Bull. Pharm. Sci., Assiut University, Vol. 45, Issue 2, 2022, pp. 1027-1042.

Bulletin of Pharmaceutical Sciences
Assiut University
Website: http://bpsa.journals.ekb.eg/
e-mail: bullpharm@aun.edu.eg

AN OVERVIEW OF INCRETIN-BASED THERAPIES: PHARMACOLOGY AND FUTURE PERSPECTIVES

Randa Ismail, Aliaa Anter, Asmaa I. Matouk and Gehan H. Heeba*

Department of Pharmacology and Toxicology, Faculty of Pharmacy, Minia University, El-Minia, Egypt

Glucagon-like peptide-1 (GLP-1) is a gut-derived incretin hormone that is released upon nutrient ingestion stimulating insulin secretion, suppressing glucagon secretion, and suppressing appetite and food intake which contribute to glucose homeostasis. The incretin system is impaired during type 2 diabetes mellitus (T2DM). Incretin-based therapies are gaining popularity in the clinical field nowadays. Current treatment guidelines for T2DM incorporate glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dipeptidyl peptidase 4 inhibitors (DPP-4i) as second-line agents with the advantages of low risk of hypoglycemia with good control of postprandial hyperglycemia (with short-acting GLP-1 RAs and DPP-4i) and weight loss (with GLP-1 RAs). GLP-1 RAs have more efficacy and are preferred with patients with preexisting cardiovascular disease. Growing evidence suggests that incretin-based therapies have beneficial effects on cardiovascular, liver, kidney, and nervous system disorders. The current review includes the biology of the incretin system, the pharmacology of incretin-based therapies, and their applications in experimental and clinical work.

Keywords: *Incretin; Glucagon-like peptide-1; Dipeptidyl peptidase 4 inhibitors; Type 2 diabetes mellitus*

INTRODUCTION

Diabetes has become one of the most serious and widespread chronic diseases in recent years. As reported by the international diabetes federation in 2021, there were 536.6 million people with diabetes worldwide and the prevalence of diabetes is expected to rise to 783.2 million by 2045[1]. Moreover, type 2 diabetes mellitus (T2DM) affects 90% of the diabetic population[2]. Currently available antidiabetics such as sulphonylureas, thiazolidinediones, and insulin have major drawback which includes weight gain and hypoglycemia which are attributed to their insulin-dependent mechanism of action[3]. Ingestion of oral glucose induces a higher insulin response than intravenous glucose does which is known as the incretin effect, which is mediated by incretin hormones, glucagon-like peptide-1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP). It was demonstrated that the incretin effect is impaired in patients with T2DM which has been attributed to the reduced GLP-1 secretion and defective GIP action [4]. GLP-1 has a 2-min half-life due to fast degradation by the dipeptidyl peptidase 4 (DPP-4) enzyme. Two ways are being used to overcome the disadvantage of endogenous GLP-1's short half-life and provide therapeutic benefits. The first is to utilize DPP-4 inhibitors (DPP-4i), such as sitagliptin, alogliptin, and vildagliptin, to block native GLP-1 degradation and the second is DPP-4 resistant GLP-1 receptor agonists (GLP-1 RAs) such as exenatide, liraglutide, Dulaglutide, lixisenatide and semaglutide[5]. Both DPP-4i and GLP-1 RAs have a low risk of hypoglycemia Moreover, GLP-1 RAs cause weight reduction whereas DPP-4i are weight neutral[6].

Biology of the incretin system

In response to nutrient ingestion incretin hormones, primarily GLP-1 and GIP are

Received in 2/9/2022 & Accepted in 11/9/2022

*Corresponding author: Gehan H. Heeba, E-mail: ghhh70@yahoo.com

released into the circulation and enhance insulin secretion in a glucose-dependent way. The incretin hormones collectively account for 50-70% of total post-prandial insulin secretion[7, 8]. The incretin effect is markedly impaired in patients with T2DM, and this is thought to contribute significantly to the postprandial hyperglycemia seen in these patients[7].

GLP-1 is released by enteroendocrine L-cells in the small bowel and colon. It regulates postprandial glucose levels through glucose-dependent insulin secretion, delaying gastric emptying and suppressing glucagon secretion[9]. Regarding post-prandial glucose (PPG) regulation, delaying gastric emptying is more important than insulin secretion by restricting the amount of PPG available to the beta cells. There is a blunted insulin response to GLP-1 in patients with T2DM. This defect can be corrected with GLP-1 infusions that achieve supraphysiologic levels[10]. The anti-diabetic actions of GLP-1 are illustrated in Figure 1.

K-cells which are mainly present in the duodenum and proximal gut release GIP in response to nutrients. In a glucose-dependent, it induces insulin secretion from pancreatic β-cells, but it does not appear to suppress glucagon secretion or gastric emptying[11]. Patients with T2DM exhibit significantly impaired GIP response. Unlike GLP-1, supraphysiologic GIP infusions do not increase the late phase insulin response to glucose in T2DM patients[12&13].

There is a limited pharmacological value of native GLP-1 and GIP due to their short half-life[14]. Either endogenous or exogenous GIP and GLP-1 are rapidly metabolized and inactivated by dipeptidyl peptidase 4 (DPP-4) which is present in the circulation and has a wide expression on cell surfaces[15].

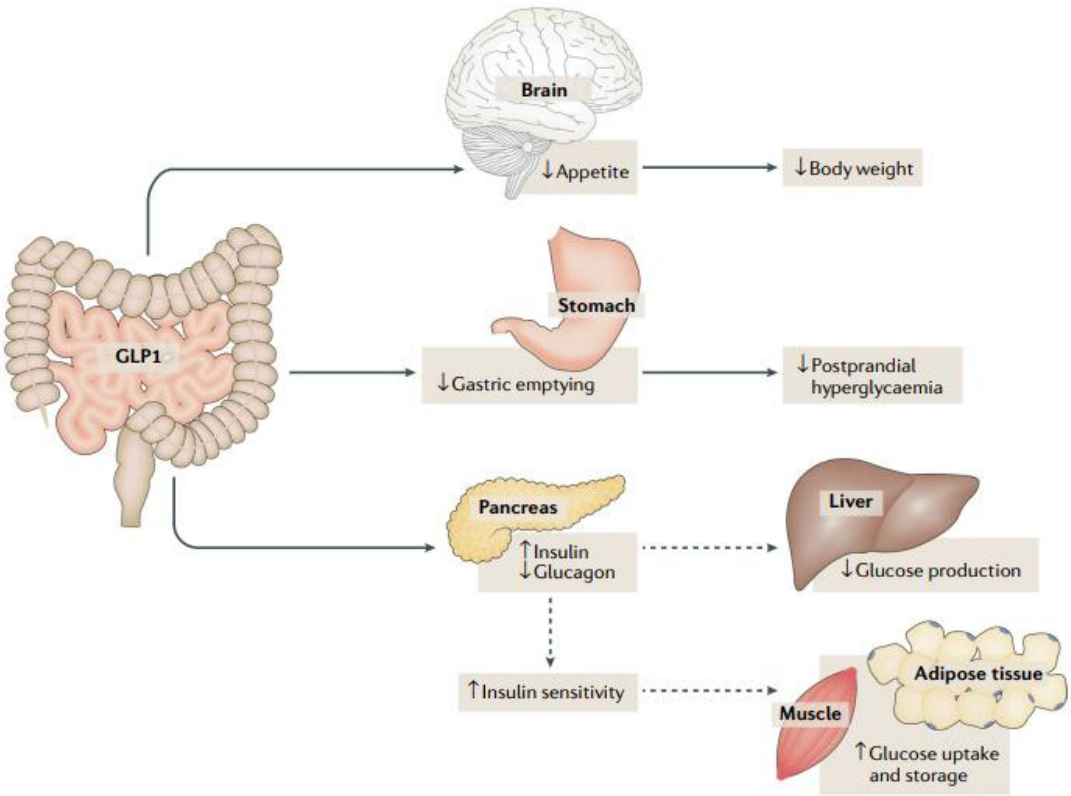

Fig. 1: Anti-diabetic actions of GLP-1. Upon nutrient ingestion, GLP-1 is released and exerts its effects through interaction with GLP-1 receptors in target tissues. GLP-1 mediates glucose-dependent insulin secretion from β-cells and glucagon suppression from α-cells of the pancreas which consequently lead to reduction of hepatic glucose production and increase of glucose uptake in adipose tissue and muscle. Gastric emptying rate is reduced, leading to lower postprandial glucose levels, while appetite is reduced, leading to decreased food intake and body weight. Solid arrows indicate direct effects mediated by GLP1. Dashed arrows show effects mediated secondary to GLP1-induced effects on pancreatic islet activity[16].

