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GLP-1 ANALOGUE AND DPP-4 INHIBITORS: A NEWER APPROACH IN THE MANAGEMENT OF TYPE 2 DIABETES MELLITUS

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ABSTRACT

Diabetes mellitus (DM), a chronic disorder with increasing prevalence worldwide. This chronic disease has been likened recently to the "Black Death" of the 14th century. It is a multifaceted disease involving multiple pathophysiological defects. The pathophysiology of type 2 diabetes mellitus (T2DM) is complex and includes impaired incretin response, among other metabolic abnormalities. Incretin hormones play a crucial role in modulating insulin and glucagon secretion, as well as regulating appetite, gastric emptying, and pancreatic beta cell functions. Increased knowledge of gut hormone in the pathophysiology of diabetes has contributed to the development of novel treatments: glucagon-like peptide-1 (GLP-1) mimetics and dipeptidyl peptidase-4 (DPP-4) inhibitors. DPP-4 inhibitors protect endogenous GLP-1 from DPP-4 degradation, thereby achieving a physiologic level of GLP-1. GLP-1 receptor agonists may also promote satiety, reduce weight, slow gastric emptying, and possibly improve hypertension and triglyceride levels; these characteristics are absent with DPP-4 inhibitors. A review of incretin based approach in the management of diabetes is presented.

Keywords: Diabetes Mellitus, Dipeptidyl Peptidase-4, Glucagon-Like Peptide-1, Insulin, Glucagon

INTRODUCTION

Diabetes mellitus (DM) is one of the most common chronic disorders, with increasing prevalence worldwide. This costly and chronic disease has been likened recently to the 'Black Death' of the 14th century **[1]**. In Type 2 diabetes (T2DM), the actions and secretion of insulin are impaired, as opposed to the absolute deficiency of insulin that occurs with type 1 diabetes mellitus. T2DM is characterized by two major pathophysiologic defects: (A) insulin resistance, which results in increased hepatic glucose production and decreased peripheral glucose disposal, and (B) impaired β-cell secretory function **[2]**. T2DM, a multifaceted disease involving multiple pathophysiological defects, accounts for nearly 85-95% of total reported cases of DM. Chances of developing T2DM are increased by obesity and physical inactivity and are augmented further with age **[3]**.

T2DM has traditionally been treated in a stepwise manner, starting with lifestyle modifications, exercise and later on pharmacotherapy with oral agents. Several classes of oral agents are available for clinical use. These mainly include insulin secretagogues, drugs that delay the absorption of carbohydrates from the gastrointestinal tract, and insulin sensitizers. Over the time, many patients with T2DM require insulin therapy. Currently available therapies for T2DM have various limitations and may also be associated with an increased risk of hypoglycemia (eg, sulphonylureas, insulin), weight gain (eg, sulphonylureas, thiazolidinediones, insulin), and gastrointestinal side effects (eg, metformin) as well as edema and heart failure (eg, thiazolidinediones) **[4]**.

Several studies have found that in diabetes there is a complex interplay of hormonal and neural stimuli, not just insulin and glucagon, are involved in the regulation of glucometabolic control **[5]**.

One new approach yielding promising results is the use of agents that are based on gut incretin hormones, which appear to be malfunctioning in T2DM and have important effects on insulin and glucagon biology as well as central nervous system effects on appetite. These new treatments include glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1) (“incretin”) mimetics as well as dipeptidyl peptidase-4 (DPP-4) inhibitors **[4]**.

An incretin hormone is a gut hormone that is released into the blood after meal ingestion and stimulates insulin secretion in a glucose-dependent manner. This accounts for the marked prandial insulin response, which

prevents prandial hyperglycemia. The incretin concept was established in the 1960s. **[6, 7]** The most important incretin hormones are the glucose dependent insulinotropic peptide (GIP) and GLP-1 **[8]**.

GIP was originally identified as a 42–amino acid peptide. It was subsequently shown to potentiate glucose-stimulated insulin secretion **[9]** whereas GLP-1 is a 30 amino acid polypeptide which is produced by the intestinal L-cells localized mainly in the distal portion of the small intestine and in the large intestine **[10]**. Plasma concentrations of both incretins increase within 5 to 15 min after meal ingestion. GLP-1 is primarily released by the ingestion of carbohydrate, fat and protein, whereas GIP is mainly liberated by the ingestion of carbohydrate and fat **[11]**.

