Treatment of type 2 diabetes mellitus by drugs modulating the incretin system

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Abstract

Diabetes, specifically type 2 diabetes mellitus (T_2DM), one of the most common non-communicable diseases, poses a major health problem throughout the world. T_2DM is characterized by insulin resistance, impaired glucose-induced insulin secretion and inappropriately regulated glucagon secretion which in combination eventually result in hyperglycemia and in the longer term microvascular and macrovascular complications of diabetes. Traditional treatment modalities, even multidrug approaches, for T_2DM are often inadequate in getting patients to achieve glycemic goals as the disease progresses due to a steady, relentless decline in pancreatic β-cell /number/function. Furthermore, current treatment modalities are often limited by inconvenient dosing regimens, safety and tolerability issues, the latter including hypoglycemia, body weight gain, edema and gastrointestinal side effects. A novel category of antihyperglycemic therapy based on modulation of the endogenous incretin system has recently evolved. The incretins, specifically glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), are gut-derived peptides secreted in response to meals, specifically the presence and absorption of nutrients in the intestinal lumen. The incretins potentiate meal-induced insulin secretion and trophic effects on the β-cell; the GLP-1 also inhibits glucagon secretion, and suppresses food intake and appetite. The activity/level of the incretins is diminished in T_2DM. Both GLP-1 and GIP are rapidly degraded by the endogenous dipeptidyl-peptidase-4 (DPP-4). Hence, stable long-acting GLP-1 analogs/GLP-1 receptor agonists (incretin mimetics) have been developed. Since, the incretin mimetics have to be injected, orally active inhibitors of DPP-4, the incretin enhancers, have also been introduced for the treatment of T_2DM. The GLP-1 receptor agonists and DPP-4 inhibitors are useful in the management of T_2DM because they provide effective reductions in levels of fasting plasma glucose (FPG) and postprandial glucose (PPG), partly through their actions on pathogenic causes of T_2DM that are not addressed by other glucose-lowering agents. In addition, the GLP-1 receptor agonists promote weight loss, whereas the DPP-4 inhibitors are mostly weight neutral, and there is a low risk of symptomatic hypoglycemia with both type of agents. The GLP-1 receptor agonists and DPP-4 inhibitors are effective as monotherapy in drug-naive patients as well as in those in whom other treatments (for example with metformin, sulfonylureas, thiazolinediones, etc.) have been inadequate to achieve glycemic control. When combined with other glucose-lowering agents, the GLP-1 receptor agonists and DPP-4 inhibitors further lower FPG and PPG levels, and hemoglobin A1c. Consequently, these agents can be used for all stages of T_2DM. However, the durability and long-term safety of these drugs remains to be determined. This review focuses on the therapeutic potential of the incretin mimetics and incretin enhancers in treating T_2DM. In addition, the review also presents some information on the mechanism of action(s), efficacy, pharmacokinetics, pleiotropic effects, drug interactions and adverse effects of the main drugs which modulate levels and activity of endogenous incretins.

Introducción

Diabetes, specifically type 2 diabetes mellitus (T_2DM), one of the most common non-communicable diseases, is emerging as an epidemic of the 21th century and a major health problem throughout the globe[1,2]. Complications from diabetes, such as cardiovascular (CV) disease, peripheral vascular disease, stroke, diabetic neuropathy, amputations, renal failure and blindness result in increasing disability, reduced life expectancy and enormous health costs for virtually every society[4]. T_2DM is a polygenic disease characterized by multiple defects in pancreatic insulin secretion and insulin action in muscle, adipose, and liver[3]. About 80-85% of T_2DM patients have insulin resistance, and impaired β-cell function occurs in 50% of newly diagnosed T_2DM[5,6], and after that there is a linear decline in β-cell number/function with time, despite therapy with sulfonylurea, metformin or insulin[7,8], as a result of glucotoxicity, lipotoxicity, proinflammatory cytokines, leptin, and islet cell amyloid leading to accelerated apoptosis and loss of β-cell function/mass. The treatment goals for T_2DM patients are related to effective control of blood glucose, as well as management of coexisting pathologies, such as hypertension, dyslipidemia, and excess body weight, and ultimately, to avert the serious complications associated with sustained tissue exposure to hyperglycemia. Although, intensive glycemic control reduces the appearance and progression of microvascular and neuropathic complications (retinopathy, nephropathy and neuropathy)[9-12], long-term intensive therapy to achieve target HbA1c in T_2DM patients has been associated with increased mortality without significant beneficial effect on major CV events[13]. In addition, tighter glycemic control (using intensive therapy) burdens the patients with complex treatment regimens, increased risk of hypoglycemia, possible weight gain, and relatively high costs, while offering uncertain benefits in return[14-16]. Hence, ideal treatment in T_2DM should be to control hyperglycemia and its adverse consequences without increasing CV or other risks such as hypoglycemia, by healthy lifestyle, preventive care, and individualizing and optimizing medications (combinations, if necessary) and their doses, for initiation and intensification of therapy to achieve a target hemoglobin A1c (HbA1c), depending on patients' circumstances.

Prevention and control of diabetes with diet, weight control and physical activity has been difficult. Treatment of T_2DM has centered on a) increasing insulin levels, either by direct insulin administration or oral agents that promote insulin secretion (insulin secretagogues, such as oral sulfonylureas), b) improving insulin sensitivity to insulin in tissues, such as by metformin or thiazolidinediones (TZDs), or c) reducing the rate of carbohydrate absorption from the gastrointestinal tract by the use of α-glucosidase inhibitors and/or agents that decrease gastric motility. Despite significant improvement achieved over the last decade in the management of T_2DM with the use of drugs such as metformin, sulphonylureas, α-glycosidase inhibitors, TZDs and insulin preparations, often in high doses and in combinations, a large proportion of patients are unable to reach recommended therapeutic targets (>60% with HbA1c > 7%)[6,7,9,17]. Furthermore, current treatments do not address the issue of progressive β-cell dysfunction/failure/loss, such that the development and continued progression of diabetes is a consequence of the failure of the β-cell to overcome insulin resistance. In addition, current therapies, with the exception of insulin, have limited glucose-lowering capacity, and become less effective over time as a result of progressive loss of β-cell function/number.[17] Also, there are major adverse effects associated with the use of current medications, especially weight gain[2,18], which may undermine the benefits of glycemic control. Therefore, strategies that aim to prevent hyperglycemia must also aim to stabilize the progressive decline of β-cells. In this regard, intensive efforts have been made and are still continuing to develop newer classes of drugs to control hyperglycemia in T_2DM patients without insulin and preserve β-cell number/function. Recent breakthroughs in the understanding of incretin-based therapies have provided additional options for the treatment of T_2DM, and one of the main strategy has been to modulate the levels of incretins (see below), the endogenous substances involved in glucose control to treat T_2DM.

This review describes the therapeutic potential in treating T_2DM (used as monotherapy or in combination with other antidiabetic drugs), mechanism of action(s), efficacy, pharmacokinetics, pleiotropic effects, drug interactions and adverse effects of the main drugs which modulate levels and activity of endogenous incretins.

The incretins

In 1902, Bayliss and Starling proposed that intestinal mucosa contains a hormone that stimulates the exocrine secretion of the pancreas ("secretin"). In 1932, La Barre proposed the name incretin for a hormone extracted from the upper gut mucosa, which caused hypoglycemia and proposed possible therapy for diabetes. In 1970, gastric inhibitory peptide (GIP) was isolated from intestinal mucosa and sequenced by Brown and co-workers. The original name gastric inhibitory peptide was dropped and GIP was renamed glucose-dependent insulinotropic peptide in 1973 after Brown and colleagues, showed that GIP (**Table 1**) stimulates insulin secretion[19]. Of the several glucagon-like peptides-1 (GLP-1) detected in the intestinal secretions, the GLP-1 (7-36) amide, was found to have the insulinotropic effect in humans[21,22]. It was determined that the incretin effect is mainly due to GLP-1(7-36) amide and GIP (**Figure 1**). GLP-1 (7-36) is a 30 amino acid peptide produced (from proglucagon) and released from the neuroendocrine L-cells of the lower small intestine (ileum) and the colon, in response to dietary fat and carbohydrates[21-24], while GIP is a 42-aminoacid peptide secreted from the K-cells of mainly the duodenum and

jejunum[20,23]. Both endogenous incretins have a very short half-life (t), of the order of minutes, as a result of degradation by the serum enzyme dipeptidyl-peptidase-IV (DPP-4, CD-26, EC 3.4.14.5)[25-28]. GLP-1 (7-36) is rapidly degraded (Table 1) to GLP-1 (9-36) with a plasma t of 1–2 minutes, while GIP is also quickly degraded with a t = 4.3 min to GIP (3-42)[20,23-27]. Earlier, it was thought that the degradation products of GIP and GLP-1 were inactive, however, it has been shown that some of the extra-pancreatic effects of GLP-1 (lowering of post-prandial glycemia by decrease in hepatic glucose production and vasodilatory effect) are mediated via the metabolite GLP-1 (9-36)[28,29], and improvement in insulin sensitivity by GIP (3-42)[29].

