The primary abnormality in type-2 diabetes is insulin resistance with subsequent failure of β-cell compensation, but others occur. Glucagon levels are raised inappropriately, possibly because of β-cell resistance to insulin. Normally, an oral glucose load elicits a substantially greater release of insulin than does the same load intravenously; this phenomenon is known as the incretin effect, and is decreased in type-2 diabetes. The incretin effect is mediated predominantly by glucagon-like peptide-1 (GLP-1), although other incretin hormones exist. GLP-1 is secreted from the small intestine in response to an oral carbohydrate load; its actions are outlined in box 1.

Thus GLP-1 may be useful for treating hyperglycaemia, causing neither weight gain nor hypoglycaemia; unfortunately, this peptide has to be given by injection, and has a half-life of only a few minutes, before it is degraded by the enzyme dipeptidyl peptidase IV (DPP-4). Possible approaches are to give an analogue of GLP-1 resistant to DPP-4 or to inhibit DPP-4, enhancing the person’s own GLP-1.

Dipeptidyl dipeptidase-4 inhibitors

Two dipeptidyl dipeptidase-4 (DPP-4) inhibitors (also known as gliptins) are available; sitagliptin (Merck Sharp & Dohme) in the UK and USA and vildagliptin (Novartis) in the UK, Mexico and Brazil, which has been approved by the European Medicines Agency for the rest of Europe. The sitagliptin UK license is a dose of 100 mg daily in patients with normal renal function (creatinine clearance>50 ml/min) as an addition to metformin, sulphonylurea, or thiazolidinedione monotherapy, or in addition to a combination regimen of metformin and sulphonylurea. The Scottish Medicines Consortium recently approved sitagliptin for restricted use with metformin. 79% of sitagliptin is excreted unchanged renally, and in the USA, sitagliptin is available in lower doses for patients with reduced creatinine clearance. The European license for vildagliptin is 50 mg twice daily with metformin or a thiazolidinedione, and 50 mg daily with a sulphonylurea. Although this drug is inactivated by hydrolysis, mainly in the kidneys, there are no data for use in moderate-to-severe renal impairment. Both gliptins can be used in patients with mild-to-moderate hepatic impairment. Vildagliptin is not a cytochrome P450 enzyme substrate, inhibitor, or inducer; sitagliptin has limited cytochrome P450 metabolism, but is not an inhibitor or inducer.

**Sitagliptin**

In a 24-week placebo-controlled trial of sitagliptin 100 mg and 200 mg daily in 741 patients with a mean HbA1c of 8-0%, HbA1c was reduced by 0-79% on 100 mg daily and 0-94% on 200 mg daily. HbA1c reduction was greatest
with higher initial HbA1c (>9%), and sitagliptin worked quickly, with most glucose reduction occurring by week 3. There were similar low rates of hypoglycaemia with both doses and there was no weight change on sitagliptin. However, sitagliptin 200 mg daily caused slightly more nausea than placebo.

**Vildagliptin**

Vildagliptin has also been investigated in several large trials over 24 weeks. Doses of 50 mg once-daily, 50 mg twice daily, and 100 mg once-daily were compared with placebo. At the higher doses, placebo-subtracted decreases in HbA1c were 0.6–0.9%. Vildagliptin was associated with low rates of hypoglycaemia and slight weight reduction.

**Vildagliptin versus rosiglitazone**

In a 24-week trial, vildagliptin 100 mg was compared with rosiglitazone 8 mg daily in 786 participants. HbA1c reduction was similar in both groups (1.1–1.3%), as were rates of hypoglycaemia (<1%) and adverse events (<3%); however, rosiglitazone treatment resulted in increased weight and double the prevalence of oedema (4.1% versus 2.1%).

**Vildagliptin versus pioglitazone**

In a 24-week study of 607 patients, once-daily doses of pioglitazone 30 mg, vildagliptin 50 mg and pioglitazone 15 mg, vildagliptin 100 mg and pioglitazone 30 mg, and vildagliptin 100 mg were studied. Mean reductions in HbA1c (baseline approximately 8.7%) were 1.4±0.1%, 1.7±0.1%, 1.9±0.1%, and 1.1±0.1%, respectively. Both combination therapies were significantly more effective than both monotherapies. Peripheral oedema was most common on pioglitazone monotherapy (9.3%) and rarest on the low-dose combination (3.5%). Hypoglycaemia was reported by two patients.

**Vildagliptin versus metformin**

Vildagliptin (100 mg daily, n=526) or metformin (titrated to 2000 mg daily, n=254) were compared in drug-naïve patients (HbA1c=7.5–11.0%). Most HbA1c reduction occurred within 12 weeks, and efficacy was sustained for a year on each agent. After 1 year, significant reductions in HbA1c were seen with both vildagliptin (−1.0±0.1%, p<0.001) and metformin (−1.4±0.1%, p<0.001). Body weight was static on vildagliptin (0.3±0.2 kg, p=0.17) and decreased on metformin (−1.9±0.3 kg, p<0.001). Adverse event rates were similar in each group, and hypoglycaemia was also low (<1%).

