



## The Role of Dipeptidyl Peptidase-4 Inhibitors in the Management of Type 2 Diabetes

a report by

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DOI:10.17925/EE.2007.00.02.45

Insulin resistance manifests itself early in life and involves multiple tissues, including the liver, muscles and adipocytes.<sup>1,2</sup> However, as long as the  $\beta$  cell is able to augment its secretion to offset the defect in insulin action, glucose tolerance remains normal.<sup>3</sup> With time, however, as the  $\beta$  cell begins to fail, the  $\beta$  cell compensatory response becomes insufficient to offset the insulin resistance, and impaired glucose tolerance (IGT)/impaired fasting glycaemia (IFG) and, eventually, overt type 2 diabetes ensues.<sup>4,5</sup> Type 2 diabetes is a chronic metabolic disorder characterised by defects in insulin secretion and insulin resistance.<sup>6</sup> Current therapeutic approaches focus on improving insulin sensitivity or preserving/augmenting  $\beta$ -cell function, or both, with the goal of re-establishing normal glucose homeostasis.

### Incretins and $\beta$ -cell Failure

Multiple factors contribute to progressive  $\beta$ -cell failure in type 2 diabetes (see *Figure 1*). Multiple studies have shown that genetic factors play an important role in the development of impaired insulin secretion.<sup>7</sup> Acquired factors – including lipotoxicity,<sup>8,9</sup> glucotoxicity<sup>10</sup> and amylin accumulation within the  $\beta$  cell<sup>11</sup> – have also been shown to contribute to the impairment in insulin secretion.

Over the last decade, considerable attention has been focused on the role of incretin hormones in the pathogenesis of progressive  $\beta$ -cell failure in type 2 diabetes.<sup>12</sup> It has been known for over 50 years that the insulin-secretory response to an oral glucose load is three- to four-fold greater following oral versus intravenous glucose administration<sup>13</sup> (see *Figure 2*). The search for the missing ‘incretin’ hormones that augment insulin secretion in response to the gastrointestinal route of glucose administration has identified two peptides – glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide, also called glucose-dependent insulinotropic polypeptide (GIP) – that together account for more than 90% of the incretin response.<sup>14–17</sup> GLP-1 and GIP are secreted by the L cells and K cells in the intestinal tract in response to meal ingestion. GLP-1 and GIP are secreted into the portal vein<sup>18,19</sup> and act on the  $\beta$  cell to stimulate glucose-dependent insulin secretion.<sup>12,20,21</sup> The secreted GLP-1 and GIP are rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4), an enzyme that is ubiquitous in plasma and cell membranes. This accounts for the short half-life (four to five minutes) of GLP-1 and GIP in the circulatory system, and ensures that after the stomach is devoid of food, insulin secretion will cease and hypoglycaemia will be avoided. Since the secretion of both GLP-1 and GIP is glucose-dependent, once the blood sugar level has returned to normal, insulin release by the  $\beta$  cell stops, providing another defence against hypoglycaemia.<sup>22,23</sup>

In individuals with impaired glucose tolerance and type 2 diabetes there is a progressive decline in plasma levels of GLP-1<sup>14</sup> and a rise in the plasma GIP concentration.<sup>24,25</sup> This suggests that the  $\beta$  cells are resistant to GIP, and this has been confirmed by the failure of the  $\beta$  cells in type 2 diabetes patients

to respond to infused GIP. The progressive decline in GLP-1 secretion in IGT and type 2 diabetes correlates closely with the impairment in insulin secretion.<sup>26</sup> The increase in plasma GIP levels and development of GIP resistance occurs in all forms of diabetes (type 2 diabetes, type 1 diabetes, cystic fibrosis, chronic pancreatitis) and can be reversed by restoration of normoglycaemia,<sup>27</sup> indicating that it is a form of glucotoxicity. Because GIP levels are elevated and the  $\beta$  cells are resistant to GIP, this has not become a target for diabetic therapy. However, if normoglycaemia can be restored by other means, this would lead to return of normal  $\beta$ -cell sensitivity<sup>27</sup> to GIP; this could become an exciting new tool to prevent  $\beta$ -cell failure and treat type 2 diabetes.