Figure 1

Gila monster (*Heloderma suspectum*)

tors, is the product of a gene mapped to the short arm of human chromosome 6 (6p21.1) and binds specifically GLP-1; it has a much lower affinity for related peptides such as GIP and glucagon[21,26,30,31]. GIP has a GIP-specific G-protein-coupled receptor with no cross-reactivity with the GLP-1 receptor. [22,30,31] Intravenous administration of GLP-1 activates the GLP-1 receptor, which results (**Table 2**) in a) increased cAMP production and activation of ATP-sensitive K channel mediated by β-arrestin-1[32,33], leading to increased synthesis and release of insulin; b) glucose-dependent enhancement of insulin release by improving β-cell responsiveness to glucose via increased expression of glucose transporter-2 (GLUT 2) and glucokinase genes; insulin release is high at high glucose level and decreases as the glucose level drops, c) increase in tissue sensitivity to insulin, d) glucose-dependent secretion of amylin from the pancreas, e) delay in gastric emptying, mediated by vagal afferents[34], f) suppression of appetite (by a central mechanism, possibly partially mediated by increased serotonin release in the hypothalamus[35], and producing a feeling of fullness[36], and satiety[37], leading to decreased body weight, g) improvement in glycemic control, and h) decrease in glucagon secretion (from α-cells), possibly mediated by increased somatostatin secretion, resulting in reduced hepatic glucose production (**Table 2**)[21-23,26,38]. Interaction of GIP with its receptor also increases glucose-dependent pancreatic insulin secretion, but it has no effect on hepatic glucose output, gastric motility, satiety or body weight (**Table 2**), however, it does induce lipogenesis and glucagon secretion, and suppress

Table 1. Amino acid sequence of incretins and analogs

		↓
GLP-1	(7-36; human)	HAEGTFTSDVSSYLEGQAAKEFIAWLVKGR-amide
GLP-1	(9-36; human)	EGTFTSDVSSYLEGQAAKEFIAWLVKGR-amide (metabolite of GLP-1)
		↓
GIP (1-42; human)		YAEGT-FISDY-SIAMD-KIHQQ-DFVNW-LAQKG-KKNDW-KHNHI-TQ
GIP (3-42; human)		EGT-FISDY-SIAMD-KIHQQ-DFVNW-LAQKG-KKNDW-KHNHI-TQ (metabolite of GIP)
		↓
Exendin-4 (synthetic) (Exenatide)		HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-amide
Exendin (9-39)		DLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-amide (major circulating metabolite of exendin-4)
		↓
Liraglutide (1-31)		HAEGTFTSDVSSYLEGQAAKEFIAWLVRGR | C-16-fatty acid-albumin

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A = Ala; D = Asp; E = Glu; F = Phe; G = Gly; H = His; I = Ile; K = Lys; L = Leu; M = Met; N = Asn; P = Pro; R = Arg; Q = Gln; S = Ser; T = Thr; V = Val; W = Trp; Y = Tyr

The position of action of the enzyme DPP-4 is indicated by↓ (above) to give the respective metabolites; other metabolites are also formed by the action of various enzymes.

Incretin receptors

Both the incretins have specific receptors. The GLP-1 receptor, a member of the seven-transmembrane domain glucagon receptor family of G-protein-coupled recep-

gastric acid secretion[23,26,28]. In addition to improving insulin sensitivity, the incretins also promote proliferation/neogenesis of β-cells and prevent loss of β-cells by apoptosis, stimulate proinsulin gene transcription and transla-

tion[39,40,23,26,28]. Additionally, there are several mechanisms of regulating hepatic and muscle glucose flux via GLP-1 receptor, independent of insulin effect[41,42]. Receptors for both GLP-1 are found in the pancreatic islet β-cells, as well as in the stomach, adipose tissue, skeletal muscle, bone, heart, kidney, stomach, lung and brain[20,21,23,27] and GIP receptors are mainly expressed in β-cells[23,27].

Table 2. Comparative actions of GLP-1 and GIP

	GLP-1	GIP
Increase glucose-dependent insulin secretion (from pancreatic β-cells)	Yes	Yes*
Enhance insulin sensitivity	Yes	Yes
Suppress glucagon secretion (from pancreatic α-cells)	Yes	No*
Stimulate insulin biosynthesis	Yes	Yes
Decrease apoptosis of β-cells	Yes	Yes
Lower blood glucose	Yes	Yes
Inhibit gastric emptying (decrease gastric motility)	Yes	No
Inhibit gastric acid secretion	Yes	Yes
Inhibit hepatic insulin extraction	Yes	Yes
Inhibit post-prandial glucose excursion	Yes	Yes
Extrapancreatic glucose lowering	Yes	Yes
Enhance satiety (suppress appetite)	Yes	No*
Decrease body weight	Yes	No*
Enhance β-cell survival	Yes	Yes
Increase β-cell neogenesis	Yes	Yes
Stimulate β-cell expansion (mass)	Yes	Yes

* = the effect is not consistent

Incretins in normoglycemic individuals and in patients with type 2 diabetes mellitus

In healthy normoglycemic individuals, plasma glucose levels are maintained within a narrow range by pancreatic insulin and glucagon (having opposite effects on glucose), and by glucoregulatory hormones, amylin and the incretins (GLP-1 and GIP)[22,23]. Ingestion of nutrients results in the release of the incretins, which stimulate the release of insulin from the pancreatic β-cells[20,21]. Incretin action is required for glucose homeostasis (24-hr blood glucose control) as well as control of postprandial glucose; about 50-70% of stimulation of insulin secretion after a meal is due to incretin effect[39,40].

In T_2DM, the amount of insulin released from the β-cells in response to a meal is insufficient and/or the target tissues (fat, liver and muscle) develop insulin resistance (decreased insulin sensitivity). In addition, the incretin effect is either greatly impaired as a result of decrease in postprandial GLP-1 secretion (about 15%) and a marked reduction in insulinotropic response of β-cells to GIP[25,43-46]; hyperglycemia decreases the levels of GIP and GLP-1[47]. The reduced incretin effect is believed to contribute to impaired regulation of insulin and glucagon secretion in T_2DM. This impaired action of incretins in T_2DM patients may be, at least partly, restored by improved glycemic control, as shown in studies involving intensive diabetic therapy[39,48].

Treatment of type 2 diabetes mellitus based upon modulation of incretins

An option for the treatment of T_2DM involves modulation of levels of endogenous incretins, mainly GLP-1, which control the release of insulin and glucagon from the pancreas in response to meals. Since, the levels of GLP-1 are decreased in T_2DM[43-46] and both GLP-1 and GIP have a very short t, of the order of minutes, as a result of degradation by DPP-4[20,23,27], enhancement of incretin action has been achieved by the development of novel metabolically stable activators of the GLP-1 receptor (incretin-mimetics)[47-70], as well as, by inhibitors of DPP-4 (incretin enhancers)[39,49,52,56-60,62-65,67,69-83,84].