These incretins exert their action through G-protein coupled receptor, which is expressed on pancreatic β-cells, is the increased formation of cyclic adenosine 30, 50-monophosphate (cAMP), which activates protein kinase A (PKA). This closes adenosine triphosphate (ATP)- regulated potassium channels in the presence of elevated glucose levels **[12,13]** and inhibits voltage-dependent potassium channels **[14]** leading to an increase in intracellular calcium enhancing exocytosis of insulin-containing granules **[12]**.

Both GIP and GLP-1 receptors are expressed in various tissues. GLP-1 receptors are found in pancreatic islets, vagal nerves, stomach, lung, kidney, and the brain, whereas GIP receptors are expressed in pancreatic islets, the brain and adipose tissue **[15, 16]**. Besides the direct stimulation of islet β-cells, GLP-1 may also promote insulin secretion indirectly through the activation of sensory nerves **[17]** suggesting an important neural contribution to GLP-1-induced insulin secretion, which could explain the rapid insulinotropic action after meal ingestion **[18]**.

Both GLP-1 and GIP are inactivated by DPP-4 resulting in a short half-life, which is 1 to 2 min for GLP-1 and 5 to 7 min for GIP **[11]** Inhibition of DPP-4 enzyme leads to an increase in plasma concentration of these incretins. This results in stimulation of insulin secretion, reduction in plasma glucose and glucagon levels, and inhibition of gastric emptying. Incretins also govern β-cell differentiation; mitogenesis and survival which is how DPP-4 inhibition can preserve β-cell mass and improve their secretory function **[19]**.

This review summarizes the incretin-based pharmacotherapy of T2DM, such as GLP-1 receptor agonists and DPP-4 inhibitors.

GLP-1 Analogues

GLP1 rapidly lowers plasma glucose in patients with T2DM **[20-22]**. Subcutaneous GLP1 injections improve postprandial glycemic control and reduce the levels of glucagon in the plasma of subjects with T2DM **[23]**. Furthermore, it also improves β cell function, and lowers fasting and postprandial glucose and hemoglobin A1c (HbA1c) levels after continuous subcutaneous GLP1 infusion. Modest weight loss and improve insulin sensitivity was also observed with this agent **[24]**. The first GLP1R agonist approved for the treatment of T2DM was exendin-4, a naturally occurring GLP1-related peptide isolated from the venom of the lizard *Heloderma suspectum* **[25]**. Exenatide is a synthetic exendin-4, GLP-1 analogue and insulin secretagogue with glucoregulatory effects. A randomized trial was conducted by Heine RJ, *et al*., **[26]**, in patients with T2DM not optimally controlled by oral agents. It was observed that exenatide and insulin glargine produced comparable reductions in HbA1c levels of approximately 1.1% after 26 weeks of therapy in patients with a mean initial HbA1c level of 8.2%–8.3%. The incidence of gastrointestinal side effects was substantially greater in patients treated with exenatide; however, exenatide therapy was associated with a mean weight loss of 2.3 kg, whereas patients treated with insulin glargine gained approximately 1.8 kg. [26] Side effect profile of exenatide includes hypoglycemia (more upon combination therapy with sulfonylureas and thiazolidinediones), nausea, vomiting, diarrhea, heartburn, indigestion, dizziness, headache and pancreatitis. Anti-exenatide antibodies were also developed **[27]**.

Lixisenatide, a once-daily injectable GLP-1 analogue, demonstrates efficacy and safety in T2DM both as monotherapy and in combination with metformin **[28]**. In a trial it has been found that lixisenatide has significantly reduced HbA1c levels and reduced weight in T2D patients **[29]**. Liraglutide, a DPP4-resistant analogue of GLP1 that binds noncovalently to albumin and is suitable for administration just once a day because it has a longer half-life than exenatide **[30, 31]**. Liraglutide lowered HbA1c levels with no associated weight gain in a 12-week monotherapy study **[32]**. In a study liraglutide induced similar glycemic control, reduced body weight and lower the occurrence of hypoglycemia compared to glimepride, both used in combination with metformin **[33]**. Liragutide is contraindicated in those with family history of medullary thyroid cancer **[34]**. Albiglutide is a recombinant human serum albumin (HAS)-GLP-1 hybrid protein with half of about a

week and is found to display resistance to DPP-4 **[35]**. Another GLP-1 analogue, taspoglutide exerts insulinotropic action in vitro and in vivo, retains the glucoincretin property of human GLP-1, is fully resistant to DPP-4 cleavage and has an extended in vitro plasma half-life **[36]**.