Emerging of Incretin-based therapies for T2DM treatment

Two approaches have been used to increase and sustain GLP-1-mediated benefits. The first depends on DPP-4 inhibition; this technique effectively increases the half-life of endogenous GLP-1 and GIP but is based on native incretin hormone production. The second technique involves the use of DPP-4-resistant GLP-1 RAs. GLP-1 RAs can produce supraphysiologic and long-term activation of the GLP-1 receptor. While these two groups of antihyperglycemic medicines work via comparable pathways, their efficacy and adverse effect profiles differ because of changes in the pharmacologic effect of DPP-4i and GLP-1RAs on increasing GLP-1 activity[6&17]. According to the American Diabetes Association guidelines (ADA), GLP-1 RAs and DPP-4i are listed as a second-line treatment for T2DM[18].

GLP-1 receptor agonists (GLP-1 RAs)

Exenatide is the first GLP-1 RA approved for the treatment of T2DM in 2005[19]. All GLP-1 RAs are used as subcutaneous preparations. However, oral daily preparation of semaglutide was recently approved, which showed close clinical effectiveness to once weekly subcutaneous preparation[20]. GLP-1 RAs all share the common mechanisms of action: they increase insulin secretion in response to hyperglycemia, decrease glucagon secretion at hyperglycemia or euglycemia, slow stomach emptying preventing high post-meal glycemic increase, and reduce calorie intake and weight loss.

GLP-1 RAs are recommended as the first preferred injectable glucose-lowering treatment for T2DM, even before insulin treatment, due to similar, if not superior, effectiveness for HbA1c reduction with further weight loss and no inherent risk of hypoglycemia. Moreover, according to guidelines, GLP-1 RAs are especially recommended for people with pre-existing atherosclerotic cardiovascular disease (ASCVD). Many studies reported that GLP-1 RAs can successfully prevent fatal cardiovascular events including stroke and acute myocardial infarction. GLP-1 RAs are classified into short-acting (exenatide and lixisenatide) and long-acting (once-weekly exenatide, liraglutide, albiglutide, semaglutide, and dulaglutide)[21&22]. Albiglutide was discontinued by Glaxo Smith Kline, the manufacturer of albiglutide, in 2017 not for safety concerns but due to its limited sales[23] so it is not included in this review.

Short-acting GLP-1 RAs are taken before a meal and have more pronounced effects on gastric motility and PPG levels mainly after the meal while long-acting GLP-1 RAs have a less pronounced effect on gastric emptying and PPG excursions, but a greater effect on fasting blood glucose (FBG) levels and weight loss[24&25]. Comparisons between different GLP-1 RAs are demonstrated in Table 1 and Figure 2.

Table 1: Comparison between various approved GLP-1 RAs.

GLP-1 RA	First approval	Uses	Elimination half-life	Approved doses	Frequency of administration
Exenatide[27] (b.i.d.)	2005 (USA) 2006 (Europe)	Antidiabetic	2-4 hrs	5 µg or 10 µg	Before breakfast and dinner (twice daily)
Lixisenatide[33, 55]	2013(Europe) 2016 (USA)	Antidiabetic	2.6 hrs	10 µg or 20 µg	Before breakfast (once daily)
Liraglutide[56]	2009 (Europe) 2010 (USA)	Antidiabetic Anti-obesity	12.6-14.3 hrs	0.6, 1.2 or 1.8 mg 3 mg	Once daily
Exenatide QW[29]	2012	Antidiabetic	2-4 hrs	2 mg	Once weekly
Dulaglutide[44]	2014	Antidiabetic	4.7-5.5 days	0.75 or 1.5 mg	Once weekly
Semaglutide (SC)[46]	2017 (USA) 2018 (Europe)	Antidiabetic Anti-obesity	5.7–6.7 days	0.5 or 1 mg 2.4 mg	Once weekly
Semaglutide (oral)[46]	2019	Antidiabetic	5.7–6.7 days	3, 7, or 14 mg	30 min before breakfast (once daily)

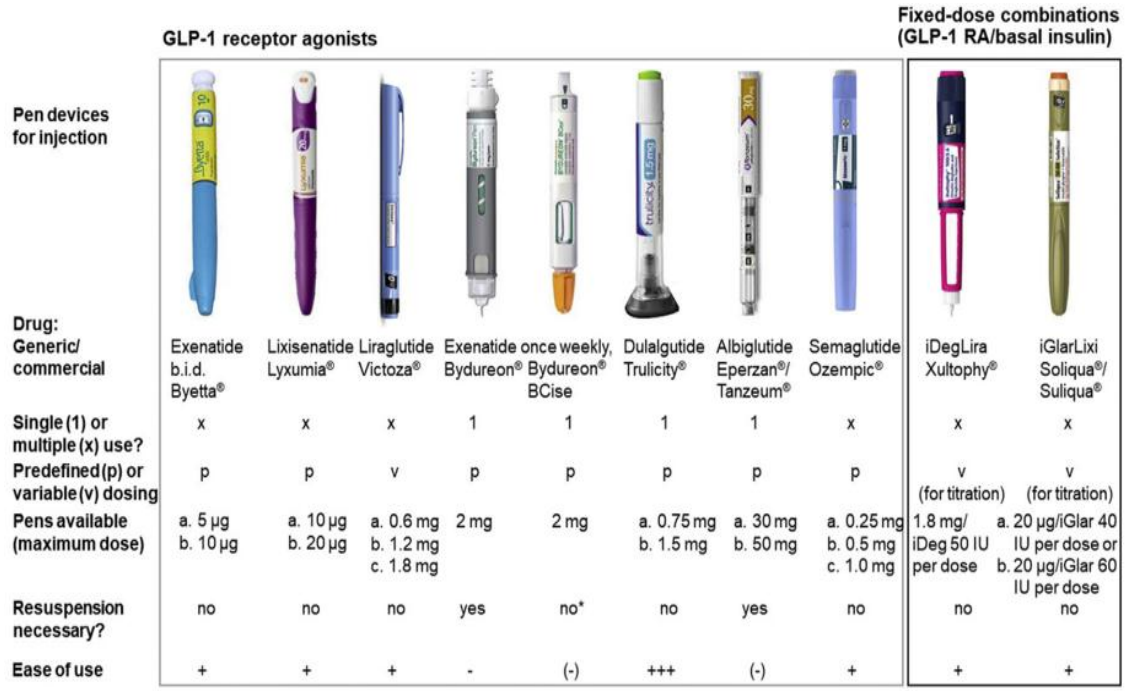

Fig. 2: Optical appearance and properties of pen injectors for approved GLP-1 RAs. [22]

Exenatide

Exenatide is a synthetic version of the natural peptide**,** exendin-4 found in Gila monster **[26].** It has 50% amino acid sequence homology with mammalian GLP-1 with the substitution of arginine amino acid with glycine at position 2, making it resistant to the proteolytic activity of DPP-4 with ~2-4 hrs half-life. It is administered twice daily (5 or 10 µg) 1 hour before breakfast and dinner with a major effect on postprandial glucose reduction**[27].** It is rapidly absorbed after subcutaneous administration and renally eliminated following proteolytic degradation by DPP-4[28]**.**

Exenatide is now available in two formulations, short-acting GLP-1 RA twice daily (BID) exenatide and long-acting GLP-1 RA 2 mg exenatide once weekly (QW). Compared with exenatide BID, exenatide QW has been demonstrated to attain a greater reduction in HbA1c with greater treatment satisfaction and less injection frequency. It has been shown to be lesser than liraglutide and semaglutide in reducing HbA1c and body weight and failed to show a significant reduction in cardiovascular risk compared to other GLP-1 RAs so within the class of GLP-1 RAs it might be selected with lower priority than other GLP-1 RAs for management of T2DM, especially for people at high cardiovascular risk[29]**.**