GLP-1 receptor agonists -- Incretin-mimetics

Because of very short t, native GLP-1 is not useful as a therapeutic agent unless administered by continuous subcutaneous infusion[24,61]. Hence, several synthetic incretin-mimetics with longer t have recently been introduced, such as the exendins, which act by stimulating the GLP-1 receptors, and thus, stimulating glucose-dependent insulin secretion and inhibiting glucagon release after meals. Exendin-4, a 39 amino acid peptide found in the saliva (venom) and isolated from the salivary gland of the lizard Heloderma suspectum (Gila monster)[85], is a naturally occurring analog of GLP-1 (53% homology to GLP-1) (**Table 4**), that binds and activates the GLP-1 receptor with the same potency as GLP-1[86-87]. A synthetic version of exendin 4 (exenatide, 39-aminoacid peptide, Byettta®) is an insulin secretagogue with glucoregulatory effect, which has been approved in the USA (2005) as add-on therapy in T_2DM patients with metformin, TZDs, sulfonylureas, and/or insulin to improve glucose control[88-90]. Though the effects of exendin-4 (exenatide) treatment on glucose control are likely due to several actions that are similar to those of GLP-1, the activity of exendin-4 is much greater than that of GLP-1 in controlling hyperglycemia, which may be due to its resistance

to degradation by DPP- 4[91]. In human plasma it has a t of 9.6 hr[92], but in the circulation the t is 2.4 hr[93]. In response to a meal, exenatide a) causes initial rapid release of insulin (from β-cells), b) suppresses pancreatic glucagon release, c) delays gastric emptying and thus decreases appearance of glucose after a meal, and d) reduces appetite - all of which function to lower blood glucose[55,90,91]. The results of the clinical studies with exenatide have been reviewed[56-58,62,65,70,94]; some data are presented in **Table 4**, which demonstrate that exenatide improves glycemic control (reduces HbA1c by 0.8%-1.4%) and decreases body weight by ~2-4 kg in T_2DM patients[88,94-110], who fail to achieve glycemic control with metformin and/or a sulfonylurea. Monotherapy with exenatide (5-10 g/dose) for 24 weeks in T_2DM patients, in addition to decreasing HbA1c (0.7-0.9%), resulted in a significant weight loss (2.8-3.1 kg)[95]. Most patients using exenatide slowly lose weight, and generally the greatest weight loss is achieved by people who are the most overweight at the beginning of exenatide therapy. Sustained glycemic control (reduction of HbA1c by about 1%) and weight loss continues with long-term therapy (>5 kg in 2-3 yr) with exetanide[97,106,108]. No ethnic differences were found in the efficacy and safety of exenatide[110]. Since metformin has been found to inhibit DPP-4 activity[114], addition of metformin to the antidiabetic regimen would enhance the beneficial effects of GLP-1 analogs. The use of exenatide with meglitinides and α-glucosidase inhibitors has not been studied. Exenatide is administered (5-10g) twice daily subcutaneously (s.c.) before or within 60

Table 4. Clinical studies with liraglutide

Reference	Dose of liraglutide (LIRA)	N	Study Duration (wk)	Other treatment	Change in HbA1c	Change in FPG (mg/dL)	Change in Weight (kg)
Seino[131]	LIRA-0.5-0.9 mg/d	226	14	Diet	- 1.7%	- 46	0
Madsbad[133]	LIRA- 0.225-0.450 mg/d.	193	12	Diet	- 0.2% to 0.5%	- 14 to - 23	- 0.7 to -1.
	LIRA- 0.60-0.75 mg/d.		12	Diet	- 0.5%	- 22 to - 34	- 0.3 to -0.4
	Placebo		12	Diet	+ 0.2%	+ 13	0.0
	Glimepiride		12	Diet	- 0.6%	- 38	+1.0
Harder[134]	LIRA 0.6 mg/d	33	8	Diet	- 0.3%	- 5	- 0.7
	Placebo		8	Diet	+ 0.5%	+ 5	- 0.9
Vilsbøll[129]	LIRA-0.6 mg/d	165	14	Diet	- 1.0%	- 36	+ 0.2
	LIRA-1.2 mg/d		14	Diet	- 1.4%	- 54	- 0.7
	LIRA-1.9 mg/d		14	Diet	- 1.5%	- 54	- 3.0
	Placebo		14	Diet	+0.2%	+ 5	- 1.8
Garber[135]	LIRA-1.2 mg/d	764	52	Diet	- 0.8%	- 15	- 2.0
	LIRA 1.8 mg/d		52	Diet	- 1.1%	- 26	- 2.5
	Glimepiride 8 mg/d		52	Diet	- 0.51%	- 5	+ 1.1
Feinglos[130]	LIRA-0.225 mg/d	210	12	Diet	+ 1.3%	+ 36	- 1.9%
	LIRA-0.450 mg/d		12	Diet	+ 0.9%	+ 11	- 1.2%
	LIRA-0.600 mg/d		12	Diet	+ 0.2%	+ 0	- 0.6%
	LIRA-0.750 mg/d		12	Diet	+ 0.3%	+ 16	- 0.9%
	Placebo		12	Metformin	+ 0.1%	- 4	- 0.6%
Nauck[132]	LIRA-0.5-2.0 mg/d	144	5	Metformin + SU	- 0.8%	- 50	- 1.5
Nauck[136]	LIRA- 0.6 mg/d	1091	26	Metformin ≥ 1 g/d	- 0.7%	- 20	- 1.8
	LIRA- 1.2 mg/d		26	Metformin ≥ 1 g/d	- 1.0%	- 29	- 2.6
	LIRA- 1.8 mg/d		26	Metformin ≥ 1 g/d	- 1.0%	- 31	- 2.8
	Glimepiride 4 mg/d		26	Metformin ≥ 1 g/d	+ 0.1%	- 23	+ 1.0
Marre[137]	LIRA-1.2-1.8 mg/d	1041	26	Glimepiride 2-4 mg/d	- 1.1%	- 31	- 0.2
	Rosiglitazone 4 mg/d		26	Glimepiride 2-4 mg/d	- 0.4%	- 18	+ 2.1
	Placebo		26	Glimepiride 2-4 mg/d	+ 0.2%	+ 16	- 2.0
Russell-Jones[139]	LIRA-1.8 mg/d			Metformin + glimepiride	- 1.3%		-1.8
	Placebo			Metformin + glimepiride	- 0.2%		
Buse[111]	LIRA-1.8 mg/d	464	26	Metformin ± SU	- 1.1%	- 29	- 3.2
	EX-10 ug b.i.d.		26	Metformin ± SU	- 0.8%	- 11	- 2 .9

Wk = week; b.i.d. = twice a day; t.i.d. = three-times a day; d = day; FPG = fasting plasma glucose levels; SU = sulfonylurea; LIRA = liraglutide; EX = exenatide. For glucose levels, to convert mg/dL to mmol/L divide by 18

min of the morning and evening meals[95,96]. Unlike sulfonylureas and meglitinides, exenatide increases insulin synthesis and secretion only in the presence of glucose, lessening the risk of hypoglycemia. However, if used in combination with sulfonylureas, exenatide may increase the risk of sulfonylurea-induced hypoglycemia[102], and therefore, the dose of sulfonylurea should be decreased if co-administered with exenatide. In patients with normal renal function, doses higher than 2.5g are needed for adequate glycemic response, but in patients with renal dysfunction dose adjustment is required[115]; it is contraindicated in patients with severe renal impairment.

The main adverse effect of exenatide is nausea, which is mild to moderate depending on the dose, and may be transient. However, in some studies, up to 14% patients had to discontinue the drug due to nausea[101-103,105]. Other gastrointestinal symptoms include dyspepsia, vomiting and diarrhea[90]. Exenatide may also cause acute pancreatitis[116], abdominal pain with or without vomiting, and sometimes renal failure[117]. In addition to being injected once or twice a day, other drawbacks of exenatide include lack of long-term studies to evaluate sustained efficacy and safety, as well as high cost.

The pharmacokinetic and pharmacodynamic profiles of exenatide have been evaluated[90,118-121]; after a single s.c. injection (5-10 g), the drug is rapidly absorbed with mean peak plasma levels (tmax) achieved in 1.0-3.0 hr[90]. Based on animal studies, the bioavailability of exenatide after s.c. injection has been estimated to be between 65% and 75%[90]. The mean apparent volume of distribution (Vd) after administration of a single s.c. dose is 28.3 L.[90] Plasma levels decrease with a mean $t_{1/2}$ of 2.4 hr (range 0.9-4.0 hr)[90,118-120]. The drug does not accumulate after repeated dosing. No ethnic differences were observed in the pharmacokinetics of exenatide[119-121]. The t of exenatide is increased in patients with renal dysfunction and it is poorly tolerated in patients with severe renal insufficiency and end-stage renal disease[115]; doses of 5-10g are unsuitable in such patients. The drug is eliminated predominantly by glomerular filtration followed by proteolytic degradation[90]. There are no significant pharmacokinetic interactions of exenatide with warfarin[121], digoxin[122], lisinopril[123], and lovastatin[124].