GLP-1 is a potent insulin secretagogue<sup>28,29</sup> and continuous intravenous/subcutaneous GLP-1 infusion has provided proof of concept that this incretin hormone could be used effectively to improve  $\beta$ -cell function and improve glycaemic control in type 2 diabetes patients.<sup>30,31</sup> The discovery of exendin-4, a long-acting GLP-1 analogue, in the salivary gland of the Gila monster has led to the development of incretin replacement therapy as an effective means to improve  $\beta$ -cell function and glycaemic control in type 2 diabetes patients.<sup>12</sup> Alternatively, inhibition of DPP-4 – the enzyme that cleaves both GLP-1 and GIP<sup>32</sup> – has proved to be an effective approach to augmenting circulating incretin levels and improving glycaemic control in type 2 diabetes patients. Sitagliptin (Januvia®, Merck) is the first DPP-4 inhibitor approved in the US for the treatment of type 2 diabetes, and vildagliptin is currently under regulatory review by the US Food and Drug Administration (FDA). A number of other DPP-4 inhibitors are currently in phase III clinical trials, and the results look quite promising.

### Mechanism of Action of Dipeptidyl Peptidase-4 Inhibitors

The major mechanism by which DPP-4 inhibitors improve glycaemic control is by augmenting plasma GLP-1 levels.<sup>33,34</sup> However, considerable



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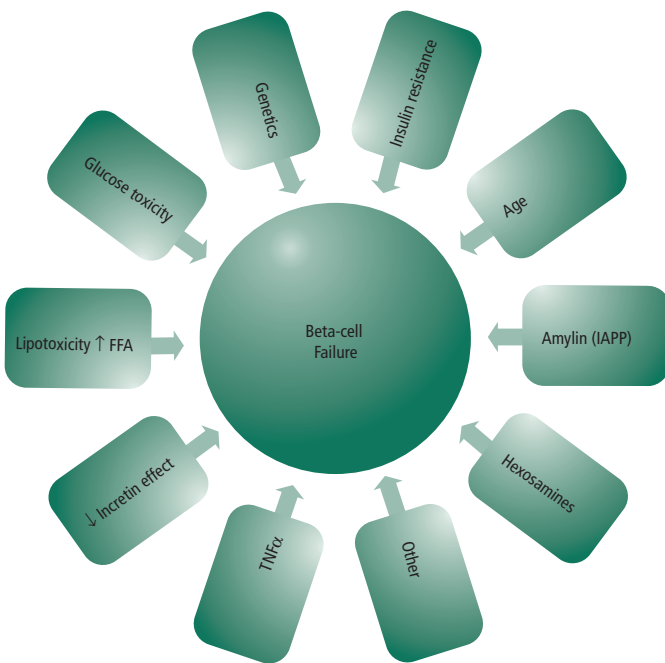
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**Figure 1: Pathogenetic Factors Implicated in the Progressive Impairment in Insulin Secretion in Type 2 Diabetes Mellitus**



*TNF-α = tumor necrosis factor-alpha.*  
 Source: DeFronzo RA, Med Clin N Am, 2004;88:787–835.

evidence suggests that factors in addition to increased plasma GLP-1 levels contribute to the beneficial effects of DPP-4 inhibitors on glucose homeostasis. Clinical studies have demonstrated that the rise in endogenous GLP-1 concentration after DPP-4 inhibition is modest,<sup>35</sup> and these drugs have a delayed effect (weeks) on improving glucose homeostasis.<sup>36,37</sup> When similar increases in GLP-1 are produced by exogenous infusion, the effect on insulin secretion and glucose levels is not nearly as robust.<sup>38</sup> It is possible that the DPP-4 inhibitors work not only by increasing GLP-1 levels, but also by augmenting the release of other deficient incretins, including GIP, pituitary adenylate cyclase-activating peptide (PACAP), gastrin-releasing peptide (GRP) and other as yet unidentified hormones.<sup>39</sup> DPP-4 inhibition may, in fact, have a multitude of pleiotropic effects since this enzyme has been shown to inhibit the degradation of over 20 peptides in the human body.<sup>40</sup> Neuropeptides stored in islet nerve terminals are also affected by DPP-4 inhibition, and this could regulate islet function.<sup>39–41</sup> Lastly, we have shown that the pattern – as well as the amplitude – of incretin release is significantly altered following DPP-4 inhibition. Thus, plasma GLP-1 and GIP concentrations do not immediately return to basal levels, but remain elevated for up to 12 hours.<sup>42</sup>