Lixisenatide

Lixisenatide is a short acting exendin-4-based GLP-1 RA is used once daily for management of T2DM[30]. Although its apparently short half-life, it reduces postprandial glucose levels with once daily dosing through the day which is primarily mediated via delayed gastric emptying**[31].** According to previous clinical studies, lixisenatide showed significant beneficial effects on postprandial blood glucose levels and HbA1c reduction in various settings, involving when used as monotherapy and add-on to oral antidiabetics and basal insulin[32]. The starting dose of lixisenatide is 10 µg daily for 2 weeks, which on day 15 is titrated to 20 µg daily. It is administrated within 1 hour of the first meal. Comparing to liraglutide, clinical studies suggest that lixinatide has more beneficial effect on PPG than FBG which suggest that it may be best fitted for a patient still requiring to lower PPG to decrease HbA1c although having a FBG which is within goal, such as a patient treated with basal insulin[33]**.**

Liraglutide

Liraglutide is a long-acting GLP-1 RA that was approved for the treatment of T2DM and obesity[34]. It is an analogue of endogenous human GLP-1 with 97% amino acid sequence homology. It is attached to palmitoyl acid, C-16 fatty acid, to lysine at position 26 via glutamine spacer and substitution lysine at position 34 with arginine[35]. Palmitoyl acid binds to Plasma albumin reversibly which prevents liraglutide degradation by DPP-4 and its depot formation at the site of injection with slow dissolution lead to prolongation of the duration of action[36].

Once daily liraglutide requires dose titration, it is usually started with once daily 0.6 mg in order to tolerate gastrointestinal adverse effects then the dose is titrated every week. To achieve glycemic goals, the dose can be titrated to 1.8 mg daily[37& 38].

Liraglutide can effectively reduce HbA1c, PPG and FBG levels. It is suggested as monotherapy for T2DM in adjunct to exercise and diet. Moreover, it is considered when metformin is unacceptable due to contraindications and intolerance. To improve glycemic control of long term T2DM, it can be used in combination with oral antidiabetics or insulin[39]. It is used now as a weight loss drug for obesity treatment even in non-diabetic patients in 3 mg daily dose[40&41]. It reduces body weight and diminishes systolic pressure[42]

Dulaglutide

Dulaglutide is a GLP-1 RA with 90% amino acid sequence homology to native GLP-1. It binds to constant fragment (Fc) of human IgG4 which protects it from proteolytic activity of DPP-4 and its large size avoids it from renal clearance so long half time[43]. a long acting once weekly GLP-1 RA was approved for treatment of T2DM in doses of 0.75 or 1.5 mg and it is used as a monotherapy or as add-on therapy to oral antihyperglycemic and insulin. It provides effective long-term glycemic control and weight loss, even in high-risk individuals (e.g., elderly or obese patients, as well as those with stage 3 or 4 chronic kidney disease (CKD) and/or cardiovascular (CV) disease)[44]. Clinical studies showed that dulaglutide is non inferior to liraglutide but superior to exenatide twice daily in HbA1c reduction[45].

Semaglutide

The structure of semaglutide is similar to liraglutide, with a free fatty acid side chain, but the half-life is much longer, apparently caused by even stronger binding to albumin[20]. Semaglutide is a long acting once weekly GLP-1 RA was approved for management of T2DM with a dose of 1 mg and obesity with a dose of 2.4 mg administrated subcutaneously. Recently, oral semaglutide was approved with a maximum 14 mg daily for management of T2DM[46]. Previous studies showed that semaglutide provides benefits beyond its long-term effects, it has more pronounced effects on weight loss and glucose lowering effects compared with liraglutide and other GLP-1 RAs[47-49]

Adverse effects of GLP-1 receptor agonists

The most reported side effects with GLP-1 RAs are gastrointestinal side effects as nausea, vomiting and diarrhea which may lead to drug discontinuation. They mostly occur upon treatment initiation with any of the GLP-1 RAs or after the dose increase during the up-titration regimens. Up to 25% of patients treated with GLP-1 RAs reported nausea while diarrhea or vomiting is reported in up to 10%. It is suggested that these adverse effects probably not related to gastrointestinal effects of GLP-1 RAs, e.g., delayed gastric emptying, but instead are related by direct interactions of GLP-1 RAs with GLP-1 receptors which located most likely in the brain stem (area postrema). For most patients, these are temporary, self-limited episodes that resolve on their own, even with continued therapy[21& 50].

Long-acting GLP-1 RAs appear to have enhanced gastrointestinal tolerability, and the incidence of nausea and vomiting decreases over time[24, 51] this may be due to tolerance development[52] However, they are more related to diarrhea[50]. The up-titration regimens are recommended to decrease the incidence of these side effects[22]. Several potential side effects, such as pancreatic cancer, acute pancreatitis and thyroid cancer, were uncertain[53& 54].

Pharmacological application of GLP-1 RAs on experimental and clinical work

Various studies showed that GLP-1 RAs have several effects beyond their pancreatic actions. GLP-1 RAs have anti-infectious, neuroprotective, metabolic regulatory and cardiovascular protective effects therefore, the potential value and therapeutic application of

GLP-1 RAs in diseases other than diabetes has become a research focus[57].

Several studies demonstrated the renoprotective effects of GLP-1 RAs as exenatide against diabetic kidney disease (DKD) which may be due to their glycemic control, antioxidant, antifibrotic, anti-inflammatory and anti-apoptotic effects[58, 59]. Besides, their modulation to natriuresis and diuresis affect sodium homeostasis in the kidney[60]. Liraglutide improved renal function in DKD rat model by decreasing expression of protein kinase B/mammalian target of rapamycin (Akt/mTOR) pathway[61].

It has been shown in secondary analysis of clinical trials that GLP-1 RAs to delay the onset and progression of diabetic nephropathy. GLP-1 RAs are considered more promising than DPP-4i in DKD the main cause is unknown, but it may be attributed to that the inhibition of DPP-4 leads to a small elevation in endogenous GLP-1 compared to supraphysiological levels attained by GLP-1 RAs[60].

It was demonstrated that GLP-1 RAs exert cardioprotective effects through anti-inflammatory effects, decreasing myocardial ischemia injury, alterations in lipid synthesis and secretion, and alleviation of endothelial dysfunction[62]. Moreover, GLP-1 RAs reduced blood pressure in a metanalysis study conducted by Wang et al.[63]. Semaglutide and liraglutide have been found to decrease blood pressure and lipid blood levels which may have a role in reducing CVDs and atherosclerosis[64-66].

Both liraglutide and exenatide showed in preclinical studies to antagonize the neurodegeneration and Alzheimer's disease (AD) progression even in non-diabetic mice[67, 68].Moreover, GLP-1 RAs such as exenatide, lixisenatide, liraglutide, semaglutide and geniposide which is a novel GLP-1 RA have showed neuroprotective effects on animal models of Parkinson's disease (PD) by protecting dopaminergic neurons via anti-inflammatory and anti-apoptotic effects[69-72]. Exenatide showed a neuroprotective effect against stroke in a preclinical study via antioxidant and anti-inflammatory effects[73]. Additionally, in cerebral ischemia/reperfusion-injured diabetic rats, lixisenatide was shown to be superior to glimepiride as a neuroprotective agent by improving behavioral/neurological functions and exhibiting antioxidant, anti-inflammatory and antiapoptotic properties[74].

GLP-1 RAs as liraglutide showed beneficial effects on women with polycystic ovary syndrome (PCO) which was attributed to weight loss, improvement of insulin resistance and positive effect on androgens level[75-78]. It is suggested that GLP-1 RAs have hepatoprotective effects against non-alcoholic fatty liver disease (NAFLD) as many studies found that GLP-1RAs may have direct effects on lipotoxicity, fatty acid oxidation, adipogenesis, and cytokines related to fibrosis and hepatitis[79, 80]. Liraglutide showed anti-fibrotic and anti-inflammatory properties in a model of NAFLD in mice[81].