GLP-1 analogs with long duration of action

A long-acting-release (LAR) formula of exenatide, which is to be injected once a week is under development. Initial trials have shown that the LAR formulation is approximately twice as effective as the original twice-daily injectable form, with a similar safety profile but with rate of nausea rates and greater weight loss[112,113,125,126]. Exenatide LAR injection (in doses of 0.8-2.0mg), administered once-weekly for 15 weeks with or without metformin, reduced HbA1c by 1.4-1.7%[113]. In a 30-week study, exenatide LAR (2.0 mg) once weekly was found to be superior to exenatide (10 g) twice daily (**Table 3**) in terms of glycemic control (HbA1c of 6.4% versus 6.8%) and the number of T_2DM patients achieving HbA1c of <7.0% (77% versus 61%)[112,113]. Adverse effects of exenatide-LAR include nausea, gastroenteritis and hypoglycemia[113,114].

Several other long-acting analogs of GLP-1 such as liraglutide (NN2211; Victoza®) and albiglutide (naliglutide, GSK716155, Albugon®, Syncria®), are being developed for the treatment of T_2DM. Liraglutide is a 30-amino acid peptide attached to a fatty acid molecule and then bonded to albumin (**Table 2**)[127,128]; it has 97% homology with GLP-1[128]. After s.c. administration, the drug is released slowly into circulation (tmax = 9-13 hr), and then cleared slowly (t of 11-15 hr) and excreted by the kidney[127,128]. The duration of action is about 24-hr, allowing once-daily s.c. dosing, which effectively reduces fasting as well as postprandial hyperglycemia (12 hr after administration) (**Table 5**) by increasing insulin secretion, delaying gastric emptying, and suppressing prandial glucagon secretion[127,128]. Liraglutide administration (0.9 mg/day for 14 weeks) resulted in 75% of patients achieving HbA1c <7.0% and 57% achieving HbA1c <6.5%[129], and once daily administration (0.75-2 mg for 5-12 weeks) caused significant improvement in glycemic control (HbA1c reduction of 0.8-1.9%) and a weight loss of up to 3.0 kg[128,130], as compared to placebo or glimepiride[131]; liraglutide administration also decreased appetite causing minimal side effects (nausea, vomiting, and diarrhea) with negligible risk of hypoglycemia[128]. The clinical efficacy of liraglutide, given as monotherapy or in combination with other antidiabetic drugs, has been amply demonstrated in a large number of clinical trials including the Liraglutide Effect and Action in Diabetes series (LEAD-1 to -6) of studies in more than 4400 T_2DM patients (**Table 6**)[111,127-141]. In addition to robust glycemic control, liraglutide reduced weight in most patients, improved beta-cell function, lowered blood pressure and triglycerides, and was well tolerated with minimal risk of hypoglycemia; addition of liraglutide to oral antidiabetic regimen improved glycemic control[128,129,139,140]. A once-a-day s.c. injection may be sufficient in normal use. Dosage adjustment may not be required in patients with renal impairment[142]. In some populations, especially at higher doses, liraglutide decreases body weight[111,129,131,134,136,138]. Some studies suggest that the efficacy and tolerability of liraglutide administered once-a-day is comparable or even better than exenatide given twice-a-day[94,111]. An ethnic difference in the effects of liraglutide was observed, in that in Japanese T_2DM patients given half the dose of the Caucasian patients, the reduction in HbA1c was more prominent, suggesting that liraglutide may be more effective in Asian than in Caucasian patients possibly due to their improvement of early phase insulin secretion[143]. The main adverse effects of liraglutide include nausea, vomiting and diarrhea[128,135-137]. The US-FDA advisory includes the risk of developing pancreatitis and papillary thyroid tumors[144,145]. After s.c. administration of 1.0 mg of liraglutide in healthy individuals, Cmax of 15-20 nmol/L was obtained at tmax of 12-14 hr; plasma t of liraglutide

Table 5. Clinical studies with Sitagliptin

Reference	Dose of sitagliptin (SITA)	N	Study Duration (wk)	Other treatment	Change in HbA1c	Change in FPG (mg/dL)	Change in Weight (kg)
Aschner[185]	SITA -100 mg/d	741	24	Diet	- 0.79%	- 13 to 18	- 0.2
	SITA -200 mg/d		24	Diet	- 0.94%	- 16 to 22	- 0.1
	Placebo		24	Diet	+ 0.18%	+ 5	- 1.1
Raz[203]	SITA -100 mg/d	521	18	Diet	- 0.48%	- 13	- 0.2
	SITA -200 mg/d		18	Diet	- 0.36%	- 11	- 0.6
	Placebo		18	Diet	+ 0.12%	+ 7	- 0.7
Hanefield191	SITA - 25-50 mg b.i.d./q.d.	555	12	Diet	- 0.4 to -0.6%	-11 to -17	0
Nonaka[205]	SITA - 50 mg b.i.d.	151	12	Diet + exercise	- 1.3%	- 49	
	SITA - 100 mg q.d.		12	Diet + exercise	- 0.8%	- 41	
	Placebo		12	Diet + exercise	- 0.2%	- 7	
Charbonnel[211]	SITA -100 mg/d	701	24	Metformin (≥1500 mg/d)	- 0.67%	- 16	- 0.6
	Placebo		24	Metformin (≥1500 mg/d)	- 0.02%	+ 9	- 0.7
Rosenstock[212]	SITA -100 mg/d	353	24	Pioglitazone 30-45 mg/d	- 0.85%	- 16	+1.8
	Placebo		24	Pioglitazone 30-45 mg/d	- 0.15%	0	+1.5
Scott[200]	SITA - 12.5 – 50 mg b.i.d.	743	12	Diet + exercise	- 0.4% to -0.8%	-13 to -18	+ 0.1 to +0.4
	Glipizide (5-20 mg/d)		12	Diet + exercise	- 0.76% to -1.38%	+ 23	
	Placebo		12	Diet + exercise	+ 0.23%	+ 8	
Nauck[215]	SITA -100 mg/d	1172	52	Metformin ≥ 1500 mg/d	- 0.67%	- 10	- 1.5
	Glipizide (5-20 mg/d)		52	Metformin ≥ 1500 mg/d	- 0.67%	- 8	+1.1
Brazg[214]	SITA - 100 mg/d	28	4	Metformin ≥ 1500 mg/d	- 22		
	Placebo		4	Metformin ≥ 1500 mg/d	- 7		
Goldstein[216]	SITA- 100 mg/d	1091	24	Diet + exercise	- 0.83%	- 23	
	SITA- 50 mg/d		24	Metformin 1000 mg/d + Diet	- 1.5%	- 53	
	SITA- 50 mg/d.		24	Metformin 2000 mg/d + Diet	- 2.07%	- 70	
	Placebo		24	Metformin 1000 mg/d + Diet	- 0.99%	- 33	
	Placebo		24	Metformin 1000 mg/d + Diet	- 1.3%	- 35	
	Placebo		24	Diet + exercise	+ 17%	+ 6	
Hermansen[217]	SITA -100 mg/d	441	24	Glimepiride	- 0.30%	- 2	+1.1
	SITA -100 mg/d		24	Glimepiride/Metformin	- 0.59%	- 7	+ 0.4
	Placebo		24	Glimepiride	+ 0.27%	+ 18	0
	Placebo		24	Glimepiride/Metformin	+ 0.30%	+ 12	- 0.7
Scott[213]	SITA -100 mg/d	273	18	Metformin ≥1500 mg/d.	- 0.7%	- 11	- 0.4
	Roziglitazone 8 mg/d		18	Metformin ≥1500 mg/d.	- 0.8%	- 23	+ 1.5
	Placebo		18	Metformin ≥1500 mg/d	- 0.2%	- 54	- 0.8
Mohan[218]	SITA -100 mg/d		18	Metformin 1500 mg/d.	- 1.0%	- 31	
	Roziglitazone 8 mg/d		18	Metformin 1500 mg/d	- 0.8%	- 23	+ 1.5
	Placebo		18	Metformin 1500 mg/d.	- 0.2%	- 54	- 0.8

Wk = week; b.i.d. = twice a day; t.i.d. = three-times a day; d = day; N = number of patients in the study; d = per day; FPG = fasting plasma glucose levels; SU = sulfonylurea; for glucose levels, to convert mg/dL to mmol/L divide by 18

was 11-15 hr[146]. There is no effect of age or gender on the pharmacokinetics of liraglutide[146]. Liraglutide is being considered for approval by the US-FDA in 2009.

