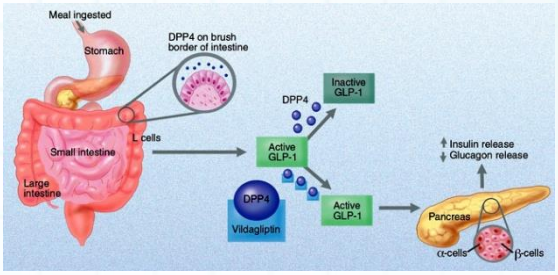
Role of DPP-IV Inhibitors in the management of Type 2 Diabetes



Patients with type 2 diabetes mellitus (T2DM) are known to have deficient meal-related incretin responses, resulting in decreased insulin secretion, increased postprandial glucagon levels, and elevated postprandial glucose. As understanding of the physiologic role of incretins has improved, a new class of incretin-based agents has been developed, the glucagon-like peptide-1 (GLP-1) receptor agonists and the dipeptidyl peptidase-4 (DPP-4) inhibitors. Both have demonstrated enhanced incretin effects and subsequent lowered glucose levels in patients with T2DM. This review discusses the clinical utility of DPP-4 inhibition in the context of DPP-4 structure and function, as well as the safety of DPP-4 inhibitors based on selectivity of enzyme inhibition.

Incretins (GLP-1 and glucose-dependent insulinotropic polypeptide [GIP]) are intestinal hormones that maintain blood glucose homeostasis and reduce postprandial blood glucose levels. They achieve these effects by potentiating glucose-dependent insulin secretion by pancreatic β-cells and inhibiting glucagon secretion by pancreatic α-cells (Figure 1). Both GLP-1 and GIP have short physiologic half-lives (5 and 4 minutes, respectively) due to rapid degradation by DPP-4. The deficient incretin response of patients with T2DM can be enhanced by competitive inhibition of DPP-4. Thus, DPP-4 inhibitors reduce blood glucose levels by augmenting the incretin effect in patients with T2DM.

Figure 1. Effects of DPP-4 inhibitors occur predominantly through GLP-1 and GIP

GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1.

Currently, both saxagliptin (Onglyza) and sitagliptin (Januvia®) are DPP-4 inhibitors approved in the United States as adjuncts to diet and exercise to improve glycemic control in adults with T2DM; vildagliptin (Galvus®) is also commercially available but only outside the United States.

DPP-4 STRUCTURE AND FUNCTION

DPP-4 is a ubiquitously expressed, homodimeric, prolyl oligopeptidase. It is involved in many physiologic functions in addition to enzymatic incretin degradation, including immune and endocrine activity, cell adhesion, and dampening of cancer growth. It is important to note that enzymatic and protein binding functions of DPP-4 are independent of one another.

The 3-dimensional structure of DPP-4 consists of a large, internal cavity containing the enzymatic active site. Its shape determines substrate specificity for proteolytic cleavage. In contrast, immunologic activity (including T-cell stimulation), which relies on protein binding, is mediated via the external surface of the molecule. Therefore, it is quite unlikely that DPP-4 inhibitors interfere with immunologic activity: not only is the enzymatic function independent of other activities, but the sites of these functions also are located distant from one another.

Figure 2. The 3-dimensional structure of DPP-4 showing the internal binding pocket for enzymatic activity and the external surface important for nonenzymatic interactions

The prolyl oligopeptidases most closely related to DPP-4 in enzymatic function are DPP-8 and DPP-9. Although DPP-4, -8, and -9 share some characteristics (eg, enzymatic activities and some independent, nonenzymatic functions), significant differences exist. For example, DPP-4 shares only 26% of its amino acid sequence with DPP-8 and -9, which share 61% with each other. They also differ with respect to cellular localization: DPP-4 is predominantly extracellular, whereas DPP-8 and -9 are exclusively intracellular (ie, cytoplasmic).

Functionally, DPP-4 has been shown to proteolytically cleave many different neuropeptides, hormones, and chemokines in vitro. However, the only in vivo physiologic substrates are the incretin hormones GLP-1, GLP-2, and GIP, and the chemokine CXCL12. In vitro analysis of DPP-8 and -9 activity has shown that these enzymes can inactivate GLP-1 and -2, though much less readily than DPP-4. However, there is no evidence suggesting in vivo activity of DPP-8 or -9 for incretin hormones.

SELECTIVE VS NONSELECTIVE INHIBITORS OF DPP-4: WHAT IS THE CLINICAL RELEVANCE?

