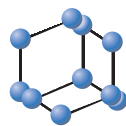


REVIEW ARTICLE

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SCIENCE

Clinical Analysis of Resemblance and Dissimilarities of Glucagon-like Peptide-1 Receptor Agonists: Therapeutic Approach Towards the Management of Diabetes Mellitus



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Abstract: One of the classes of injective antidiabetic agents includes Glucagon-like peptide-1 receptor agonists (GLP-1RA) which ameliorate glycemia and numerous atherosclerosis-related factors in individuals prone to Type 2 diabetes mellitus (T2-DM) disorder.

Methods: The review paper targeted the role of GLP-1RA in managing DM. The literature published during the last decades in several data-based searches (PubMed, Scopus, ScienceDirect) was reviewed and compiled the therapeutic uses of GLP-1 RA in the management of DM. In this review, we have discussed GLP-1RA and its role in the management of diabetes mellitus.

Results and Discussion: Disrupted homeostasis marks insulin resistance and β -cell deterioration as two major indications of T2-DM. β -cells failure (~80% of functioning of β -cell) and insulin resistance in the liver and muscles are primarily susceptible to physiological defects. GLP-1RAs if administered for a prolonged period also cause a loss in weight through the activation of receptors of GLP-1 found in hypothalamic satiety centers which control appetite and decrease intake of calories. They not only assist in controlling blood glucose but also improve β -cell function and post-diabetic conditions namely hyperlipidemia, obesity, and hypertension.

Conclusion: It was concluded that GLP-1RA has a new therapeutic approach to the management of DM. Hence, GLP-1RA provides distinctive and innovative evolution for the treatment of T2-DM.

Keywords: GLP-1, type 2 diabetes mellitus, β -cells, insulin, exenatide, incretin mimetics.

1. INTRODUCTION

One of the classes of injective antidiabetic agents includes Glucagon-like peptide-1 receptor agonists (GLP-1RA) which ameliorate glycemia and numerous parameters associated with atherosclerosis in individuals prone to Type 2 diabetes mellitus (T2-DM) [1, 2]. There are no episodes of hypoglyce-

mia by GLP-1RA when given in combination therapy with thiazolidinediones or metformin, but the incidence of hypoglycemia may be minimized by sulfonylurea or insulin. Various metabolic effects of GLP-1RA include decreased gastric emptying, obstructed food intake, modulation of rodent β -cell proliferation, induced glucose-dependent insulin secretion, and elevated natriuresis and diuresis. Besides, GLP-1 also possesses neuroprotective effects, cardioprotective effects, apoptosis, and decrease inflammation. Similarly, GLP-1 acts by binding to GLP-1R, thus increasing insulin secretion when oral and intravenous glucose is administered [3-5]. DM is a metabolic disorder caused by restricted or entire deficit of in-

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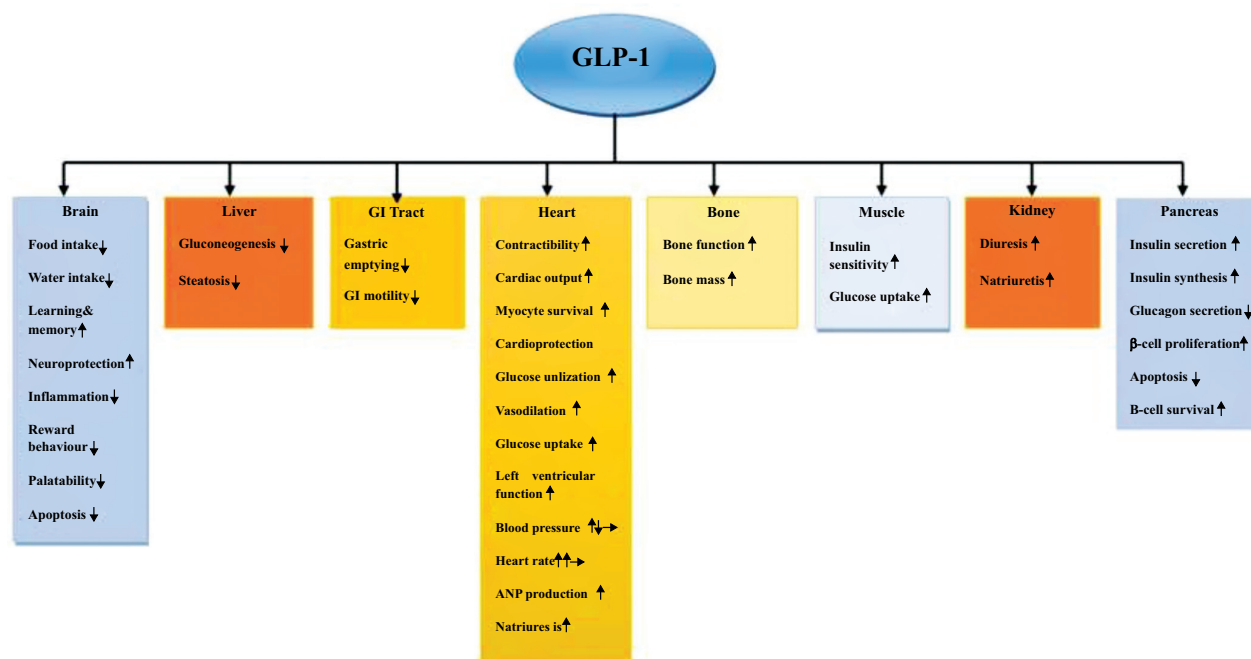


