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REVIEW ARTICLE

Incretin-based therapy: a new horizon in diabetes management

Malek Zarei[1] · Navideh Sahebi Vaighan[1] · Mohammad Hadi Farjoo[1] · Soosan Talebi[1] · Mohammad Zarei[2,3]

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Abstract
Diabetes mellitus, a metabolic syndrome characterized by hyperglycemia and insulin dysfunction, often leads to serious complications such as neuropathy, nephropathy, retinopathy, and cardiovascular disease. Incretins, gut peptide hormones released post-nutrient intake, have shown promising therapeutic effects on these complications due to their wide-ranging biological impacts on various body systems. This review focuses on the role of incretin-based therapies, particularly Glucagon-like peptide-1 (GLP-1) agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors, in managing diabetes and its complications. We also discuss the potential of novel agents like semaglutide, a recently approved oral compound, and dual/triple agonists targeting GLP-1/GIP, GLP-1/glucagon, and GLP-1/GIP/glucagon receptors, which are currently under investigation. The review aims to provide a comprehensive understanding of the beneficial impacts of natural incretins and the therapeutic potential of incretin-based therapies in diabetes management.

Keywords Diabetes mellitus · Incretins · Glucagon-like peptide-1 agonists · Dipeptidyl peptidase-4 inhibitors

Introduction

Diabetes mellitus (DM) is a metabolic syndrome disorder characterized by high blood glucose levels (hyperglycemia), defective action and/or secretion of insulin, impaired adipocyte's secretory function, and multiple organ or tissue dysfunctions. Diabetes mellitus (DM), which is defined by hyperglycemia, describes a group of chronic metabolic disorders. DM complications, such as microvascular and neuropathic disorders may affect the lives of millions of people worldwide in the long term. It has been estimated that around 700 million people will live with DM by 2045 [1]. Apart from health problems, it will impose an economic burden of 776 billion USD on the health systems throughout the world [1]. The two primary forms of this disorder are type 1 (T1DM) and type 2 (T2DM). T1DM is an autoimmune disorder in which immune cells such as CD4 + and CD8 + T cells and macrophages invade the pancreatic islets and demolish the β cells, resulting in diminished insulin secretion [2]. However, the primary mechanism of T2DM is the dysfunction of synthesis, secretion, and response to insulin, which is known as insulin resistance [3]. Obesity and sedentary lifestyles are responsible for about 80% of T2DM [4]. Obese or non-obese T2DM patients develop insulin resistance due to alterations in cell receptors and post-receptor levels, respectively [5].

Long-term uncontrolled diabetes can lead to various complications, most importantly micro-and macrovascular, responsible for significant morbidity and mortality. In this regard, neuropathy, nephropathy, and retinopathy are categorized as microvascular complications, while macrovascular complications include cardiovascular, cerebrovascular, and peripheral artery diseases [6]. Besides, lung microvascular complications, nonalcoholic fatty liver disease (NAFLD), cancer, and atherosclerosis are the other nonclassical chronic complications of diabetes.

To date, various drugs and therapies have been used to control diabetic manifestations and complications, some of which have been relatively effective. Incretin-based therapy using the novel anti-diabetic agents, including injectable glucagon-like peptide-1 (GLP-1) agonists (Exenatide, Liraglutide, Albiglutide, dulaglutide, semaglutide (oral)) and

✉ Navideh Sahebi Vaighan
navideh.sahebi@sbmu.ac.ir

[1] Department of Pharmacology, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[2] Renal Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

[3] John B. Little Center for Radiation Sciences, Harvard T.H Chan School of Public Health, Boston, MA, USA

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oral dipeptidyl peptidase-4 (DPP-4) inhibitors (Alogliptin, Linagliptin, Saxagliptin, Sitagliptin, Vildagliptin) has shown promising impacts on diabetes and its complications [7, 8] (Table 1). Some of which, such as liraglutide, have had meaningful effects on obesity [9]. The newer agents, so-called twincretins and triple agonists such as tirzepatide, cotadutide (under development), and some molecules acting on GLP-1, GIP, and GLP-1/GIP/glucagon receptors respectively, have exerted substantial effects on glycemic control and bodyweight in various studies. The gut peptide hormones, incretins, are released after nutrient intake and provoke insulin secretion. GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 (glucagon-like peptide-1) are known incretin hormones that exert an activity so-called the incretin effect, a phenomenon whereby oral glucose administration provokes further insulin release compared to intravenous injection at the same plasma glucose concentration [10]. Furthermore, GLP-1 is released in a lesser amount in the Central Nervous System (CNS) [11–13]. In addition to pancreatic β-cells, GLP-1 receptors are also expressed in the kidney, lung, heart, walls of arteries, and gastrointestinal tract [14], indicating the potential role of GLP-1R agonists in the therapy of diabetic complications. Moreover, there is evidence regarding the multiple biologic effects of incretin hormones on fat deposition, bones, cardiovascular system, nerve growth, appetite, obesity, blood glucose, and lipid metabolism [15–22], dysfunction of which is the leading cause of T2DM and its complications.

Hence, fat deposition, obesity, glucose, and lipid metabolism disorders are the leading causes of diabetes (T2DM), which in the long-term lead to multiple organ involvement, so-called diabetic complications. The present literature aims to review the beneficial impacts of natural incretins on human body systems, advantageous effects of incretin-based therapy on diabetes and its complications (Fig. 1), and finally, the novel incretin-based agents will be summarized.

Incretin hormones

The incretin hormones, GLP-1 and GIP are gut-derived peptide hormones, secreted by endocrine intestinal cells of L and K–types, respectively, [23, 24]. The K-cells are found in the duodenum and proximal jejunum, whereas the L–cells are expressed more in the ileum and less in the duodenum and even in the colon and rectum [25, 26]. Due to their crucial role in glucose homeostasis and the pathophysiology of T2DM, incretins have been broadly investigated so far [27].

Soon after nutrient intake, plasma concentrations of GIP and GLP-1 increase to reach their peak in almost one hour. Glucose and other carbohydrates, such as starch, sucrose, triglycerides, various amino acids and proteins provoke GIP and GLP-1 secretion, consequently stimulating insulin secretion [28, 29]. Incretins exert a phenomenon called the incretin effect, meaning that at the same plasma glucose concentration, oral glucose stimulates higher insulin secretion levels than glucose infusion [27, 30]. Besides their effect on insulin secretion, incretin hormones also affect glucagon release, so that while GLP-1 suppresses glucagon release, GIP stimulates it [31, 32]. Therefore, the insulinotropic

Table 1 Anti diabetic agents: incretin-based agents

Drug	Mechanism of action	Effects	Clinical Applications
*GLP-1RECEPTOR AGONISTS Exenatide, liraglutide, albiglutide, dulaglutide, semaglutide, tirzepatide	Activation of GLP-1 receptors	Reduce postprandial glucose levels: Increase glucose-stimulated insulin release, inhibit glucagon secretion, retard gastric emptying, produce a feeling of satiety	Type 2 diabetes, liraglutide: obesity
*DPP-4 INHIBITORS Sitagliptin, saxagliptin, linagliptin, alogliptin, vildagliptin	Inhibition of GLP-1 degradation, raise circulating GLP-1 levels	Reduce postprandial glucose levels: Increase glucose-stimulated insulin release, inhibit glucagon secretion, retard gastric emptying, produce a feeling of satiety	Type 2 diabetes

*GLP-1 receptor agonists are mostly injectable, except for semaglutide, which is available orally and injectable. DPP-4 inhibitors are taken orally.