Another drug of this class, albiglutide, a recombinant human GLP-1-albumin-fusion protein (genetic fusion of a DPP-4-resistant GLP-1 dimer to human albumin) has a long duration of action (t = 6-8 days) and is to be injected every 5-8 days to control hyperglycemia[147,148]. In (**Table 5**) addition to controlling blood sugar, it also suppresses appetite. In T_2DM patients, albiglutide (16-64 mg given by s.c. injection) improved fasting plasma glucose and post-prandial glucose with a low adverse effect profile (mainly, headache, nausea and flatulence)[147,148]. After injection, albiglutide is readily absorbed but tmax is reached in 3-5 days and its plasma t is between 6 and 8 days[147,148].

Although, the GLP-1 receptor agonists (incretin mimetics) are effective in reducing HbA1c and post-prandial glucose in patients failing sulphonylurea and/or metformin therapy, the role of these drugs in the treatment of T_2DM is still debated. An earlier consensus algorithm of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)[149], http://www.eje-online.org/cgi/content/full/160/6/909 - BIB4 suggested to limit the use of GLP-1 receptor agonists only to some specific cases, without considering those agents as the main-line drugs. The reasons for this exclusion were their perceived limited efficacy in decreasing HbA1c in comparison with other agents, their poorly defined safety profile, and their cost[94]. However, the newer Consensus algorithm issued by ADA/EASD suggests that GLP-1 receptor agonists can be used, in selected cases, as an add-on treatment to metformin[150].

GIP analogs and GIP receptor antagonists

In addition to the insulinotropic action of GIP on the pancreatic β-cell, GIP also has been shown to stimulate β-cell proliferation and inhibit apoptosis in islet cell lines. Additionally, functional GIP receptors have been identified on adipocytes, which have been shown to stimulate glucose transport, increase fatty acid synthesis, and stimulate lipoprotein lipase activity in animal models. Thus, there is some interest in GIP analogs as novel therapeutic option for the treatment of T_2DM. However, there are several limitations to using GIP itself as a therapeutic agent: a) GIP (1-42) has a short biological t in the circulation due to rapid cleavage and degradation by DPP-4, b) the cleaved metabolite (GIP 3-42) (**Table 2**) is not only inactive but may also function as a GIP receptor antagonist in vivo, c) clinical GIP infusion studies in T_2DM patients have resulted in blunted insulin responses, since GIP no longer modulates glucose-dependent insulin secretion in T_2DM even at supraphysiological plasma levels.[22] However, the interaction of GIP with its functional receptor on adipocytes results in a) increase in lipoprotein lipase, b) stimulation of lipogenesis, c) enhancement of fatty acid and glucose uptake, d) augmentation of insulin-mediated fatty acid incorporation, and e) inhibition of both glucagon- and adrenergic-receptor mediated lipolysis.[23,55] Thus, GIP promotes energy storage and reduces insulin at the adipocyte level while it stimulates insulin secretion from the β-cells. Hence, there is interest in developing GIP receptor agonist for the treatment of obesity and insulin resistance.[55] Although, several GIP analogs have been synthesized, no human studies with GIP analogs have been reported.

Pleiotropic effects of incretins and incretin-mimetics

The incretins have a number of pleiotropic (extrapancreatic) actions which have therapeutic benefits beyond controlling hyperglycemia[20,21,151-153]. As mentioned earlier, GLP-1 and exenatide delay gastric emptying, suppress appetite and cause satiety by central mechanism(s), which translates into reduction in body weight. GLP-1, exenatide and liraglutide have been shown to increase insulin sensitivity and β-cell function (**Table 3**)[111,128,135,139,140,154-156] In animal experiments, both exenatide and liraglutide increased β-cell mass, by increasing proliferation and neogenesis and reduction in apoptosis [27,38,157-159]; it is not known if these effect on β-cells are also applicable to humans. GLP-1 and analogs regulate cell proliferation and apoptosis in various tissues (such as pancreas, gut and the CNS)[158]. Exenatide also improves lipid profile (decrease in total cholesterol, LDL-cholesterol and triglycerides, apo B, and an increase in HDL-cholesterol)[100]. Liraglutide administration also decreases triglyceride levels[111,128]. Furthermore, exenatide treatment in patients with the metabolic syndrome produced significant improvement in cardiometabolic risk factors and anthropometric parameters[160]. Since exendin-4 was shown to reverse hepatic steatosis in ob/ob mice[161], the GLP-1 mimetics may be a therapeutic option for (human) hepatic steatosis[162].

Activation of GLP-1 receptors by GLP-1 in the endothelium, and cardiac and vascular myocytes, has been shown to increase levels of cAMP and cGMP resulting in vasodilation, enhanced coronary blood flow, and increased functional recovery and cardiomyocyte viability after ischemia-reperfusion injury in experimental studies[163,164]. Exenatide has also been reported to prevent ischemic-reperfusion injury in experimental animal models[165]. It is possible that the incretins and incretin-mimetics may protect the heart against ischemia-reperfusion injury in humans. The central action of GLP-1 also contributes to central regulation of metabolic and cardiovascular homeostasis[155], GLP-1 decreases BP and increases myocardial contractility[151], and in heart failure patients, infusion of GLP-1 improves endothelial function and symptoms of heart failure[43,159,166,167]. Some of these beneficial effects are mediated via a nitric oxide synthase-requiring mechanism that is independent of the interaction of GLP-1 with its receptor[168]. Exenatide decreased both the systolic and diastolic BP in patients following 82-week treatment, probably as a secondary consequence of improvements in blood levels of glucose and lipids and a reduction in body weight[97]. In other short term (24-week)[95] and long term (82-week)[107] studies, exenatide (5-10g bid) lowered