Fig. (1). Pharmacological action of GLP-1. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

ulin secretion or insulin response which results in impairment of the metabolism of lipids, carbohydrates, and proteins resulting in chronic hyperglycemia. Disrupted homeostasis marks insulin resistance and β -cell deterioration as two major indications of T2-DM. β -cells failure (~80 percent of β -cell functioning) and insulin resistance in the liver and muscles are primarily susceptible to physiological defects [6, 7]. T2-DM is depicted by insulin unresponsiveness due to insulin resistance, diminished insulin formation, and ultimately β -cell failure in the pancreas. The conditions reduce glucose transport into the muscle cells, fat cells, and liver. Hyperglycaemic episodes stimulate lipolysis. Altered α -cell function elicits hepatic glucose and glucagon levels that rise during fasting are not depleted with meals. Hyperglycemia results from inadequacy in insulin levels and enhanced insulin resistance. The incretins act as significant mediators of insulin release and about GLP-1, glucagon inhibition. A greater class of individuals having Type 2 diabetes are obese having central visceral adiposity. Thus, advancing in Type 2 diabetes, the adipose tissue plays an essential role [6, 8-11]. The adverse effects associated with GLP-1RA include gastrointestinal events such as nausea, vomiting, and diarrhea. Trials reports showed nausea of mild to moderate form and tend to lessen with time. GLP-1 assists in the glucose-dependent relative release of insulin from β -cells of the pancreas [12-15]. This response is mediated by a prompt, kinase phosphorylation-dependent mechanism; however, gene expression is not altered [16, 17]. Exogenous GLP-1 when administered intravenously to people suffering from T2-DM tends to maintain the normal fasting glucose level by lowering the plasma glucose concentration, even in cases that showed insufficient response to oral anti-hyperglycaemic agents [7, 16, 18, 19].

In this review paper, an attempt was made to highlight the therapeutic approach towards the GLP-1RA in the treatment of T2-DM based on clinical trials and also discuss the mechanism behind the GLP-1RA.

2. MATERIALS AND METHODS

For the assessment of the function of the GLP-1RA in treating diabetes mellitus, the literature present in various database search engines like Science Direct, PubMed, and Scopus was studied. The research or review papers published in the last decades (2010-2022) related to the selected topic were searched by using keywords such as, "Glucagon-like peptide-1 (GLP-1) receptor agonists". Several articles were found and relevant papers include the GLP-1RA and its function in diabetes mellitus (DM). The selected literature was reviewed and functions of GLP-1 RA in DM were discussed.

3. PHARMACOLOGICAL ACTIONS OF GLP-1

Exogenous GLP-1 on administration intravenously to people suffering from T2-DM tends to maintain the normal fasting glucose level by lowering the plasma glucose concentration, even in cases that showed insufficient response to oral antihyperglycaemic agents [20-23]. The pharmacological actions of GLP-1RA are summarized in Fig. (1). Exogenous GLP-1 administration to people with T2-DM showed multiple effects such as lowered A1C, steady gastric emptying, elevated satiety, low free fatty acid concentrations, reduced glucagon concentration, enhanced insulin sensitivity, and reduced body weight [2]. Recently, US FDA has accepted the 5 GLP-1 RAs namely exenatide, dulaglutide, liraglutide, lixisenatide, and albiglutide which are briefed in Table 1.

4. GLP-1 MECHANISM OF ACTION

GLP-1 has several actions such as enhancing insulin secretion & diminishing glucagon which results in the depletion of glucose formation [24]. Administration of a pharmacological dose of GLP-1 can improve incretin defects. However, weight loss and decreased appetite are the effects exerted on the brain. Somatostatin activity is enhanced by sodium-glucose cotransporter-2 (SGLT-2) [25]. Liraglutide elevates intracellular cyclic adenosine monophosphate (cAMP) by activating GLP-1R triggering insulin secretion and reducing postprandial glucagon [26]. Glucagon triggers definite G protein-coupled receptors (GPCR) on pancreatic β -cells, which ultimately activate the adenylate cyclase and intensify the glucose-reliant release of insulin from β -cells in the pancreas. Promoting insulin release enhances the release of insulin

and diminishes glucagon release in a glucose-dependent relative mode *via* mimicking incretin. Dulaglutide mediates steady motility in the gastric region and reduces endogenous glucose synthesis, and food intake [27-29]. The detailed mechanism is summarised in Fig. (2). As depicted in Fig. (2), signaling of GLP-1 in pancreatic β -cells elicits metabolic/bio-energetic reprogramming leading to excessive glycolytic/higher ATP-making phenotype. This metabolic reprogramming plays a definitive role in mechanism(s) triggering stimulation of GLP-1 and hence insulin secretion. Studies revealed an essential mechanism that discusses GLP-1 analogues potentiate glucose homeostasis in type 2 DM patients, disclosing latest aspects that lead to the advancement of the latest therapeutic strategies [16, 30]. Fig. (2) depicts the function of GLP-1 RA in preventing T2DM.

