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REVIEW ARTICLE

Role of Glucagon-like Peptide-1 (GLP-1) Agonists in the Management of Diabetic Patients with or without COVID-19

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Abstract:

Glucagon-like peptide 1 (GLP-1) is a gut-derived hormone released after a meal, which alleviates hyperglycemia, increases β-cell survival, reduces body weight, and reduces inflammation. These thrilling effects motivated clinical studies to discover the potential use of GLP-1 receptor agonists (GLP-1 RAs) in the management of T2D. GLP-1 RAs are potential anti-diabetic agents that can reduce blood pressure, glucose levels, HbA1c and, weight loss without hypoglycemia risk. This manuscript reviews the importance of GLP-1 RAs and their role in the management of T2D with or without COVID-19 infection. Hence, this manuscript can help physicians and researchers to choose the most appropriate drugs for the individualized treatment of subjects.

Keywords: COVID-19, Coronavirus, GLP-1R agonist, Glucagon-like peptide-1, Incretin.

1. INTRODUCTION

To date, about 100 million cases and 2 million deaths have been reported globally due to coronavirus disease 2019 (COVID-19). The mortality of COVID-19 climbs up instantly, in particular with a high prevalence of comorbidities, such as hypertension, cardiovascular disease, obesity, and diabetes [1, 2]. Type 2 diabetes (T2D), classified as a chronic disease and considered as an epidemic in many developed and developing countries, is currently inducing serious complications to the COVID-19 pandemic, causing a higher mortality rate all over the world [3, 4]. Impaired insulin action, pancreas β-cell impairment, and hyperglucagonemia have been determined for T2D metabolic diagnosis, resulting in hyperglycemia with toxic effects that lead to various complications [5]. However, the pathophysiological effects of these disorders remain to be fully revealed, but they might usually cause incretin deficiency. Incretin disorder function is a hallmark in diabetes, and current studies showed that incretin is also diminished in T2D and obesity [6]. According to this theory, lipotoxicity and insulin resistance can cause subtle changes in β-cell function, leading to decreased insulinotropic effects of glucagon-like peptide-1

(GLP-1) and further promoting high blood glucose levels and β-cell damage [7, 8]. Consequently, abnormal incretin is a very initial sign of pre-diabetic situation in obese subjects who are still glucose tolerant [5].

Insulinotropic effects of GLP-1 are decreased in T2D subjects, causing the development of incretin-based treatments in the recent decade. In this respect, two classes of incretin-based therapy, including dipeptidyl peptidase-IV (DPP-IV) inhibitors and GLP-1 receptor agonists (GLP-1 RAs), are available for the management of T2D.

Current medicines used for T2D treatment are not efficient for inhibiting the continuous decrease in β-cell function; this may lead to hypoglycemia and weight gain. All of the GLP-1 RAs and DPP-IV inhibitors are attractive options due to their glucose-reducing properties with minimal adverse effects of weight gain and hypoglycemia. These drugs exert their influences by reducing gastric emptying and thereby reducing appetite, inhibiting beta-cell apoptosis and glucagon release, preventing β-cell glucolipotoxicity, normalizing glucose-dependent insulin secretion, reducing liver glucose production, and improving beta-cell survival. Some prevention strategies, vaccines, and different pharmaceutics have already been examined, and some are still under examination to evaluate their safety and efficacy as potential treatments for COVID-19

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[9, 10]. Diabetic patients are frequently treated with GLP-1 RAs with daily or weekly subcutaneous administration. In the interest of improving clinical practices and developing novel approaches, we aim to highlight the valuable role of GLP-1 agonists in the management of T2D regarding the current clinical outcomes in the setting of COVID-19 infection and the further advancements for the improvement of patient compliance and convenience.

2. METHOD

The words "GLP-1", "incretin", "incretin-based therapies", "COVID-19", "coronavirus", "GLP-1R agonist and "dipeptidyl peptidase-IV (DPP-IV) inhibitors", were entered into databases, such as ScienceDirect, PubMed, EMBASE, EBSCOHost, and Googlescholar were reviewed.