Table 3. Clinical studies with exenatide and exenatide LAR

Reference	Dose of exenatide (EX)	N	Study Duration (wk)	Other treatment	Change in HbA1c	Change in FPG	Change in Weight (kg) (mg/dL)
Moretto[95]	EX- 5 µg b.i.d.	232	24	Diet/exercise	- 0.7%	- 18	- 2.8
	EX-10 ug b.i.d.		24	Diet/exercise	- 0.9%	- 19	- 3.1
	Placebo		24	Diet/exercise	- 0.2%	- 5	- 1.4
Nelson[96]	EX-10 µg b.i.d.	99	4	Diet/exercise	- 0.4%	- 36	---
	Placebo		4	Diet/exercise	+ 0.2%	+ 11	---
Nelson[96]	EX-10 µg b.i.d./20 q.d.	127	30	Diet/metformin	- 0.9%		- 4.3
	EX-10 ug b.i.d./20 q.d.		30	Diet/exercise	- 1.0%		- 3.7
Fineman[88]	EX-0.08 µg b.i.d./t.i.d.	109	4	SU ± Metformin	- 1.0- -1.1%	---	---
	Placebo		4	SU ± Metformin	- 0.3%	---	---
Ratner[97]	EX-10 µg b.i.d.	92	82	Metformin	- 1.3%	- 31	5.3
Poon[98]	EX-5 µg b.i.d.	156	4	Diet/exercise/metformin	- 0.4%	- 20	- 1.4
	Ex-10 ug b.i.d.		4	Diet/exercise/metformin	- 0.5%	- 17	- 1.8
	Placebo		4	Diet/exercise/metformin	+ 0.1%	+ 7	0
Barnett[99]	Ex-10 ug b.i.d.	138	16	Metformin/SU	- 1.4%	- 52	- 2.2
	Insulin glargine		16	Metformin/SU	- 1.4%	- 74	+2.3
Klonoff[100]	EX-5-10 ug b.i.d.	217	16	Metformin ± SU	- 1.0%		- 5.3
	Placebo.		16	Metformin ± SU	- 0.4%	- 0.2	- 0.1
Monami[94]	EX-5-10 ug b.i.d.	466	16	Metformin ± SU	- 1.2%	- 1.3	- 1.2
	Placebo.		16	Metformin ± SU	- 0.4%	- 0.2	- 0.1
deFronzo[101]	EX- 5µg b.i.d.	336	30	Metformin (1000 mg/d)	- 0.4%	- 7	- 1.6
	EX-10 µg b.i.d.		30	Metformin (1000 mg/d)	- 0.8%	- 11	- 2.8
	Placebo		30	Metformin (1000 mg/d)	+ 0.2%	+14	- 0.3
Buse[102]	Ex- 5 µg b.i.d.	377	30	Glimepiride (4 mg/d)	- 0.5%	- 5	- 0.9
	EX-10 µg b.id		30	Glimepiride (4 mg/d)	- 0.9%	- 11	- 1.6
	Placebo		30	Glimepiride (4 mg/d)	+ 0.1%	+ 7	- 0.6
Kendall[103]	EX-5 µg b.i.d.	733	30	Metformin + SU	- 0.6%	- 9	- 1.6
	EX-10 µg b.i.d.		30	Metformin + SU	- 0.8%	- 11	- 1.6
	Placebo		30	Metformin + SU	+ 0.2%	+14	- 0.9
Zinman[104]	EX-10 µg b.i.d.	233	16	Metformin + TZD	- 0.9%	- 29	- 1.8
	Placebo		16	Metformin + TZD	+ 0.1%	+ 2	- 0.2
Heine[105]	EX-10 µg	551	26	Metformin + SU	- 1.1%	- 26	- 2.3
	Insulin glargine		26	Metformin + SU	- 1.1%	- 52	+1.8
Nauck[106]	EX-10 µg b.i.d.	501	52	Metformin + SU	- 1.0%	- 32	- 2.5
	Biphasic insulin		52	Metfromin + SU	- 0.9%	- 31	+ 2.9
Blonde[107]	EX-5-10 µg b.i.d.	314	82	Metformin ± SU	- 1.1%		- 4.4
	EX-5-10 µg b.i.d.	551	82	Metformin ± SU	- 0.9%		- 3.5
Buse[108]	EX-5-10 µg b.i.d.	283	30	Metformin ± SU	- 0.9%		- 2.1
	EX-5-10 µg b.i.d.		52	Metformin ± SU	- 1.1%		- 4.7
Brodows[109]	EX-5-10 µg b.i.d.	314	24	Metformin ± SU	- 0.7% to -0.9%	- 18	- 2.8 to -3.1
Gao[110]	EX-5-10 ug b.i.d.	466	16	Metformin ± SU	- 1.2%	- 1.3	- 1.2
	Placebo.		16	Metformin ± SU	- 0.4%	- 0.2	- 0.1
Buse[111]	EX-10 ug b.i.d.	464	26	Metformin ± SU	- 0.8%	- 11	- 2.9
	Liraglutide 1.8 mg/d		26	Metformin ± SU	- 1.1%	- 29	- 3.2
Drucker[112]	EX-10 µg b.i.d.	295	30	Metformin ± SU	- 1.5%	- 25	- 3.8
	EX-LAR 2.0 mg/wk		30	Metformin ± SU	- 1.9%	- 41	- 4.3
Kim[113]	EX-LAR 0.8 mg/wk	45	15	Metformin/diet/exercise	- 1.4%	- 43	0.0
	EX-LAR 2.0 mg/wk		15	Metformin/diet/exercise	- 1.7%	- 40	- 3.8
	Placebo		15	Metformin/diet/exercise	+ 0.4%	+18	0.0

Wk = week; b.i.d. = twice a day; t.i.d. = three-times a day; d = day; EX = exenatide; EX-LAR = Long-acting exenatide;
FPG = fasting plasma glucose levels; SU = sulfonylurea; TZD = thiazolinedione. For glucose levels, to convert mg/dL to mmol/L divide by 18

BP, which was independent of weight loss. Liraglutide administration also decreased systolic BP[128,129], which occurs even before the weight loss.

Exenatide treatment has been shown to prevent early diabetic retinopathy in experimental animals[169]. The incretins may also be involved in the regulation of taste function, since GLP-1 signaling in taste buds modulates taste sensitivity[170]. The apparent ability of exendin-4 (exenatide) to arrest progression of, or even reverse nigral lesions once established, normalize dopamine imbalance, and increase the number of cells positive for markers of dopaminergic neurons in the substantia nigra in a model of Parkinson's disease suggests that pharmacological manipulation of the GLP-1 receptor system could be of therapeutic value in Parkinson's disease[171,172]. Furthermore, GLP-1 has been shown to decrease endogenous amyloid-beta peptide (Abeta) levels and protect hippocampal neurons from death induced by Abeta and iron[173]; these observations suggest that GLP-1 and analogs may be useful in the therapy of Alzheimer's disease[174,175]. Since, exenatide potently decreases ghrelin levels in fasting rats, incretin-mimetics could offer a therapeutic option for syndromes characterized by substantial amounts of circulating ghrelin[176]. Additionally, exendin-4 improves glycemic control, ameliorates brain and pancreatic pathologies, and extends survival in a mouse model of Huntington's disease[177]. It is expected that other GLP-1-receptor agonists and inhibitors of DPP-4 will have some of the above mentioned pleiotropic effects of GLP-1 and agonists.

Dipeptidyl-peptidase-4 inhibitors - incretin enhancers

Since the incretin-mimetics have to be given subcutaneously, efforts to find orally active compounds that enhance the endogenous incretin effect, have resulted in the development of inhibitors of DPP-4[71,76,78,79,84], the enzyme which rapidly inactivates the endogenous incretins. DPP-4, a serine protease/peptidase, involved in many important processes related to nutrition, excretion and immune function (such as maintaining lymphocyte composition and memory T cell generation), is present in many tissues of the body but mostly in the kidney[178,179]. Serum levels of DPP-4 have been shown to increase with prolonged hyperglycemia[180], and its levels decrease with normalization of blood glucose. Increased levels of DPP-4 could contribute to the reduction in circulating active GLP-1 and to the consequent postprandial hyperglycemia in T_2DM patients with poor metabolic control[180]. Inhibitors of DPP-4, called the gliptins, block the active site of DPP-4 and thereby prevent the inactivation of incretins, thus prolonging the duration of action of GLP-1 and GIP[181]. These "incretin enhancers" increase postprandial insulin secretion, effectively improve glycemic control (reduce HbA1c), suppress glucagon release and endogenous glucose production (in the liver), and improve islet cell function (increased β-cell sensitivity to glucose), without a significant effect on gastric motility or body weight[57,80,82,182-199]. The DPP-4 inhibitors are more effective in patients with significant residual β-cell function as compared to those with long-standing insulin deficiency. The data on the effect of gliptins on appetite and body weight are not consistent in that some investigators claim that gliptins do not have any effect on these parameters[57,58,63,75,76,200,201], while others indicate that the gliptins have a modest effect on appetite (slowing gastric motility and inducing a feeling of satiety) and reduction in body weight[189,202,203]. Preclinical studies have demonstrated that an approximately 80% inhibition of DPP-4 activity is necessary to achieve a near-maximal effect on glucose concentration[204]. In humans, 80-88% inhibition is achieved with DPP-4 inhibitors given at the therapeutic doses[182,192,205,206], which results in significant rise in GLP-1 and GIP levels[192,197]. If animal studies turn out to be applicable to man, chronic treatment with DPP-4 inhibitors may prevent the decline in β-cell function and increase basal GLP-1 levels[207]. Interestingly, the observation that atorvastatin inhibits DPP-4[208] suggests that the statin may offer clinical benefit in treating T_2DM patients with dyslipidemia.

In general, the DPP-4 inhibitors are well tolerated and the risk of hypoglycemia is low when used as monotherapy or in combination with metformin or TZDs. In addition, these drugs have a low gastrointestinal side effect profile and drug administration does not require injection, thus enhancing patient compliance. However, the risk of nasopharyngitis, urinary tract infection and upper respiratory infection increases with the use of these drugs[56,71,189]. The effect of inhibition of DPP-4 could potentially have some adverse consequences, since DPP-4 has a large number of physiological (endogenous) substrates, and DPP-4 has been implicated in the control of lymphocyte and immune function, cell migration, viral entry, cancer metastasis, and inflammation[71]. It is possible that inhibition of neuropeptides, other closely related serine proteases such as DPP-2, DPP-8, DPP-9, fibroblast activation protein-alpha/seprase, prolyl endopeptidase, and tryptase may account for the occasional anemia, thrombocytopenia, neurogenic inflammation, allergic reactions, hypertension and splenomegaly that have been reported with certain non-selective DPP-4 inhibitors[177,178,209]. However, no such adverse effects have been reported in humans with short-term (12 months) use of the approved selective inhibitors at the therapeutic doses[81]. On the other hand, the DPP-4 inhibitors may be useful to decrease liver inflammation and steatosis, in conditions in which DPP-4 levels are high[210]. However, the durability and long-term safety of these drugs remains to be determined.