Table 1. FDA Approved available GLP-1RA.

Study	Drug	Adverse Drug Reactions	Clinical Applications
Tran <i>et al</i> (2017) [58]	Exenatide	- Nausea, Diarrhoea, Vomiting, Infection in the urinary tract, - Nasopharyngitis, Infection Upper respiratory tract, Viral gastroenteritis, Arthralgia, Sinusitis, Back pain, - Hypertension, Cough, Bronchitis, Pain in extremities, musculoskeletal pain.	- Stimulate insulin production - Reduce release of postprandial glucagon - Reduce gastric emptying rate and reduced appetite - Reduce nutrient absorption rate in the bloodstream.
Davies <i>et al</i> (2015) [59]	Liraglutide	- Nausea, - Vomiting, - Diarrhea	- Enhance glucose-dependent insulin release and inhibit levels of postprandial glucagon - Reduces HbA1c in people with T2-DM.
Trujillo <i>et al</i> (2014) [60]	Albiglutide	- Infections in the upper-respiratory system - Diarrhea, - Nausea, and injection-site reactions	- Lowers glycosylated haemoglobin (A1C) and reduces weight - Inhibiting secretion of glucagon - Hindering rate of gastric emptying, and favouring satiety
Thompson <i>et al</i> (2015) [61]	Dulaglutide	- Nausea, - Vomiting, - Diarrhea, and dizziness	- Augments secretion of insulin and lessens the release of glucagon - Reduces motility in the gastric region and supports satiety. - Pre-prandial and postprandial levels of glucose in the blood are reduced
Anderson <i>et al</i> (2016) [62]	Lixisenatide	- Nausea, - Vomiting, - Diarrhea	- Reduce postprandial glucose (PPG) - Suppresses inappropriate glucagon secretion - Stimulates glucose-dependent insulin secretion - Enhances concern of satiety by reducing the rate of gastric emptying.

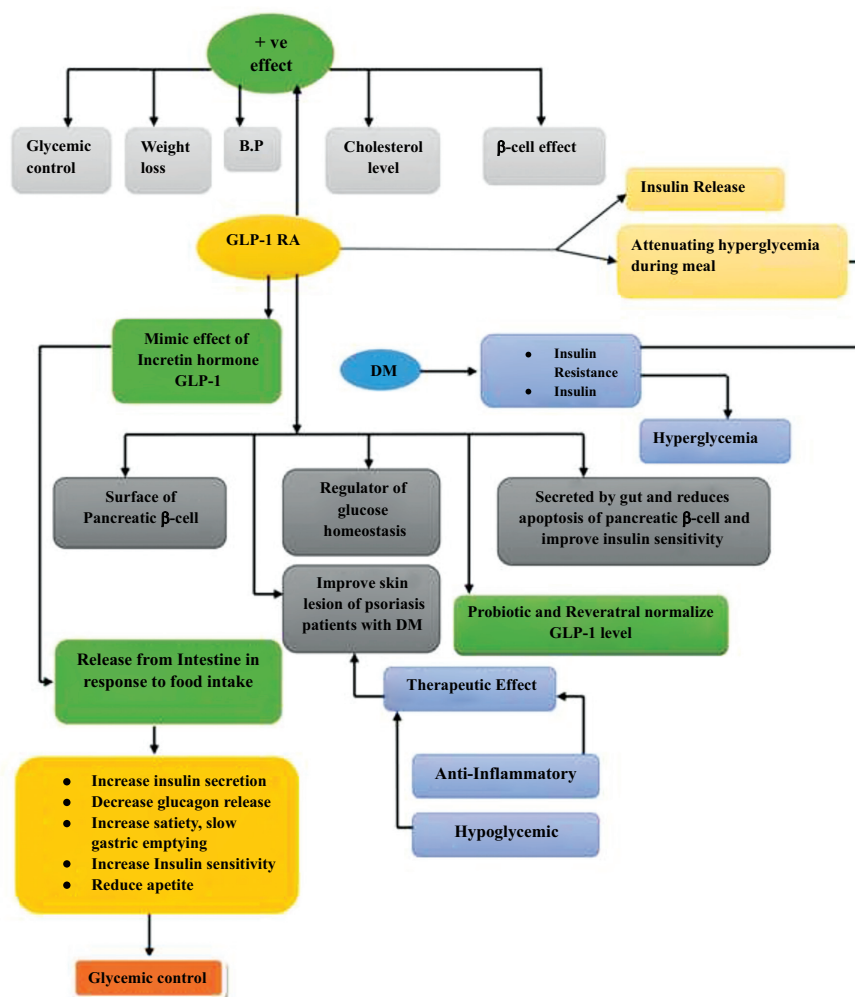


Fig. (2). The function of GLP-1 RA in preventing T2DM. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