The clinical relevance of selectivity has been extensively investigated due to the functional homology of DPP-4, -8, and -9. One preclinical study by Lankas showed that nonselective inhibition of these enzymes led to a litany of toxicities in rodent and canine models, including alopecia, thrombocytopenia, reticulocytopenia, enlarged spleen, multiorgan histopathologic changes, gastrointestinal toxicity, and mortality. In the same study, similar toxicities were observed when using an inhibitor of DPP-8 and -9.

These findings led to controversy concerning the increased potential for adverse events with nonselective inhibition of DPP family members DPP-4, -8, and -9. However, the interpretation of the data has been disputed: subsequent preclinical studies showed no relationship between DPP-8 and -9 inhibition and adverse events in animals, as demonstrated in an exhaustive study of DPP-4, -8, and -9 inhibition by Burkey et al. Furthermore, experiments in which DPP-8 and -9 were selectively inhibited in vivo did not result in toxicities. Wu and colleagues strongly suggested that the reported toxicities associated with certain DPP inhibitor compounds relate to their chemical—rather than their pharmacologic—properties. Moreover, no clinical data suggest that toxicities analogous to those found by Lankas et al are associated with DPP inhibition. It has therefore become clear that no link exists between DPP inhibition and these adverse events in humans.

Today, clinical data are available for several selective DPP-4 inhibitors in use or under investigation for the treatment of T2DM. These agents include alogliptin, dutogliptin, linagliptin, saxagliptin, sitagliptin, and vildagliptin Clinically approved selective DPP-4 inhibitors exhibit >1 log selectivity for DPP-4 over DPP-8 and -9

this degree of selectivity is significant. These selective DPP-4 inhibitors have not been associated with human toxicities analogous to those observed in the Lankas et al animal study. It should also be

noted that the US Food and Drug Administration has not required any statement regarding pathologic effects of DPP-4 inhibition within the product labeling information of the approved products saxagliptin and sitagliptin.

TABLE: Clinically approved DPP-4 inhibitor selectivity: Potencies in inhibiting DPP-4 vs DPP-8 and DPP-9

	Fold Selectivity		
DDP-4 Inhibitor	**Sitagliptin (IC50) 33**	**Saxagliptin (Ki) 27**	**Vildagliptin (Ki) 24**
Selectivity vs DPP-8	3000	400	300
Selectivity vs DPP-9	>5000	75	30
DPP, dipeptidyl peptidase; IC50, concentration that inhibits 50%; Ki, inhibition constant.			

CLINICAL UTILITY OF DPP-4 INHIBITORS

DPP-4 inhibitors have demonstrated efficacy in significantly lowering glycosylated hemoglobin (HbA1c), fasting plasma glucose, and postprandial glucose, as well as in increasing the percentage of patients reaching HbA1c goal (ie, <7% or <6.5%). The average ranges of placebo-adjusted HbA1c mean decreases over 24 weeks reported in the package inserts for saxagliptin and sitagliptin are 0.6% to 0.8% for monotherapy and 0.7% to 2.1% for combination therapy with metformin. Additionally, clinical trials of saxagliptin in combination with metformin and sitagliptin both as monotherapy and in combination with metformin have demonstrated significant glycemic efficacy, including sustained HbA1c reductions for up to 2 years.

DPP-4 inhibitors are generally well tolerated with no identifiable link to toxicities reported in the Lankas et al animal studies. The safety profiles of DPP-4 inhibitors are well documented. The most commonly reported adverse events for saxagliptin and sitagliptin have been mild infections (ie, nasopharyngitis, urinary tract infection, and upper respiratory tract infection) and headache No clinically relevant changes in laboratory immunologic parameters have been found in studies of DPP-4 inhibitors. Results from 2 pooled analyses, one with saxagliptin as add-on to metformin and another with sitagliptin as monotherapy or as add-on to metformin for up to 2 years' duration, showed a well-tolerated profile with similar adverse event profiles as those observed at 24 weeks. Advantages over existing diabetes agents include a low risk for hypoglycemia as well as weight neutrality.

DPP-4 has important functions as both an enzyme (metabolic regulation) and as a receptor (immunologic activation); these functions act independently of one another. Importantly, selective DPP-4 inhibition does not affect the immunologic functioning of other DPP-4 family proteins. Several studies have shown that no significant toxicities indicating a risk for humans are associated with DPP-4, -8, and -9 inhibition in animal models, and clinical data on DPP-4 inhibitors provide confirmatory evidence. GLP-1 and GIP half-lives and protein levels are dramatically increased when DPP-4 inhibitors are administered. Selective DPP-4 inhibitors have demonstrated consistent clinical efficacy and are generally well tolerated in patients with T2DM.

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