3. INCRETIN

The incretin effects reflect the elevated insulin release in response to a glucose load transported to the intestine compared with that reached by intravenous glucose when the blood concentration of glucose, under both situations, are comparable [11]. This effect is involved for about 60% of the insulin secretion after an oral glucose load due to insulinotropic properties of incretins that are secreted from enteroendocrine cells of the gastrointestinal. The gastric inhibitory polypeptide (GIP) and GLP-1 are known as the main incretin hormone [12].

3.1. Advantage of Incretin Therapy

The main challenge in diabetes therapy is preventing hypoglycemia development, especially with insulin and sulfonylureas (SUs). Hypoglycemia in diabetic patients causes some complications, such as brain damage, unconsciousness, and even death, if uncontrolled. The other main adverse effect experienced by diabetes patients is weight gain, which happens with using most anti-diabetes drugs, including thiazolidinediones, SUs, and insulin [13]. Since obesity is closely related to insulin resistance, the efficacy of these components in treating T2D becomes relatively limited due to their association with weight gain [13]. Physicians prescribe chemical agents and herbal medicine or nutrients for the treatment of T2D and related disorders [14 - 19]. However, they have some limitations and drawbacks [20]. Incretin-based treatments offer new options for the treatment of T2D by controlling hyperglycemia and body weight. As mentioned above, incretin is secreted in response to a meal and high glucose concentration, which consequently leads to the release of more insulin. Previous data reported that T2D patients have a reduced incretin effect, probably due to declined active GLP-1 concentration [11].

However, all GLP-1 RAs seem to have a crucial role, given by their glucose-reducing properties with minimal side effects, such as weight gain and hypoglycemia [21]. In a study, a continuous infusion of GLP in T2D patients led to a significant weight loss of 1.9 kg and a decline in appetite from baseline in comparison with placebo [22]. These findings revealed that GLP-1 could be valuable in the treatment of T2D patients [23]. Currently, there are growing interestsin therapeutic approaches based on the stimulation of GLP-1 actions and GLP-1 receptors

on the pancreas [21]. As well documented, GLP-1 regulates several genes expression in β-cell by suppressing β-cell apoptosis, inhibiting β-cell glucolipotoxicity, and increasing β-cell survival and function [24]. Furthermore, it has been reported that GLP-1 reduces hepatic glucose production and prevents glucagon secretion [24]. This incretin also reduces acid secretion, gastric emptying, and reduces appetite [21].

3.2. Enteroendocrine Cells

The intestine is the main energy sensor that sends signals to the brain via hormones and neurons [25]. Enteroendocrine cells are found in the gut mucosa and sparsely spread in the epithelial lining. These cells secrete various peptides with deep influences on body homeostasis [26]. The peptide YY (PYY) and GLP-1 are among the main ones. These incretin hormones are released by intestinal L-cells mainly located in the colon and distal part of the small intestine and have numerous physiological functions ranging from managing appetite, controlling gut transit, stomach emptying, and stimulating β-cell survival and proliferation. GLP-1 and PYY decrease gastrointestinal transit and participate in the ileal brake where stomach emptying is suppressed to regulate food delivery to the intestine with absorption and digestion rate [25]. PYY and GLP-1 levels in the blood are increased within 15 min after a meal and reach peak concentration at about one hour [25]. Besides the alterations between L-cells in various compartments, there are also studies proposing that GLP-1 may have different functions depending on where it is secreted. Colon has a maximum GLP-1 density but will not sense nutrients from a meal until later, indicating that the L-cells of the colon are not responsible for the postprandial rise in GLP-1. Additionally, GLP-1 is recognized as an anorectic hormone that inhibits appetite, but at the same time, concentrations of GLP-1 are elevated in the conditions of low energy as in anorexic cases and germ-free animals that have augmented food intake in comparison with conventionally elevated counterparts [27, 28].