### Effect on Insulin Secretion

The main effect of DPP-4 inhibition in type 2 diabetes is to augment GLP-1 and GIP secretion, leading to increased secretion of insulin and inhibition of glucagon secretion.<sup>43,44</sup> Because the  $\beta$  cell in type 2 diabetes is resistant to the stimulatory effect of GIP on insulin secretion, and because GIP does not inhibit glucagon secretion,<sup>45</sup> GLP-1 is the primary incretin hormone that mediates the beneficial glycaemic effect of the DPP-4 inhibition.

Circulating plasma insulin levels are unchanged or increased after short-term treatment with sitagliptin<sup>46</sup> and vildagliptin.<sup>47,48</sup> However, we

have shown that the insulin secretory rate is increased following a single-dose administration of vildagliptin.<sup>42</sup> It is important to note, however, that plasma glucose levels decline significantly following both short-term and chronic administration of DPP-4 inhibitors. Both the absolute and the incremental plasma glucose levels are important determinants of the insulin secretory response, and they both decline after DPP-4 inhibition. A similar insulin response in the face of a reduced plasma glucose stimulus indicates an important stimulatory effect of the DPP-4 inhibitors on insulin secretion. Thus, the incremental insulin response divided by the incremental glucose response has been shown to increase following administration of both sitagliptin<sup>46</sup> and vildagliptin.<sup>49,50</sup> Homeostatic model assessment (HOMA)  $\beta$  cell,<sup>48,51,52</sup> as well as insulin secretion, measured with the minimal model,<sup>53</sup> has been shown to increase following DPP-4 inhibition.

Because the main mechanism of action of the DPP-4 inhibitors is mediated by GLP-1, and because GLP-1 potentiates insulin release only during conditions of hyperglycaemia, the glucose-lowering effect of the DPP-4 inhibitors is self-limiting.<sup>12,22</sup> In theory, therefore, hypoglycaemia should not be a problem with the DPP-4 inhibitors, and this has been proved in clinical studies.<sup>54,55</sup> Moreover, when given in association with insulin sensitisers such as metformin and the thiazolidinediones, hypoglycaemia is also distinctly uncommon.<sup>49,56–58</sup> DPP-4 inhibitors are not approved for use with insulin, and appear to be less effective in reducing glycated haemoglobin (HbA<sub>1c</sub>) when combined with this agent.<sup>59</sup>