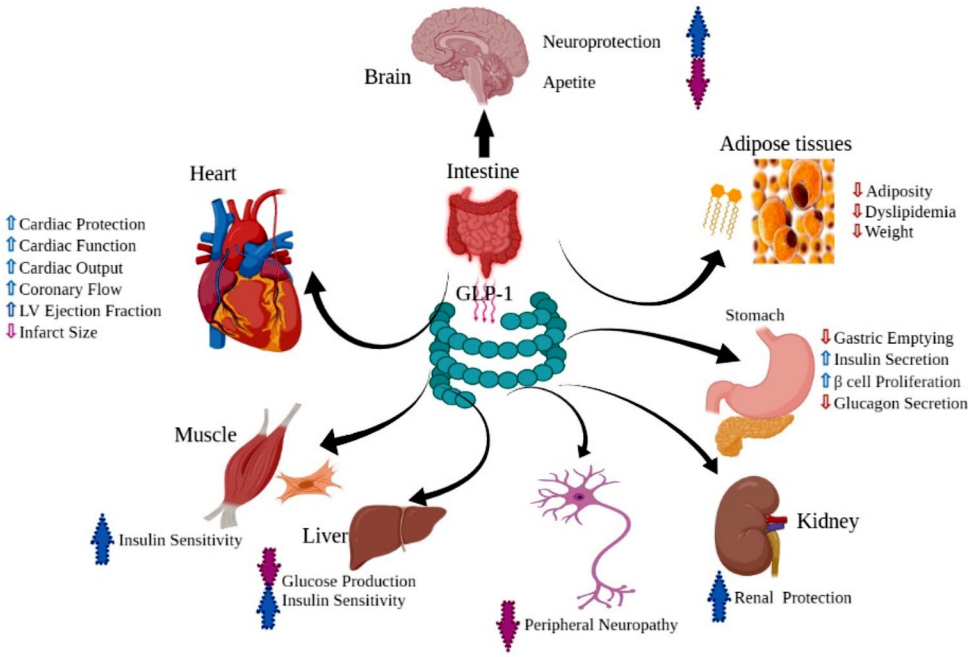

Fig. 1 The beneficial effects of incretin-based therapy on diabetes and its complications. Incretins, the gut peptide hormones, are released after nutrient intake and provoke insulin secretion. In addition to pancreatic β-cells, incretin receptors are also expressed in the kidney, lung, heart, walls of arteries, CNS, and gastrointestinal tract which result in multiple biologic effects in various body tissues. The advantageous effects of incretins on diabetic complications have been demonstrated. The newer anti-diabetic agents (GLP-1 agonists and DPP-4 inhibitors) are supposed to improve diabetic complications

effect, together with glucagon secretion inhibition of GLP-1, count as the prominent glucose-lowering mechanism of this hormone [33, 34]. However, it should be noticed that the function and activity of incretin hormones are not similar and completely equivalent in different tissues [24]. In contrast to GIP, which does not affect gastric emptying, GLP-1 slows it. On the other hand, GIP induces triglyceride storage, an activity that is unlikely to be done by GLP-1 [32, 35, 36]. As mentioned previously, the beneficial role of incretin receptors in improving diabetic complications can be postulated.

Incretin hormones in T2DM

Insulin resistance, inadequate insulin secretion, and hyperglucagonaemia are the main reasons for T2DM occurrence [37]. Regarding the role of incretin hormones in stimulating insulin secretion and the GLP-1 effect on glucagon release suppression, a review on the role of incretin hormones in T2DM would be rational. Although various studies and meta-analyses have not found significant differences in nutrient-induced incretin secretion between healthy individuals and T2DM subjects [38–40], different experiments indicated that GIP could not stimulate insulin secretion in patients with T2DM [31, 41, 42]. Nonetheless, the insulinotropic and glucagonostatic effects of GLP-1 have been well documented [31, 43–45]. Insulin secretory response to glucose decreases by 25% in patients with T2DM compared to healthy individuals [46]. This level of activity of GLP-1 in T2DM patients, however is adequate for a proportional reduction in plasma glucose [47]. Considering the prominent role of GIP in the incretin effect in healthy subjects, this phenomenon is decreased or even lost in T2DM patients [48, 49]. Despite the minimal impact of GIP on insulin secretion in patients with Type 2 Diabetes Mellitus (T2DM), and the hormone's glucagonotropic effect, dual agonists that target both GLP-1 and GIP (such as tirzepatide) have demonstrated promising results in promoting weight loss. Besides, based on data indicating the effect of GIP on enhancing triglyceride deposition, GIP receptor antagonists have been suggested for the therapy of pre-diabetic subjects and metabolic disorders [50, 51]. On the contrary, as mentioned above, because GLP-1 sustains its effect on glucose metabolism, insulin secretion, and glucagon suppression in patients with T2DM, receptor agonist of this hormone has been widely used in the therapy of diabetes [27, 52].

Effect of incretins on appetite, caloric intake, and body weight

Approximately 80% of T2DM is linked to obesity and physical inactivity, as the crucial role of these factors in T2DM improvement is well-documented [4, 53]. Obesity causes excessive triacylglycerol (a fatty acid metabolite) and other fatty acid metabolites to deposit in the sarcoplasm of skeletal muscles [4], resulting in insulin signal inhibition [54, 55]. Moreover, insulin signaling suppression is associated with the level of circulated fatty acids [56]. Therefore, in obese patients with T2DM, insulin resistance impairs the ability of β-cells to compensate for decreased insulin

sensitivity [57]. Besides, it has been documented that there is a profound relationship between physical activity and a reduction in T2DM incidence [4].

Incretins influence obesity through different mechanisms, such as fat storage promotion, gastric emptying slowness, appetite suppression, and satiety increase. In animal models, GIP enhanced fat storage in subcutaneous adipose tissue by lipoprotein lipase induction [17, 32, 36]. However, animals with a GIP receptor knockout did not get fat during a high-fat diet [17]. Furthermore, some studies have documented the hypersecretion of GIP in obesity to prevail over the metabolic disorders resultant from insulin resistance [32, 58]. Conversely, GLP-1 secretion is decreased in obese subjects for an unknown reason. Besides, GLP-1 injection increases satiety and decreases food intake and appetite [59], indicating this hormone's potential role in the pathogenesis of obesity. Consequently, various studies have focused on the potential therapeutic effect of GLP-1 on obesity in diabetic and non-diabetic subjects [60–65]. Moreover, the subjects with obesity and T2DM receiving GLP-1 analogs exerted metabolic and appetite responses comparable to healthy individuals [16, 66–69]. Therefore, studies on GLP-1R agonists (GLP-1RAs) and DPP4 inhibitors were raised, eventually leading to the introduction of two groups of therapeutic agents used as incretin-based therapy [27, 70]. In addition to being broadly used as a blood sugar lowering agent, GLP-1RAs have recently been approved for weight management in the United States [71, 72]. In this regard dual agonists affecting on GLP-1/GIP (tirzepatide) have shown encouraging impacts on weight loss [73, 74]. Semaglutide, the only oral GLP-1R agonist (currently) has exerted inspiring effects on bodyweight reduction as well [75, 76]. Besides, various studies have shown that through some surgical methods, such as bariatric surgery and Roux-en-Y gastric bypass, GLP-1 secretion increases significantly, associated with further excess weight loss and blood glucose improvement [77–79]. However, as reviewed above, the potential therapeutic role of incretins in weight loss is not negligible. Differential effects of GLP-1 and GIP on various biological functions are summarized in Table 2.

Table 2 Differential effects of GLP-1 and GIP on various biological functions

Effet	GLP-1	GIP
Orgin	Secreted by L-cells in the ileum, colon and rectum	Secreted by K-cells in the duodenum and proximal jejunum
Insulin secretion	Stimulates insulin secretion	Stimulates insulin secretion
Glucagon release	Suppresses glucagon release	Stimulates glucagon release
Triglyceride storage	No effect on triglyceride storage	Promotes triglyceride storage
Effect on T2DM	Maintains insulinotropic and glucagonostatic effects in T2DM patients	Minimal effect on insulin secretion in T2DM patients
Appetite and caloric intake	Increases satiety and decreases food intake	No significant effect on appetite and caloric intake
Body weight	Promotes weight loss	No significant effect on weight
Neural effects	Found in CNS and PNS; may improve neuronal complications and cognitive function	Limited information available; GIP receptors are expressed in some brain areas but less is known about their roles.
Cardiovascular effects	Cardioprotective; improves endothelial function, reduces apoptosis, and oxidative stress	Limited information available; may have beneficial effects but less well-studied than GLP-1.