5. GLP-1 RA AND TYPE 2 DM - CLINICAL ANALYSIS

The incretin system secretes a hormone namely GLP-1 that mediates several gluco-regulatory consequences, namely glucose-dependent relative release of insulin and reduction of glucagon secretion, these outcomes deteriorate in participants having T2-DM. Clinical data from over a decade implies that this deficiency could be treated by using GLP-1RAs as a tool in T2-DM. Clinical trial studies using GLP-1RAs subcutaneously implicate that such drugs have glycated hemoglobin (HbA1c) reducing tendency, a congenitally less possibility for hypoglycemia, and decreased weight of the body. GLP-1RAs have been found safe when undergoing cardiovascular trials and three of them reported a decreasing threat of main adverse cardiovascular episodes (MACE) in cases with the confirmed cardiovascular disorder or a major threat [31, 32]. The frequently harmful effects susceptible to GLP-1RAs are GIT effects, which occur at the initial stage and diminish over time. Several research studies regarding GLP-1 RA are discussed in this section. For example, Stephen *et al.* reported that majority of patients opt for oral medicines, the formulation of GLP-1RA orally is a beneficial strategy for enhancing

the prophylaxis of T2DM. Semaglutide, being the recently approved first oral GLP-1RA, is the co-formulation having penetration enhancer that exhibits the capability to enhance the usage of GLP-1RAs in the clinical procedure [33]. Several studies reported the effectiveness of GLP-1RAs, their function in the management of T2-DM, and the potential of GLP-1RAs is also summarized. Regarding the effectiveness of GLP-1RAs, Alatorre *et al.* compared adherence (proportion of days covered [PDC]), treatment, and persistence prototypes between T2-DM people by introducing GLP-1 RAs. T2-DM patients were given dulaglutide, albiglutide, and exenatide once a week, exenatide and liraglutide two times a day (BID). It was found that mean adherence was considerably greater for dulaglutide concerning exenatide and liraglutide. The proportion of participants attaining PDC ≥ 0.80 was noteworthy more for dulaglutide in contrast to exenatide and liraglutide. The mean days on therapy for all matched participants was considerably greater for dulaglutide in relation to exenatide and liraglutide. A considerably lower percentage of dulaglutide patients withdraw treatment in contrast to exenatide and liraglutide. It was concluded from the above study, significantly greater adherence, higher persistence, and

less discontinuation were shown by Dulaglutide inhibitors compared to exenatide or liraglutide when examined after a 6-month follow-up [34]. On the other hand, Overgaard *et al.* reported that Semaglutide, GLP-1 analog, had been accepted for improving type 2 DM. It was observed from the above study, that the potency-attuned efficient GLP-1RA levels raised after replacing semaglutide from another GLP-1RA and decreased from ~0.3 to ~0.8 %- points for HbA1c and body weight from ~2 to ~4% by administrating 1.0 mg of semaglutide. Limited depletion in HbA1c was noticed after substitution to semaglutide 0.25 mg from liraglutide 1.2/1.8 mg or dulaglutide 1.5 mg. Thus, it was concluded that the exposure-response model substituted semaglutide with exenatide, dulaglutide, or liraglutide sustained-release for more depletion in HbA1c and body weight [35]. Earlier minor depletion in outcomes, when switched to semaglutide 0.25 mg, might be neglected by starting semaglutide therapy at a larger dosage. Similarly, Roth *et al.* explained the efficiency, tolerability, and assurance of a GLP1RA determined in hypothalamic obesity (HO) patients. Participants were given once-a-week injections by subcutaneous route of exenatide 2mg or placebo for 36 weeks randomly. The fundamental efficiency endpoint was measured at 36-week presenting a change in BMI. 42 individuals were given exenatide 2 mg (ExQW) or a placebo randomly. Patients were 5±2 years post-diagnosed and had progressed HO. In studies, the consequence of a 36-week ExQW *versus* placebo on percentage BMI was insignificant; though total body fat mass decreased. There was a convincing decrement in waist circumference. All participants administered with placebo had enhanced percent adipose tissue, while 50% examined with ExQW had decrements. No significant changes were observed in mean HbA1c, glucose tolerance, and serum lipid levels post-therapy. ExQW was well accepted. The utmost adverse effects were short-term gastrointestinal effects. It was concluded that the GLP1RA is an assured and safer treatment approach to potentiate or manage HO in young adults and children [36]. In another research, Santiago Tofé *et al.* estimated the effectiveness and adequacy of available GLP-1 RA agents in T2-DM patients after a tedious follow-up in a real-world setting. It was observed from the study that 735 patients were of an average age group of 59.7 years, the extent of diabetes was about 9.01 years, 8.18% HbA1c, and 38.56 kg/m² BMI. The average observation was for 18.97 months. All HbA1c, fasting plasma glucose (FPG), and BMI were approximately decreased from baseline and managed during the follow-up. About 13.81% of patients were prone to gastrointestinal (GI) adverse effects when evaluated after the first follow-up, 37.07% of people withdrew from the GLP-1 RA therapy, and 38.63% did not reveal much efficacy. Thus, GLP-1 RA agents are majorly recommended for obese participants with prolonged and inadequately controlled T2-DM. All agents recommended GLP-1 RAs with considerably lower FPG, HbA1c, and BMI. GI adverse effects were shown in fewer patients. It was concluded from the study that a larger portion of patients did not find efficient and/or disrupted GLP-1 RA treatment [37]. In the same way, Razavi *et al.*, 2020 reported that clinical trial studies have illustrated their efficiency concerning other oral antihyperglycemic agents, gained body weight, and improved hypoglycaemic episodes. Both Dipeptidyl peptidase-4 (DPP-4) inhibitors and GLP-1 RAs proved their efficacy in cardiovascular outcome tests, while certain