**Sitagliptin and metformin**

In 677 patients with poorly controlled diabetes (HbA1c>8%) on at least 1500 mg metformin daily, the addition of sitagliptin 100 mg daily resulted in a significant reduction in HbA1c (placebo-subtracted reduction of 0.65%), with low incidence of hypoglycaemia, and gastrointestinal upset and weight reduction similar to those of placebo. Initial therapy with sitagliptin and metformin was more effective than was monotherapy with either metformin or sitagliptin. 1091 patients with HbA1c of 7.5–11% were randomly assigned one of six treatments of 0–100 mg sitagliptin and 0–2000 mg of metformin per day, for 24 weeks. The placebo-subtracted reductions in HbA1c were 2.07% on sitagliptin 100 mg and metformin 2000 mg, 0.99% on metformin 1000 mg, and 0.83% on sitagliptin 100 mg. In the sitagliptin 100 mg arm metformin 2000 mg group, 66% of patients achieved an HbA1c of less than 7% and 44% achieved an HbA1c less than 6.5%. Hypoglycaemia was infrequent in all groups, and was similar to that seen with placebo. The incidence of gastrointestinal upset in combination treatments was comparable to that of metformin alone.

**Sitagliptin versus glipizide**

Sitagliptin has been compared with glipizide in patients with poorly controlled diabetes despite treatment with metformin. 1172 patients received either 100 mg sitagliptin or up-titrated glipizide (mean final dose 10.3 mg) over a year. Although the reductions in HbA1c were the same in each group (0.67%), sitagliptin was associated with less hypoglycaemia (4.9% against 32%) and a reduction in weight, although the glipizide dose is not maximum, hypoglycaemia limits further up-titration.

**Vildagliptin and metformin**

In a 24-week study with 544 participants (mean baseline HbA1c 8.4%) on at least 1500 mg metformin, the addition of vildagliptin 100 mg resulted in a placebo-subtracted reduction in HbA1c of 1.1%. Hypoglycaemia incidence was similarly low (<1%) in both vildagliptin and placebo groups. On vildagliptin, weight was stable and there was a small but significant reduction in diastolic blood pressure.

**Vildagliptin and pioglitazone**

A 24-week study compared vildagliptin (50 mg or 100
mg daily) with placebo in addition to pioglitazone (45 mg daily) monotherapy in 463 patients. The placebo-subtracted mean change in HbA1c was \(-0.8\pm0.1\%\) (p=0.001 versus placebo) for vildagliptin 50 mg and \(-1.0\pm0.1\%\) (p<0.001 versus placebo) for vildagliptin 50 or 100 mg daily, with similar side-effects and low occurrence of hypoglycaemia in each group.

**Summary and evidence in elderly**

Gliptins reduce HbA1c 0.6–1.1%, with hypoglycaemia rates similar to placebo. In comparative studies, sitagliptin was as effective as glipizide but with less hypoglycaemia, and vildagliptin was as effective as rosiglitazone, but without the oedema. Gliptins give slight or no reduction in weight, but weight reduction is significant when compared with sulphonylurea. The gliptins are well tolerated, with low incidence (<1.5%) of nausea and vomiting. Sitagliptin in addition to metformin does not increase gastrointestinal upset, and evidence suggests that vildagliptin reduces the gastrointestinal side-effects of metformin. So far, the gliptins have not caused abnormal liver-function tests.

The efficacy of vildagliptin in older and younger patients was compared in a pooled analysis of five trials of vildagliptin of 24–52 weeks’ duration, and safety was compared in eight 12–52 week trials (table 1). Safety was similar in both groups, but reductions in HbA1c and weight were greater in elderly patients. Vildagliptin and insulin in patients aged 65 years and older decreased HbA1c placebo by 0.6% compared with placebo, but in younger participants, the HbA1c reduction was 0.1%; in both groups, vildagliptin decreased rather than increased the hypoglycaemia rate.

**Where do these new agents fit in diabetes care?**

Hyperglycaemia inevitably progresses, requiring more treatment as time passes. Metformin is the first-line oral drug, although its use in elderly people will often be limited by renal impairment; next, as additional or alternative therapy to metformin, a commonly used, well studied oral agent such as a sulphonylurea or pioglitazone should be considered. One would consider a DPP-4 inhibitor if a patient has a contraindication to pioglitazone such as heart failure, or risk of hypoglycaemia on sulphonylurea in patients with erratic lifestyle or diet. Renal impairment may limit use of gliptins; lower strength tablets of sitagliptin and safety data for vildagliptin are urgently required in moderate-to-severe renal impairment. Thus, patients may benefit from gliptin monotherapy or combination therapy if they have contraindications to other agents. However, each oral agent reduces HbA1c by 0.7–1.5%; will this reduction be adequate?

Table 1: Vildagliptin in elderly and young patients

<table>
<thead>
<tr>
<th></th>
<th>Elderly (n=238)</th>
<th>Young (n=1231)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>70</td>
<td>50</td>
</tr>
<tr>
<td><strong>Baseline weight (kg)</strong></td>
<td>83.4*</td>
<td>92</td>
</tr>
<tr>
<td><strong>Weight loss (kg)</strong></td>
<td>0.9±1</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Number of other medications</strong></td>
<td>9.8</td>
<td>4.4</td>
</tr>
<tr>
<td><strong>Baseline HbA1c</strong></td>
<td>8.3±1</td>
<td>8.7</td>
</tr>
<tr>
<td><strong>Reduction in HbA1c</strong></td>
<td>1.2%*</td>
<td>1.0%*</td>
</tr>
<tr>
<td><strong>Any adverse event</strong></td>
<td>63.6%*</td>
<td>60.6%</td>
</tr>
<tr>
<td><strong>Hypoglycaemia</strong></td>
<td>0.8%</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

*p=0.05 versus baseline (within group). †p=0.05 versus younger patients. *Safety data for 374 older and 1890 younger participants. Data are mean.
comorbidities, clinicians will need to apply evidence-based medicine carefully to make full use of all available agents.

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References