Dipeptidyl peptidase 4 inhibitors (DPP4i)

Since 2006, DPP4i, gliptins, are available for T2DM management. All members of DPP4i are small and orally administered molecules. DPP4i do not have intrinsic glucose-lowering activity, therefore their effectiveness as anti-hyperglycemic agents are associated directly to their ability to inhibit DPP-4 activity and is mediated via the effects of the protected substrates, incretin hormones mainly GLP-1. The risk of hypoglycemia is low as the effects of GLP-1 are glucose dependent[16]. Sitagliptin, vildagliptin, saxagliptin and alogliptin and linagliptin are widely available globally while, gemigliptin, anagliptin and teneliptin are used mainly in the Asian countries[82]. DPP4i are incorporated in treatment of T2DM without ASCVD according to ADA guidelines[18]. It was demonstrated that DPP4i have moderate glucose-lowering effects and are well tolerated[83]. The comparison between the most common DPP4i are shown in table 2.

Table 2: Comparison between common approved DPP-4 inhibitors.

DPP-4i	First approval	Elimination half-life	Approved doses	Frequency of administration
Sitagliptin[84, 86]	2006	12.5 hrs	100 mg	Once daily
Vildagliptin[18, 102]	2007	2 hrs	50 mg	Twice daily
Saxagliptin[91, 103]	2009	2.5 hrs	5 mg	Once daily
Alogliptin [104, 105]	2013	21 hrs	25 mg	Once daily
Linagliptin[94, 97]	2011	12 hrs	5 mg	Once daily

Sitagliptin

In 2006, sitagliptin was the first DPP4i to be approved with convenient once-daily regimen. It is used as monotherapy or in combination with other antidiabetics for T2DM management in adults with good efficacy and tolerability and low risk of hypoglycemia and bodyweight neutral effects and not related to increased CVD risk[84]. It is a derivative of β-amino acid-based triazolopiperazine [85] which does not undergo significant metabolism with a half-life 12.5 hrs[86].

Vildagliptin

Vildagliptin was the second approved DPP-4i which belongs to the chemical class cyanopyrrolidine[87]. It undergoes significant hydrolysis with short half-life ~2 hrs so it is administered twice daily[18&86]. It is well tolerated when administered as monotherapy or in combination with other anti-diabetics for T2DM management[88]. There is a fixed dose of vildagliptin/metformin combination available in the market. Vildagliptin improves glycemic control in the elderly and in patients with moderate to severe renal impairment[89].

Saxagliptin

Saxagliptin has a methanoprolinenitrile structure which was approved in 2009 [90]. It is a highly potent, orally active, competitive and selective DPP-4i which used in T2DM treatment at doses of 2.5 or 5 mg once daily. It is mainly metabolized by cytochrome P450 (CYP) 3A4/5 to 5-hydroxy saxagliptin which is an active metabolite so once daily 2.5 mg is

recommended upon coadministration with strong CYP inhibitors and in patients suffer from moderate or severe renal impairment due to elevated saxagliptin exposure[91]. There is a concern about the increased risk of heart failure with the use of saxagliptin which was reported by a study conducted to evaluate the cardiovascular outcomes of saxagliptin[92]. The food and drug administration (FDA) recently approved a fixed-dose combination (FDC) product containing saxagliptin and a sodium glucose cotransporter-2 (SGLT2) inhibitor; it has been suggested that the drugs contained in this combination have additive effects on blood glucose lowering and that the potential risk of heart failure linked to the use of saxagliptin alone may be minimized using this drug combination[83].

Alogliptin

Alogliptin was approved for T2DM management as monotherapy, with a dose of 25 mg or as add-on /combination therapy with other antidiabetics as metformin or pioglitazone, with a dose of 12.5 or 25 mg It is generally well tolerated in T2DM patients, including the elderly, those with renal and/or hepatic impairment, and patients who are high risk of cardiovascular events[93].

Linagliptin

Linagliptin is a methylxanthine derivative which was approved in 2011[94]. It does not undergo significant metabolism so has a long half-life ~12 hrs[86&95]. Unlike other DPP-4i, it does not require dose adjustment according to the renal function as it is minimally cleared through the kidney but most of the dose is excreted in the bile and eliminated with the feces[86&95&96]. It is used as monotherapy with 5 mg once daily or in combination with other

antidiabetics as metformin in a dose 2.5 mg twice daily for T2DM treatment [97].

Adverse effects of DPP-4 inhibitors

In both short and long-term studies, DPP-4i were well tolerated. they are weight neutral with no increased risk of hypoglycemia (in the absence of concurrent therapy with insulin or sulfonylureas)[98]. The most common described adverse effects including nasal pharyngitis, headache, and upper respiratory tract infections. Minimal elevated risk of gastrointestinal side effects was reported by some studies with sitagliptin[6].

Post-marketing reports have linked sitagliptin, linagliptin, saxagliptin, and alogliptin to hypersensitivity responses such as anaphylaxis, angioedema, and more severe blistering skin conditions such as Stevens-Johnson syndrome[99]. Some of DPP-4i, but not all, have been linked to severe joint pain [100]. There has been considerable concern about an increase in pancreatitis and possibly pancreatic cancer with DPP-4i[101].

Pharmacological application of DPP-4i on experimental and clinical work

Several clinical and experimental studies demonstrated that DPP-4i have beneficial effects on diabetic nephropathy which are mediated by anti-oxidant, anti-inflammatory and anti-fibrotic effects independent of their glycemic control[106]. Sitagliptin was found to exert renoprotective effects in rats with T2DM[58] and renal ischemia reperfusion injury in diabetic rats[107] through antioxidant, anti-fibrotic, anti-inflammatory and anti-apoptotic properties. Saxagliptin lowered serum blood urea nitrogen and creatinine levels in animal models of T1DM and T2DM as well as low levels of TNF-α, C-reactive protein, IL-1, IL-6, and IL-18 levels[106]. Linagliptin evoked several renoprotective benefits in animal models of kidney disease, including reductions in glomerulosclerosis, albuminuria, and tubulointerstitial fibrosis, independent of changes in GLP-1 and glucose levels[108]. As observed in clinical studies, DPP-4i have modest renoprotective effects compared to GLP-1 RAs as they only attenuate albuminuria with no effect on estimated glomerular filtration rate (eGFR)[60]. Moreover, DPP-4i showed nephroprotective effects on non-diabetic CKD models. Sitagliptin showed anti-inflammatory effects on a model of salt-hypertension CKD[109].

DPP-4i showed neuroprotective effects in various preclinical and clinical studies. Linagliptin was suggested to have neuroprotective effects through upregulation of Akt/mTOR pathway, anti-inflammatory and antiapoptotic effects in mice with mild hyperglycemia and stroke [110]. Alogliptin showed neurovascular protective effects in a stroke model of middle cerebral artery occlusion through amelioration of disrupted vascular permeability of the brain and cerebral infarction and restoration of the expression of occludin and zona occludens-1 proteins of endothelial tight junction[111]. Vildagliptin protected against diabetic peripheral neuropathy development through restoration of Na^+/K^+ ATPase activity, improvement of nociception and partial recovery of nerve conduction velocity deficit[112]. Preclinical and clinical studies showed that sitagliptin has neuroprotective effect by antioxidant, anti-inflammatory and anti-apoptotic properties against Alzheimer's disease[113].

DPP-4i showed some favorable cardiac and vascular benefits in preliminary studies, and initial data from clinical trials suggested a decrease in major cardiovascular events. However, later CV outcome trials with saxagliptin, alogliptin, and sitagliptin demonstrated noninferiority but no superiority compared to placebo in patients with T2DM and high CV risk. Saxagliptin was linked to an unexpectedly greater incidence of heart failure hospitalization [114].

Different DPP-4i showed hepatoprotective effects. Sitagliptin ameliorated hepatic ischemia reperfusion injury induced by Pringle's maneuver in rats by modulation of nuclear factor erythroid derived 2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) signaling pathway[115]. Vildagliptin showed hepatoprotective effects in a model of diabetic nonalcoholic steatohepatitis and associated liver fibrosis in rats through antioxidant, anti-inflammatory and anti-fibrotic properties[116]. Linagliptin had hepatoprotective effects against carbon tetrachloride induced liver fibrosis in mice by suppression of transforming growth factor beta 1 (TGF-β1), oxidative stress and mTOR[117].

Alogliptin attenuated doxorubicin-induced testicular toxicity via downregulation of TGF-

β1/ NF-κB (nuclear factor kappa B) signaling pathway, oxidative stress and apoptosis[118].