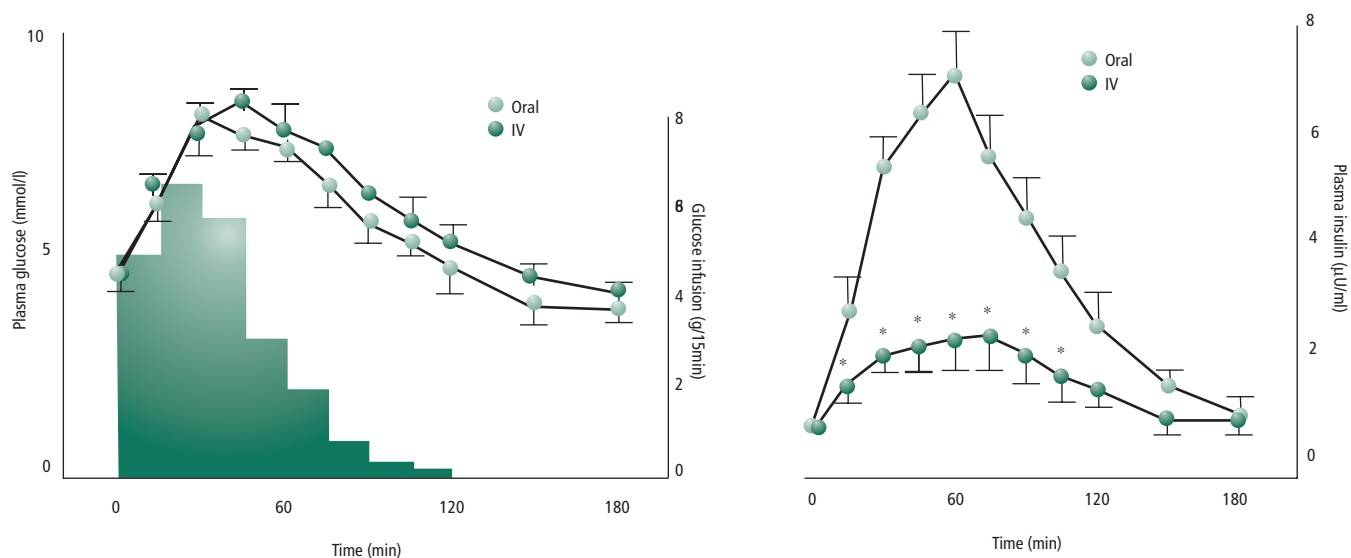
### Effect on Glucagon Secretion

GLP-1 is a potent inhibitor of glucagon secretion by the pancreatic  $\beta$  cells,<sup>60</sup> and this inhibitory effect is glucose-dependent.<sup>61,62</sup> Not surprisingly, a decline in plasma glucagon concentration has consistently been observed in diabetic patients treated with DPP-4 inhibitors.<sup>47,50</sup> The decrease in plasma glucagon concentration has been correlated with the suppression of basal and post-meal<sup>42</sup> rate of hepatic glucose production in type 2 diabetes patients treated with DPP-4 inhibitors. Although GIP levels increase during treatment with DPP-4 inhibitors, GIP has no suppressive effect on glucagon secretion, and some studies have shown an increase in circulating glucagon levels in response to GIP.<sup>45</sup>

The main effect of dipeptidyl peptidase-4 inhibition in type 2 diabetes is to augment glucagon-like peptide-1 and gastric inhibitory polypeptide secretion, leading to increased secretion of insulin and inhibition of glucagon secretion.

### Effect on Insulin Sensitivity

The effect of long-term DPP-4 inhibition on insulin sensitivity has been less well studied in humans. There are no insulin clamp data, and most existing human studies rely on surrogate indices – the HOMA-Insulin Resistance (HOMA-IR) index, Quantitative Insulin Sensitivity Check Index (Quicky) and

**Figure 2: Plasma Insulin Response to Oral Glucose (50g) and Isoglycaemic Intravenous Glucose in Controls**

Adapted from: Nauck, Creutzfeldt, et al., *Diabetologia*, 1986;29:46–52.

Oral Glucose Insulin Sensitivity (OGIS) index. Both sitagliptin and vildagliptin have been shown to improve insulin sensitivity after both short- and long-term administration.<sup>48,50</sup> However, whether this is a direct effect of the drug or simply reflects amelioration of glucotoxicity remains to be established. In one study in normal, glucose-tolerant subjects in whom plasma glucose/insulin/glucagon levels during a typical mixed meal were reproduced by intravenous glucose/hormone administration in the presence and absence of GLP-1, no effect on insulin sensitivity was noted.<sup>63</sup> Animal models of diabetes have more consistently demonstrated a beneficial effect of DPP-4 inhibition on insulin sensitivity.<sup>64–66</sup>

GLP-1 receptors are expressed in the liver and, when stimulated, could improve hepatic insulin sensitivity, suppress hepatic glucose production (HGP) and reduce fasting plasma glucose concentration.<sup>67</sup> With regard to this, we have shown that a single dose of vildagliptin given with the evening meal significantly suppresses post-meal HGP and post-prandial glycaemic excursion from 6pm until 8am the following morning (see *Figure 3*).<sup>42</sup> The suppression of HGP correlated closely with the decline in plasma glucagon concentration ( $r=0.49$ ;  $p<0.05$ ), but a direct effect of GLP-1 on the liver cannot be excluded.