Incretin effects on the peripheral and central nervous system

GLP-1R is also found in the central nervous system in the hypothalamus and brainstem, and in the peripheral nervous system (PNS), on afferent branches of the vagus nerve which originate from the vicinity of the intestinal L cells [80–82]. Since many diabetic patients suffer from neuronal or psychological complications of diabetes, pharmaceutical agents capable of ameliorating both hyperglycemia and neuronal complications of the disease may be of great importance. These agents might offer new treatment approaches for neurodegenerative diseases, such as Alzheimer's disease, as well as debilities in cognition and memory [83]. Even some unrelated diabetes complications, such as obesity may be affected by the CNS which is partially regulated by GLP-1 receptors [82]. The benefits of incretin mimetics are also seen in non-diabetic patients, suggesting favorable central or peripheral neuronal roles which may be detached from their effect on plasma glucose levels [83, 84].

As mentioned above, GLP-1Rs are located on the vagus nerve and their stimulation by incretin ligands can hinder stomach emptying. This phenomenon, which is not merely insulin-dependent, can decrease postprandial glucose levels [85]. GLP-1 can ameliorate postprandial lipemia by diminishing chylomicron biosynthesis in the intestine [86]. It is mediated via the interaction of GLP-1 with melanocortin-4 receptors in the CNS in a brain-gut axis which may be a promising therapeutic strategy for hyperlipidemia and hyperchylomicronemia in diabetic patients [87]. Apart from its effect on gastric transit time, GLP-1 has an anti-appetite effect by stimulating its relevant receptors in the CNS. It seems that the vagus nerve mediates the transition of the satiety signals between the alimentary tract and the CNS, where signals are received

by the solitary tract nucleus and are relayed to the hypothalamus to be sent back for food intake control [88].

Diabetic neuropathy spans a vast spectrum of sufferings from simple pain to death. Considering various groups of anti-diabetic agents, the incretin-based drugs (GLP-1 agonists and dipeptidyl peptidase-4 inhibitors) stand at the top of the anti-diabetic agents for managing peripheral neuropathy of diabetes [89]. Besides the incretins' possible role in improving axonal regeneration and neural repair, hippocampal expression of GLP-1R and GIPR suggests their involvement in memory formation and synaptic plasticity, a concept highlighted by learning defects in GLP-1R knockout mice. Incretins also hinder the progression of neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease. These agents also impede associated memory and cognitive defects in animal models of the diseases, as mentioned earlier [89, 90]. In myelinated motor nerves and unmyelinated pain neurons, GLP-1R may have some roles in their function regardless of its glycemic controlling effects [90]. Some studies show that DPP-4 inhibitors can inhibit diabetic neuropathy in rodents [91].

The animal model findings are not confirmed unequivocally in human studies, maybe because of the small sample sizes and the paucity of clinical trials. For instance, concerns regarding the increased risk of pancreatitis due to GLP-1RAs observed in animal studies have not been consistently replicated in human trials, likely due to variations in study design and participant characteristics [92, 93]. In one clinical trial, exenatide did not improve diabetic peripheral neuropathy or the electrophysiologic profile of the nerves [94]. In another clinical trial, the liraglutide effect on improving polyneuropathy was discouraging [95]. It seems that further studies are required before concluding about the effect of GLP-1 and its receptor in human diabetic neuropathy [96].

Cardiovascular effects of incretin system

DM-associated cardiovascular disease (CVD) and stroke are the leading causes of morbidity and mortality in patients with diabetes [97]. Death due to coronary heart disease occurs much more frequently in diabetic patients than non-diabetic subjects (3 to 5-fold) [98, 99], especially those with other comorbidities such as hypertension and dyslipidemia who are at increased risk. Management of these risk factors may improve cardiovascular health. However, there is not adequate evidence regarding the favorable effect of conventional oral anti-diabetic drugs on cardiovascular disorders in diabetes [100]. Studies have shown the multiple effects of GLP-1 on the cardiovascular system [18, 19]. Various reports have presented the contradictory effects of GLP-1 and GLP-1RAs on endothelial function, atherosclerosis progression, and cardiac blood supply [18, 19]. The embryonic development of the cardiovascular system seems to be associated with GLP-1 activity. In a human study, treatment with GLP-1 decreased the ability of tumor necrosis factor-alpha (TNF-α) to induce gene and protein expression of plasminogen activator inhibitor type-1 (PAI-1), a prominent factor of endothelial cell dysfunction [101, 102]. Similarly, a randomized study indicated that GLP-1 administration in patients with T2DM increased the flow-mediated vasodilation, an effect absent in healthy individuals, suggesting the potential role of GLP-1 in improving endothelial dysfunction associated with atherosclerosis [103]. However, data on the effect of GLP-1 and/or GLP-1RAs on blood pressure have been controversial [104–107]. On the other hand, GLP-1RA agonists, like exenatide demonstrated cardioprotective effects by lowering apoptosis and oxidative stress [108]. The GLP-1 signaling pathway leads to a decrease in the pro-apoptotic markers such as caspase-3&9, Bax/Bcl-2, and p53 in cardiac Tissue (Fig. 2) [109]. Many human studies have been carried out to evaluate the cardioprotective effects of GLP-1 and GLP-1RAs. For example, GLP-1 infusion (4 weeks) in patients with severe heart failure improved left ventricular function, functional status, and Quality of Life (QoL) scores in subjects with and without diabetes. GLP-1 administration also improved left ventricular ejection fraction (LVEF) in patients with acute myocardial infarction [110, 111]. It is suggested that GLP-1 acts through two main pathways. The first one is through GLP-1R activation, which induces glucose uptake, ischemic preconditioning, and mild vasodilatory actions; and the second pathway is GLP-1R–independent, meaning that GLP-1 independently affects the cardiac post-ischemic recovery and vasodilation, probably via NOS-induced-cGMP formation [112]. In this regard, treatment with liraglutide in mice has improved the reduction of the endothelial nitric oxide synthase (eNOS), a crucial enzyme for vascular nitric oxide (NO) synthesis [113]. NO induces the production of cGMP, an intracellular second messenger that consequently stimulates phosphodiesterases (PDE) and cGMP-dependent protein kinases (PKGs) effectors. Hypertrophy inhibition, vaso-relaxation, and cellular proliferation are mediated by these effector molecules in the cardiovascular system [114]. Besides, the correlation between eNOS induction and reduction in TNF expression and NF-κB stimulation in cardiomyocytes has been documented (Fig. 2) [113]. However, these findings altogether indicate the cardiovascular protective effects of GLP-1R stimulation.