Sitagliptin (MK-0431, Januvia®) has been approved (2006) in the USA, and vildagliptin (LAF 237, Galvus®) in Europe (2008), as oral antidiabetic agents, to be used either as monotherapy in T_2DM patients inadequately controlled with diet and exercise, or as add-on therapy in combination with metformin, TZDs, or insulin, who have failed oral agents[73,185,190, 194]. If used as monotherapy, sitagliptin is re-

ported to be less effective than sulfonylurea and metformin in lowering HbA1c[211]. The efficacy of sitagliptin has been demonstrated in least 11 clinical trials conducted in 6781 randomized patients[57,59,65,84,185,186,191,195,200,203,205,211,212-220]; some data are presented in **Table 6**. Sitagliptin monotherapy (50-100 mg/day) usually results in a reduction in HbA1c of 0.8-0.9% and glucose levels of 18-22 mg/dL[195,200,203], while addition of metformin[211,213,216,219,221] or TZDs[212,220] to the antidiabetic regimen improves the efficacy; combination with metformin increases the efficacy in part by the reported inhibition of DPP-4 by metformin[114]. The drug (at doses of 100-200 mg/d) is well-tolerated in trials lasting up to 52 weeks, and it has a low risk of hypoglycemia[57,186,200,203,215,219-222]. Sitagliptin may be used as monotherapy in patients who cannot tolerate metformin or sulfonylureas and it may also be used as an alternative to metformin in renal insufficiency[57], however, the dose has to be decreased in patients with moderate to severe renal dysfunction or end-stage renal disease[223,224]. An ethnic difference in the efficacy of the gliptins (sitagliptin and vildagliptin) was observed in that at the same doses, the reduction in HbA1c was 1.5 times higher in Japanese T_2DM patients as compared to the Caucasian patients[225]. Sitagliptin improves β-cell function and decreases insulin resistance[157,191,211,214-216]. Sitagliptin has a favorable effect on lipid profile (decrease in free fatty acids, triglycerides and increase in HDL-cholesterol)[200].

Sitagliptin may cause gastrointestinal side effects, nasopharyngitis, upper respiratory infection and headache[57]; cases of severe idiosyncratic hepatotoxicity have also been reported[63]. Since, sitagliptin is highly selective for DPP-4 and shows little interaction with other proteas (**Table 6**) es or closely related enzymes, in particular DPP-8 and DPP-9, it is not associated with multiorgan toxicities exhibited by inhibitors of DPP-8/DPP-9 in animal studies[209]. Never-the-less, another DPP-4 inhibitor, vildagliptin, has been reported to cause skin lesions and kidney impairment in animals, but, no such adverse effects have been reported with short-term (12 months) use of sitagliptin or vildagliptin at therapeutic doses[81]. Some drawbacks of using sitagliptin include a lack of long-term safety and efficacy data, as well as high cost.

After oral administration, sitagliptin is rapidly absorbed (t_{max} = 1-4 hr), the absorption is not influenced by food intake[182,192]. The oral bioavailability of sitagliptin is 87%; it exhibits low and reversible binding to plasma proteins (approximately 38%) and is widely distributed in tissues (Vd = 198 L)[182,192]. The C_{max} and AUC are dose-dependent in the 25–400 mg dose range[226]. Plasma levels decline in a biphasic pattern (t of the alpha phase = 2-4 hr; terminal t = 8-14 hr), independent of the dose[182,192]. Sitagliptin is mostly excreted (80-87%) by the kidney[182,192,227]; metabolism by hepatic CYP 3A4 and CYP2C8 accounts for 17% of the administered drug[192,227]. Pharmacokinetic and pharmacodynamic parameters of sitagliptin are not significantly altered in moderately obese subjects[228] or in diabetic patients[192,221]. However, pharmacokinetic parameters of sitagliptin are altered in patients with renal insufficiency, with values of Cmax, AUC, and terminal $t_{1/2}$ increasing with the degree of renal dysfunction: AUC increase 4-5-fold, and Cmax and terminal $t_{1/2}$ increase 2-fold in patients with end-stage renal disease[223,224]. The pharmacokinetics of sitagliptin is not significantly affected by mild to moderate hepatic dysfunction.[229] Sitagliptin does not alter the pharmacokinetic parameters of glyburide[196,230], metformin[196,221], rosiglitazone[231], simvastatin[196,232], warfarin[196] or oral contraceptives[196].

Vildagliptin is used as monotherapy or in combination with metformin, sulfonylureas or TZDs in T_2DM patients with inadequate glycemic control following monotherapy; it is also used as monotherapy or in combination with a TZD in patients who cannot tolerate metformin or sulfonylureas[194,220]. At an oral dose of 100 mg, vildagliptin almost completely inhibits DPP-4 for up to 24 hr[233]. At least 19 clinical trials have been conducted in more than 7000 randomized patients[56-58,65,74,80,82,84]; results of some of these studies are presented in **Table 6**[183,188,201,202,235-248]. Vildagliptin dose-dependently improves glycemic control in T_2DM patients: at doses of 25 to 50 mg b.i.d., the decrease in HbA1c ranges between 0.8% and 1.1%, and fasting glucose levels (by 15 mg/dL to 30 mg/dL) after monotherapy[201,202,234], with further improvement in these parameters when given in combination with metformin[188,194,197,198,239,244,246], the effect on weight is minimal[237,243,244,246]. Vildagliptin is as effective as pioglitazone, and In T_2DM patients failing TZD monotherapy, vildagliptin in combination with pioglitazone improved glycemic control[240,241,247,249] without additional risk of hypoglycemia[240,241]. Vildagliptin in combination with metformin, a sulfonylurea or a TZD (given for 24-52 wk) not only improved glycemic control in T_2DM patients but also appeared to slow the progression of β-cell degeneration[187,194,250]. Vildagliptin has a low risk of hypoglycemia and is generally well-tolerated at doses of up to and including 200 mg a day in trials lasting up to 52 wk[201,251]. The drug is also available as a fixed-dose formulation with metformin (Eucreas®)[252-254]. Vildagliptin improves islet-cell function by increasing both α- and β-cell responsiveness to glucose; improvement in β-cell function (assessed by increase in HOMA-β), insulin sensitivity (reduction in HOMA-insulin resistance), postprandial insulin secretion, and a reduction in postprandial glucagon secretion were observed with vildagliptin (at doses of 25-200 mg/day)[75,187,193,194,199,253-264]. Vildagliptin improves lipid profile[237].

After oral administration, vildagliptin is rapidly absorbed giving rise to dose-dependent Cmax (t_{max} = 1.0-2.0 hr) across the dose range of 25- 200 mg; its oral bioavailability is 85%[256,265-268]. Food has no effect on the absorption of vildagliptin[268]. Vildagliptin exhibits low protein binding (9.3%), and it is quickly eliminated (t of ≃ 2-3 hr)[256,265,266]; the t is dose-dependent (range 1.6-2.5 hr)[267-269]. There is