### Effect on $\beta$ -cell Neogenesis

In rodents, GLP-1 stimulates proliferation and inhibits apoptosis of  $\beta$  cells and promotes the differentiation of  $\beta$  cells from ductal cell-derived precursor cells.<sup>68–71</sup> Because DPP-4 inhibitors increase GLP-1 levels, the effect of these drugs on  $\beta$ -cell mass has been examined. In rats and mice, DPP-4 inhibition has been shown to stimulate  $\beta$ -cell replication and neogenesis and to inhibit apoptosis.<sup>72</sup> DPP-4 inhibition has been shown to reduce streptozotocin-induced  $\beta$ -cell injury.<sup>73</sup> However, it remains to be determined whether such potential to augment  $\beta$ -cell mass exists in man.<sup>74</sup>

In a double-blind, placebo-controlled study in which vildagliptin was administered for 52 weeks to patients inadequately treated with metformin, there was a sustained improvement in glycated haemoglobin (HbA<sub>1c</sub>) in the vildagliptin-treated group.<sup>58</sup> This sustained effect indicates that DPP-4 inhibitors may have  $\beta$ -cell protective effects

that persist long after initiation of therapy. Whether these beneficial effects will continue to persist after three to five years remains to be determined. Moreover, in man it is not possible to discern whether the

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increase in insulin secretion is due to an enhanced  $\beta$ -cell function or increased  $\beta$ -cell mass. It also remains to be determined whether initiation of DPP-4 therapy at the initial onset of type 2 diabetes or at the stage of IGT can prevent the progressive  $\beta$ -cell failure that characterises the natural history of type 2 diabetes.

### Regulation of Appetite and Weight

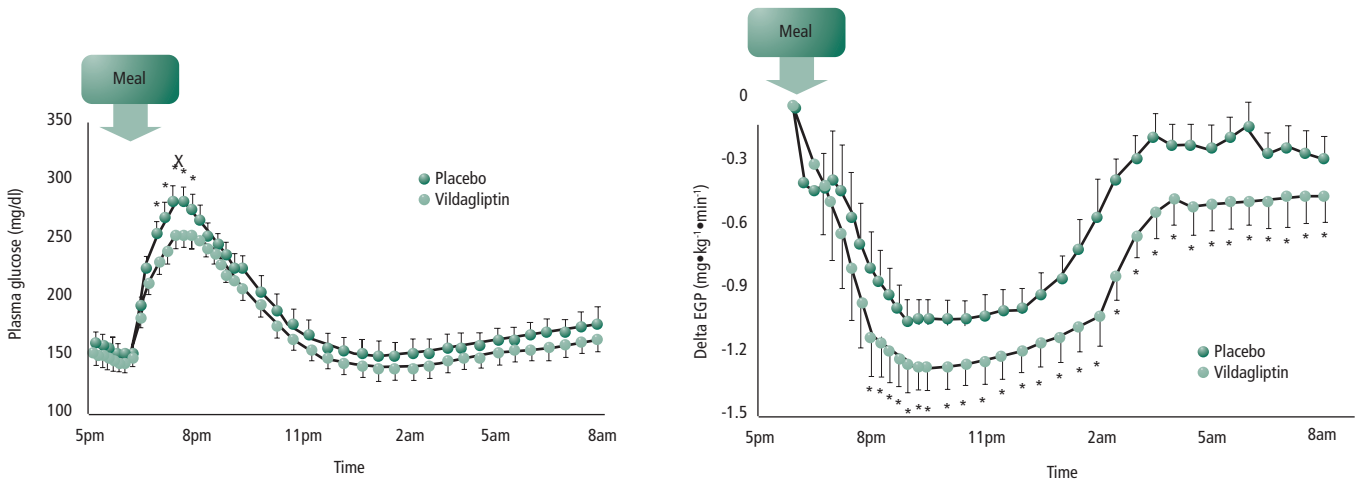
Unlike the GLP-1 analogues, which have a potent effect on suppressing appetite and promoting weight loss,<sup>75,76</sup> the DPP-4 inhibitors have no effect on appetite regulation and are weight-neutral.<sup>58</sup> This difference is most likely explained by the fact that the DPP-4 inhibitors increase plasma GLP-1 level to or only modestly above normal,<sup>47</sup> whereas GLP-1 administration leads to a pharmacological elevation in the circulating incretin concentration.<sup>77</sup>