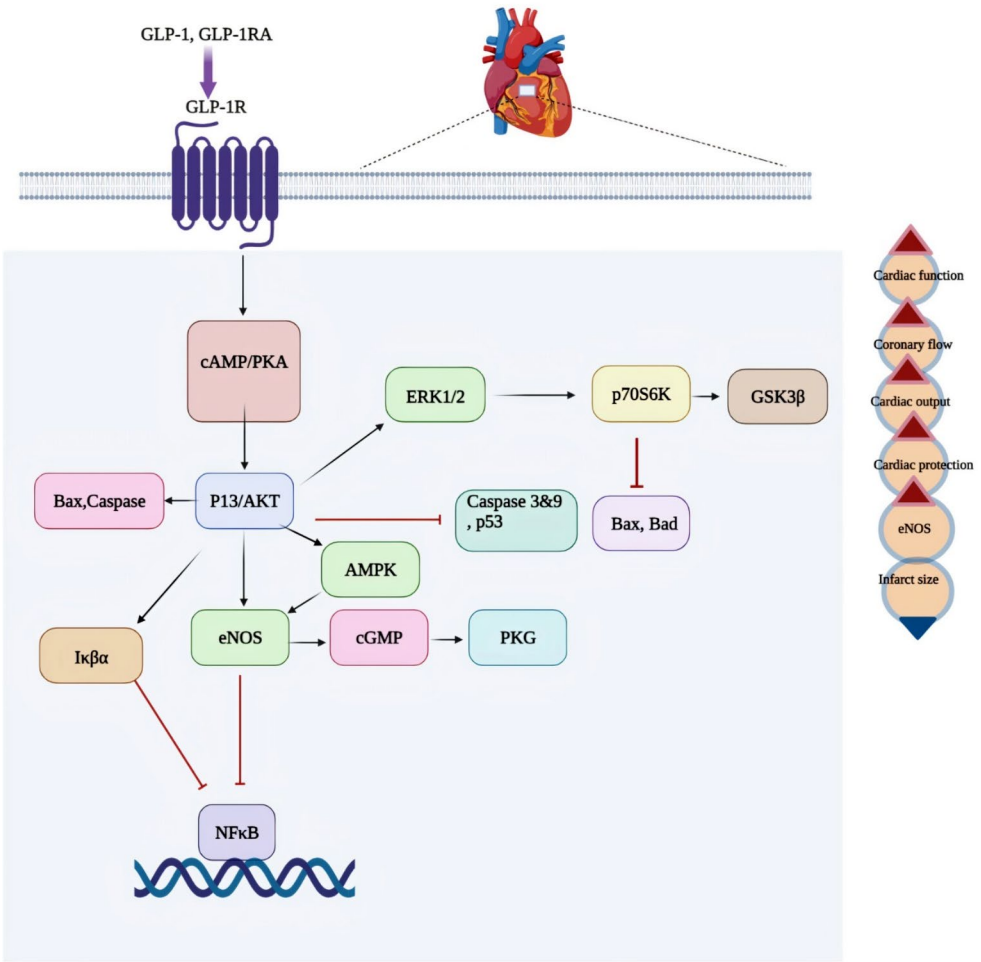

Fig. 2 GLP-1 signaling pathway in the cardiac tissue. Activation of GLP-1R in the cardiovascular system results in multiple cascades which lead to beneficial effects on the system

Effect of incretin-based therapy on cardiovascular activity in T2DM

Compared to non-diabetic individuals, diabetic subjects are at a much higher risk of cardiovascular (CV) events, so CVD accounts for almost 80% of the mortality in individuals with T2DM. Metabolic risk factors, such as insulin resistance, dyslipidemia, obesity, and hypertension contribute to CVD manifestation [115]. The beneficial cardiovascular effects of GLP-1RAs have been approved. In this regard, Nathanson et al. showed that two-day administration of exenatide in patients with T2DM and heart failure improved cardiac output and reduced pulmonary capillary pressure [116]. Notably, these promising effects of GLP-1RAs on the CV system are reported to be independent of glycemic control, likely through improvements in vascular risk factors and atherosclerosis [115, 117, 118].

Several significant trials have focused on the impact of GLP-1RAs on cardiovascular outcomes in patients with T2DM and elevated cardiovascular risk. These studies specifically examined the impact on cardiovascular mortality, non-fatal myocardial infarction (MI), and non-fatal stroke [119–122]. All trials confirmed the cardiovascular safety of GLP-1RAs, with several showing significant efficacy in reducing cardiovascular events. Noteworthy among these are the LEADER outcomes trial for liraglutide [117], the HARMONY trial for albiglutide [122], the REWIND trial for dulaglutide [121], and the SUSTAIN-6 trial for injectable semaglutide [118]. Liraglutide significantly lowered both cardiovascular and all-cause mortality, and both liraglutide and injectable semaglutide demonstrated improvements in kidney outcomes [117, 118]. Variations in trial outcomes may be due to the cardiovascular risk profiles of participants and the specific GLP-1RA class used. While A recent meta-analysis showed a 14% overall reduction in major adverse cardiovascular events another meta-analysis indicated greater benefits of GLP-1RAs in patients with established CVD compared to those without, highlighting the need for more studies on primary prevention [123]. Emerging evidence suggests GLP-1RAs could significantly reduce MI risk. Clinical studies have shown that GLP-1RAs, such as exenatide and liraglutide, administered during acute MI, can reduce infarct size and improve cardiac function [124, 125]. Furthermore, a prospective observational study with 17,868

diabetic patients discharged after their first MI event found that GLP-1RA use was associated with a reduced risk of stroke, heart failure, re-infarction, and cardiovascular death compared to standard diabetes care [126]. While GLP-1 RAs have demonstrated cardiovascular benefits, some evidence suggests that they may increase the risk of hospitalizations in patients with heart failure with reduced ejection fraction (HFrEF). Therefore, until more randomized studies are conducted, it is advisable to avoid using GLP-1 RAs in patients with HFrEF [127].

Evidence regarding the impact of DPP4 inhibitors on cardiovascular events is paradoxical [164, 165]. Some studies have suggested that diabetic patients treated with DPP4 inhibitors experience fewer cardiovascular events compared to those on other anti-diabetic drugs [128, 129]. For instance, a meta-analysis reported that DPP4 inhibitors treatment is associated with a reduced risk of main adverse cardiovascular events [128]. Another one meta-analysis study on 40 trials suggested that long-term treatment of patients with T2DM with DPP-4 inhibitors and GLP-1As is associated with a lower risk of myocardial infarction compared to those receiving sulfonylurea drugs [130]. Despite this, several randomized controlled trials have been conducted to evaluate the cardiovascular outcomes of DPP4 inhibitors in diabetic patients, and none demonstrated significant cardiovascular benefits [131–133]. Notably, the SAVOR-TIMI 53 trial found that saxagliptin was linked to an increased risk of hospitalization for heart failure [134].

Anti-atherogenic role of incretin-based therapy

Numerous preclinical and experimental studies have highlighted the anti-atherogenic properties of GLP-1 by reducing aortic macrophage recruitment and atherosclerotic lesion formation [135]. Sudo et al. demonstrated that lixisenatide improves advanced atherosclerotic plaques in rabbits, increasing fibrotic areas and decreasing necrotic and calcified areas, without changing the overall plaque size [136]. Incretin treatment, specifically with GLP-1RAs, is linked to stable plaque characteristics, showing increased collagen and sirtuin-6, with reduced inflammation and oxidative stress in carotid plaques from diabetic patients [137]. The long-term effects of GLP-1RAs on atherosclerosis and during percutaneous coronary interventions remain unclear, with mixed evidence. Some studies suggest a link between GLP-1 levels and coronary artery disease progression [138], while others show GLP-1's protective role after myocardial ischemia, such as exenatide reducing infarct size in both animal models and clinical settings [108].

DPP4 inhibitors have shown promising protective effects against atherosclerosis through multiple mechanisms. These inhibitors improve endothelial cell dysfunction, which is crucial for maintaining vascular health and preventing atherosclerosis [139, 140]. They regulate blood lipids by reducing LDL cholesterol and triglycerides and increasing HDL cholesterol, thereby mitigating atherosclerotic risk factors [141, 142]. Additionally, DPP4 inhibitors lower both systolic and diastolic blood pressure, contributing to a reduction in atherosclerotic progression [143, 144]. Inflammation and oxidative stress, key factors in the development of atherosclerosis, are significantly suppressed by DPP4 inhibitors [139, 143, 145]. They also affect mononuclear macrophages by reducing foam cell formation, which is essential in early atherosclerotic plaque development [146–148]. The inhibitors further inhibit the proliferation and migration of smooth muscle cells, thereby reducing intimal hyperplasia and stabilizing atherosclerotic plaques [149, 150]. By reducing the levels of MMP2 and MMP9, DPP4 inhibitors (Sitagliptin) enhance plaque stability, which lowers the risk of plaque rupture and subsequent cardiovascular events [151, 152]. Additionally, these inhibitors increase the levels of circulating endothelial progenitor cells (EPCs), aiding in vascular repair and maintenance [153, 154]. In conclusion, DPP4 inhibitors hold significant potential in preventing and treating atherosclerosis and related cardiovascular diseases through various mechanisms. However, more research is needed to fully understand their long-term effects and underlying mechanisms..

