Dipeptidyl-Peptidase IV Inhibitors and glycemic control in type 2 Diabetes Mellitus

Lokendra Bahadur Sapkota,1 Sangita Thapa2
1Department of Biochemistry, 2Department of Microbiology, Chitwan Medical College, Bharatpur, Nepal

Correspondence
Dr Lokendra B Sapkota,
Department of Biochemistry,
Chitwan Medical College,
Bharatpur, Nepal
Email: sdrloken@gmail.com

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ABSTRACT
Background & Objectives: Type 2 diabetes mellitus (T2DM) is a progressive disease, characterized by insulin resistance, impaired glucose-induced insulin secretion, inappropriately elevated glucagon concentrations, and hyperglycemia. Many patients cannot obtain satisfactory glycemic control with current therapies. New and more effective agents, targeted not only at treatment, but also at prevention of the disease, its progression, and its associated complications, are, therefore, required. The dipeptidyl peptidase-4 (DPP-4) inhibitors are a newer class of oral drugs for the treatment of T2DM. They inhibit the breakdown of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulino tropic polypeptide (GIP) thereby increasing the incretin effect in patients with T2DM. In clinical practice they are associated with significant reductions in HbA1c, no weight gain and a low risk of hypoglycemia. Since incretin response is markedly diminished in Asian populations, these agents can be used to achieve satisfactory glycemic control in Nepalese T2DM patients.

Key words: DPP-4 inhibitors; incretin hormones; type 2 DM

INTRODUCTION
The prevalence of type 2 DM is increasing at an alarming rate both in the developed and developing countries of the world.1 It is characterized by insulin resistance and impaired β-cell secretory function.2 Many studies have already proven that people with type 2 DM have reduced β-cell function (~50%) at the time of diagnosis which continues to decline regardless of treatment.3 This shows that the defect occurs early and is important in the pathogenesis of the disease, rather than simply arising as a consequence of hyperglycemia. Many patients cannot obtain satisfactory glycemic control with current therapies, and eventually develop microvascular and macrovascular diabetic complications.4 To prevent such complications, new and more effective pharmacological agents are required which not only targets treatment of type 2 DM, but also its prevention, progression, and associated complications. One new approach which is rapidly undergoing trials worldwide with promising results is the use of agents that are based on gut incretin hormones glucagon like peptide-1 (GLP-1) and glucose dependent insulino tropic peptide (GIP). These two hormones are secreted by intestinal mucosal cells as a result of food ingestion and regulate the endocrine secretion of pancreas; hence the name incretins.5 These incretins undergo degradation by the action of enzyme Dipeptidyl peptidase-IV, which are ubiquitously distributed in a number of sites, including the endothelial cells of small gut arterioles.6 As a result, the majority of GLP-1 and GIP is inactivated before reaching the systemic circulation.

Biology of DPP-4
DPP-4 is a 766-amino acid serine protease that preferentially cleaves peptide hormones containing a position two alanine or proline. The human gene encoding DPP-4 has been localized to chromosome 2 locus 2q24.3,7 Majority of the DPP-4 protein is extracellular, with a hydrophobic transmembrane sequence anchoring the protein in the cell membrane.8 It is a single-pass type II integral transmembrane glycoprotein with its carboxy-terminus outside the membrane and a short N-terminal cytoplasmic extension. It was originally identified as a protein on lymphocytes. DPP-4 is widely expressed in several cell types, particularly in exocrine glands and absorptive epithelia. In humans, DPP-4 found in the brush borders of epithelial cells of the proximal convoluted tubules in the kidney and of the small and large intestine as well as in prostate, liver hepatocytes, and activated leukocytes (T-, B- and natural killer cells).9

DPP-4 is also known as adenosine deaminase binding protein (ADBP) or T-cell activation antigen CD26.10 It catalyses the release of an N-terminal dipeptide provided that the next to last residue is proline, hydroxyproline, dehydroproline or alanine.11 Only oligopeptides in the trans conformation are able to bind to the active site of DPP-4. Several peptides have been identified...
as DPP4 substrates. These substrates include neuropeptides, chemokines, and the incretin hormones.\textsuperscript{12} 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.\textsuperscript{13} Almost 50% of this degradation occurs at the intestinal capillaries close to the site of GLP-1 and GIP release.