Conclusion

There are different agents used for management of T2DM including GLP-1 RAs and DPP-4i. GLP-1 RAs and DPP-4i have advantages of low risk of hypoglycemia and weight reduction with GLP-1 RAs. GLP-1 RAs are often favored over DPP-4i due to better glucose reduction and clinically meaningful weight loss shown in clinical trials. Moreover, GLP-1 RAs showed cardiovascular protective effects, but DPP-4i failed to show cardiovascular benefits, so GLP-1 RAs are preferred by the guidelines in patients with preexisting Atherosclerotic Cardiovascular Disease (ASCVD) risk. Both GLP-1 RAs and DPP-4i showed benefits in many disorders as nervous system, liver, kidney disorders so they may have therapeutic potential in diseases other than diabetes which become a research hotspot.

REFERENCES

1. H. Sun,P. Saeedi,S. Karuranga,M. Pinkepank *et al.*, "IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045," ***Diabetes Res Clin Pract,*** 183,109119 (2022).
2. S. Khunti,M. J. Davies and K. Khunti, "Clinical inertia in the management of type 2 diabetes mellitus: a focused literature review", ***ABCD (Diabetes Care),***15(2), 65-69 (2015).
3. "Diagnosis and classification of diabetes mellitus," ***Diabetes Care,*** 35 Suppl 1(Suppl 1), S64-S71 (2012).
4. K. Kazafeos, "Incretin effect: GLP-1, GIP, DPP4," ***Diabetes Res Clin Pract,*** 93 Suppl 1(S32-36 (2011).
5. L. Sun,C. Wang,Y. Dai,Y. Chu *et al.*, "Coumaglutide, a novel long-acting GLP-1 analog, inhibits β-cell apoptosis in vitro and invokes sustained glycemic control in vivo," ***Eur J Pharmacol,*** 767, 211-219 (2015).
6. M. P. Gilbert and R. E. Pratley, "GLP-1 Analogs and DPP-4 Inhibitors in Type 2 Diabetes Therapy: Review of Head-to-Head Clinical Trials," ***Front Endocrinol (Lausanne),*** 11, 178 (2020).
7. M. Nauck,F. Stöckmann,R. Ebert and W. Creutzfeldt, "Reduced incretin effect in type 2 (non-insulin-dependent) diabetes," ***Diabetologia*** 29(1), 46-52 (1986).
8. M. A. Nauck,E. Homberger,E. G. Siegel,R. C. Allen *et al.*, "Incretin effects of increasing glucose loads in man calculated from venous insulin and C-peptide responses," ***J Clin Endocrinol Metab,*** 63(2), 492-498 (1986).
9. D. J. Drucker, "The biology of incretin hormones," ***Cell Metab,*** 3(3), 153-165 (2006).
10. M. A. Nauck,U. Niedereichholz,R. Ettler,J. J. Holst *et al.*, "Glucagon-like peptide 1 inhibition of gastric emptying outweighs its insulinotropic effects in healthy humans," ***Am J Physiol,*** 273(5), E981-988 (1997).
11. J. F. Gautier,S. P. Choukem and J. Girard, "Physiology of incretins (GIP and GLP-1) and abnormalities in type 2 diabetes," ***Diabetes Metab,*** 34 Suppl 2, S65-72 (2008).
12. N. Mentis,I. Vardarli,L. D. Köthe,J. J. Holst *et al.*, "GIP does not potentiate the antidiabetic effects of GLP-1 in hyperglycemic patients with type 2 diabetes," ***Diabetes,*** 60(4), 1270-1276 (2011).
13. T. Vilsbøll,T. Krarup,S. Madsbad and J. J. Holst, "Defective amplification of the late phase insulin response to glucose by GIP in obese Type II diabetic patients," ***Diabetologia,*** 45(8), 1111-1119 (2002).
14. R. Mentlein,B. Gallwitz and W. E. Schmidt, "Dipeptidyl-peptidase IV hydrolyses gastric inhibitory polypeptide, glucagon-like peptide-1(7-36)amide, peptide histidine methionine and is responsible for their degradation in human serum," ***Eur J Biochem,*** 214(3), 829-835 (1993).
15. T. P. Vahl,B. W. Paty,B. D. Fuller,R. L. Prigeon *et al.*, "Effects of GLP-1-(7-36) NH2, GLP-1-(7-37), and GLP-1- (9-36) NH2 on intravenous glucose tolerance and glucose-induced insulin secretion in healthy humans," ***J Clin Endocrinol Metab,*** 88(4), 1772-1779 (2003).
16. C. F. Deacon, "Dipeptidyl peptidase 4 inhibitors in the treatment of type 2

diabetes mellitus," ***Nat Rev Endocrinol*** 16(11), 642-653 (2020).
17. J. J. Neumiller, "Incretin-based therapies," ***Med Clin North Am,*** 99(1), 107-129 (2015).
18. B. Draznin,V. R. Aroda,G. Bakris,G. Benson *et al.,* "9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2022," ***Diabetes Care,*** 45(Suppl 1), S125-s143 (2022).
19. F. K. Knop,A. Brønden and T. Vilsbøll, "Exenatide: pharmacokinetics, clinical use, and future directions," ***Expert Opin Pharmacother,*** 18(6), 555-571 (2017).
20. M. Davies,T. R. Pieber,M. L. Hartoft-Nielsen,O. K. H. Hansen *et al.,* "Effect of Oral Semaglutide Compared With Placebo and Subcutaneous Semaglutide on Glycemic Control in Patients With Type 2 Diabetes: A Randomized Clinical Trial," ***Jama,*** 318(15), 1460-1470 (2017).
21. M. A. Nauck,J. J. Meier, "MANAGEMENT OF ENDOCRINE DISEASE: Are all GLP-1 agonists equal in the treatment of type 2 diabetes?," ***Eur J Endocrinol,*** 181(6), R211-r234 (2019).
22. M. A. Nauck,D. R. Quast,J. Wefers and J. J. Meier, "GLP-1 receptor agonists in the treatment of type 2 diabetes - state-of-the-art," ***Mol Metab,*** 46(101102 (2021).
23. M. S. Rendell, "Albiglutide for the management of type 2 diabetes," ***Expert Rev Endocrinol Metab,*** 13(1), 1-8 (2018).
24. J. B. Buse,J. Rosenstock,G. Sesti,W. E. Schmidt *et al.,* "Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6)," ***Lancet,*** 374(9683), 39-47 (2009).
25. C. Wysham,T. Blevins,R. Arakaki,G. Colon *et al.,* "Erratum. Efficacy and Safety of Dulaglutide Added Onto Pioglitazone and Metformin Versus Exenatide in Type 2 Diabetes in a Randomized Controlled Trial (AWARD-1). Diabetes Care 2014,37:2159-2167," ***Diabetes Care,*** 38(7), 1393-1394 (2015).
26. J. Eng,W. A. Kleinman,L. Singh,G. Singh *et al.,* "Isolation and characterization of exendin-4, an exendin-3 analogue, from Heloderma suspectum venom. Further evidence for an exendin receptor on dispersed acini from guinea pig pancreas," ***J Biol Chem,*** 267(11), 7402-7405 (1992).
27. O. G. Kolterman,J. B. Buse,M. S. Fineman,E. Gaines *et al.,* "Synthetic exendin-4 (exenatide) significantly reduces postprandial and fasting plasma glucose in subjects with type 2 diabetes," ***J Clin Endocrinol Metab,*** 88(7), 3082-3089 (2003).
28. C. Triplitt,R. A. DeFronzo, "Exenatide: first-in-class incretin mimetic for the treatment of Type 2 diabetes mellitus," ***Expert Rev Endocrinol Metab,*** 1(3), 329-341 (2006).
29. J. Inaishi,Y. Saisho, "Exenatide Once Weekly for Management of Type 2 Diabetes: A Review," ***Clin Pharmacol***, 14, 19-26 (2022).
30. L. Van Gaal,E. Souhami,T. Zhou and R. Aronson, "Efficacy and safety of the glucagon-like peptide-1 receptor agonist lixisenatide versus the dipeptidyl peptidase-4 inhibitor sitagliptin in young (<50 years) obese patients with type 2 diabetes mellitus," ***J Clin Transl Endocrinol,*** 1(2), 31-37 (2014).
31. J. J. Meier, "GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus," ***Nat Rev Endocrinol,*** 8(12), 728-742 (2012).
32. Y. Handelsman,M. H. A. Muskiet and G. S. Meneilly, "Combining GLP-1 Receptor Agonists and Basal Insulin in Older Adults with Type 2 Diabetes: Focus on Lixisenatide and Insulin Glargine," ***Adv Ther,*** 36(12), 3321-3339 (2019).
33. D. McCarty,M. Coleman and C. L. Boland, "Lixisenatide: A New Daily GLP-1 Agonist for Type 2 Diabetes Management," ***Ann Pharmacother,*** 51(5), 401-409 (2017).
34. N. Mikhail, "Cardiovascular Effects of Liraglutide," ***Curr Hypertens Rev,*** 15(1), 64-69 (2019).
35. K. Madsen,L. B. Knudsen,H. Agersoe,P. F. Nielsen *et al.,* "Structure-activity and protraction relationship of long-acting glucagon-like peptide-1 derivatives: importance of fatty acid length, polarity,

