



# The role of incretin-based therapies in the management of type 2 diabetes

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## Introduction

Type 2 diabetes mellitus (T2DM) is associated with a greatly increased risk of cardiovascular (CV) disease.<sup>1–3</sup> This risk is related to the degree of hyperglycaemia, and can occur with elevated fasting glucose or impaired glucose tolerance.<sup>1–3</sup> Many patients also exhibit other CV risk factors such as obesity, hypertension and dyslipidaemia.<sup>4</sup> Guidelines for the management of T2DM advocate rigorous control of blood glucose, blood pressure (BP) and other risk factors (Table 1).<sup>4–8</sup> Recently, novel classes of drug derived from the incretin system have been introduced into the management of T2DM. This review discusses the potential role of these agents in achieving the goals of therapy.

## Management of glucose in patients with T2DM

Lifestyle interventions alone are generally insufficient to maintain long-term glycaemic control in patients with T2DM; therefore, guidelines advocate the early introduction of pharmacological treatment. Metformin is widely recommended as first-line therapy, particularly for overweight patients, although other agents may be appropriate for selected cases.<sup>4,6,7</sup> If first-line therapy does not achieve glycaemic control (usually expressed in terms of HbA<sub>1c</sub> level), intensification of therapy is indicated. A medium dose of an antidiabetic agent yields about 70–80% of the maximal hypoglycaemic effect possible with that agent.<sup>9</sup> Addition of a second agent is therefore more logical than a very high dose of the first. Depending on the patient, a combination of two or more oral agents or initiation of insulin may be

## ABSTRACT

In patients with type 2 diabetes mellitus (T2DM), goals for blood glucose and other cardiovascular risk factors, such as blood pressure and body weight, can be difficult to achieve. Recent clinical trials indicate that incretin-based therapies – dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 (GLP-1) agonists – help to achieve glycaemic goals and are generally well tolerated, with a low prevalence of hypoglycaemia. GLP-1 agonists also improve weight, blood pressure and markers of  $\beta$ -cell function. Addition of an incretin-based agent may be appropriate for selected patients with T2DM and unsatisfactory glycaemic control on conventional therapies. Copyright © 2009 John Wiley & Sons.

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## KEY WORDS

type 2 diabetes; incretin-derived therapies; liraglutide; exenatide; glucagon-like peptide-1 (GLP-1); sitagliptin; vildagliptin

indicated.<sup>4–7</sup> Even combination therapy may not achieve satisfactory glycaemic control. For example, in the STENO-2 trial only approximately 15% of patients reached HbA<sub>1c</sub> <6.5%, despite intense therapy.<sup>10</sup> In a more recent study, only 26% of patients with a mean baseline HbA<sub>1c</sub> of 9.1% reached HbA<sub>1c</sub> <8% despite support with a glucose monitoring manual.<sup>11</sup>

## Potential new targets for glycaemic control FPG and PPG

The contributions of fasting plasma glucose (FPG) and postprandial glucose (PPG) levels to HbA<sub>1c</sub> depend on the severity of T2DM: PPG predominates in fairly well controlled patients, whereas the contribution of FPG increases as the condition worsens.<sup>12,13</sup> If a patient has a close to normal FPG level but HbA<sub>1c</sub> above the target, persistent elevation of PPG may be making an important contribution to hyperglycaemia. Addition of an agent that reduces PPG excursions may improve glycaemic control.<sup>9</sup>

## The $\beta$ -cell as a target of therapy

Pancreatic islet function is approximately 50% of normal by the time of diagnosis of T2DM.<sup>14</sup> Agents that preserve  $\beta$ -cell function could influence the progression of T2DM if introduced early in the disease. The  $\beta$ -cell could thus be considered a target of therapy and, in the future, markers of  $\beta$ -cell function may be included among the goals of treatment.