### Clinical Trials

#### Dipeptidyl Peptidase-4 Inhibitors as Monotherapy

Vildagliptin monotherapy has been evaluated in five trials ranging in duration from four to 52 weeks.<sup>47,52,56,78–80</sup> The decrease in HbA<sub>1c</sub> ranged from -0.31% when administered as 50mg/day<sup>52</sup> to -1.1% when given in a dose of 100mg/day.<sup>80</sup> 100mg/day of vildagliptin was

**Figure 3: Plasma Glucose and Change from Baseline in the Rate of Endogenous Glucose Production**



Left: during the meal tolerance test. Right: during the post-absorptive period after ingestion of vildagliptin and placebo. Taken from Balas et al., J Clin Endocrinol Metab, 2007;92:1249–55.

shown to be non-inferior to rosiglitazone 8mg/day, with no weight gain in the vildagliptin group,<sup>56</sup> but was inferior by 0.4% in HbA<sub>1c</sub>, with 1% reduction versus 1.4% reduction over 52 weeks, to metformin 2,000mg/day. However, vildagliptin showed a superior gastrointestinal side effect profile.<sup>81</sup>

Sitagliptin monotherapy has been shown to be similarly effective to vildagliptin.<sup>51,82–84</sup> Across the dose range, the reduction in HbA<sub>1c</sub> ranged from -0.4% (25mg/day)<sup>82,83</sup> to -0.94% (200mg/day).<sup>84</sup> There are no available non-inferiority data on sitagliptin monotherapy.

### Combination Therapy

DPP-4 inhibitors have been proved most successful in reducing HbA<sub>1c</sub> when used in combination with metformin. In two separate studies, addition of vildagliptin to metformin reduced HbA<sub>1c</sub> by 1.1%.<sup>58,85</sup>

Dipeptidyl peptidase-4 inhibitors have emerged as promising new treatments for patients with type 2 diabetes mellitus, and they can be used both as monotherapy and in combination with other oral agents.

In three studies, addition of sitagliptin 100mg/day to metformin reduced HbA<sub>1c</sub> by 0.67%.<sup>46,53,57</sup> In initial combination, sitagliptin and metformin showed HbA<sub>1c</sub> reductions of -2.07%.<sup>86</sup>

Addition of vildagliptin 100mg/day to pioglitazone reduced HbA<sub>1c</sub> by 1%, an amount similar to that seen with metformin;<sup>49</sup> addition of sitagliptin to pioglitazone reduced HbA<sub>1c</sub> by 0.7%.<sup>87</sup> In initial combination, vildagliptin and pioglitazone showed HbA<sub>1c</sub> reductions of -1.9%.<sup>88</sup> The combination of sitagliptin plus metformin was similarly effective to glipizide plus metformin,<sup>57</sup> although the starting HbA<sub>1c</sub> (~7.6%) was only modestly

elevated, which would have minimised any differences between the two groups. It is noteworthy that DPP-4 inhibitors, unlike the GLP-1 analogues (exenatide), do not promote weight loss.<sup>58</sup> No phase III data have been published with any other DPP-4 inhibitor.