Table 6. Clinical studies with Vildagliptin

Reference	Dose of vildagliptin (VILD)	N	Study Duration (wk)	Other treatment	Change in HbA1c	Change in FPG (mg/dL)	Change in Weight (kg)
Kikuchi [234]	VILD – 25-50 mg b.i.d.	291	12	Diet	-1.0% to - 1.2%		0
	Placebo		12	Diet	+0.1%	- 9	- 0.2
Dejager[202]	VILD - 50 mg q.d.	632	24	Diet	- 0.8%	- 18	- 1.8
	VILD - 50 mg b.i.d		24	Diet	- 0.8%	- 14	- 0.3
	VILD -100 mg q.d.		24	Diet	- 0.9%	- 14	- 0.8
	Placebo		24	Diet	- 0.3%	- 4	- 1.4
Pi-Sunyer[201]	VILD - 50 mg q.d.	354	24	Diet	- 0.5%	- 9	- 0.4
	VILD - 50 mg b.i.d		24	Diet	- 0.7%	- 22	0
	VILD -100 mg q.d.		24	Diet	- 0.8%	- 20	- 0.4
	Placebo		24	Diet	0.0	+ 2	- 1.4
Pan[235]	VILD - 50 mg b.i.d.	660	24	Diet	- 1.4%	- 16	
	Acarbose 300 mg/d		24	Diet	- 1.3%	- 27	
Schweizer[236]	VILD - 50 mg b.i.d.	780	52	Diet	- 1.0%	- 16	+ 0.3
	Metformin 1000 mg b.i.d.		52	Diet	- 1.4%	- 31	+ 1.6
Rosenstock[237]	VILD - 50 mg b.i.d.	598	52	Diet	- 0.9%		0
	Rosiglitazone 8 mg/d.		52	Diet	- 1.1%		+ 4.7
Scherbaum[238]	VILD - 50 mg q.d.	306	52	Diet	- 0.2%	- 7	- 0.5
	Placebo		52	Diet	+0.1%	+ 8	- 0.2
Ahren[239]	VILD - 50 mg q.d.	107	12	Metformin	- 0.6%	- 18	- 0.4
	Placebo		12	Metformin	+ 0.1%	+ 4	- 0.5
Rosenstock[240]	VILD -100 mg q.d.	607	24	Diet	- 1.1%	- 23	- 0.6
	VILD - 50 mg q.d.		24	Pioglitazone 15 mg q.d. + Diet	- 1.7%	- 43	+ 1.4
	VILD -100 mg q.d.		24	Pioglitazone 30 mg q.d. + Diet	- 1.9%	- 50	+ 2.1
	Placebo		24	Pioglitazone 30 mg q.d. + Diet	- 1.4%	- 34	+ 1.5
Garber[241]	VILD - 50 mg q.d.	463	24	Pioglitazone 45 mg/d.	- 0.8%	- 14	+ 0.1
	VILD - 50 mg b.i.d.		24	Pioglitazone 45 mg/d.	- 1.0%	- 18	+ 1.3
	Placebo		24	Pioglitazone 45 mg/d	- 0.3%	- 9	+ 1.4
Garber[242]	VILD - 50 mg q.d.	515	24	Glimepiride	- 0.6%	- 5	- 0.1
	VILD - 50 mg b.i.d.		24	Glimepiride	- 0.6%	- 7	+ 1.3
	Placebo		24	Glimepiride	+ 0.1%	+ 4	- 0.4
Fonseca[243]	VILD - 50 mg b.i.d.	296	24	Insulin 82U/d	- 0.5%	- 14	+ 1.3
	Placebo		24	Insulin 82U/d	- 0.2%	- 4	+ 0.3
Bosi[188]	VILD - 50 mg q.d.	544	24	Metformin ≥1500 mg/d	- 0.7%	- 14	- 0.4
	VILD - 50 mg b.i.d.		24	Metformin ≥1500 mg/d	- 1.1%	- 31	+ 0.2
	Placebo		24	Metformin ≥1500 mg/d	+0.2%	+ 13	- 1.0
Bosi[244]	VILD - 50 mg b.i.d.	1179	24	Metformin 2000 mg/d	- 1.8%	- 47	0
	VILD - 50 mg b.i.d.		24	Metformin 1000 mg/d	- 1.6%		0
	VILD - 50 mg b.i.d.		24	Diet	- 1.1%	- 27	0
	Placebo		24	Metformin 2000 mg/d	- 1.4%	- 35	0
Rosenstock[245]	VILD - 50 mg b.i.d.	786	24	Diet	- 1.1%	- 23	- 0.3
	VILD - 50 mg q.d.		24	Rosiglitazone 8 mg q.d. + Diet	- 1.3%	- 41	+ 1.6
Bolli[246]	VILD - 50 mg b.i.d.	576	24	Metformin 2000 mg/d	- 0.9%	- 38	+ 0.2
	Pioglitazone 30 mg q.d.		24	Metformin 2000 mg/d	- 1.0%	- 25	+ 1.9
Goke[247]	VILD - 50 mg b.i.d.	305	52	Diet ± pioglitazone	- 1.0%		- 0.5
	Metformin 2000 mg/d		52	Diet ± pioglitazone	- 1.5%		+ 2.5
Ferrannini[248]	VILD - 50 mg b.i.d.	2789	52	Metformin 2000 mg/d	- 0.44%	- 18	- 0.23
	Glimepiride 4.5 mg/d		52	Metformin 2000 mg/d	- 0.53%	- 21	

N = number of patients in the study; b.i.d. = twice a day; q.d. = once a day; d = day; FPG = fasting plasma glucose levels; SU = sulfonylurea;
For glucose levels, to convert mg/dL to mmol/L divide by 18

no accumulation after repeated dosing. The metabolism of vildagliptin is mainly by hydrolysis to inactive metabolites[265]. Some 80% to 85% of an oral dose is eliminated in urine, including 22% to 29% of unchanged drug in Chinese subjects, which is similar to that observed in non-Chinese subjects[256,265-269]. There is no significant effect of gender or obesity on the pharmacokinetics of vildagliptin, however, total exposure (AUC) of the drug increases, but clinically insignificantly in the elderly[267]. Hepatic dysfunction does not have any effect on the pharmacokinetics of vildagliptin, therefore, dosage adjustment is not necessary[269]. Vildagliptin does not have a significant effect on the pharmacokinetics of digoxin[270], amlodipine[271] valsartan[271], ramipril[271], simvastatin[272] and warfarin[273].

Several other DPP-4 inhibitors, including alogliptin (SYR-322)[84,274,275,276,277] and saxagliptin (BMS-477118; Onglyza ®)[84,275,278,279], etc., are in various stages of development. Both vildagliptin and saxagliptin are apparently close to being approved by the USA-FDA. Monotherapy with alogliptin (12.5-25 mg per day) improved glycemic control (decrease in HbA1c by 0.6%) in T_2DM patients without raising the risk of hypoglycemia[274,276.280]. It appears to be effective and safe in treating T_2DM, when added to metformin in patients not sufficiently controlled on metformin monotherapy.[281] In addition to metformin, alogliptin can also be combined with TZDs, sulfonylureas and insulin[274,277]. The drug is well tolerated and has an excellent safety profile, except that hypoglycemia is significant at 800 mg dose[282]; it appears to be weight neutral. Combination of alogliptin with pioglitazone (in ob/ob mice) increased GLP-1 and insulin levels and reduced glucagon concentration, and exhibited a complementary effect in terms of improved glycemic control and lipid profile[283]. Never-the-less, studies in diabetic patients are needed to evaluate the long-term safety and efficacy of alogliptin[284]. After single oral doses (25-800 mg), alogliptin is rapidly absorbed (t_{max} = 1-2 hr) and is slowly eliminated (t = 12 – 21 hr). A small fraction of the dose is metabolized (8%), and 60 - 71% of the dose of the drug is eliminated by the renal route[282,285]. Results of clinical studies with saxagliptin appear to be encouraging, in that a dose-dependent inhibition of DPP-4 is achieved resulting in reduction in HbA1c (by 0.7-0.9%), fasting serum glucose, postprandial glucose levels, with low incidence of adverse effects, and no significant effect on body weight[84,275,278, 279,286].

Conclusions

Traditional first-line therapy (sulfonylureas, metformin, TZDs, etc.) might not be appropriate for all T_2DM patients. In addition, these drugs have significant adverse effects, such as hypoglycemia and weight gain. The recently developed diabetes therapies based upon GLP-1 receptor agonists (e.g., exenatide, liraglutide) and DPP-4 inhibitors (e.g., sitagliptin, vildagliptin) are useful in the management of T_2DM because they provide effective reductions in fasting plasma glucose and postprandial glucose levels. In addition, the GLP-1 receptor agonists promote weight loss, whereas the DPP-4 inhibitors are weight neutral, and there is a low risk of symptomatic hypoglycemia. These drugs are effective as monotherapy in drug-naive patients as well as in those in whom other treatments (for example with metformin, sulfonylureas, thiazolinediones, etc.) have been inadequate to achieve glycemic control. When combined with other glucose-lowering agents, the GLP-1 receptor agonists and DPP-4 inhibitors the efficacy of treatment is increased. These drugs appear to have beneficial effects on β-cell dysfunction, although, the ability of GLP-1 receptor agonists to reduce and/or reverse the progressive β-cell loss remains unclear. Also, it is not known that long-term therapy based upon incretin-mimetics/incretin-enhancers will have sustained benefits, especially in later-stages of the disease; the long-term safety has also not been established. Never-the-less, the current consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes about the medical management of hyperglycemia in T_2DM patients has included GLP-1 receptor agonists as an option when weight loss or risk of hypoglycemia are major considerations. In general, antidiabetic agents should be individualized on the basis of their efficacy as hypoglycemic agents and their extraglycemic effects (on lipids, BP and weight), tolerability and safety, complication of long-term use, ease of drug administration, and costs.

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