and bulkiness," ***J Med Chem,*** 50(24), 6126-6132 (2007).
36. D. B. Steensgaard, J. K. Thomsen, H. B. Olsen and L. B. Knudsen, "The molecular basis for the delayed absorption of the once-daily human GLP-1 analoge, liraglutide," ***Diabetes*** 57, A164(2008).
37. American Diabetes Association"8. Obesity Management for the Treatment of Type 2 Diabetes: Standards of Medical Care in Diabetes-2019," ***Diabetes Care,*** 42(Suppl 1), S81-S89 (2019).
38. I. Romera,A. Cebrián-Cuenca,F. Álvarez-Guisasola,F. Gomez-Peralta *et al.,* "A Review of Practical Issues on the Use of Glucagon-Like Peptide-1 Receptor Agonists for the Management of Type 2 Diabetes," ***Diabetes Ther,*** 10(1), 5-19 (2019).
39. M. Hasanzad,N. Sarhangi,S. Nikfar,S. N. Ostad *et al.,* "A narrative review of current trends in liraglutide: insights into the unmet needs in management of type 2 diabetes and obesity," ***J Diabetes Metab Disord,*** 19(2), 1863-1872 (2020).
40. A. Astrup,R. Carraro,N. Finer,A. Harper *et al.,* "Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide," ***Int J Obes (Lond),*** 36(6), 843-854 (2012).
41. M. E. Lean,R. Carraro,N. Finer,H. Hartvig *et al.,* "Tolerability of nausea and vomiting and associations with weight loss in a randomized trial of liraglutide in obese, non-diabetic adults," ***Int J Obes (Lond),*** 38(5), 689-697 (2014).
42. K. B. Harris and D. J. McCarty, "Efficacy and tolerability of glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes mellitus," ***Ther Adv Endocrinol Metab,*** 6(1), 3-18 (2015).
43. W. Glaesner,A. M. Vick,R. Millican,B. Ellis *et al.,* "Engineering and characterization of the long-acting glucagon-like peptide-1 analogue LY2189265, an Fc fusion protein," ***Diabetes Metab Res Rev,*** 26(4), 287-296 (2010).
44. L. J. Scott, "Dulaglutide: A Review in Type 2 Diabetes," ***Drugs*** 80(2), 197-208 (2020).
45. D. Sharma,S. Verma,S. Vaidya,K. Kalia *et al.,* "Recent updates on GLP-1 agonists: Current advancements & challenges," ***Biomed Pharmacother,*** 108(952-962 (2018).
46. A. M. Chao,J. S. Tronieri,A. Amaro,T. A. Wadden, "Semaglutide for the treatment of obesity," ***Trends Cardiovasc Med, S1050-1738(21)00158-4,*** (2021).
47. A. J. Ahmann,M. Capehorn,G. Charpentier,F. Dotta *et al.,* "Efficacy and Safety of Once-Weekly Semaglutide Versus Exenatide ER in Subjects With Type 2 Diabetes (SUSTAIN 3): A 56-Week, Open-Label, Randomized Clinical Trial," ***Diabetes Care,*** 41(2), 258-266 (2018).
48. I. Lingvay,C. V. Desouza,K. S. Lalic,L. Rose *et al.,* "A 26-Week Randomized Controlled Trial of Semaglutide Once Daily Versus Liraglutide and Placebo in Patients With Type 2 Diabetes Suboptimally Controlled on Diet and Exercise With or Without Metformin," ***Diabetes Care,*** 41(9), 1926-1937 (2018).
49. R. E. Pratley,V. R. Aroda,I. Lingvay,J. Lüdemann *et al.,* "Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial," ***Lancet Diabetes Endocrinol,*** 6(4), 275-286 (2018).
50. K. Bettge,M. Kahle,M. S. Abd El Aziz,J. J. Meier *et al.,* "Occurrence of nausea, vomiting and diarrhoea reported as adverse events in clinical trials studying glucagon-like peptide-1 receptor agonists: A systematic analysis of published clinical trials," ***Diabetes Obes Metab,*** 19(3), 336-347 (2017).
51. D. J. Drucker,J. B. Buse,K. Taylor,D. M. Kendall *et al.,* "Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study," ***Lancet,*** 372(9645), 1240-1250 (2008).
52. C. Orskov,S. S. Poulsen,M. Møller and J. J. Holst, "Glucagon-like peptide I receptors in the subfornical organ and the area postrema are accessible to circulating glucagon-like peptide I," ***Diabetes,*** 45(6), 832-835 (1996).

53. P. C. Butler, M. Elashoff, R. Elashoff and E. A. J. D. c. Gale, "A critical analysis of the clinical use of incretin-based therapies: are the GLP-1 therapies safe?," 36(7), 2118-2125 (2013).
54. M. A. Nauck and N. Friedrich, "Do GLP-1-based therapies increase cancer risk?," ***Diabetes Care,*** 36 Suppl 2(Suppl 2), S245-S252 (2013).
55. R. H. Becker,J. Stechl,A. Steinstraesser,G. Golor *et al.*, "Lixisenatide reduces postprandial hyperglycaemia via gastrostatic and insulinotropic effects," ***Diabetes Metab Res Rev,*** 31(6), 610-618 (2015).
56. E. W. Iepsen,S. S. Torekov and J. J. Holst, "Liraglutide for Type 2 diabetes and obesity: a 2015 update," ***Expert Rev Cardiovasc Ther,*** 13(7), 753-767 (2015).
57. X. Zhao,M. Wang,Z. Wen,Z. Lu *et al.*, "GLP-1 Receptor Agonists: Beyond Their Pancreatic Effects," ***Front Endocrinol (Lausanne)*** 12, 721135 (2021).
58. H. A. Habib,G. H. Heeba and M. M. A. Khalifa, "Comparative effects of incretin-based therapy on early-onset diabetic nephropathy in rats: Role of TNF-α, TGF-β and c-caspase-3," ***Life Sci,*** 278, 119624 (2021).
59. H. A. Habib,G. H. Heeba and M. M. A. Khalifa, "Effect of combined therapy of mesenchymal stem cells with GLP-1 receptor agonist, exenatide, on early-onset nephropathy induced in diabetic rats," ***Eur J Pharmacol,*** 892, 173721 (2021).
60. R. Z. Alicic,E. J. Cox,J. J. Neumiller and K. R. Tuttle, "Incretin drugs in diabetic kidney disease: biological mechanisms and clinical evidence," ***Nat Rev Nephrol,*** 17(4), 227-244 (2021).
61. T. T. Liao,L. B. Zhao,H. Liu,R. L. He *et al.*, "Liraglutide protects from renal damage via Akt-mTOR pathway in rats with diabetic kidney disease," ***Eur Rev Med Pharmacol Sci,*** 23(3 Suppl), 117-125 (2019).
62. A. Sharma and S. Verma, "Mechanisms by Which Glucagon-Like-Peptide-1 Receptor Agonists and Sodium-Glucose Cotransporter-2 Inhibitors Reduce Cardiovascular Risk in Adults With Type 2 Diabetes Mellitus," ***Can J Diabetes,*** 44(1), 93-102 (2020).
63. B. Wang,J. Zhong,H. Lin,Z. Zhao *et al.*, "Blood pressure-lowering effects of GLP-1 receptor agonists exenatide and liraglutide: a meta-analysis of clinical trials," ***Diabetes Obes Metab,*** 15(8), 737-749 (2013).
64. S. Hamal,L. Cherukuri,K. Shaikh,A. Kinninger *et al.*, "Effect of semaglutide on coronary atherosclerosis progression in patients with type II diabetes: rationale and design of the semaglutide treatment on coronary progression trial," ***Coron Artery Dis,*** 31(3), 306-314 (2020).
65. L. B. Knudsen and J. Lau, "The Discovery and Development of Liraglutide and Semaglutide," ***Front Endocrinol (Lausanne),*** 10,155 (2019).
66. X. Ma,Z. Liu,I. Ilyas,P. J. Little *et al.*, "GLP-1 receptor agonists (GLP-1RAs): cardiovascular actions and therapeutic potential," ***Int J Biol Sci,*** 17(8), 2050-2068 (2021).
67. T. R. Bomfim,L. Forny-Germano,L. B. Sathler,J. Brito-Moreira *et al.*, "An anti-diabetes agent protects the mouse brain from defective insulin signaling caused by Alzheimer's disease- associated Aβ oligomers," ***J Clin Invest,*** 122(4), 1339-1353 (2012).
68. P. L. McClean,V. Parthsarathy,E. Faivre and C. Hölscher, "The diabetes drug liraglutide prevents degenerative processes in a mouse model of Alzheimer's disease," ***J Neurosci,*** 31(17), 6587-6594 (2011).
69. D. Athauda and T. Foltynie, "The glucagon-like peptide 1 (GLP) receptor as a therapeutic target in Parkinson's disease: mechanisms of action," ***Drug Discov Today,*** 21(5), 802-818 (2016).
70. Y. Chen,Y. Zhang,L. Li,C. Hölscher, "Neuroprotective effects of geniposide in the MPTP mouse model of Parkinson's disease," ***Eur J Pharmacol,*** 768, 21-27 (2015).
71. W. Liu,J. Jalewa,M. Sharma,G. Li *et al.*, "Neuroprotective effects of lixisenatide and liraglutide in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of Parkinson's disease," ***Neuroscience,*** 303,42-50 (2015).

