Current and emerging pharmacotherapy for managing diabesity

Caroline Day, Clifford J Bailey

Treatment of diabesity requires agents that will improve glycaemic control and facilitate a reduction in adiposity. Beyond metformin, currently available antidiabetes therapies that lower blood glucose levels without weight gain include glucagon-like peptide-1 receptor agonists and agents that inhibit dipeptidyl peptidase-4, both of which exploit the "incretin effect". In the future, renal elimination of excess glucose via the inhibition of sodium-glucose co-transporter 2 offers a novel approach to reducing hyperglycaemia and facilitating weight loss. Other possible strategies include tissue-specific inhibitors of glucocorticoid action, and intestinal and adipocyte hormones that modulate nutrient homeostasis and regulate cellular energy metabolism. Weight loss is a valuable antidiabetes strategy, but the only currently approved pharmacotherapy for obesity is the intestinal lipase inhibitor, orlistat. Other weight-reducing therapies are advancing in development, mostly based on lessons from bariatric surgery, and involving mechanisms to limit food consumption.

The coexistence of overweight and obesity with type 2 diabetes (diabesity) presents a particularly difficult therapeutic challenge. Lifestyle measures, which should underpin all management approaches, are seldom successful in the long term and pharmacotherapy is necessary but often complicated by failure to maintain both weight loss and glycaemic control. This article explores the use of recently available and potentially new pharmacological agents to treat diabesity. The initial section considers agents that primarily have a blood glucose-lowering action, while the latter section assesses agents that primarily have an antiobesity action.

Blood glucose-lowering agents

Glycaemic control is essential to reduce the incidence and severity of microvascular complications in type 2 diabetes and to help reduce the risk of macrovascular disease (Holman et al, 2008). Obesity precipitates and potentiates many of the endocrine and metabolic derangements of type 2 diabetes (*Figure 1*). Obesity also superimposes its own well recognised burden of morbidity and premature mortality upon that of type 2 diabetes, and more than doubles the risk of a cardiovascular event compared with normal weight (Maggio and Pi-Sunyer, 2003). Clearly, strategies to control hyperglycaemia without weight gain, and preferably with weight loss, are advantageous.

When lifestyle measures alone are unable to achieve or maintain glycaemic control in diabesity, the preferred add-on pharmacological therapy is metformin. This counters insulin resistance without weight gain, sometimes enables weight loss, is associated with a low risk of hypoglycaemia and may confer independent benefits against cardiovascular disease (Bailey et al, 2007; Golay, 2008). However, contraindications and gastrointestinal tolerability issues limit the universal use of this agent and illustrate the need for antidiabetes weight-reducing interventions.

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Article points

1. This article explores the use of recently available and potentially new pharmacological agents to treat diabesity.
2. The initial section considers agents that primarily have a blood glucose-lowering action, while the latter section assesses agents that primarily have an antiobesity action.
3. Diabesity is highly heterogeneous and a variety of differently acting agents – of which there are several in development – would be a welcome boost to the therapeutic armamentarium in the recognised battle to target concurrent control of hyperglycaemia and excess adiposity.

Key words

- Adipokines
- Glucose lowering
- Incretin
- Orlistat
- SGLT2 inhibitor
- Weight loss

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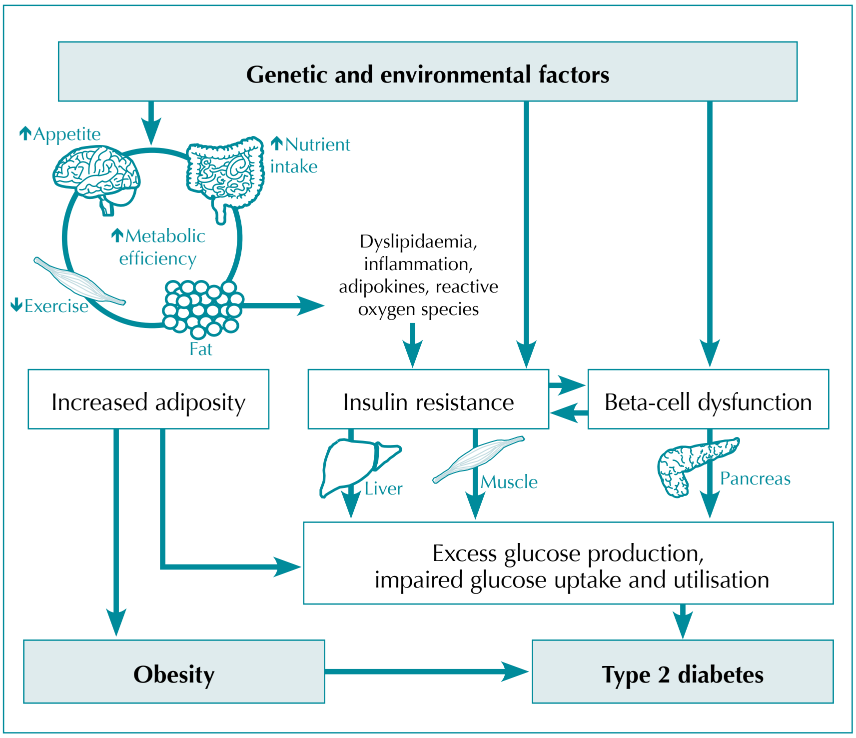