3.3. GLP-1 Receptor (GLP-1R)

GLP-1R is a seven-transmembrane G-protein coupled receptor (GPCR) with a molecular weight of 64 kDa, which was cloned from rat pancreatic, gut tumor cell line, and a human pancreatic insulinoma [21]. The GPCR family is known by a long N-terminal extracellular domain (ECD) containing six conserved Cys residues that form a constraint structure required for ligand binding. This receptor is chiefly expressed in pancreatic β-cells, and after activation by GLP-1, it motivates the increase of cAMP and the influx of intracellular Ca^{2+} which stimulates insulin secretion [29].

In the human being, the gene of this receptor is located on the long arm of chromosome 6p21 [21]. Glucagon, GLP type 1, and 2 are encoded by a similar gene and result from post-translational modifications of the proglucagon molecule. Nevertheless, the interaction of the ligand to its receptor is specific with no relevant cross-reactivity with other receptors except for glucagon, which binds GLP-1R with 100-1000 fold less affinity compared with GLP-1. Glucagon family of GPCRs with coupling with $G\alpha_s$ subunit activate adenylyl cyclase (AC)

and increase cAMP levels, but certain members, such as GLP-1R, are able to express owing to additional G-protein subunits [30].

3.4. Structure-Activity Studies of GLP-1

The incretin family (e.g., GLP-1) has up to 40 amino acids (AA) in length, contributing similarities in the AA sequence. The N-terminal domains of GLP-1 form a random coil shape, whereas the central sections of these incretins have an alpha-helical structure. For examining the function and importance of AA residues, alanine scanning experiments have been done by Adelhorst *et al.* They have substituted each residue with alanine and recognized crucial AA that was involved in receptor interaction, except if it was already alanine, in which case it was replaced by its equal in glucagon (alanine[25]) [31]. Obviously, histidine[7], glycine[10], phenylalanine[12], threonine [13], aspartic acid [15], phenylalanine [28], and isoleucine [29] have a potent role in receptor binding, as a noticeable reduction in binding affinity was caused by each alanine replacement. Alanine replacements of these positions lead to a significant decline in cAMP production. Hence, it seems that the N-terminal region is more important for the activation of the receptor, while the C-terminal region is mostly involved in receptor binding [32].

It has been established that the free N-terminal histidine[7] is vital for insulinotropic effects. histidine[7] (position 1) is a key and vital residue for GLP-1R activation and binding and presents different types of GLP-1 agonists. The existence of this AA is essential for DPP-4 cleavage, and alterations of *N*-terminal histidine can result in resistance to proteolysis. Moreover, des-amination, α-methylation, *N*-methylation, and imidazole lactic acid increase the stability of GLP-1 against the DPP-4 enzyme. The whole elimination of histidine[7] caused the loss of activity. The replacement of alanine [8] (position 2) with d-alanine reduces the peptide affinity less than 2-fold. Therefore, the alanine[8] is less important to the peptide's function compared with histidine[7]. In position 3, glutamic acid is critical for receptor interaction, and it does confer good receptor binding affinity and strength. Replacement of glutamic acid[9] with lysine can lead to significant loss of GLP-1 potency. Glycine[10] is essential for the interaction of GLP-1 with its receptor, and all the GLP-1 agonists having glycine[10], threonine[11], phenylalanine[12], threonine[13], and serine[14] sequence, are important for GLP-1 activity [33].

In position 9, the aspartic acid is vital for GLP-1 activity and can be replaced by glutamic acid with a small reduction of affinity. Of note, a d-aspartic acid replacement can lead to noteworthy loss of binding affinity, showing the significance of stereochemical conformation. In position 10, valine can be substituted with alanine, tyrosine, and other hydrophobic amino acids with little loss in activity and affinity. Replacement of position 12 serine with alanine did not change activity and binding affinity. Lysine at position 20 is recognized as a conjugation location for fatty acids, binding directly or via a γ-glutamyl spacer, to extend the half-life by means of elevated albumin binding [33 - 35].

