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

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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. Moreover, type 2 diabetes mellitus (T2DM) affects 90% of the diabetic population. Currently available antidiabetics such as sulphonylureas, thiazolidinediones, and insulin have major drawbacks which include weight gain and hypoglycemia which are attributed to their insulin-dependent mechanism of action. 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. 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. 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.

Biology of the incretin system

In response to nutrient ingestion incretin hormones, primarily GLP-1 and GIP are
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 T2DM1,8.

GLP-1 receptor agonists (GLP-1 RAs)

Exenatide is the first GLP-1 RA approved for the treatment of T2DM in 200519. 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 hypoglycemia, 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 sales23 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.

<table>
<thead>
<tr>
<th>GLP-1 RA</th>
<th>First approval</th>
<th>Uses</th>
<th>Elimination half-life</th>
<th>Approved doses</th>
<th>Frequency of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide46 (b.i.d.)</td>
<td>2005 (USA) 2006 (Europe)</td>
<td>Antidiabetic</td>
<td>2-4 hrs</td>
<td>5 µg or 10 µg</td>
<td>Before breakfast and dinner (twice daily)</td>
</tr>
<tr>
<td>Lixisenatide33, 35</td>
<td>2013 (Europe) 2016 (USA)</td>
<td>Antidiabetic</td>
<td>2.6 hrs</td>
<td>10 µg or 20 µg</td>
<td>Before breakfast (once daily)</td>
</tr>
<tr>
<td>Liraglutide46</td>
<td>2009 (Europe) 2010 (USA)</td>
<td>Antidiabetic Anti-obesity</td>
<td>12.6-14.3 hrs</td>
<td>0.6, 1.2 or 1.8 mg 3 mg</td>
<td>Once daily</td>
</tr>
<tr>
<td>Exenatide QW27</td>
<td>2012</td>
<td>Antidiabetic</td>
<td>2-4 hrs</td>
<td>2 mg</td>
<td>Once weekly</td>
</tr>
<tr>
<td>Dulaglutide24</td>
<td>2014</td>
<td>Antidiabetic</td>
<td>4.7-5.5 days</td>
<td>0.75 or 1.5 mg</td>
<td>Once weekly</td>
</tr>
<tr>
<td>Semaglutide (SC)46</td>
<td>2017 (USA) 2018 (Europe)</td>
<td>Antidiabetic Anti-obesity</td>
<td>5.7-6.7 days</td>
<td>0.5 or 1 mg 2.4 mg</td>
<td>Once weekly</td>
</tr>
<tr>
<td>Semaglutide (oral)46</td>
<td>2019</td>
<td>Antidiabetic</td>
<td>5.7-6.7 days</td>
<td>3, 7, or 14 mg</td>
<td>30 min before breakfast (once daily)</td>
</tr>
</tbody>
</table>
Exenatide

Exenatide is a synthetic version of the natural peptide, exendin-4 found in Gila monster. 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. It is rapidly absorbed after subcutaneous administration and renally eliminated following proteolytic degradation by DPP-4.

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.

Lixisenatide

Lixisenatide is a short acting exendin-4-based GLP-1 RA is used once daily for management of T2DM. 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. 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. 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.

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

![GLP-1 receptor agonists and Fixed-dose combinations](source)

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Liraglutide

Liraglutide is a long-acting GLP-1 RA that was approved for the treatment of T2DM and obesity. 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. 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.

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.

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. It is used now as a weight loss drug in non-diabetic patients in 3 mg daily dose. It reduces body weight and diminishes systolic pressure.

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, 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). Clinical studies showed that dulaglutide is non inferior to liraglutide but superior to exenatide twice daily in HbA1c reduction.

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. 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. 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.

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.

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

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-inflammatory, 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-1 RAs may have direct effects on lipotoxicity, fatty acid oxidation, adipogenesis, and cytokines related to fibrosis and hepatitis.\(^{79, 80}\) Liraglutide showed antifibrotic 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.