Figure 1. Obesity and type 2 diabetes usually arise through the interaction of a variety of genetic susceptibilities and environmental impositions. Polymorphisms and small variations in the expression levels of many genes with the potential to alter feeding behaviour and nutrient metabolism give rise to excess adiposity. Excess adiposity exacerbates genetic predispositions for the development of insulin resistance and defective insulin secretion through unhealthy nutrient choices, excess energy intake, inadequate physical activity, inflammatory factors from adipose tissue, oxidative stress and disturbances of metabolic homeostasis such as an altered glucose-fatty acid (Randle) cycle.

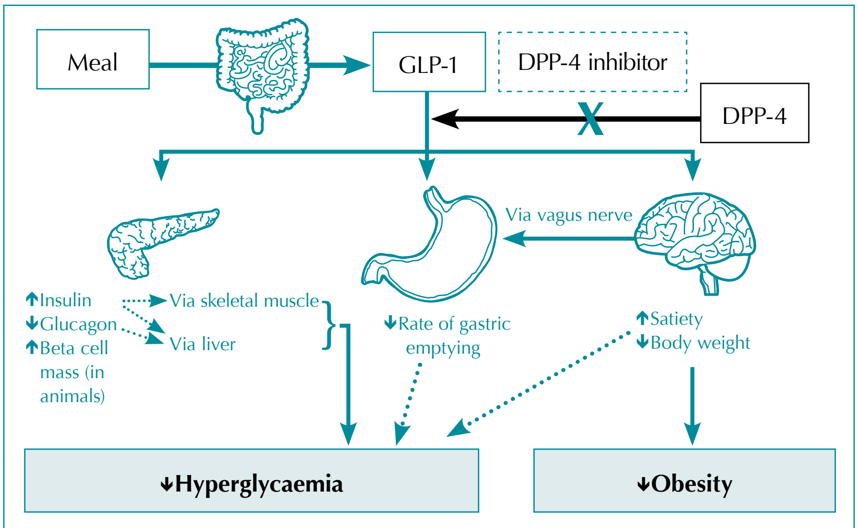

Figure 2. The incretin hormone glucagon-like peptide-1 (GLP-1) exerts effects that reduce hyperglycaemia and reduce weight in diabesity. GLP-1 receptor agonists (such as exenatide and liraglutide) are agents that mimic the effects of endogenous GLP-1. Dipeptidyl peptidase-4 (DPP-4) inhibitors enhance the action of endogenous GLP-1 by preventing its breakdown by the enzyme DPP-4.

Alpha-glucosidase inhibitors, of which acarbose is the only example available in the UK, reduce the rate of carbohydrate digestion, lowering postprandial hyperglycaemia without weight gain. Although acarbose has a good safety record, efficacy is limited when complex carbohydrate is not a major part of the diet. Alpha-glucosidase inhibitors can also cause considerable gastrointestinal disruption, which limits their application (Lebovitz, 1998).

In STOP-NIDDM (Study To Prevent Non-Insulin-Dependent Diabetes Mellitus), acarbose reduced the relative risk of developing diabetes by 25% in a population with IGT, compared with placebo (Chiasson et al, 2002). Furthermore, the acarbose-treated group experienced a relative reduction in the risk of cardiovascular events and hypertension (Chiasson et al, 2003).

Fibre supplements such as galactomannan guar have been used as dietary adjuncts to reduce postprandial peaks in blood glucose levels. They do not cause weight gain, but efficacy is modest and tolerability often limiting (Jenkins et al, 1980). Other established blood glucose-lowering agents such as sulphonylureas, meglitinides, pioglitazone and insulin are prone to causing weight gain (Bailey, 2011a).