Renoprotective effect of incretin-based therapy in T2DM

Diabetic kidney disease (DKD) happens in 20-40% of patients with diabetes and is the main leading cause of the end-stage renal disease (ESRD) that requires dialysis treatment and affects their QoL [155, 156]. Moreover, DKD not only increases the risk of cardiovascular disease in patients, even in the early stages [157], but the negative linear relationship between the glomerular filtration rate (GFR) and mortality is reported [158]. Several pathogeneses have been described, such as hemodynamic alterations causing glomerular hypertension, oxidative stress [157], mitochondrial dysfunction [159], endoplasmic reticulum stress [160], activation of cytokines, profibrotic factors, inflammation, and growth factors [161, 162]. The current interventions to slow down the DKD development consist of controlling blood pressure and blood glucose level, decreasing urinary albumin excretion, and stopping smoking [157].

An experiment in rats has shown the GLP-1R mRNA expression in the proximal tubules and glomeruli (1).

Moreover, a human study indicated that GLP-1R was expressed in tubules and glomeruli (2); however, another study stated that proximal tubules were the dominant location of GLP-1R expression (3). This discrepancy can be explained by the limitation of sensitivity and specificity of antibodies against these receptors (4). Studies on rats have shown the enhancement of DPP-4 activity in response to a high-fat diet or obese state (5) and downregulation of the expression of GLP-1R in the tubules of diabetic rats (6), demonstrating the potential role of incretin-based therapies against diabetic nephropathy. The probable mechanism underlying the beneficial effect of GLP-1RA and DPP-4 is mainly through the inhibition of sodium–hydrogen exchanger 3 (NHE3), which ultimately results in natriuresis as a result of inhibition of sodium reabsorption from the proximal tube. Moreover, tubuloglomerular feedback is activated because of enhanced sodium chloride delivery to distal tubules, leading to diminished glomerular hyperfiltration and pressure [163]. Furthermore, calcium, phosphate, chloride, and bicarbonate are excreted as well; however, the excretion of potassium is not influenced (Fig. 3) [164]. It has been shown that in the urine of individuals with T2DM, DPP-4 was found to correlate with albuminuria [165], which offers DPP-4 as a marker of tubular injury in diseases affecting the glomerulus, including DKD, lupus nephritis, and glomerulonephritis in this population [166].

Various studies in DKD models have demonstrated the beneficial effects of GLP-1RAs and DPP-4 inhibitors in lowering proteinuria and glomerular sclerosis by reducing oxidative stress and inflammation and protecting against endothelial injury [157]. The administration of DDP-4 inhibitors in rats with T1DM increased the serum concentration of active GLP-1, declined urinary albumin excretion, and improved diabetic nephropathy histology. They inhibited macrophage infiltration, inflammatory molecules, and downregulated nuclear factor NF-κB activity in the kidney [167]. Along with these effects, no significant change in glycemic profiles was observed, indicating anti-inflammatory and antifibrotic renoprotective impacts of DDP-4 inhibitors, such as sitagliptin, linagliptin, and vildagliptin through amplifying serum concentration of active GLP-1 [168]. Sitagliptin has decreased tubulointerstitial, glomerular, and vascular lesions in type 2 diabetic Zucker diabetic fatty (ZDF) rats [169]. Moreover, this drug attenuated the inflammatory cytokines and apoptosis of cells in the kidney, which diminished the glomerulosclerosis and tubulointerstitial fibrosis [170]. In addition, exenatide decreased the

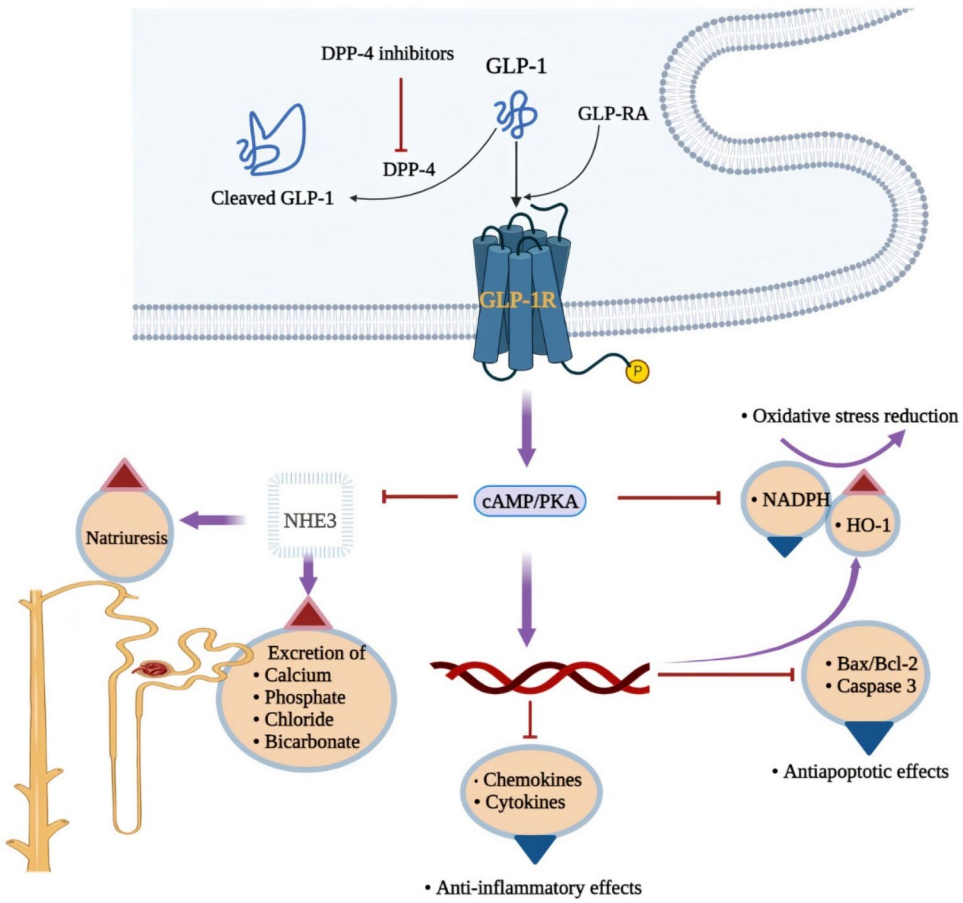

Fig. 3 Beneficial effects of incretin based-therapy on kidney activities. GLP-1R stimulation causes stress oxidative reduction and anti-inflammatory and anti-apoptotic effects. It can also increase natriuresis and calcium, phosphate, bicarbonate, and chloride excretion

concentration of TGFβ (Transforming growth factor), a diabetic nephropathy-related cytokine [171].