## The incretin response

Oral administration of glucose to healthy humans causes a greater stimulation of insulin secretion than intravenous administration of a similar glucose load. The augmented insulin response to oral glucose – the incretin response – is reported to be reduced or abolished in patients with T2DM.<sup>15,16</sup> Restoration of the incretin response could improve glycaemic control in such patients. The incretin response is partly mediated by glucagon-like peptide-1 (GLP-1), synthesised by enteroendocrine cells in the gastrointestinal tract.<sup>15,16</sup> Administration of native GLP-1

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**Table 1.** Recommended goals in the treatment of type 2 diabetes mellitus

Organisation	Fasting plasma glucose	Post-prandial glucose	HbA <sub>1c</sub>	Low-density lipoprotein-cholesterol	Blood pressure	BMI/weight
UK National Institute for Health and Clinical Excellence <sup>7</sup>	–	<8.5mmol/L (<140mg/dL)	<6.5%	– <sup>†</sup>	<140/80mmHg <130/80mmHg in high-risk patients	Weight loss 5–10%
European Society of Cardiology/European Association for the Study of Diabetes <sup>‡,4,8</sup>	<6mmol/L (<108mg/dL)	<7.5mmol/L (<135mg/dL)	≤6.5%	<2.5mmol/L (100mg/dL) Option of <2.0mmol/L (80mg/dL) ≤1.8–2.0mmol/L (70–77mg/dL) for patients with CVD	<130/80mmHg	<25kg/m <sup>2</sup>
American Association of Clinical Endocrinologists <sup>5</sup>	<110mg/dL (<6mmol/L)	<140mg/dL (<8.5mmol/L)	≤6.5%	<100mg/dL (<2.5mmol/L) <70mg/dL (<1.8mmol/L) in selected patients	<130/80mmHg	–

CVD, cardiovascular disease. <sup>†</sup>An explicit lipid target is not stated, but the importance of lipid lowering (mainly with statins) is discussed. <sup>‡</sup>The guidelines discuss type 1 and type 2 diabetes and refer to guidelines issued by the Fourth Joint Task Force on Cardiovascular Disease Prevention in Clinical Practice.<sup>8</sup>

increases glucose-dependent stimulation of insulin secretion in patients with T2DM, but it is rapidly inactivated, mainly by the enzyme dipeptidyl peptidase-4 (DPP-4).<sup>15,16</sup> Two types of agents are thus being developed: those that prevent the rapid degradation of GLP-1 by inhibiting DPP-4 (to preserve the endogenous peptide), and stable GLP-1 receptor agonists resistant to the enzyme. Agents from both classes have received regulatory approval. Two DPP-4 inhibitors, sitagliptin and vildagliptin, are currently licensed. Exenatide is presently the only marketed GLP-1 agonist. A new GLP-1 agonist, liraglutide, is in advanced clinical development but is not yet licensed.

### Incretin-based therapies' effects on glycaemic targets

#### DPP-4 inhibitors

Sitagliptin is licensed for use in patients with T2DM at a dose of 100mg once daily, added to other oral agents when these do not achieve glycaemic control.<sup>17</sup> In clinical trials, sitagliptin 100–200mg/day improved glycaemic control when given as monotherapy<sup>18</sup> or added to metformin,<sup>19–22</sup> glimepiride (with or without metformin)<sup>23</sup> or pioglitazone<sup>24</sup> ( $p < 0.001$  *vs* placebo in each trial). The reduction in HbA<sub>1c</sub> with sitagliptin was approximately 0.5–1.0% greater

than with placebo ( $p \leq 0.001$ ); PPG was also significantly reduced ( $p \leq 0.05$  *vs* placebo).<sup>18–23</sup> In another trial, sitagliptin 100mg/day was non-inferior to glipizide 5mg/day for the reduction of HbA<sub>1c</sub> in patients inadequately controlled with metformin.<sup>25</sup>

Vildagliptin is licensed for use in patients with T2DM, at a dose of 50mg once or twice daily as dual oral therapy, with insufficient glycaemic control on first-line treatment.<sup>26</sup> Vildagliptin 50–100mg/day has been reported to reduce HbA<sub>1c</sub> by 0.6–1.1% compared with placebo when given as monotherapy<sup>27</sup> or when added to glimepiride,<sup>28</sup> metformin<sup>29</sup> or pioglitazone<sup>30</sup> ( $p \leq 0.003$  *vs* placebo in all studies). Vildagliptin 100mg/day significantly reduces PPG ( $p < 0.01$  *vs* placebo).<sup>28–30</sup> Initial therapy with vildagliptin plus pioglitazone reduces HbA<sub>1c</sub> and PPG significantly more than pioglitazone alone ( $p < 0.05$ ).<sup>31</sup> In comparative trials, vildagliptin 100mg/day produced a similar reduction in HbA<sub>1c</sub> to pioglitazone (each added to metformin)<sup>32</sup> or rosiglitazone (each as monotherapy),<sup>33</sup> but in another study it did not meet the criteria for non-inferiority compared with metformin monotherapy.<sup>34</sup> Vildagliptin 50mg/day has been reported to attenuate the progressive loss of glycaemic control in drug-naïve