Phenylalanine at position 22 and isoleucine at position 23 is vital for both receptor activity and binding and can be substituted with *hexafluoroleucine* with a slight loss in the activity of GLP-1. Alanine at position 24 and tryptophan at position 25 are both important for the activity of GLP-1. Furthermore, leucine at position 26 is an essential residue for GLP-1 activity and can be substituted with hexafluoro analog with a modest loss of affinity and potency. Valine at position 27 is a vital AA and is existent in both synthetic and natural GLP-1 RA. Glycine at position 29 can be replaced with 2-aminobutyric acid to offer more potent GLP-1 RA with outstanding resistance to proteolysis. This change was significant in the taspoglutide discovery. Arginine at position 30 and glycine at position 31 is vital for receptor activation and binding [33 - 35].

The GLP-1 is quickly degraded by enzymes, particularly DPP-4 at the histidine[7]-alanine[8] position. Hence, the therapeutic value of natural GLP-1 is limited. This trouble can be overcome by the administration of DPP-IV inhibitors or stable GLP-1 analogs. Furthermore, other approaches, including pegylation, *N*-alkylated amino acids, α,α-dialkylated aminoacids, d-amino acids, β-amino acids, stapling, and other structural changes were involved to protect the peptides from proteolysis [33 - 35].

3.5. GLP-1 RAs and DPP-4 Inhibitors

Experiments on native GLP-1 have reported the beneficial effects of this incretin in the treatment of T2D. It is well documented that GLP-1R was not down-regulated even by long-time stimulation with its native ligand and provided 'proof-of-concept' for the pharmacological industry to develop GLP-1R-based treatment [21]. However, due to native GLP-1 short half-life time of 1.5 min and their quick degradation and inactivation by DPP-4 enzyme, T2D subjects would need 24-h administration of native GLP-1 to achieve the antidiabetic effects [30, 36]. Otherwise, developing longer-acting forms of GLP-1 seems to be critical for the improvement of patient safety and compliance [30]. Also, continuous GLP-1 injection is not a practical approach for normalizing hyperglycemia [21]. Two main problems in the administration of GLP-1 are associated with its fast inactivation in blood and its delivery via injection [37]. In this fact, there are two clear options to solve this problem, which include administration of GLP-1 RAs or GLP-1 analogs that are resistant to DPP-IV activity and/or suppress the DPP-1V activity [21, 38].

GLP-1 RAs resistant to DPP-4 degradation have been prepared and can be considered in two categories: long and short-acting GLP-1 RAs, which are different in pharmacokinetic profiles and structure. Because of their peptidic structure, all up to now available GLP-1 RAs are prescribed as subcutaneous injections in the thigh, upper arm, and abdomen [39]. The short-acting GLP-1 RAs (i.e., lixisenatide and exenatide) are resistant to DPP-4 activity, leading to a circulating half-life of about 2–4 h. These GLP-1 RAs are prescribed once or twice daily, and because of their short half-life, they display fluctuations in blood level during the day and hence intermittent activation of the GLP-1 receptors [7, 11, 39]. The long-acting GLP-1 RAs (dulaglutide, liraglutide, albiglutide, and exenatide) continuously stimulate the GLP-1 receptor and can be used with much more intervals

up to once weekly (i.e., exenatide). Because of alterations in pharmacokinetics, their pharmacodynamic profile is also different [23]. Hence, short-acting agents show a significant decrease in gastric emptying, which might participate in the short-term effects on reducing postprandial plasma glucose levels and food intake. The long-acting agents have a potential influence on fasting glucose levels and have a slight effect on gastric emptying, which displays quick tachyphylaxis [40]. The changes in pharmacokinetics, size, and structure of the GLP-1 RAs should be taken into attention when choosing the optimal therapy choice based on both tolerability and efficacy for the individual subjects [5, 38].

The suppression of DPP-1V enzymatic activity has been reported for GLP-1 lengthen action, normalization of hyperglycemia in T2D, and the delay of diabetes onsets in animal models [37, 41].[REMOVED HYPERLINK FIELD] DPP-IV, which exists in the circulation and cell membranes, cleaves GLP-1 to yield the inactive form of GLP-1. Consequently, several alterations have been done to GLP-1 to elevate its biological half-life and subsequently its efficacy *in vivo*. Exenatide (exendin-4), a GLP-1RA, is accessible for the treatment of T2D. This agent is synthesized in the salivary glands of the Gila monster lizard or Heloderma Suspectum. Exendin-4 does not have the DPP-IV recognition site and is an effective insulinotropic compound [21].