In several clinical studies, the renoprotective effects of incretin-based therapies have been reported [172, 173]. For instance, in studies evaluating semaglutide [118] and liraglutide [117] effects on renal function, they lowered the rate of new-onset or deterioration of established nephropathy compared to the placebo group. Moreover, lixisenatide lowered the risk of new-onset macroalbuminuria even after adjustment for HbA1c concentration [174]. Importantly, liraglutide in the LEADER trial not only improved albuminuria, but reduced secondary kidney outcomes, such as the persistent doubling of the serum creatinine level, new-onset persistent macroalbuminuria, kidney failure, or death due to kidney disease, which was not observed by exenatide [175], albiglutide [176], linagliptin [132], dulaglutide [121], saxagliptin [177] and alogliptin [178] treatment in other studies. Linagliptin diminished albuminuria and UACR independent of HbA1c and systolic blood pressure (32). In two distinct studies about the effects of linagliptin and alogliptin, no beneficial effect was observed when the drugs were used as monotherapy. Nevertheless, adding these drugs to patients' established treatment based on blocking the renin-angiotensin system remarkably diminished the albuminuria in patients with type 2 DM [179, 180]. It should be noted that though several studies failed to indicate the renoprotective impacts of DDP-4 inhibitors, they emphasized the safety and tolerability of these medications in patients with renal disorders [181–183].

The renoprotective effects of incretin-based therapies can be attributed to the modification of renal risk factors as well. In this regard, GLP1RA has been shown to reduce waist circumstance, body weight, visceral and trunk fat, and systolic blood pressure [184, 185]. This blood pressure reduction was significant when liraglutide and albiglutide were used. However, with exenatide and dulaglutide, this effect was insignificant compared to placebo [186]. On the other hand, the direct impact of GLP-1RA on the kidney is presumed to have a positive effect on albuminuria regardless of changes in hyperglycemia, blood pressure, and body weight [187]. It creates a consensus about the presence of GLP-1R in the kidney vessels [188]. Nonetheless, different trials failed to demonstrate the desirable effect of GLP-1Ras on renal hemodynamics, mainly on eGFR, reduction of which over time manifests a decline in intraglomerular pressure [187, 189–196]. Besides, sodium secretion resulting from inhibition of NHE3 was not persistent in the long term [187]. The central role of inflammation in DKD is demonstrated by several studies [197, 198], which motivated the scientists to seek the effect of incretin-based therapies on inflammation. In this regard, numerous studies on animals and humans showed the anti-inflammatory effect of GLP-1RA and DPP-4 inhibitors through attenuating inflammatory cytokines and markers, such as IL-1β, TNF-α, chemoattractant protein-1 (MCP1), and high-sensitivity C-reactive protein (hs-CRP) in DKD cases and models [170, 174, 199–202]. Moreover, these results strongly suggest that the renoprotective impact of GLP-1RAs might be exerted through inflammation suppression [203]. Furthermore, the mechanism behind the favorable effects of GLP-1RAs is speculated to be through reducing inflammation, improvement of renal substrate metabolism resulting in improved insulin sensitivity, production of valuable systemic metabolites through activation of GLP-1R agonism [204], or direct effect of GLP-1 on tubules of the kidney regardless of the mechanism mediated by the receptor [205]. Furthermore, GLP-1RAs show an antioxidant effect by lowering oxidative markers and improving oxidative damage, as reported by various investigations [200, 203, 206, 207]. For instance, exenatide is shown to exert an anti-inflammatory effect by directly inhibiting the generation of H2O2-induced free radical species, attenuating the lactate dehydrogenase (LDH), creatine kinase-MB (CK-MB), and malondialdehyde (MDA) levels [200, 207]. It is stated that the cAMP-dependent pathway could be responsible for the observed antioxidant impact [208]. Teneligliptin is shown to reduce free radical species generated by NADPH oxidase activity and act as an antioxidant [209]. According to the evidence, GLP-1 can regulate NO synthesis [210, 211], which can be beneficial for preventing renal failure progression in diabetes [212]. Moreover, NO synthesis modulation by exenatide lowered blood pressure [213]. Thomson et al. revealed that exenatide improved renal hemodynamics and GFR by NO synthesis-related mechanism [212]. In a study by Jensen and coworkers, hypertensive animals with problems in kidney functions GLP-1 receptors were reduced in the renal tissues, indicating the major role of GLP-1 in the homeostasis of the renal vasculature and renal function [214]. Other studies have confirmed the modulatory function of GLP-1 agonists on the renal renin-angiotensin system as well.

Effect of incretin-based therapy on diabetic retinopathy

Various clinical trials and studies have been carried out to scrutinize the effects of GLP-1RAs and DPP-4 inhibitors on diabetic retinopathy. It has been shown that subcutaneous injection of semaglutide, but not oral administration, in the SUSTAIN-6 study resulted in an increase in retinopathy in Type 2 DM patients [118, 120]. Nevertheless, a posthoc analysis of the SUSTAIN-6 trial did not demonstrate any difference in the incidence of diabetic retinopathy between the semaglutide and placebo groups in patients with no

pre-existing diabetic retinopathy [215]. Moreover, liraglutide [117], albiglutide [216], and exenatide [217] in different studies showed progression of diabetic retinopathy. It should be noted that this increase in the liraglutide group was not statistically significant, and in follow-up of patients receiving exenatide the improvement or stability of diabetic retinopathy was reported. Besides, when GLP-1 RAs were compared to two or more oral glucose-lowering drugs in a study, the overall incidence of diabetic retinopathy was not enhanced. Nevertheless, the secondary analysis showed that GLP-1RA was associated with a transient 44% increased risk of diabetic retinopathy over 6–12 months, particularly in patients with arterial hypertension [218]. The possible explanations for these results seem to be due to a short period of diabetic retinopathy follow-up, lack of baseline diabetic retinopathy staging, a rapid drop in HbA1c, and retinal microvascular angiogenesis [219]. On the other hand, no association between GLP-1RA exposure and severe diabetic retinopathy has been reported by several studies [175, 215, 218, 220–223], even among patients with pre-existing ocular disease [224]. A meta-analysis revealed the safety of GLP-1RAs for diabetic retinopathy treatment [225]. Based on the FDA (Food and Drug Administration) report regarding ocular adverse events due to GLP-1RAs, such as vitreous hemorrhage, diabetic retinopathy, proliferative diabetic retinopathy, macular edema, or blindness, GLP-1RAs did not enhance the diabetic retinopathy development risk [226]. Hernandez and coworkers found that systemic administration of liraglutide in db/db mice inhibited retinal neurodegeneration by stimulating the AKT pathway, a vital pathway for retinal neurons to survive [227]. Moreover, they observed these desirable effects via administered liraglutide, native GLP-1, lixisenatide, or exenatide topically, suggesting that the neuroprotective effects are independent of the type of GLP-1 RA and blood glucose levels [227]. Besides, GLP-1RA therapy in diabetic rats improved B wave and OPs [228], the most sensitive index of electrophysiology of diabetic retinopathy declined in diabetic retinopathy. The differences in the structure of the medication could explain the observed discrepancy. It is essential to state that in the various studies examining GLP-1RA-related diabetic retinopathy, a standard AE report was used instead of a retinal image, except for one retrospective study in which a robust method was applied [229]. The results of a clinical trial (FOCUS), which will analyze semaglutide-related ocular events via retinal imaging, are expected to provide significant insights into this issue [135].

The detrimental effect of DDP-4 inhibitors on diabetic retinopathy has been reported recently. Lee and coworkers stated that DPP-4 inhibitors in their murine diabetic retinopathy model aggravated diabetic retinopathy after one week of treatment due to increased retinal vascular leakage [230].

On the other hand, Kolibabka et al. indicated the anti-angiogenic effects of linagliptin, a DPP-4 inhibitor [231]. Vildagliptin could inhibit the thrombogenic reactions and inflammation in the retina of Otsuka Long-Evans Tokushima Fatty rats (OLETF rats), models of obese type 2 diabetes [232]. Moreover, topical DPP-4 inhibitors have shown preventive effects on vascular leakage and neurodegeneration in the retinas of mice [233]. Besides, in a study by Kim et al., the overall risk of diabetic retinopathy did not increase with DPP-4 inhibitor treatment. At the same time, it was significantly raised within 12 months after treatment initiation and later decreased with no rational explanation.