patients with mild hyperglycaemia ( $p < 0.01$  *vs* placebo).<sup>35</sup>

#### GLP-1 agonists

Exenatide is approximately 50% homologous with mammalian GLP-1<sup>15</sup> and is resistant to degradation by DPP-4.<sup>15</sup> It is identical to exendin-4, a peptide isolated from the salivary glands of the Gila monster. Exenatide is licensed at a dose of 5–10µg twice daily in combination with metformin and/or sulphonylureas if maximally tolerated doses of these agents have not achieved glycaemic control in patients with T2DM.<sup>36</sup> Exenatide 10µg twice daily reduces HbA<sub>1c</sub> by approximately 0.8–1.0% more than placebo ( $p < 0.001$ ) in patients not adequately controlled by metformin,<sup>37</sup> sulphonylureas,<sup>38</sup> glitazones (with or without metformin)<sup>39</sup> or metformin plus sulphonylureas.<sup>40</sup> It also significantly reduces FPG ( $p < 0.05$  *vs* placebo)<sup>37–40</sup> and PPG ( $p < 0.01$  *vs* placebo).<sup>37,39,40</sup> Exenatide monotherapy is as effective as insulin glargine<sup>41</sup> and biphasic insulin aspart<sup>42</sup> in patients suboptimally controlled by metformin plus sulphonylurea. A once-weekly formulation of exenatide, currently in development, has been reported to reduce HbA<sub>1c</sub> significantly more than the twice-daily formulation ( $p < 0.01$ ).<sup>43</sup>



Liraglutide is a GLP-1 analogue that is 97% homologous with native human GLP-1.<sup>15</sup> It is resistant to DPP-4 and has a half-life of approximately 11–15 hours,<sup>44,45</sup> permitting once-daily subcutaneous injection. Liraglutide monotherapy with 1.2 and 1.8mg/day decreases HbA<sub>1c</sub> and FPG significantly ( $p < 0.002$ ) more than glimepiride 8mg/day.<sup>46</sup> Added to metformin plus rosiglitazone, liraglutide 1.2 and 1.8mg/day reduces HbA<sub>1c</sub> by approximately 1.5% ( $p < 0.01$  *vs* placebo).<sup>47</sup> In further trials, liraglutide added to background therapy was compared with placebo and an active comparator. Liraglutide 1.8mg/day reduced HbA<sub>1c</sub> by approximately 1.0–1.3% ( $p < 0.0001$  *vs* placebo),<sup>48,49</sup> was as effective as glimepiride,<sup>49</sup> and was significantly more effective than rosiglitazone ( $p < 0.0001$ )<sup>48</sup> and insulin glargine ( $p < 0.0001$ ).<sup>50</sup> Compared with placebo, liraglutide significantly ( $p < 0.01$ ) increased the proportion of patients reaching HbA<sub>1c</sub> targets of  $< 7\%$  or  $\leq 6.5\%$ <sup>47,48,50</sup> and reduced PPG.<sup>47,49</sup> In a comparative trial between once-daily liraglutide and twice-daily exenatide (each added to oral therapy), liraglutide was associated with significantly greater reductions in HbA<sub>1c</sub> and FPG ( $p < 0.0001$  for both) and with significantly ( $p \leq 0.015$ ) more patients reaching HbA<sub>1c</sub>  $< 7\%$  and  $\leq 6.5\%$ .<sup>51</sup>