Although the clinical use of both DPP-IV inhibitors and GLP-1 RAs increased recently, some drawbacks still persist. The long-term influences of these medicines and their biologically active components are unknown. These derivatives have various physiological functions, such as a vasoactive intestinal peptide, glucagon, neuropeptide Y, glucose-dependent insulinotropic polypeptide, and substance P [37]. Various DPP-IV inhibitors and GLP-1 RAs have been accessible globally since 2006 [42]. These drugs are approved to use as monotherapy or along with other antidiabetic drugs [23].

3.6. Different Type of GLP-1 RAs

GLP-1 RAs are classified as short-acting (lixisenatide and exenatide), and long-acting (liraglutide, albiglutide, and dulaglutide). Injection of GLP-1 receptor agonists to T2D patients was reported to decrease plasma glucose levels to the normal range, even in subjects who had an insufficient response to oral antidiabetic drugs. The effects of GLP-1 receptor agonists observed after injection to T2D patients, resulting in a decreased glucagon levels, reduced HbA1c levels (semaglutide>liraglutide>exenatide>lixisenatide), reduced insulin resistance, elevated satiety, reduced free fatty acid levels, reduced gastric emptying, and reduced body weight (semaglutide >> liraglutide > exenatide > lixisenatide) [43, 44].

3.6.1. Exenatide

Exenatide is approved by the FDA to control hyperglycemia in diabetes, either as a monotherapy or along with other drugs. Exenatide is a synthetic form of exendin-4 and is a potent GLP-1 receptor agonist. This drug is resistant to DPP-4, and its half-life is very more than the natural GLP-1 (about 2.4 hours compared with l.5 min) [45]. It has been established that exenatide decreases postprandial hyperglycemia by suppressing hepatic glucose production, increasing peripheral tissue glucose disposal, delaying gastric emptying, and reducing gastrointestinal glucose absorption. Suppression of glucagon releases by exenatide (which inhibits endogenous glucose production by about 56%) is also known as another mechanism for the reduction of postprandial hyperglycemia [46].

3.6.2. Liraglutide

Liraglutide was approved by the FDA for reduction of blood glucose in diabetic patients that were not controlled by antihyperglycemic agents or lifestyle changes. It is also approved for obesity treatment. Moreover, it has 97% AA sequence homology to native GLP-1. Significant changes of the peptide structure delay its absorption, make it resistant to DPP-4 degradation, and enable reversible binding to albumin. About 2% of liraglutide is free in the blood (not bound to protein) and is metabolized by endogenous peptidases. This agent does not undergo substantial hepatic or kidney clearance. Hence, its half-life is about 13 hours after subcutaneous injection [45]. Treatment with liraglutide markedly improved insulin secretion, protected β-cells against lipotoxicity and liver fat content, reduced oxidative stress, and inhibited inflammation. Vanderheiden *et al.* reported that liraglutide normalized hypoglycemia by improving insulin secretion and did not markedly impact insulin sensitivity or glucagon secretion [47].

3.6.3. Semaglutide

The molecular structure of semaglutide (with a half-life of one week, once-daily administration) is similar to liraglutide, except the alanine in position 2 as a site of DPP-4, has been replaced by α-aminobutyric acid to make it entirely resistant to DPP-4. The fatty acid side chain binding seems to be stable, has a slower clearance and supports once-weekly dosing. This agent is in clinical development for non-alcoholic fatty liver disease (NASH) (phase 2) and obesity (phase 3) treatment. Moreover, phase 3 clinical trials in diabetes are ongoing with semaglutide injection. Semaglutide injection significantly normalized glucose levels, reduced body weight, and cardiovascular risk. This drug showed greater weight loss compared with liraglutide and other GLP-1 RAs. Likely, semaglutide affected various genes involved in inflammation and atherosclerosis [44].