GLP-1 RAs were reported to considerably lower the chances of severe harmful cardiovascular episodes in T2-DM patients with pre-defined cardiovascular disorder. Various clinical trial studies have precisely differentiated between the efficiency and safety of GLP-1 RAs and DPP-4 inhibitors. These findings have typically revealed that the GLP-1 RA showed better management of glycemia and weight reduction compared to the DPP-4 inhibitor. Both treatment schedules tend to decrease the occurrence of hypoglycemia, but GLP-1 RAs were prone to more GI adverse effects [17, 38]. In some studies, evaluation was done by substituting DPP-4 inhibitors in comparison to GLP-1RAs and the latter showed enhanced glycaemic control and weight reduction post-substitution [19]. Present clinical guidelines depict that both DPP-4 inhibitors and GLP-1RAs are associated with the management of glycemia in T2DM patients. GLP-1RAs might be chosen over DPP-4 inhibitors among participants as they showed more decreased HA1c and reduction of weight in the clinical trials. Amongst participants with pre-defined cardiovascular disease, GLP-1 RAs with validated cardiovascular benefits are proved in addition to metformin therapy [17]. A systematic investigation of the literature was conducted using several databases. Random controlled trials were performed that compared exenatide and liraglutide with once-a-week GLP-1RAs in type 2 diabetes. The results were investigated by glycaemic control, body weight reduction, hypoglycemia, and GI adverse effects. The output indicated that 5531 patients were examined under eight trials. Dulaglutide, taspeglutide and Exenatide-long-acting release (LAR) showed more favorable results than exenatide BID in decreasing glycosylated HbA1c and FBG amounts and attaining HbA1c targets. Liraglutide was as efficient as dulaglutide and more significant than exenatide-LAR and albiglutide in glycemia management. Once a week, GLP-1RAs, exenatide, and liraglutide showed the identical prevalence of hypoglycemia and GI adverse events. It was observed that once a week administered GLP-1RAs were more efficient in glycaemic control and identically potent in reducing body weight than exenatide administered two times a day but was substandard to liraglutide in managing these 2 factors (dulaglutide was equivalent to liraglutide in glycaemic control). GLP-1RAs administered once a week, exenatide and liraglutide had similar chances of causing AEs [39]. Similarly, Patel *et al.* reported a literature review to examine the potency data of GLP-1 RAs administered once a week (QW) in terms of controlling glycemia, cardiovascular events, decreased body weight, and possible renal defensive actions to reinforce pharmacy professionals and various healthcare workers to guide patients about the treatment. In this detailed review, 31 clinical trials were conducted taking into consideration the Phase 3 clinical trials of the QW GLP-1 RAs dulaglutide, exenatide controlled-release, and semaglutide administered subcutaneously. All QW GLP-1 RAs were preferable to placebo for lowering HbA1c and weight of the body. Last, in QW GLP-1 RA *versus* insulin tests, all QW GLP-1 RAs were as potent as insulin, primarily when body weight and hypoglycemia were also expressed. QW GLP-1 RAs are approaching a significant curative preference for T2-DM patients as they emerge as an asset apart from just glycaemic control. Their possible potency differences must be taken care of while prescribing them to the patients. Thus, GLP-1 RAs are attributed to a variety of profits for T2-DM patients that are confirmed through their place