72. L. Zhang,L. Zhang,L. Li,C. Hölscher, "Semaglutide is Neuroprotective and Reduces α-Synuclein Levels in the Chronic MPTP Mouse Model of Parkinson's Disease," ***J Parkinsons Dis,*** 9(1), 157-171 (2019).
73. V. Darsalia,M. Larsson,D. Nathanson,T. Klein *et al.*, "Glucagon-like receptor 1 agonists and DPP-4 inhibitors: potential therapies for the treatment of stroke," ***J Cereb Blood Flow Metab,*** 35(5), 718-723 (2015).
74. R. G. Abdel-Latif,G. H. Heeba,A. Taye and M. M. A. Khalifa, "Lixisenatide, a novel GLP-1 analog, protects against cerebral ischemia/reperfusion injury in diabetic rats," ***Naunyn Schmiedebergs Arch Pharmacol,*** 391(7), 705-717 (2018).
75. H. Cena,L. Chiovato and R. E. Nappi, "Obesity, Polycystic Ovary Syndrome, and Infertility: A New Avenue for GLP-1 Receptor Agonists," ***J Clin Endocrinol Metab,*** 105(8), e2695-2709 (2020).
76. K. Elkind-Hirsch,O. Marrioneaux,M. Bhushan,D. Vernor et al., "Comparison of single and combined treatment with exenatide and metformin on menstrual cyclicity in overweight women with polycystic ovary syndrome," ***J Clin Endocrinol Metab,*** 93(7), 2670-2678 (2008).
77. S. Frøssing,M. Nylander,E. Chabanova,J. Frystyk *et al.*, "Effect of liraglutide on ectopic fat in polycystic ovary syndrome: A randomized clinical trial," ***Diabetes Obes Metab,*** 20(1), 215-218 (2018).
78. E. M. Lamos,R. Malek and S. N. Davis, "GLP-1 receptor agonists in the treatment of polycystic ovary syndrome," ***Expert Rev Clin Pharmacol,*** 10(4), 401-408 (2017).
79. P. N. Newsome,K. Buchholtz,K. Cusi,M. Linder et al., "A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis," ***N Engl J Med,*** 384(12), 1113-1124 (2021).
80. J. M. Petit and B. Vergès, "GLP-1 receptor agonists in NAFLD," ***Diabetes Metab,*** 43 Suppl 1, 2s28-22s33 (2017).
81. E. Somm,S. A. Montandon,U. Loizides-Mangold,N. Gaïa *et al.*, "The GLP-1R agonist liraglutide limits hepatic lipotoxicity and inflammatory response in mice fed a methionine-choline deficient diet," ***Transl Res,*** 227, 75-88 (2021).
82. N. A. Subrahmanyan,R. M. Koshy,K. Jacob and J. M. Pappachan, "Efficacy and Cardiovascular Safety of DPP-4 Inhibitors," ***Curr Drug Saf,*** 16(2), 154-164 (2021).
83. K. Orime and Y. Terauchi, "Efficacy and safety of saxagliptin for the treatment of type 2 diabetes mellitus," ***Expert Opin Pharmacother,*** 21(17), 2101-2114 (2020).
84. L. J. Scott, "Sitagliptin: A Review in Type 2 Diabetes," ***Drugs,*** 77(2), 209-224 (2017).
85. D. Kim, L. Wang, M. Beconi,G. J. Eiermann *et al.*, "(2 R)-4-Oxo-4-[3-(trifluoromethyl)-5, 6-dihydro [1, 2, 4] triazolo [4, 3-a] pyrazin-7 (8 H)-yl]-1-(2, 4, 5-trifluorophenyl) butan-2-amine: a potent, orally active dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes," ***J Med Chem,*** 48(1), 141-151 (2005).
86. C. F. Deacon, "Dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes: a comparative review,"***Diabetes Obes Metab,*** 13(1), 7-18 (2011).
87. E. B. Villhauer,J. A. Brinkman,G. B. Naderi,B. F. Burkey *et al.*, "1-[[(3-hydroxy-1-adamantyl) amino] acetyl]-2-cyano-(S)-pyrrolidine: a potent, selective, and orally bioavailable dipeptidyl peptidase IV inhibitor with antihyperglycemic properties," 46(13), 2774-2789 (2003).
88. S. Henness and S. J. Keam, "Vildagliptin," ***Drugs,*** 66(15), 1989-2001, discussion 2002-1984 (2006).
89. G. M. Keating, "Vildagliptin: a review of its use in type 2 diabetes mellitus," ***Drugs,*** 74(5), 587-610 (2014).
90. B. Ahrén, "DPP-4 Inhibition and the Path to Clinical Proof," ***Front Endocrinol (Lausanne),*** 10, 376 (2019).
91. D.W. Boulton, "Clinical Pharmacokinetics and Pharmacodynamics of Saxagliptin, a Dipeptidyl Peptidase-4 Inhibitor," ***Clin Pharmacokinet*** 56(1), 11-24 (2017).
92. B. M. Scirica,D. L. Bhatt,E. Braunwald,P. G. Steg *et al.*, "Saxagliptin and cardiovascular outcomes in patients with