3.6.4. Lixisenatide

Lixisenatide (with a half-life of □3.5 hours, 2–3 times daily administration) is currently being synthesized to treat T2D [48]. Lixisenatide was reported to potentially normalize insulin secretion, reduce β-cell apoptosis, increase insulin secretion, reduce postprandial glucose (PPG), delay gastric emptying, and preserve β-cell function. Moreover, this drug increased the biosynthesis of insulin and stimulated β-cell proliferation, proposing the potential to change the progression of T2D. Lixisenatide is commonly used in combination with basal insulin [48].

3.6.5. Dulaglutide

Dulaglutide (with a half-life of 90 hours, once-weekly administration) consists of two GLP-1 analogues with identical AA sequences, and are covalently linked by modified human IgG Fc. This change causes less kidney clearance due to the large size of the dulaglutide, and consequently increases the duration of action [49]. Dulaglutide decreases glucagon secretion increases insulin secretion, and delays gastric emptying. Dulaglutide injection decreases fasting and postprandial glucose levels in T2D patients. Dulaglutide may elevate the risk of thyroid C-cell cancer and pancreatitis. Hence, in T2D patients with the risk of pancreatitis development, the administration of this drug should be stopped. Furthermore, this drug is not recommended in cases with severe gastrointestinal (GI) disease (i.e., colitis, inflammatory bowel syndrome, GI perforation, GI obstruction, pseudomembranous colitis, Crohn's disease, ileus, ulcerative colitis, gastroparesis, and/or undiagnosed GI bleeding) [50].

3.6.6. Albiglutide

Albiglutide (half-life of 5 days, once-weekly injection) is a modified form of GLP-1 fused to human albumin and has 97% AA sequence homology to native GLP-1. At the position of 8, alanine is replaced by glycine and this change leads to its resistance to DPP-4 proteolysis. Because of limited knowledge in severe kidney damage, it is proposed that this drug should be administrated with care in such patients. Due to the large molecular size, this incretin has not interacted with drug-metabolizing enzymes. Like other types of GLP-1 RAs, this drug reduced fasting glucose decreased PPG, stimulated insulin secretion, inhibited glucagon secretion during hyperglycemia, and delayed gastric emptying [51].

3.7. Administration of GLP-1 Receptor Agonists in A Diabetic Patient Infected with COVID-19

Hyperglycemia is proved as the main risk factor for COVID-19 infection [52]. Based on numerous reports, hyperglycemia can aggravate COVID-19 pneumonia and increase the hospitalization rate [53, 54]. It has been proposed that GLP-1 agonists have a useful effect on diabetes patients with or without COVID-19, owing to their several beneficial properties on hyperglycemia, obesity, and extreme inflammation-induced acute lung damage [55].

Lockdown during the COVID-19 is associated with unbalanced nutrition, low physical activity, and diabetes risk. Hence, GLP-1RAs can be favorable for managing body weight and hyperglycemia during long COVID-19 lockdown times. The GLP-1RAs, especially semaglutide and liraglutide, have useful properties on inflammatory mediators and obesity, and both are related to severe COVID-19 infection [56]. Furthermore, GLP-1 RAs motivated the synthesis of the surfactant proteins in the lung, which show immune-modulating protective and anti-inflammatory effects against viral and bacterial infections [55].

Inflammation is the main cause of COVID-19 severity and death [57]. A bidirectional relationship between hyperglycemia and chronic inflammation had been described for chronic complications of diabetes. Severe pneumonia in diabetes with COVID-19 is related to cytokine storm and hyperglycemia. An improvement of hyperglycemia management with lower blood concentration of IL-6, lactate dehydrogenase (LDH) activity inhibition, and high sensitivity C-reactive protein (hsCRP) have been observed in COVID-19 patients [58]. However, GLP-1 RAs show potential anti-inflammatory effects, and lung protection should be assessed since preclinical experiments have proposed that GLP-1 RAs may reduce lung inflammation and preserve lung function in animal models with experimental lung damage and respiratory syncytial virus infection [1]. Various preclinical experiments performed in animal models with experimental induced lung injury established that GLP-1 agonists alleviate lung inflammation by the inhibition of nuclear factor kappa B (NF-κB) signaling pathways and cytokine release [59]. However, GLP-1 RAs may exacerbate anorexia and should be stopped in severely ill cases with COVID-19 due to a potential risk of aspiration pneumonia. Accordingly, diabetic patients with COVID-19 infection who use GLP-1 agonists should be carefully monitored and provided with sufficient fluid consumption and a regular diet to prevent the risk of dehydration [54].