## Effects on other goals of therapy

### Other CV risk factors

Sitagliptin has been reported to significantly ( $p < 0.05$ ) increase high-density lipoprotein-cholesterol compared with glipizide<sup>25</sup> and to reduce triglycerides compared with placebo ( $p < 0.05$ ),<sup>22,24</sup> but it appears to have no significant effects on weight or BP.<sup>19,22,24,25</sup> Vildagliptin is weight neutral and has no consistent effects on BP or lipids.<sup>27–35</sup> Liraglutide is associated with body weight reductions of approximately 2–3kg compared with baseline, which are significant ( $p < 0.0001$ ) compared with rosiglitazone,<sup>48</sup> glimepiride<sup>49</sup> or insulin glargine.<sup>50</sup> Liraglutide reduces systolic BP by approximately 2–3mmHg compared with baseline<sup>49</sup> and by approximately 3–4.5mmHg *vs* comparators ( $p < 0.05$ ).<sup>52</sup> The effects of exenatide on body weight and

## Key points

- DPP-4 inhibitors and GLP-1 agonists have been introduced into the management of T2DM. Both are derived from the incretin system, which is involved in endogenous regulation of meal-stimulated insulin secretion
- Clinical trials indicate that DPP-4 inhibitors and GLP-1 agonists, added to conventional therapies, improve glycaemic control in patients with T2DM and are generally well tolerated, with a low prevalence of hypoglycaemia. GLP-1 agonists also improve weight, blood pressure and markers of  $\beta$ -cell function
- Addition of an incretin-based agent may be appropriate for selected patients with T2DM who have unsatisfactory glycaemic control on first-line therapies, particularly if weight gain or hypoglycaemia are a concern

systolic BP appear to be similar to those of liraglutide.<sup>37–42</sup>

## $\beta$ -cell function

Significant ( $p < 0.05$ ) improvements in markers of  $\beta$ -cell function compared with baseline values, placebo or comparators have been reported with sitagliptin,<sup>19,21,23–25</sup> vildagliptin,<sup>28,29</sup> exenatide<sup>39,42</sup> and liraglutide.<sup>48–50,53</sup>

## Safety issues

Incretin-based therapies are generally well tolerated. Sitagliptin is associated with slightly higher rates of constipation, nasopharyngitis, urinary tract infections, hypertension and dizziness than placebo.<sup>18–25</sup> The most common adverse effects of vildagliptin are headache, nasopharyngitis, dizziness, back pain, peripheral oedema and arthralgia.<sup>27–35</sup> Those of exenatide are nausea, hypoglycaemia and vomiting, reported in approximately 35–60%, 5–35% and 10–15% of patients, respectively.<sup>37–40</sup> Around 40–50% of patients develop antibodies to exenatide.<sup>37–40</sup> Generally, this does not appear to impair glycaemic control or increase the rate of adverse events.<sup>37–40</sup> However, approximately 6% of patients develop high titres of antibodies; approximately half of these have no apparent glycaemic response to exenatide.<sup>36</sup> The most common adverse effects of liraglutide are nausea and vomiting, which occur in approximately 10–30% and 5–12% of patients, respectively, and are generally transient.<sup>46–51</sup> Minor hypoglycaemia was reported in approximately 3–12% of patients in most liraglutide studies,<sup>46,47,49</sup> but higher rates occurred in patients also receiving a sulphonylurea.<sup>50</sup> Antibodies

against liraglutide develop in 9–12% of patients, but the presence of antibodies does not appear to have a significant effect on glycaemic control or the tolerability of treatment.<sup>48,50</sup>

## Conclusions

The incretin-based therapies represent a new approach to the management of T2DM. They reduce HbA<sub>1c</sub>, FPG and PPG, and are generally well tolerated; the low risk of hypoglycaemia is an advantage over several conventional treatments. The effects of incretin-based therapies on markers of  $\beta$ -cell function suggest that they could influence the course of T2DM if introduced early in the disease. In addition to improving glycaemic control, GLP-1 agonists produce clinically relevant reductions in body weight and systolic BP and may thereby help to achieve other goals of treatment. Evidence to date indicates that incretin-based therapies are a reasonable choice for selected patients when first-line therapy does not achieve glycaemic control. Some guidelines for the management of T2DM now include incretin-based therapies as a treatment option in such cases.<sup>6,7</sup> They may be particularly useful if weight gain or hypoglycaemia are a concern.

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