It should be noted that the impact of undesirable glycemic control on diabetic retinopathy risk in the treatment group compared to the control one cannot be excluded [234]. Sitagliptin is shown to inhibit the breakdown of the blood-retina barrier in type 1 and 2 diabetes models through the alteration made in dispersing tight junction proteins, inflammatory cytokines, like IL-1β, and apoptosis-induced cell death. Moreover, it prevented the decline of endothelial progenitor cells (EPCs) adhesion to the retinal vessels [235, 236]. In a double-blind, placebo-controlled trial scrutinizing the six-week saxagliptin treatment effect on microvascular changes in retina in type 2 diabetes, it normalized the retina capillary flow (RCF) and ameliorated central hemodynamics [237]. These findings suggest that the beneficial effects of DPP-4 inhibitors are attributed to inhibiting retinal cell nitrosative stress, inflammation, and apoptosis; however, it should be tested to determine whether these effects are related to GLP-1 [90].

Novel incretin-based agents at a glance

Semaglutide

Semaglutide, initially designed as an injectable long-acting GLP-1RA, was approved in the United States in September 2019 as an oral compound [238]. With a slight change in the amino acid sequence of natural GLP-1, semaglutide has been developed to improve albumin binding, renal clearance, DPP-4 cleavage, and gastric mucosa absorption [239]. To protect the peptide-based construction of Semaglutide from proteolytic enzymes and gastric pH, the absorption enhancer sodium N-[8-(2-hydroxybenzoyl) amino] caprylate was added to the oral tablet [239, 240]. For predictable absorption, it should be given on an empty stomach with limited volumes of water (120 ml) [241]. The impacts of Semaglutide on glycemic control and body weight reduction have been demonstrated in different clinical trials [75, 76, 242]. The PIONEER clinical trial program consisted of eight Phase 3 trials designed to evaluate the efficacy and

safety of oral semaglutide, a novel GLP-1 receptor agonist, in patients with type 2 diabetes [243]. In the PIONEER trials, oral semaglutide (14 mg) exerted a large reduction in HbA1c compared to placebo, empagliflozin, sitagliptin, liraglutide, and dulaglutide [75, 76, 242, 244, 245]. In addition, the efficacy of semaglutide in weight reduction across the PIONEER trials has been documented. Besides, 14 mg of oral semaglutide resulted in greater weight loss compared to the drugs mentioned above [75, 76, 242, 244, 245]. The cardiovascular safety of oral semaglutide was investigated in the PIONEER 6 trial. Compared to the placebo group (4.8%), the major adverse cardiovascular events were lower (3.8%) in the oral semaglutide group [120]. Given the oral dosage form of the drug compared to other GLP-1 analogues, its efficacy in glycemic control and weight loss, and its relatively safe cardiovascular profile, it can improve patient compliance.

Dual and triple agonists

Besides the GLP-1 receptor agonists with encouraging efficacy in glycemic control and weight loss, new agents acting on two or more different enteropancreatic receptors, including dual agonists acting on GLP-1/GIP or GLP-1/glucagon, and triple agonists stimulating GLP-1/GIP/glucagon receptors, are under development.

Dual agonists stimulating GLP-1 and GIP receptors (twincretins)

Tirzepaptide, a novel, once-weekly injectable agent recently approved for chronic weight management in adults with obesity or overweight and also to be used along with diet and exercise to help improve blood sugar (glucose) in adults with type 2, is a synthetic peptide with dual agonist activity on GLP-1 and GIP receptors [246, 247]. It has shown significant A1C and weight reductions in the SURPASS global clinical development program. The SURPASS trials (SURPASS-1-6) were a global series of Phase 3 clinical studies designed to evaluate the efficacy and safety of tirzepatide in various patient populations with type 2 diabetes. Across all SURPASS trials, tirzepatide consistently met its primary and key secondary endpoints for efficacy. Participants experienced sustained A1C reductions and progressive weight loss. The safety profile of tirzepatide was favorable, with gastrointestinal, nausea, diarrhoea and vomiting side effects being the most commonly reported adverse events [248, 249]. It decreases insulin resistance associated with lowering fasting insulin level and HOMA2-IR (an Insulin resistance index) that attenuates pancreatic beta cell stress to secrete insulin and improves insulin sensitivity [246]. The advantageous insulin-sensitizing action of tirzepatide seems to be mediated by weight reduction and activation of glucose, lipids and branched-chain amino acids oxidation [9]. Moreover, insulin-like growth factor-binding protein 1,2 (GFBP-1, 2) deficiency which is associated with insulin resistance and fatty liver respectively [250, 251] are increased after treatment with tirzepatide [246].

In T2DM, the conversion of proinsulin to insulin is impaired due to pancreatic beta cell dysfunction. However, tirazepatide dose-dependently attenuates proinsulin level, proinsulin/insulin and proinsulin/C-peptide ratios, indicative of ameliorated beta cell function [252, 253]. Different randomized clinical trials investigated the efficacy of various doses of tirzepatide in lowering HbA1c and body weight as monotherapy or add-on therapy to metformin in patients with T2DM when compared to dulaglutide, semaglutide or placebo [73, 254–257]. The results showed the superiority of tirzepatide in reducing body weight and glycated hemoglobin levels in a dose-dependent manner. The fasting hyperglucagonemia, commonly seen in diabetic patients that dysregulates hepatic glucose metabolism, was improved resulting in better HbA1c control in patients treated with the tirzepatide [258, 259]. Moreover, a meta-analysis study demonstrated a dose-dependent superiority of tirzepatide on glycaemic control and bodyweight reduction compared to placebo, GLP-1 RAs and basal insulin [74].

Furthermore, tirzepatide had favorable impacts on a range of cardiovascular risk factors, such as blood pressure and lipid profile. In this regard, a 26-week study demonstrated dose-dependently reduction of apoC- III, apoB levels, small low-density lipoprotein and large triglyceride-rich lipoprotein particles following treatment with tirzepatide. Besides, the effect of tirzepatide on lipid profile is mainly similar to that of semaglutide and dulaglutide, except for HDL-C level improvement which was significantly greater by tirzeatide than other drugs [260]. Moreover, several systemic inflammation and endothelial dysfunction biomarkers associated with atherosclerotic cardiovascular disease, including hsCRP, intercellular adhesion molecule-1and N-terminal-pro hormone B-type natriuretic peptide (NT-proBNP) have been shown to be suppressed after administration of tirzepatide [261].

Although the SURPASS-4 study found no tirzepatide-related cardiovascular adverse effects [262], increased heart rate without alteration in laboratory values, ECG or vital signs was reported by some studies as the serum concentration of the drug rose [255, 263]. However, in the phase 2 trial systolic and diastolic blood pressure as well as pulse rate were not significantly different in the tirzepatide treatment group compared to placebo or dulaglutide [256]. On the other hand, in the SURPASS-1 trial [257], tirzepatide in a dose of 10 mmHg lowered systolic blood pressure significantly when compared to placebo. A meta-analysis

and systematic review of GLP-1RA- related cardiovascular outcomes reported a reduction of major cardiovascular side effects and all-cause mortality [264]. Moreover, its long-term cardiovascular safety is still being investigated in different RCTs (A Study of Tirzepatide (LY3298176) Compared with Dulaglutide on Major Cardiovascular Events in Participants with Type 2 Diabetes [249, 265, 266].

It has been shown that the serum markers such as keratin-18 (K-18) and adiponectin which are associated with Non-alcoholic fatty liver disease (NAFLD) (occurring in the most of diabetic patients) have been improved after tirzepatide therapy [267, 268]. The rodent models of obesity and human studies demonstrated the inverse association between adiponectin and insulin resistance [269].