**Physiology of DPP-4 Inhibitors**

DPP-4 inhibitors are a newer class of oral hypoglycemic agents (OHA’s) that regulates blood glucose level by inhibiting the action of DPP-4. Meal ingestion with increased glucose concentration in blood stimulates release of the endogenous incretins GLP-1 and GIP which in turn stimulates insulin release and inhibit glucagon release resulting in lower blood glucose.\textsuperscript{14} They are rapidly inactivated by DPP-4. Therefore DPP-4 inhibitors prolong the action of endogenous incretins, enhancing the first-phase insulin response.\textsuperscript{15,16}

DPP-4 inhibitors were first introduced in 2006 for the management of hyperglycemia in type 2 DM. Currently, sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin have been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency for use in patients with type 2 diabetes. DPP-4 inhibitors only enhance the body’s own ability to release insulin and regulate blood glucose, hence these drugs are applicable only in the management of type 2 DM.\textsuperscript{17} Their effect is dependent on some function of the insulin-releasing beta cells in the pancreas, and people with type 1 diabetes generally do not have a significant number of functioning pancreatic beta cells.

Examples of DPP-4 inhibitors which are commonly used worldwide.

- **Sitagliptin** (First discovered and FDA approved 2006, marketed by Merck & Co. as Januvia),\textsuperscript{18}
- **Vildagliptin** (EU approved 2007, marketed in the EU by Novartis as Galvus),\textsuperscript{19}
- **Saxagliptin** (FDA approved in 2009, marketed as Onglyza),
- **Linagliptin** (FDA approved in 2011, marketed as Tradjenta by Eli Lilly Co and Boehringer Ingelheim),\textsuperscript{20}
- **Alogliptin** (approved in Japan in 2012, marketed by Sanwa Kagaku Kenkyusho Co., Ltd. and Kowa Company, Ltd.)\textsuperscript{21}
- **Teneligliptin** (approved in Japan in 2012),\textsuperscript{22}
- **Gemigliptin** (being developed by LG Life Sciences),\textsuperscript{23}
- **Dutogliptin** (being developed by Phenomix Corporation), Phase III\textsuperscript{24}

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The combined incretin response (GLP-1 and GIP) accounts for 50–70% of total postprandial insulin production.\textsuperscript{25} Both insulin secretion and biosynthesis are enhanced, while over-secretion of glucagon is suppressed, restoring the normal glucagon: insulin relationship, which is important for the regulation of hepatic glucose metabolism.\textsuperscript{26} Though $\beta$-cell trophic effects have been demonstrated in animal and in vitro studies, clinical studies have shown that $\beta$-cell function improves.\textsuperscript{27}

In patients with type 2 DM the incretin response is markedly diminished. Circulating levels of DPP-4 activity have been reported to be higher in some studies of subjects with chronic hyperglycemia and type 2DM.\textsuperscript{28,29} So, there exist a clear relationship between type 2 DM, incretin response and DPP-4 inhibitors. This newer group of drugs help in prolonging the incretin effects by inhibiting the action of DPP-4. By DPP-4 inhibition, high concentration of endogenously produced GLP-1 and GIP is available in the circulation. As a result, there is enhancement in insulin secretion, suppression of glucagon secretion and improvement in beta-cell function.