<table>
<thead>
<tr>
<th>DPP-4i</th>
<th>First approval</th>
<th>Elimination half-life</th>
<th>Approved doses</th>
<th>Frequency of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin</td>
<td>2006</td>
<td>12.5 hrs</td>
<td>100 mg</td>
<td>Once daily</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>2007</td>
<td>2 hrs</td>
<td>50 mg</td>
<td>Twice daily</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>2009</td>
<td>2.5 hrs</td>
<td>5 mg</td>
<td>Once daily</td>
</tr>
<tr>
<td>Alogliptin</td>
<td>2013</td>
<td>21 hrs</td>
<td>25 mg</td>
<td>Once daily</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>2011</td>
<td>12 hrs</td>
<td>5 mg</td>
<td>Once daily</td>
</tr>
</tbody>
</table>

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\(^\text{84}\). It is a derivative of \(\beta\)-amino acid-based triazolopiperazine\(^\text{85}\) which does not undergo significant metabolism with a half-life 12.5 hrs\(^\text{86}\).

Vildagliptin
Vildagliptin was the second approved DPP-4i which belongs to the chemical class cyanopyrrolidine\(^\text{87}\). It undergoes significant hydrolysis with short half-life \(~2\) hrs so it is administered twice daily\(^\text{88}\). It is well tolerated when administered as monotherapy or in combination with other anti-diabetics for T2DM management\(^\text{88}\). 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\(^\text{89}\).

Saxagliptin
Saxagliptin has a methanoprolinenitrile structure which was approved in 2009\(^\text{90}\). 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\(^\text{91}\). 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\(^\text{92}\). 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\(^\text{83}\).

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\(^\text{93}\).

Linagliptin
Linagliptin is a methylxanthine derivative which was approved in 2011\(^\text{94}\). It does not undergo significant metabolism so has a long half-life \(~12\) hrs\(^\text{86,95}\). 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\(^\text{86,95,96}\). 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 and renal ischemia reperfusion injury in diabetic rats 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 anti-apoptotic 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-
\( \beta \)-NF-κB (nuclear factor kappa B) signaling pathway, oxidative stress and apoptosis.

**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.

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نظرية عامة على العلاجات القائمة على الأنكورتين: علم الأدوية وجهات النظر المستقبلية

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إن الجلوكوجون شبيه البيبتيد-1 هو أحد الهرمونات المعوية (هرمون الأنكورتين) الذي يتم إفراغه بعد تناول الأكل فهو يقوم بزيادة إفراز الإنسولين وتقليل إفراز الجلوكوجون وتنبئ الشهية بذلك يقوم بالحفاظ على مستويات الجلوكوز في الدم. يضعف نظام الأنكورتين أثناء الإصابة بمرض السكري من النوع الثاني.

تكتسب العلاجات المرتزمة على الأنكورتين شهيرة في المجال السريري في الوقت الحاضر. تتضمن ارشادات العلاج الحالية على كلا من محفزات مستقبلات الجلوكوجون شبيه البيبتيد-1 ومثبطات ثنائي بيبتيد بيبتيداز-4. كما أن خصائص خطر الإصابة بنقص السكر في الدم والتحكم الجيد في ارتفاع سكر الدم بعد الأكل (مع محفزات مستقبلات الجلوكوجون شبيه البيبتيد-1: قصير المفعول) ومثبطات ثنائية بيبتيد بيبتيداز-4) ونقص الوزن (مع محفزات مستقبلات الجلوكوجون شبيه البيبتيد-1) يجمع من الفاعلية وتفضيل مع المرضى الذين يعانون من أمراض القلب والأوعية الدموية الموجودة مسبقا. تشير الأدلة المتزايدة إلى أن العلاجات القائمة على الأنكورتين لها أثر مفيدة على اضطرابات القلب والأوعية والكبد والكلي والجهاز العصبي.

تتضمن المراجعة الحالية بيوطولوجي نظام الأنكورتين وعلم الأدوية للعلاجات القائمة عليه وتطبيقاتها في العمل التجريبي والسريري.