3.8. Glucose Lowering Affects GLP-1

T2D is recognized by both abnormal insulin secretion and peripheral insulin resistance [60]. Sulfonylurea drug is used as the current treatment for the pancreas islet cell impairments, which is the first-line of therapy against inadequate insulin release. Nevertheless, these agents increase insulin release independent of plasma glucose levels and may cause potential hypoglycemia [61]. Moreover, as obviously established in the U.K. Prospective Diabetes Study, the capability of these drugs to motivate insulin secretion reduces in a long time, probably showing a worsening effect on β-cell function [61]. In this respect, there is an essential need to find new medicines for treating the β-cell function of T2D. As mentioned above, antidiabetic properties of GLP-1, including insulin release and the increase of β-cell mass and survivals, accompanied by the suppression of food intake and glucagon secretion, could be effective for β-cell therapies. Both intravenous and subcutaneous injection of GLP-1 in T2D subjects have been revealed for reducing blood glucagon levels, stimulating insulin secretion, improving overall glycemic, and suppressing gastric emptying [60][REMOVED HYPERLINK FIELD]. It has been reported that GLP-1 was able to reduce plasma glucose levels even in subjects with long-standing and severe T2D and even in subjects who no longer responded to SUs [21]. One week of administration of GLP-1 before dinner, lunch, and breakfast markedly normalized PPG and lipid levels [62]. In another experiment, overnight intravenous administration of GLP-1 reduced PPG and fasting glucose concentration to near-normal levels in T2D subjects [63]. Short and long period administrations of GLP-1 and GLP-1 RAs significantly raise insulin release and improve hyperglycemia in T2D. Their long-term properties on animals' β-cells are causing an increase of β-cell mass by elevating its differentiation and proliferation in both diabetic and healthy rodents [40].

The hypoglycemic properties of DPP-4 inhibitors are mainly mediated by suppressing the postprandial decrease of

GLP-1, thus prolonging and improving insulin release and glucagon inhibition [64]. DPP-4 inhibitors lead to 1.5 – 3.0-fold elevation of active GLP-1 level in blood. This rise is low in comparison with the therapeutic levels of GLP-1 RAs, which are about a 10-fold rise in GLP-1 levels. Besides elevating GLP-1 concentration, experiments in humans and animal models show the presence of non-classical glucose-reducing mechanisms of DPP-4 inhibitors [65]. These include: 1) suppression of DPP-4 activity in the gut, which enhances GLP-1-motivated activation of autonomic nerves and high portal GLP-1 concentration that inhibits liver glucose production, 2) suppression of DPP-4 activity in the pancreas, which enhances islet cell-produced GLP-1, directly inhibiting glucagon and stimulatinginsulin secretion, 3) decreased inactivation of DPP-4 substrates other than GLP-1, which may increase pancreas function and lead to other effects [23, 64, 65].

3.9. Lipid-Lowering Effects GLP-1

High triglyceride levels have been well accepted as a risk factor for insulin resistance. Diabetic patients are recognized by elevated circulating low-density lipoprotein cholesterol (LDL-C) and triglyceride as well as decreased high-density lipoprotein (HDL) levels [66]. It should be noted that GLP-1 can normalize some of these changes, besides its crucial role in intestinal lipid metabolism [67 - 73]. A previous study reported that GLP-1 agonists reduced liver VLDL overproduction and de novo lipogenesis in animal models [72], which led to a decrement of lipid accumulation in the liver and circulating VLDL-bound triglyceride and plasmatic ApoB-100 levels [74]. Administrations of DPP-IV inhibitors and GLP-1 RAs have been examined for normalizing postprandial and basal lipaemia in human and animal models [74, 75]. Hepatic and intestinal lipoproteins and lipids metabolism are the two main factors affecting lipaemia. Numerous experiments propose that GLP-1 may affect the intestine with direct local action and indirect modulation on the liver. GLP-1 RAs can decrease the activity of jejunal microsomal triglyceride transfer protein and jejunal triglyceride availability in animal models. Moreover, decreased chylomicron levels were because of decreased production rather than elevated clearance of these compounds. Therefore, DPP-IV inhibitors and GLP-1 RAs in humans and animal models lead to a direct decline in intestinal lipoprotein synthesis so that less triglyceride and less ApoB-48 reached circulation after oral lipid supplementation [69, 72]. It has been shown that Sitagliptin or Exendin-4 also decreased postprandial free fatty acid concentration in human subjects [76, 77]. GLP1 also directly changed triglyceride homeostasis by the declining liver and adipose tissue lipid accumulation [66].