Dual agonists stimulating GLP-1 and glucagon receptors

Dual agonists targeting GLP-1 and glucagon receptors (GLP-1R/GCGR) can decrease plasma glucose and bodyweight. Improvements in energy expenditure and reductions in food intake highlight the potential value of glucagon pharmacology as a treatment for metabolic syndrome. However, the hindrance posed by its hyperglycemic effects has rendered practical implementation non-existent. Data showed that glucagon receptor agonists enhance resting calorie consumption, which leads to greater bodyweight loss compared to GLP-1 receptor stimulation alone [270–272]. While it might appear that stimulating glucagon receptors could potentially elevate plasma glucose levels, simultaneous targeting of both receptors may likely act as a compensatory mechanism to mitigate this effect. Cotadutide (MEDI0382) was the first GLP-1R/GCGR dual agonist to enter clinical trials. [273]. Cotadutide revealed an adverse-effect profile similar to liraglutide in a phase I research on healthy participants, with dose-escalation associating with vomiting, nausea, dizziness, and small elevations in heart rate. There were dose-dependent effects on peak glucose levels and food intake, with the maximum dosage (300 g) showing a significant decrease in food intake but with a high rate of adverse effects [274]. In subsequent trials (Ib, IIa) involving individuals with T2DM and those who were overweight, Cotadutide demonstrated general safety and tolerability, as well as efficacy in reducing fasting blood glucose, post-prandial glucose flactuations, body weight, and liver fat [273]. The improvements in post-prandial glucose glycemic variation found with Cotadutide administration are related to increased insulin release and postponed stomach emptying. [275]. In a long-term investigation (54 weeks), both Cotadutide dosages (100 µg and 200 µg) reduced body weight to the same extent as the GLP-1R agonist liraglutide. Cotadutide, on the other hand, had a greater rate of adverse reactions resulting in study discontinuation. However, both doses of Cotadutide resulted in marginal enhancements in total cholesterol and triglyceride levels compared to liraglutide, but these improvements were not statistically significant [276].

However, AstraZeneca, the developer of cotadutide, has revealed plans to discontinue its clinical program for the daily GLP-1R/GCGR in favor of prioritizing the advancement of AZD9550, its once-weekly injectable GLP-1RA/GCGR. [277].

SAR425899, another dual agonist, has shown glycemic control, bodyweight reduction, and reduced gastric emptying effects in human studies. [278, 279]. Sanofi's GLP-1R/GCGR dual-agonist SAR425899 has been evaluated in a phase I clinical study using single and multiple ascending subcutaneous doses daily. The experiment comprised healthy/overweight and overweight/obese type 2 diabetics. In healthy/overweight individuals and overweight/obese type 2 diabetes patients, SAR425899 reduced body weight by 5.32 kg and 5.46 kg, respectively, over 21–28 days. In the latter group, fasting plasma glucose and glycated hemoglobin decreased significantly. [278]. The research assessed the effect of SAR425899 on the functioning of β-cells in 36 obese individuals with type 2 diabetes. These patients were randomly assigned to receive either a placebo or different doses of SAR425899 (low or high) for a period of 28 days. The results demonstrated enhancements of 23% (placebo), 163%, and 95%, correspondingly. [279]. Despite the encouraging outcomes, SAR425899 was terminated during Phase II clinical trials owing to a significant prevalence of gastrointestinal side effects among patients.

Efinopegdutide also referred to as MK-6024, JNJ-64,565,111, and HM12525A, was investigated in a clinical study including individuals who were both obese and diagnosed with T2DM. During a 12-week treatment period, dosages of 5.0 mg, 7.4 mg, and 10 mg were administered once weekly, resulting in substantial decreases in body weight of -4.6%, -5.9%, and −7.2% respectively, when compared to the placebo. Significantly, there were no considerable changes seen in HbA1C%, fasting insulin, or blood sugar levels [280]. Efinopegdutide (at 5.0, 7.4, and 10.0 mg) showed significant placebo-corrected body weight decreases of 6.7%, 8.1%, and 10.0% in non-diabetic obese individuals during 26 weeks, compared to 5.8% for Liraglutide (3 mg). For all Efinopegdutide dosages, side events caused 18–32% of patient discontinuation, whereas Liraglutide had 17% [281]. Efinopegdutide is being evaluated for non-alcoholic fatty liver disease after discontinuation for obesity and T2D.

Another dual agonist, once-weekly Mazdutide (IBI362 or LY3305677), showed therapeutic effectiveness in overweight and obese individuals with dose-escalation in a 12-week phase I clinical study. Body weight decreased by

4.8% for 3 mg, 6.4% for 4.5 mg, and 6.0% for 6 mg in the research. adverse events did not cause individuals to stop therapy. Gastrointestinal adverse effects were prevalent but insignificant. Three individuals had asymptomatic cardiac issues [282]. Both 4.5 mg and 6 mg Mazdutide provide comparable fasting glucose and HbA1c decreases to 1.5 mg dulaglutide over 12 weeks, but results in more weight loss [283].

BI 456,906, a Boehringer-Ingelheim GLP-1R/GcgR dual-agonist, reduced body weight in a repeated escalating dosage phase Ib clinical research. At maximum doses, decreases were − 5.8% in 6 weeks and − 13.8% in 16 weeks. Due to gastrointestinal, vascular, and cardiac side effects, 12.5% of patients discontinued at 6 weeks and 17.8% at 16 weeks. Plasma amino acid and glucagon decreases indicated GcgR and GLP-1R targeting, according to the research [284].

NNC9204–1777, a drug developed by Novo Nordisk, reduced obesity-related body weight by 12.6% in a 12-week multiple ascending dosage phase I clinical study. The research indicated safety concerns owing to dose-dependent heart rate increases, reticulocyte count decreases, higher markers of inflammation and liver abnormalities, and reduced glucose tolerance at high doses. The study consequently concluded that NNC9204–1777 had unacceptable safety risks. [285].

Triple agonists

Triple agonists, which activate GLP-1, GIP, and glucagon receptors, are primarily in the developmental stage. Three such triple-agonists, SAR441255, LY3437943 and, HM15211 have advanced to clinical trials. SAR441255, a triple-agonist utilizing the exendin-4 sequence, exhibits enhanced glycemic control and body weight reduction in phase Ia trials involving healthy humans and phase I trials with diabetic obese monkeys [286]. LY3437943, characterized by its C20-diacid acylated compound, demonstrates a harmonious interplay of activity between GLP-1R and GcgR in vitro. In a phase Ia trial, a single dose of LY3437943 induces body weight loss comparable to four weeks of Tirzepatide, with sustained effects beyond its six-day half-life exposure. A subsequent phase Ib trial validates significant reductions in blood glucose and body weight over 12 weeks [287, 288]. HM15211, incorporating a human Fc fragment for prolonged half-life, proves effective in reducing liver fat and body weight in obese subjects with non-alcoholic fatty liver disease during phase Ia and Ib studies. It is currently undergoing phase II trials for non-alcoholic steatohepatitis [289]. Despite their promise, these triple-agonists are in early development, requiring further clinical trials to address safety concerns and confirm their effectiveness in combating obesity and diabetes.

Conclusion

Diabetes and its complications are responsible for remarkable mortality all over the world. Conventional anti-diabetic agents have not been able to control these life-threatening complications efficiently. Incretins, the gut peptide hormones, along with insulin release stimulation, have some other effects on the cardiovascular system, appetite, obesity, lipid metabolism, and others. Incretin-based therapy relying on novel anti-diabetic agents like GLP-1 agonists and DPP-4 inhibitors acting on the incretin system has shown encouraging therapeutic effects on diabetic manifestations and complications. In this regard, semaglutide, initially designed as an injectable long-acting GLP-1RA, was recently approved in the United States as an oral compound. Dual and triple agonists targeting GLP-1, GIP, and glucagon receptors such as tirzepatide and cotadutide with inspiring impacts on glycemic control, bodyweight, live fatty acid, and plasma triglyceride levels are currently under investigation.

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Declarations

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