### Who Should Receive Treatment with Dipeptidyl Peptidase-4 Inhibitors?

The primary mechanism of action of the DPP-4 inhibitors is to increase plasma incretin levels, leading to the stimulation of insulin secretion and inhibition of glucagon release. Because individuals with IGT/IFG have lost 80% of their  $\beta$ -cell function<sup>4,5</sup> and have a 40–50% reduction in  $\beta$ -cell mass,<sup>89</sup> it makes more sense that DPP-4 inhibitor therapy should be initiated early in the natural history of type 2 diabetes when significant  $\beta$ -cell function remains. One might predict that the DPP-4 inhibitors could be least effective if started late in the natural history of type 2 diabetes when little  $\beta$ -cell function remains. One would argue that individuals with IGT/IFG who still possess significant  $\beta$ -cell function are most likely to benefit from DPP-4 inhibitor therapy. The combination of a DPP-4 inhibitor with metformin seems especially effective. This can be explained by the fact that metformin monotherapy significantly increases the circulating levels of GLP-1<sup>90</sup> and, when added to the increase in plasma GLP-1 concentration elicited by DPP-4 inhibitors, leads to a critical GLP-1 level that synergistically augments insulin secretion, inhibits glucagon secretion and acts as the missing 'gut factor'<sup>91</sup> to augment hepatic glucose uptake following ingestion of an oral glucose load. Lastly, the combination of a DPP-4 inhibitor with a thiazolidinedione may prove to be very effective in enhancing/maintaining insulin secretion, since the thiazolidinediones are well established to exert clinically relevant effects to preserve  $\beta$ -cell function.<sup>92–96</sup>

### Dipeptidyl Peptidase-4 Inhibitors or Incretin Mimetics?

Incretin mimetics (exenatide) and DPP-4 inhibitors appear to have comparable effectiveness in achieving glucose control, although no direct head-to-head comparisons are available.<sup>97</sup> This is most likely explained by the fact that exenatide is given as a pharmacological injection and results in supraphysiological levels of the GLP-1 analogue, which cause a greater increase in insulin secretion than those seen after DPP-4 inhibition.<sup>97</sup> These supraphysiological levels of

GLP-1 also produce sustained weight loss,<sup>76</sup> which exerts its own beneficial effect to improve glycaemic control. The DPP-4 inhibitors do not promote weight loss, most likely because they only normalise or only modestly increase plasma GLP-1 levels. Moreover, if a beneficial effect of incretin replacement therapy is to be observed on preservation of/increase in  $\beta$ -cell function/mass, it is more likely to be observed with the supraphysiological incretin levels reached with injection of exenatide. However, due to the possibility of the above-mentioned 'pleiotropic' effects of DPP-4 inhibition, it is possible that there will be additional benefits of the DPP-4 inhibitors that are currently not recognised. With regard to this, decreases in plasma triglyceride<sup>46,56</sup> and apolipoprotein B<sup>98</sup> levels have been described with DPP-4 inhibition. In patients treated with exenatide, significant reductions in plasma triglyceride concentration and blood pressure and increases in plasma high-density lipoprotein (HDL) cholesterol have been observed. These beneficial effects are largely related to the associated weight loss. Combination therapy with exenatide and a DPP-4 inhibitor has not yet been evaluated, but, because the pleiotropic effects of the DPP-4 inhibitors have yet to be elucidated, the possibility of using these two classes of drugs together remains to be examined.

### Safety

Since DPP-4 is ubiquitously present in the body, initially it was postulated that DPP-4 inhibition might be associated with a multitude

of adverse events. However, this has not proved to be the case, and the safety profile of the DPP-4 inhibitors has been shown to be excellent.

Special attention has been paid to the immune system, since DPP-4 (CD 26) is present in abundant amounts on lymphocytes.<sup>99</sup> However, inhibition of DPP-4 activity on lymphocytes does not seem to have a deleterious effect on the immune response.<sup>100</sup>

A theoretical risk associated with DPP-4 inhibition is the prolongation of action of a multitude of small peptide hormones, neuropeptides, growth factors, cytokines and chemokines that are normally cleaved by this protease.<sup>40</sup> Despite these theoretical concerns, clinical studies have shown a particularly good safety profile,<sup>47,52,78,80,82,84</sup> although long-term (three- to five-year) studies will be required to establish definitively the safety of this new class of oral antidiabetic drugs.

### Conclusions

DPP-4 inhibitors have emerged as promising new treatments for patients with type 2 diabetes, and they can be used both as monotherapy and in combination with other oral agents. Although they appear to be no more or slightly less potent than other oral antidiabetic medications, they offer advantages in the form of simple administration (once-daily oral dose), lack of hypoglycaemia and excellent safety profile. Whether the DPP-4 inhibitors can restore/preserve  $\beta$ -cell function remains to be determined. ■

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