DPP-4 Inhibitors

The current DPP-4 inhibitors are reversible competitive inhibitors of DPP-4 **[37]**. Sitagliptin and vildagliptin have been explored in detail; both possess such pharmacokinetic properties that support a once-daily dosing regimen. Clinically important pharmacokinetic parameters are summarized in **Table 1**. Sitagliptin was approved by the U.S. Food and Drug Administration (FDA) on October 17, 2006, **[38]**, Vildagliptin was approved in February 2008 by European Medicines Agency for use within the EU, While this drug is still not approved for use in the US as it was rejected from FDA twice; firstly because in early study on animals, it was found that it elevate liver enzymes 2.5 over normal folds and it cause rare cases of acute hepatitis and the second time, it causes skin ulceration for the experimental animals however these findings were not occurred in human trials **[39]**. Both Sitagliptin and vildagliptin are orally active, rapidly absorbed, and mainly excreted by the kidneys. Dose adjustments are required in patients with renal impairment **[40]**. Vildagliptin is not recommended for patients with severe liver problems. It is recommended that renal function is assessed prior to the start of sitagliptin treatment. The recommended dosage of sitagliptin is 100 mg orally once daily, either as monotherapy or in antidiabetic combination therapy, taken with or without food, whereas it is 100 mg for vildagliptin when used with metformin or a thiazolidinedione or 50 mg in combination with a sulphonylurea **[41, 42]**. The pharmacokinetics of vildagliptin and sitagliptin do not seem to be affected by age, gender, ethnicity, or body mass index **[4]**. The European Medicines Agency has also approved a new oral treatment released by Novartis, called Eucreas, a combination of vildagliptin and metformin **[43]**. Sitagliptin has been shown to lower HbA1c level by about 0.7% points versus placebo. It is slightly less effective than metformin when used as a monotherapy and does not cause a weight gain compared to sulfonylureas. Sitagliptin is recommended as a second line drug (in combination with other drugs) after the treatment based on a combination of diet and metformin fails **[44]**.

In a 24 - week study on 741 patients, it was found that in once daily regimen, sitagliptin

as monotherapy improves glycaemic control in fasting and postprandial states; β - cell functions were also improved and this regimen was well tolerated **[45]**. In another study carried by Sahelian R on 2719 patients, it was observed that sitagliptin improved blood sugar control when used alone or in diabetes patients; not satisfactorically managed with metformin or a peroxisome proliferator - activated receptor (PPAR) agonist **[46]**. In a double blind, randomized, multicentric study; safety and efficacy of vildagliptin was evaluated by Ferrannini E, *et al*., **[47]**, in which it was found that apart from DPP-4 inhibition, vildagliptin is also known to enhance α- cell responsiveness to both the suppressive effects of hyperglycemia and stimulatory effects of hypoglycemia. The addition of vildagliptin to metformin showed comparable efficacy to that of glimepride after 52 weeks **[47]**.

Saxagliptin , previously identified as BMS-477118, is a new oral anti-diabetic drug of the new DPP-4 inhibitor class of drugs **[48]**. It was approved by FDA on July 31, 2009 **[49]**. Saxagliptin 2.5 or 5 mg once daily suppresses DPP-4 activity for 24 hours **[50]** , It significantly improves mean HbA1c levels (relative to placebo) in treatment-naive patients with type 2 diabetes. It was found that combination therapy with saxagliptin 5 mg once daily and metformin was more effective than saxagliptin or metformin monotherapy **[51]**. Saxagliptin is metabolized via CYP 3A4/A5, whereas DPP-4 inhibitors are in general not substrates for cytochrome P450 and do not act as inducers or inhibitors of this system. Several metabolites have been documented but most of them are inactive; however, the main metabolite of saxagliptin also exerts a significant DPP-4 inhibition and is half as potent as the parent compound **[52]**.