within the therapy rules of diabetes [40]. Potts *et al.* demonstrated the actions of GLP-IRAs in comparison to placebo and different antidiabetic drugs on the reduction of body weight in obese or overweight T2-DM patients. Meta-analyses were conducted in pairs and mixed therapy comparisons were accompanied to assess the variable changes in weight after six months duration between each comparator and the GLP-IRAs. Among 27 trials in the mixed therapy comparison, the GLP-IRAs were primarily used in reducing weight; exenatide 2mg/week, liraglutide 1.2mg, exenatide 20µg; and liraglutide 1.8mg with respect to placebo. No significant differences were noticed amongst various GLP-1 RAs relative to weight loss. This review implies that treatment with GLP-IRAs is involved in the diminution of weight in obese or overweight T2-DM participants. No considerable difference in reduction of weight was assessed amongst various GLP-1 Ras [41]. Similarly, clinical benefits of GLP-1R agonists were appreciated from largely randomized clinical trial data which were performed to evaluate cardiovascular safety. In placebo-controlled clinical studies, improvement of renal biomarkers was seen with effects supposedly being independent of glycemic control actions. In this review, GLP-1R agonist's action on the metabolism of glucose and physiological functions of the kidney, and the mechanisms both direct and indirect of renal protection of these drugs were described [42]. In another trial, 126 obese and overweight T2-DM people were the part of initial analysis. Among these, 13 stopped dulaglutide (DU) owing to gastrointestinal side effects after a mean follow-up of 6 months and 18 months duration of regular treatment was achieved by 65 of them. At 6 months, a remarkable reduction of mean HbA1c by -0.85% exhibited a steady value during the follow-up of 18 months. A moderate loss in weight over time was seen with these results. Logistic regression analysis confirmed the defensive outcome of obesity against discontinuation of the drug. Along with the benefit of a once-weekly regime, at an 18-month follow-up, a major chunk of participants on DU medication achieved glycemic targets in comparison to those on liraglutide (LIRA). These findings suggested the beneficial outcome of DU as an add-on to metformin (MET) or MET added to insulin secretagogues is promising and lasting, specifically in the view of obesity and bigger HbA1c impairment although it has its limitation in the form of its retrospective design and inability to titrate LIRA to its highest dose [43]. Likewise, Neil *et al.*

studied the double-blind, randomized, active-controlled and placebo, multicentric, phase 2 trial. The researchers collaborated with 08 countries having 71 clinical locations. Non-diabetic participants with a BMI of 30 kg/m² or more were selected for the project. Participants (6:1) were randomly distributed to the active treatment group (*i.e.* semaglutide (started at 0.05 mg/ day and increased proportionally each 4 weeks) or liraglutide (started at 0.6 mg/ day and increased by 0.6 mg/ week)) or matching placebo group employing a block size of 56. All the dosages were given through a subcutaneous route once daily. All semaglutide groups *versus* placebo were noteworthy and continued to be significant even after being adjusted for multiple tests. The mean weight of the body decreased for 0.2 mg or more of semaglutide in contrast to liraglutide were all considerable, and weight loss of 10% or more was estimated to have occurred in 10 percent of participants who were given a placebo in comparison to 37-65% who were administered 0.1 mg or more of semaglutide. All dosages of semaglutide were well accepted, with no newer safety worries [44]. Another study analyzed 932 eligible participants having T2-DM who were prescribed GLP-1 RA between the index date of September 2016 to July 2018 for the first time. The average age was 63.8 years and 56.0% were males. Dulaglutide (65.7%) or liraglutide (29.1%) were the index GLP-1 RA of most people. Usual comorbidities associated were hypertension, obesity, dyslipidemia, nephropathy, and retinopathy. Average hemoglobinA1c (HbA1c) levels were reduced above 6 months after GLP-1 RA commencement. A decrease in mean body weight, triglycerides, body mass index, low-density lipoprotein, total cholesterol, and attuned urinary albumin occurred above 6 months. Anti-diabetic drug usage reduced after GLP-1 RA commencement, although non-antidiabetic therapy prescribing underwent little or no change. Thus, prominent advantages of GLP-1 RA management are evident in the study for T2-DM, including betterment in HbA1c, blood lipid profile, and body weight (28) [45]. Rapuch *et al.* reported the major result was treatment perseverance with no discontinuity (gap after index management prescription ≥ 2 -fold the likely period of that medication) or change over new non-index glucose-dropping prescription prescribed ≤ 30 days before or after index treatment discontinuity [46]. Some of the significant work carried out by the study of the role of GLP-1RA in the management of DM is summarized in Table 2.

Table 2. Functions of GLP-1 RA in prevention of T2-DM.

Study	GLP-1 Category Drug/dose/Duration of Action	Route of Administration	Adverse Effects	Remarks/Conclusion
Linnebjerg <i>et al.</i> , 2008 [63]	Exenatide three management categories (placebo, 5 µg and 10 µg b.i.d. sc for 5 days each)	Subcutaneous injection	Nausea, vomiting, headache, diarrhea, and hypoglycemia	- Sustained reduction in HbA1c, - Decrease in weight of the body and stringent postprandial control of glucose.
Buse <i>et al.</i> , 2004 [64]	Exenatide 5 µg dose b.i.d. for 26 weeks	Subcutaneous	Nausea, vomiting, and recurrent adverse episodes were usually of gastrointestinal type	- Considerably decreased Hb1Ac in T2-DM failing maximally significant doses of sulfonylurea. - Usually well accepted and concerned with loss in weight.

(Table 2). Contd...

