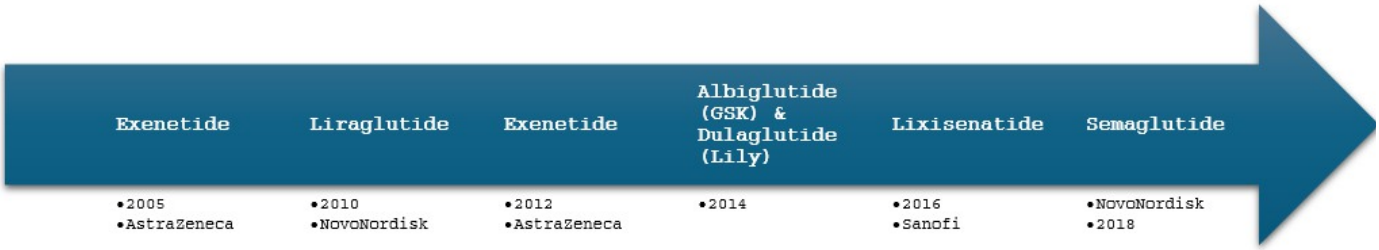

Figure 4: Timeline of GLP-1 Agents

Treatments based on GLP-1 often result in weight loss[45,46]. Possible causes of weight reduction include diminished slow gastric emptying and increased satiety[46]. When GLP-1-based therapy is stopped, weight comes back on, just like with other pharmacotherapies for weight loss.

Compared to once-weekly exenatide (-2 kg), dulaglutide (-3 kg), or 1.2 mg liraglutide (-2 kg), subcutaneous semaglutide (-6 kg) resulted in more weight loss after adjusting for placebo in trials. Similarly, 1.8 mg liraglutide (-3.5 kg) produced somewhat more weight loss than once-weekly exenatide (-2.5 kg) or dulaglutide (-3 kg)A[47]. When compared to 1 mg of subcutaneous semaglutide, tirzepatide led to more weight loss[48].

In patients with diabetes and preexisting cardiovascular disease, GLP-1-based treatments reduce overall mortality[49,50]. In a meta-analysis of seven trials that compared placebo with GLP-1 receptor agonists (lixisenatide, exenatide, albiglutide, liraglutide, semaglutide) in patients with diabetes and CVD, the risk of all-cause mortality was reduced to 60 versus 68 events per 1000 persons (OR 0.88, 95% CI 0.82-0.95)[51].

Reported Adverse Effects

Common gastrointestinal side effects of GLP-1-based treatments include upset stomach, flatulence, and vomiting[52]. Between 10% and 50% of patients experience them in clinical trials[53]. A network meta-analysis of 236 clinical studies found that GLP-1 receptor agonists were more likely to cause treatment cessation due to adverse events compared to oral medications[54].

When comparing patients using semaglutide (14 mg orally daily, formulation R1) to those taking sitagliptin (100 mg daily), one study found that 15.9% of patients on semaglutide and 12.3% on sitagliptin experienced nausea, vomiting, and diarrhea, respectively, compared to 6.9%, 4.1%, and 7.9% of patients on sitagliptin, respectively[55]. Nausea 17.4 to 22.1 percent, diarrhea 11.5 to 16.4 percent, and decreased appetite 5.3 to 8.9 percent were the same in the tirzepatide group as in the subcutaneous semaglutide group in a trial comparing the two[56]. The frequency of nausea has been found to be lower with once-weekly administration of liraglutide (9 versus 21 percent) or twice-daily administration of exenatide (26 versus 50 percent), both of which are no longer available in the US or Canada[57].

GLP-1-based medicines have been linked to more severe gastrointestinal concerns, such as blockage and symptomatic gastroparesis, when they are consumed for the purpose of reducing body weight[58].

Ketoacidosis has been recorded in patients who are receiving therapy that are based on GLP-1, with certain cases being connected with the use of tirzepatide and subcutaneous semaglutide[59]. Ketoacidosis is a condition that manifests itself in these instances when there is neither normoglycemia nor hypoglycemia present, and when there is no present insulin deficit. The onset of ketoacidosis is characterized by severe nausea, vomiting, and/or diarrhea, which may be caused by the GLP-1-based medication on its own or in conjunction with a superimposed cause (for example, gastroenteritis, other severe condition, or excessive use of alcohol). Fluids containing dextrose and electrolyte replenishment are administered intravenously as part of the management process. When compared to diabetic ketoacidosis, insulin therapy is not required for the management of ketoacidosis that is linked with GLP-1-based therapy. However, insulin therapy may be suggested if there is a suspicion of concomitant diabetic ketoacidosis or insulin insufficiency[60].

The results of studies that have been conducted on the topic of a relationship between therapy with GLP-1-based medicines and the risk of suicidality have been contradictory[61]. A meta-analysis of findings from 27 trials involving 59,403 participants found that GLP-1-based treatment for diabetes or weight management was not associated with an increased risk of death by suicide, suicide attempts, suicidal ideation, or self-harm (33 events among 32,357 participants versus 27 events among 27,046 participants for GLP-1-based treatment and placebo, respectively)[62]. This was the conclusion reached after comparing the use of GLP-1-based therapies with placebo.

CONCLUSION

There is a wide range of pleiotropic effects that GLP-1 analogs have on metabolism, and these effects vary depending on the molecule (native or recombinant long-acting) and the mode of administration. The regulation of blood glucose, the reduction of body weight through the inhibition of food intake and the reduction of gastric motility, the stimulation of cell proliferation, the reduction of inflammation and apoptosis, the improvement of cardiovascular function, and neuroprotection are just some of the numerous beneficial effects that are mediated by GLP-1R agonists. In the treatment of type 2 diabetes, recombinant GLP-1R analogs that have enhanced pharmacokinetics and sustained action have proven to be effective. Furthermore, there is a significant and continuous effort being made to further optimize their action profile in order to improve therapeutic outcome and patient compliance. For the treatment of diabetes and obesity, novel peptides that combine the pharmacology of GLP-1 with those of other gut peptides are now being evaluated in clinical settings. It is reasonable to be cautiously optimistic that enhanced GLP-1-based pharmacology may one day be safely employed to further reduce body weight in comparison to GLP-1R agonists that are already accessible. This is despite the fact that long-term clinical investigations are still being conducted.

CONFLICT OF INTEREST: None

FINANCIAL SUPPORT: None

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