type 2 diabetes mellitus," ***N Engl J Med,*** 369(14), 1317-1326 (2013).
93. K. Kaku,K. Kisanuki,M. Shibata and T. Oohira, "Benefit-Risk Assessment of Alogliptin for the Treatment of Type 2 Diabetes Mellitus," ***Drug Saf,*** 42(11), 1311-1327 (2019).
94. M. Eckhardt,E. Langkopf,M. Mark,M. Tadayyon *et al.,* "8-(3-(R)-aminopiperidin-1-yl)-7-but-2-ynyl-3-methyl-1-(4-methyl-quinazolin-2-ylmethyl)-3, 7-dihydropurine-2, 6-dione (BI 1356), a highly potent, selective, long-acting, and orally bioavailable DPP-4 inhibitor for the treatment of type 2 diabetes," 50(26), 6450-6453 (2007).
95. U. Graefe-Mody,S. Retlich and C. Friedrich, "Clinical pharmacokinetics and pharmacodynamics of linagliptin," ***Clin Pharmacokinet,*** 51(7), 411-427 (2012).
96. U. Graefe-Mody,C. Friedrich,A. Port,A. Ring *et al.,* "Effect of renal impairment on the pharmacokinetics of the dipeptidyl peptidase-4 inhibitor linagliptin(*)," ***Diabetes Obes Metab,*** 13(10), 939-946 (2011).
97. K. McKeage, "Linagliptin: an update of its use in patients with type 2 diabetes mellitus," ***Drugs,*** 74(16), 1927-1946 (2014).
98. F. Salvo, N. Moore, M. Arnaud, P. Robinson *et al.,* "Addition of dipeptidyl peptidase-4 inhibitors to sulphonylureas and risk of hypoglycaemia: systematic review and meta-analysis," ***Bmj,*** 353, i2231 (2016).
99. K. Gooßen and S. Gräber, "Longer term safety of dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes mellitus: systematic review and meta-analysis," ***Diabetes Obes Metab,*** 14(12), 1061-1072 (2012).
100. T. Chaicha-Brom and T. Yasmeen, "DPP-IV inhibitor-associated arthralgias," ***Endocr Pract,*** 19(2), 377 (2013).
101. A. G. Egan,E. Blind,K. Dunder,P. A. de Graeff et al., "Pancreatic safety of incretin-based drugs--FDA and EMA assessment," ***N Engl J Med,*** 370(9), 794-797 (2014).
102. L. Cai,Y. Cai,Z. J. Lu,Y. Zhang *et al.,* "The efficacy and safety of vildagliptin in patients with type 2 diabetes: a meta-analysis of randomized clinical trials," ***J Clin Pharm Ther,*** 37(4), 386-398 (2012).
103. R. Baetta and A. Corsini, "Pharmacology of dipeptidyl peptidase-4 inhibitors: similarities and differences," ***Drugs*** 71(11), 1441-1467 (2011).
104. X. W. Chen,Z. X. He,Z. W. Zhou,T. Yang *et al.,* "An update on the clinical pharmacology of the dipeptidyl peptidase 4 inhibitor alogliptin used for the treatment of type 2 diabetes mellitus," ***Clin Exp Pharmacol Physiol,*** 42(12), 1225-1238 (2015).
105. G. M. Keating, "Alogliptin: a review of its use in patients with type 2 diabetes mellitus," ***Drugs,*** 75(7), 777-796 (2015).
106. D. Kawanami,Y. Takashi,H. Takahashi,R. Motonaga *et al.,* "Renoprotective Effects of DPP-4 Inhibitors," ***Antioxidants (Basel),*** 10(2), 246 (2021).
107. J. Vaghasiya,N. Sheth,Y. Bhalodia and R. Manek, "Sitagliptin protects renal ischemia reperfusion induced renal damage in diabetes," ***Regul Pept,*** 166(1-3), 48-54 (2011).
108. K. Kanasaki, "The role of renal dipeptidyl peptidase-4 in kidney disease: renal effects of dipeptidyl peptidase-4 inhibitors with a focus on linagliptin," ***Clin Sci (Lond),*** 132(4), 489-507 (2018).
109. D. Cappetta,L. P. Ciuffreda,A. Cozzolino,G. Esposito *et al.,* "Dipeptidyl Peptidase 4 Inhibition Ameliorates Chronic Kidney Disease in a Model of Salt-Dependent Hypertension," ***Oxid Med Cell Longev,*** 2019, 8912768 (2019).
110. G. Zhang,S. Kim,X. Gu,S. P. Yu *et al.,* "DPP-4 Inhibitor Linagliptin is Neuroprotective in Hyperglycemic Mice with Stroke via the AKT/mTOR Pathway and Anti-apoptotic Effects," ***Neurosci Bull,*** 36(4), 407-418 (2020).
111. F. L. Hao,X. F. Han,X. L. Wang,Z. R. Zhao *et al.,* "The neurovascular protective effect of alogliptin in murine MCAO model and brain endothelial cells," ***Biomed Pharmacother,*** 109, 181-187 (2019).
112. R. Bianchi,I. Cervellini,C. Porretta-Serapiglia,N. Oggioni *et al.,* "Beneficial effects of PKF275-055, a novel, selective, orally bioavailable, long-acting dipeptidyl

peptidase IV inhibitor in streptozotocin-induced diabetic peripheral neuropathy," ***J Pharmacol Exp Ther,*** 340(1), 64-72 (2012).

113. M. Wiciński,E. Wódkiewicz,M. Słupski,M. Walczak *et al.*, "Neuroprotective Activity of Sitagliptin via Reduction of Neuroinflammation beyond the Incretin Effect: Focus on Alzheimer's Disease," ***Biomed Res Int,*** 2018, 6091014 (2018).
114. A. J. Scheen, "Cardiovascular Effects of New Oral Glucose-Lowering Agents: DPP-4 and SGLT-2 Inhibitors," ***Circ Res,*** 122(10), 1439-1459 (2018).
115. S. A. Abdel-Gaber,A. Geddawy and R. A. Moussa, "The hepatoprotective effect of sitagliptin against hepatic ischemia reperfusion-induced injury in rats involves Nrf-2/HO-1 pathway," ***Pharmacol Rep,*** 71(6), 1044-1049 (2019).
116. A. S. Hendawy,N. M. El-Lakkany,E. M. Mantawy,O. A. Hammam et al., "Vildagliptin alleviates liver fibrosis in NASH diabetic rats via modulation of insulin resistance, oxidative stress, and inflammatory cascades," ***Life Sci*** 304, 120695 (2022).
117. M. Abd Elmaaboud,H. Khattab and S. Shalaby, "Hepatoprotective effect of linagliptin against liver fibrosis induced by carbon tetrachloride in mice," ***Can J Physiol Pharmacol,*** 99(3), 294-302 (2021).
118. A. M. Kabel, "Zinc/alogliptin combination attenuates testicular toxicity induced by doxorubicin in rats: Role of oxidative stress, apoptosis and TGF-β1/NF-κB signaling," ***Biomed Pharmacother,*** 97,439-449 (2018).

Bull. Pharm. Sci., Assiut University, Vol. 45, Issue 2, 2022, pp. 1027-1042.

نشرة العلوم الصيدلية
جامعة أسيوط

BULL. PHARM. SCI. Assiut Univ.

نظرة عامة على العلاجات القائمة على الإنكريتين: علم الأدوية ووجهات النظر المستقبلية

رندا اسماعيل – علياء عنتر – اسماء ابراهيم معتوق – جيهان حسين هيبة*

قسم الأدوية والسموم ، كلية الصيدلة ، جامعة المنيا ، مصر

إن الجلوكاجون شبيه البيبتيد-١ هو أحد الهرمونات المعوية (هرمون الأنكريتين) الذي يتم افرازه بعد تناول الأكل فهو يقوم بزيادة إفراز الانسولين وتقليل إفراز الجلوكاجون وتثبيط الشهية بذلك يقوم بالحفاظ علي مستويات الجلوكوز في الدم. يضعف نظام الأنكرتين أثناء الإصابة بمرض السكري من النوع الثاني.

تكتسب العلاجات المرتكزة علي الأنكرتين شهرة في المجال السريري في الوقت الحاضر. تتضمن ارشادات العلاج الحالية علي كلا من محفزات مستقبلات الجلوكاجون شبيه البيبتيد-١ ومثبطات ثنائي بيبتيديل بيبتيدايز-٤ كعوامل خط ثانٍ مع مزايا انخفاض خطر الإصابة بنقص السكر في الدم و التحكم الجيد في ارتفاع سكر الدم بعد الأكل (مع محفزات مستقبلات الجلوكاجون شبيه البيبتيد-١ قصير المفعول و ومثبطات ثنائي بيبتيديل بيبتيدايز-٤) ونقص الوزن (مع محفزات مستقبلات الجلوكاجون شبيه البيبتيد-١). تتمتع محفزات مستقبلات الجلوكاجون شبيه البيبتيد-١) بمزيد من الفاعلية وتفضل مع المرضى الذين يعانون من أمراض القلب والأوعية الدموية الموجودة مسبقا. تشير الأدلة المتزايدة إلى أن العلاجات القائمة على الأنكرتين لها آثار مفيدة على اضطرابات القلب والأوعية والكبد والكلي والجهاز العصبي. تتضمن المراجعة الحالية بيولوجيا نظام الأنكريتن وعلم الادوية للعلاجات القائمة عليه وتطبيقاتها في العمل التجريبي والسريري.