Study	GLP-1 Category Drug/dose/Duration of Action	Route of Administration	Adverse Effects	Remarks/Conclusion
Kim <i>et al</i> 2007 [65]	2.0mg exenatide once weekly	Subcutaneous	Nausea, Gastroenteritis/diarrhea	• Capability of 24-hrs glycemic control & diminution in weight with novel once-weekly management for T2-DM. • Lessened fasting plasma glucose, reduction of body weight, decreased self-monitored postprandial hyperglycemia
Yousef <i>et al</i> 2021 [66]	Liraglutide	Oral/ Subcutaneous	Gastrointestinal, endocrine/metabolic, central nervous system	• Employed either alone or in amalgamation with additional drugs were significant at lessening HbA1c and regulating weight in people suffering from T2-DM
Janssen <i>et al</i> 2020 [67]	Exenatide 12 weeks 2 mg s.c	Intravenous	Nausea, vomiting adverse effects of a gastro-intestinal nature, and subcutaneous nodule in dermatological origin	• Agonism of GLP-1R enhances FDG uptake by brown adipose tissue without showing obesity or T2-DM. • Exenatide decreased body weight, without influencing REE or oxidation of the substrate, and momentarily reduced appetite ratings for the period of the first week. It also diminished levels of total cholesterol and triglycerides, and inclined to lessen glucose amounts. • Remarkably, it raised BAT metabolic volume and mean standardized uptake value without influencing supraclavicular adipose tissue fat proportion (MRI).
Ekberg <i>et al</i> 2021 [68]	Semaglutide Initial dose of semaglutide, 0.25 mg, 0.5mg, 1.0mg	Standard pen injector	GI hemorrhage hypoglycemia,	• It was concerned with glycemic and loss in weight advantages in various adults with T2-DM, favoring real-world use. • For the latter, predictable mean changes in body weight and HbA1c between baseline and EOS were -1.2 %-points and -5.4 kg respectively, with comparable outcomes in Sweden and Denmark. At EOS, 67.5% of people attained HbA1c.
Chen xi <i>et al</i> 2021 [69]	Exenatide	Subcutaneous	Incidence of Nausea, vomiting, and diarrhoea. The occurrence of hypoglycemia was alike in the two groups (27% for exenatide and 38% for part 70/30).	• In premixed human insulin-managed people with T2-DM with insufficient glycemic control, replacing exenatide two times a day plus glargine was better as part 70/30 two times a day for glycemic and control of weight.

(Table 2). Contd...

Study	GLP-1 Category Drug/dose/Duration of Action	Route of Administration	Adverse Effects	Remarks/Conclusion
Dalmazi <i>et al.</i> 2020 [70]	Exenatide 2mg	Subcutaneous	Gastrointestinal side effects and site reactions at injection followed by allergic reactions and headache.	- Unceasing and significant glycemic control and loss of weight - Duration of diabetes and basal insulin treatment, though, might influence the result of EOW management, indicating that the initial beginning of EOW can enhance glycemic control and lessen the risk of discontinuation of management.
Tsimikas <i>et al.</i> 2019 [71]	Exenatide Once weekly 2mg	-	Gastrointestinal disorders, Nausea, occurrence of myocardial infarction, ischemic stroke, and congestive heart failure	- Management with exenatide QW for about 7 years was concerned with unceasing progress in glycemic control and various factors of cardiovascular risk. - Efficient perfection in various cardiovascular risk factors, namely diastolic blood pressure, the weight of the body, low and high-density lipoprotein cholesterol, and total cholesterol concentration.
Basolo <i>et al.</i> 2018 [72]	Exenatide twice daily 10µg	Subcutaneous	Nausea	- In comparison to placebo, it reduced early ad libitum energy intake but did not modify 24 h-EE. - These results depict that although it decreases intake of food, it can be more useful in diminishing overeating and thus can aid to more weight regain of weight following weight loss initially.
Trautmann <i>et al.</i> 2017 [73]	Exenatide Once Weekly	Subcutaneous	Constipation, Diarrhea, Dyspepsia, Gastroesophageal reflux Nausea, and Vomiting	- It enhanced glycemic results once weekly and was well accepted in people with T2DM for up to 156 weeks. - It was administered once weekly in a group of N=329, fasting glucose levels, a decline from baseline in HbA1c and body weight were sustained.
Trautmann <i>et al.</i> 2016 [74]	Exenatide 2mg once weekly	-	Nausea or vomiting through the course of the study, though people with at least 1 nausea/vomiting episode depicted higher loss of weight at week 24 than those who did not.	- It administered once weekly exhibits a direct influence on systolic BP and glycemic effects during the first 2 to 4 weeks of management. - It once weekly exhibited effective progress in HbA_{1c}, weight, FG, and systolic BP at weeks of 2 and 4, with incessant advancement through week 24.
Tofe <i>et al.</i> 2021 [37]	Dulaglutide subcutaneous Semaglutide	-	GI side effects, 03 people died due to cardiovascular reasons during follow-up (two were on Dulaglutide and one on Semaglutide subcutaneously)	Patients starting with Dulaglutide were older, exhibited a greater extent of diabetes and greater baseline FPG and HbA_{1c}, and were given more sulfonylurea and insulin and lesser SGLT-2 inhibitors vs. people taking Semaglutide subcutaneously.
Kazim <i>et al.</i> 2019 [75]	Dulaglutide	Subcutaneous	-	A Few months later incorporating dulaglutide into the regimen the patient, HbA_{1c} reduced to 6.3% despite an effective decline in the dosage of insulin daily to 20 units that was associated with a 20-pound loss of body weight.