3.10. GLP-1 as an Energy Sensor

The GLP-1 mainly exists in L-cells of the colon, but food reach the colon long after a meal (about 1 h). However, the peak of insulin reaches after 15 min [25]. The small intestine absorbs a high amount of nutrients, which makes it unlikely for colonic GLP-1 to participate in the incretin effect. Furthermore, it has been reported that increased concentration of GLP-1 detected in germ-free animals did not contribute to normalized glucose homeostasis, which proposes that colonic-produced GLP-1 has other functions [78]. It has been shown that expression of GLP-1 from colonic L-cells acts as an energy sensor to reduce intestinal motility for allowing more time for food harvesting in the small intestine. This is probably an interesting benefit whereby in energy scarcity, the small intestinal transit is slow, causing more time for food extraction, while in energy sufficient condition, it has a benefit for making quick transition to eject potential pathogenic microbes. Moreover, this is a solid agreement with the orexigenic properties of insulin-like peptide 5 (INSL5) released from colonic L-cells and contrasts the anorexic effects of GLP-1. Supportively, anorexic subjects have elevated GLP-1 concentration and lower intestinal transit [25, 27]. Lee *et al.* reported that colonic INSL5 stimulates liver[REMOVED HYPERLINK FIELD] glucose output, which is also in line with the hypothesis of colonic L-cells function as energy sensors involved for adaptation to famine [79]. Hence, colonic L-cells might act as energy sensors and contribute to low energy concentration by elevating appetite and liver glucose production through INSL5 and reducing intestinal transit through GLP-1 [25].

3.11. GLP-1 Control of Appetite and Weight

The potential effects of GLP-1 on feeding behavior were reported in previous studies. Although these effects may be in part associated with intestinal motility, it appears that GLP-1 has a direct effect on hypothalamic feeding centers as GLP-1 receptors, which are presented in certain nuclei within the hypothalamus [80]. It has been established that acute administrations of GLP-1 can lead to satiety and decrease food consumption in humans and animal models [80]. GLP-1 antagonist exendin 9-39 supplementation in animal models abrogates the effect of GLP-1 and can itself stimulate weight gain. Long-term treatment of Zucker rats with exendin 4 decreased calorie intake and reduced weight gain [81]. In T2D subjects, administration of short-term GLP-1 or exendin-4 curbed food intake and appetite besides its insulinotropic effects [81, 82].

CONCLUSION

The DPP-IV inhibitors and GLP-1RAs are valuable choices for the treatment of T2D as monotherapy or adjunctive therapy. Furthermore, there is huge evidence documenting the useful effects of these agents in overweight or obese subjects or those who are suffering froma high risk of hypoglycemia-usual comorbidities of T2D. Clinical trials established the superiority of GLP-1 RAs to other anti-diabetes agents in the reducing of blood pressure, glucose levels, HbA1c, and weight loss, without hypoglycemia risk. However, selecting among the available GLP-1R agonist and DPP-IV inhibitors will likely depend on reaction to adverse effects, cost, and patient preferences. GLP-1 agonists have been established to be effective and safe anti-hyperglycemia and anti-inflammatory effects. However, COVID-19 is a new unknown viral infection that requires more clinical trials to use these agents in diabetic patients with severe COVID-19 infection in the view of increasing the safety and convenience of therapy.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial, or otherwise.

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