**Clinical trials, safety and efficacy of DPP-4 inhibitors**

Numerous studies have been carried out so far to evaluate the effects of DPP-4 inhibitors in people with type 2 DM. Clinical trials have demonstrated that sitagliptin is safe and efficacious for the management of hyperglycemia in type 2 diabetes. Sitagliptin administered in a dose of 100-mg to 200-mg daily reduced hemoglobin A1c (HbA1c) levels ranging from 0.7 to 1.0 %, within a duration of 24 weeks. These differences were statistically significant when compared to placebo (P < 0.001).\textsuperscript{30} Improvements in fasting plasma glucose and postprandial glucose levels were also reported in those treated with sitagliptin. In one trial, 701 patients with a mean baseline HbA1c of 8% (range: 7-10%) who were previously treated with metformin continued therapy with metformin and were randomized to receive either 100 mg sitagliptin or placebo daily for 24 weeks.\textsuperscript{31} Patients in the placebo group experienced no changes in HbA1c, whereas those treated with sitagliptin plus metformin realized a 0.65% reduction in HbA1c at 24 weeks. Similar results have been published from other clinical trials evaluating the efficacy of combination metformin and sitagliptin therapy.\textsuperscript{32,33} Significant reduction in HbA1c have been achieved with concomitant use of DPP-4 inhibitors with pioglitazone.\textsuperscript{34}

Kim et al. in their review of DPP-4 inhibitors provided evidence that this class of agents may be more effective in Asian patients.\textsuperscript{35} The findings of Seino et al. suggest a better response of Asian patients to DPP-4 inhibitors, raising the possibility that patients of Asian ethnicity have relatively more
defects in meal associated insulin secretion. Unlike traditional treatments which do not seem to address the progressive decline in β-cell function, DPP-4 inhibitors could theoretically preserve and even reverse the progressive loss of insulin secretory capacity, although long-term studies in type 2 diabetic patients will be required to demonstrate this change.

DPP-4 inhibitors augment insulin secretion in a glucose-dependent manner, thus preventing hypoglycemia when used as monotherapy or in combination with other OHA’s. They are not associated with increased risk for diarrhea, nausea or vomiting. Compared with other antidiabetic agents, gastrointestinal adverse events were more common in patients receiving metformin or a GLP-1 agonist than a DPP-4 inhibitor. Preclinical data have indicated a potential cardioprotective effect of DPP-4 inhibitors by increasing the concentration not only of GLP-1, but of other vasoactive peptides as well. Renal excretion is the main elimination pathway for most DPP-4 inhibitors. It is therefore necessary to adjust their dose in patients with moderate or severe renal impairment. Sitagliptin has not been found to be nephrotoxic in clinical trials and was well tolerated at adjusted doses in patients with moderate or severe renal insufficiency, including those with end-stage renal disease treated with dialysis.

Clinically approved DPP-4 inhibitors are generally well tolerated in T2DM patients. As a drug class, the DPP-4 inhibitors have become accepted in clinical practice due to their excellent tolerability profile, with a low risk of hypoglycemia, a neutral effect on body weight, and once–daily dosing. The National Institute for Health and Clinical Excellence (NICE) clinical guideline for T2DM issued in 2009 in the United Kingdom suggests adding a DPP-4 inhibitor instead of a sulfonylurea as a second–line treatment to first line metformin if there is a considerable risk for hypoglycemia or if a sulfonylurea is contraindicated or not tolerated.

**CONCLUSION**

The DPP–4 inhibitors represent a highly promising, novel class of oral agents for the treatment of T2DM. Their novelty lies in their dual action on α– and β–cell function, leading to an improved profile of glucagon and insulin secretion patterns after meal. These drugs are weight–neutral, do not cause hypoglycemia, and are not associated with severe gastrointestinal adverse events. They seem likely to be as efficacious as currently available oral anti-diabetic agents, giving sustainable and clinically meaningful reductions in HbA1c levels, both as monotherapy and in combination with other anti-diabetic agents, and apparently can be used across a broad spectrum of patient groups (elderly; obese, poorly controlled diabetes; hepatic or renal failure). As a class, DPP-4 inhibitors appear to have an excellent safety profile, with little or no risk for hypoglycemia, no weight gain, and the potential benefit of addressing the islet dysfunction that characterizes type 2 DM. Since incretin response is more diminished in Asian populations this group of drugs can address the therapeutic needs of Nepalese type 2 diabetic population and can be effectively used as a monotherapy or combination therapy in the glycemic control.

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