6. FUTURE DIRECTIONS

A glucose-dependent insulintropic polypeptide (GIP) and GLP-1 are the hormones of incretin which are released by enteroendocrine cells present in the small intestine in the presence of nutrients. These hormones mediate the control of glucose by enhancing the glucose-dependent release of insulin while inhibiting glucagon secretion. Type 2 DM patients showed an altered insulin effect to GIP and GLP-1 which performs a function in hyperglycemia. The degradation of GLP-1 and GIP is blocked by Dipeptidyl peptidase-4 inhibitors (DPP-4) to elevate levels of these active hormones. Inhibitors of DPP-4 have shown moderate control of glycemia in clinical trials. These are usually well-accepted, neutral weight, and do not potentiate the chances of hypoglycemia. To resist the action of DPP-4, GLP-1 RA was discovered, these are the peptide analogues of either human GLP-1 or exendin-4 and hence, have an extended half-life [17]. The most preferred treatment measure for T2-DM patients and inadequate glycaemic control were GLP-1 RAs. This review procures a common clinical analysis of resemblance and dissimilarities in the mechanism of the response of weekly administered a GLP-1 RA category of drugs, focussing on the understanding of pharmacy professionals to manage optimal medicine, education, and responsibility for diabetic patients [47, 48].

According to various reports, GLP-1 RAs have proved a defining safety and potency profile. GLP-1RAs are known to reduce blood glucose levels, which occur by pancreatic β -cell elicited glucose-reliant insulin release and inhibited release of glucagon, and their tendency to lower gastric emptying rate and induce satiety [27, 49]. GLP-1 RAs tend to have potential consequences on various organ systems where receptors of GLP-1 are located, namely renal and cardiovascular systems. Variations in individuals among GLP-1 RAs concerning their extent of action, structure, and molecular size contribute to different pharmacodynamics and various clinical responses including the extent of glycaemic control, loss in weight tendency, cardiovascular outcomes, and reliabilities profiles [27].

Thus, various data reported that GLP-1 RAs work as a potential treatment tool for T2DM patients reported to attain diverse clinical advantages. The outcome implies that when choosing or recommending therapies, pharmacy professionals should be aware of how these various GLP-1 RAs given once weekly act on the body and their mechanism of action alter clinical results to assure optimal treatment for individuals [50]. Based on clinical evidence, professional societies recommend GLP-1 RAs for diabetes treatment and management despite their high cost, which can be out of pocket for many patients [51]. However, another study indicates the cost-effectiveness of GLP-1 RAs against insulin therapy for hospitalized and all-cause mortality cases [52-54]. Along with the cost, associated side effects are also a major limitation for clinical implications. It contributes to the reduction in hemoglobin and weight loss. Gastrointestinal symptoms are the common adverse effects of GLP1-RAs. However, GLP1-RAs are preferred in the case of patients with high cardiovascular risk and where weight reduction is the main precedence [55-57].

CONCLUSION

A detailed review regarding the role, release, and regulation of GLP-1 in patients of T2-DM and how it affects the secretion of insulin from β -cells in the pancreas has been described. In this review, a scientific update on GLP-1RAs, a category of incretin-based, antidiabetic injectable therapy that enhances fasting and postprandial glucose level control in blood *via* glucose-reliant cells hormone release in the pancreas with no remarkable risk of hypoglycemia is provided. Clinical data from over a decade imply that this deficiency could be treated by using GLP-1RAs as a tool in T2-DM. Clinical trial studies using GLP-1RAs subcutaneously implicate that such drugs possess glycated haemoglobin (HbA1c) reducing tendency, a congenitally less possibility for hypoglycemia, and decreased weight of the body. GLP-1RAs have been found safe when undergoing cardiovascular trials and three of them were reported to decrease the threat of chief adverse cardiovascular episodes in cases with confirmed cardiovascular disorder or at major cardiovascular threat. The frequent harmful responses susceptible to GLP-1RAs are GIT-associated adverse effects, that occur at an initial stage and diminish over time. Several studies reported that with major patients opting for oral medicines, the formulation of GLP-1RA orally is a beneficial strategy for improving the prophylaxis of people with T2-DM. In addition, chronic usage of GLP-1RAs favors weight loss in the body through the acceleration of GLP-1 receptors situated in satiety centers in the hypothalamus which control appetite, leading to a decrease in the intake of calories.

AUTHORS' CONTRIBUTIONS

The authors confirm contribution to the paper as follows: study conception and design: Study Concept or Design: V.M; P.B, M.P, A.A; Data Analysis or Interpretation: D.K, M.D, T.K, N.J; Data Collection: K.R, A, Draft manuscript: S, K.R. All authors reviewed the results and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

T2-DM	=	Type 2 Diabetes Mellitus
BMI	=	Body Mass Index
SC	=	Subcutaneous
HBA1c	=	HemoglobinA1C
FPG	=	Fasting Plasma Glucose
OW	=	Once Weekly
BAT	=	Brown Adipose Tissue
SGLT	=	2 Sodium-glucose Cotransporter-2

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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

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