Linagliptin is a new long acting xanthine based DPP inhibitor with high selectivity to DPP- 4 in comparison to DPP-8 and DPP-9. It was approved by FDA in 2011 **[53]**. It is associated with minimal risk of hypoglycemia. It produces a significant and sustained improvement in glycemic control. Improvement in β- cell functions were also observed with this agent **[54]**.

Dutogliptin is being developed by Phenomix Corporation. It is a small-molecule DPP-4 inhibitor for the potential oral treatment of T2DM **[55]**. A 12-week, double-blind, randomized, placebo-controlled, multicentre trial was conducted by Pattzi HM, et al. to determine the efficacy and tolerability of dutogliptin in patients with type 2 diabetes mellitus. It was observed that dutogliptin treatment for 12 weeks improved glycaemic

control in patients with type 2 diabetes who were on a background medication of metformin, a thiazolidinedione (TZD) or metformin plus a TZD. It was very well tolerable in a dose of 200 mg & 400 mg. The 400 mg dose of dutogliptin resulted in larger changes of HbA1c and fasting plasma glucose and more subjects reached an HbA1c target of < 7% than the 200 mg dose **[56]**.

Alogliptin was approved by FDA in 2013. It is an orally administered anti-diabetic drug in the DPP-4 inhibitor class. Oral bioavailability is nearly 100 percent. Twenty percent of drug binds to protein. Half life is 12-21 hours. It metabolizes in liver with microsomal enzyme mainly with CYP2D6- and 3A4. Major route of excretion is renal and minor amount is excreted by fecal route **[57]** . Seino, *et al*. conducted a randomized clinical trial in 2011 to determine the efficacy and safety of alogliptin versus placebo and voglibose among newly diagnosed type 2 diabetes patients in Japan. The main outcome indicated that alogliptin was statistically superior to both comparators **[58]**.

An herbal dietary supplement berberine, too inhibits DPP-4, which at least partly explains its antihyperglycemic activity **[59]**.

Various adverse effects including nausea, headache, skin reactions and rarely hypersensitivity reactions and pancreatitis are reported with DPP-4 inhibitors. These effects occur due to probably via ductal proliferation and metaplasia **[60]**. The DPP-4 enzyme is known to be involved in the suppression of certain malignancies, particularly in limiting the tissue invasion of these tumours. Inhibiting the DPP-4 enzymes may allow some cancers to progress **[61, 62]**. A study of DPP-4 inhibition in human nonsmall cell lung cancer (NSCLC) concluded "DPP-4 functions as a tumor suppressor, and its down regulation may contribute to the loss of growth control in NSCLC cells **[63]**. Some other adverse effects including nasopharyngitis and upper respiratory infections were also reported (probably via immunomodulation) **[64]**.

CONCLUSIONS

The pathophysiology of type 2 diabetes mellitus (T2DM) is complex and includes impaired incretin response, among other metabolic abnormalities. There is rapid and accelerated progress in the development of anti-diabetes drugs. Incretin-based treatments for T2DM, such as GLP-1 receptor agonists and DPP-4 inhibitors, mimic or prolong the actions of incretin hormones and function in a glucose-dependent manner. Most antidiabetic agents are often associated with weight gain over time, whereas exenatide therapy is frequently associated with weight loss, an

important clinical feature that differentiates GLP1 receptor agonists from all other available therapies for T2DM. DPP-4 inhibitors have some theoretical advantages over existing therapies. DPP-4 inhibitors will be a first-line treatment strategy of the early stages of type 2 diabetes in the future, particularly in combination with metformin. However long-term data on cardiovascular outcomes and safety are needed before widespread use of these new agents.

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Table 1: Clinically Important Pharmacokinetic Parameters

	Sitagliptin	Vildagliptin
Selectivity for DPP-4 over DPP-8/9 (fold)	>2600	32–250
Absolute bioavailability [%]	87	85
Time to reach maximum plasma concentration, Tmax [hr]	2	1-2
Volume of distribution [L]	198	70.5
Plasma protein binding [%]	38	9
Terminal half life, T1/2 [hr]	11.0	1.7
Renal clearance [L/hr]	21	13
Elimination in urine [%]	87	85
Recommended dosage [mg/day]	100	100