GLP-1 receptor agonists

Incretin hormones are released by the intestine during meal digestion and augment the prandial insulin response. The incretin hormones potentiate nutrient-induced insulin secretion in a glucose-dependent manner, which is associated with a low risk of hypoglycaemia between meals. The two main incretin hormones are glucagon-like peptide-1 (GLP-1), secreted from L-cells mainly in the ileum, and glucose-dependent insulinotropic polypeptide (GIP), secreted from K-cells in the upper small intestine (*Figure 2*). GLP-1 offers other properties suited to therapeutic use (Holst, 2006). In particular, GLP-1 reduces glucagon secretion at high (but not low) glucose concentrations and exerts a weight-reducing satiety effect; neither effect is shared by GIP, which has a mild adipogenic effect. Moreover, the secretion of GLP-1 may be reduced in type 2 diabetes but its biological effectiveness is largely retained, whereas the effect of GIP tends to decline in type 2 diabetes (Nauck et al, 2011a).

Although pharmacological doses of human GLP-1 can slow gastric emptying, causing nausea and limiting dose titration, this is usually temporary, and may contribute to the initial satiety and blood glucose-lowering effects (Flatt et al, 2009a).

Since incretin hormones are rapidly degraded by dipeptidyl peptidase-4 (DPP-4) (Flatt et al, 2008), several DPP-4-resistant forms of GLP-1 receptor agonist have been produced; a twice-daily injectable preparation of exenatide received marketing authorisation in 2007 and was followed by once-daily injected liraglutide in 2009. Exenatide is a synthetic version of exendin-4, a peptide discovered in the saliva of a lizard (*Helloderma suspectum*); it has 53% homology with human GLP-1, is resistant to degradation by DPP-4 and retains full GLP-1 receptor agonism. Liraglutide is a human GLP-1 analogue with a single amino-acid substitution linked to a fatty acid; this aggregates the molecules into heptamers and binds them to albumin in the circulation, which gives protection from degradation by DPP-4 (Holst et al, 2010).

To date, these specific agents have shown utility throughout the natural history of diabesity as monotherapy* and in combination with other antidiabetes agents. Clinical trials with GLP-1 receptor agonists have typically shown reductions in HbA_{1c} >11 mmol/mol (>1 percentage point) and in body weight by 2–3 kg over periods of 6–12 months (for example, Wilding, 2009). Economic considerations in the UK have largely restricted their use to the more obese people – for example, NICE (2009; 2010) recommends their use in people with a BMI ≥35 kg/m^2 although it allows for use in people with a BMI <35 kg/m^2 in specific circumstances.

Exenatide once weekly

Most recently approved is the GLP-1 receptor agonist exenatide once weekly. This is a subcutaneously injected depot of exenatide encapsulated in biodegradable microspheres. It has been clinically investigated in the DURATION (Diabetes Therapy Utilisation: Researching Changes in A_{1c}, Weight and Other Factors Through Intervention with Exenatide Once-Weekly) studies – a series of open-label randomised trials. When administered for 30 weeks to people with type 2 diabetes and a BMI of 25–45 kg/m^2, exenatide once weekly (2 mg) lowered HbA_{1c} levels more than regular 10 µg twice-daily exenatide (–21 mmol/mol [–1.9 percentage points] versus –16 mmol/mol [–1.5 percentage points]; P=0.0023). More participants in the exenatide once weekly group achieved the target HbA_{1c} level of <53 mmol/mol (<7%) than those administering exenatide twice daily (77% versus 61%, respectively; P=0.0039), with similar weight loss in both groups (exenatide once weekly –3.7 kg; exenatide twice daily –3.6 kg; P=0.89) (Drucker et al, 2008).

A potential advantage of exenatide once weekly is the convenience of once-weekly dosing, although this must be balanced against possible injection site reactions (Electronic Medicines Compendium [EMC], 2011a) and the potential for persistent stimulation to cause antibody formation (Drucker et al, 2008).

At the time of going to print, NICE (2012) has issued draft guidance regarding the use of exenatide once weekly.

Other considerations regarding therapy with GLP-1 receptor agonists

While preclinical evidence indicates that GLP-1 can sustain islet growth in animals, clinical studies have not yet shown that GLP-1 receptor agonists can restore islet mass after years of dysfunction in human type 2 diabetes (Kim and Egan, 2008). There is also emerging evidence that GLP-1 receptor agonists can improve the lipid profile, lower blood pressure and exert beneficial effects on markers of endothelial function, although they may also exert a small chronotropic effect (Verge and López, 2010).

Other studies have shown that GLP-1 may have added benefits to cardiovascular function partly through its metabolite GLP-1(9-37) (Croom and McCormack, 2009; Holst et al, 2010). Furthermore, there is preliminary evidence that GLP-1 may also benefit some neural cognitive functions and reduce bone resorption (Nuche-Berenguer et al, 2009; Hamilton et al, 2011).

Debate is ongoing regarding pancreatitis and pancreatic cancer with GLP-1 receptor agonist therapy, but the occurrence of these events is probably no more than for the diabetes population in general (Elashoff et al, 2011).

GLP-1 therapies in development

GLP-1 agents in advanced development include lixisenatide, which is a shorter-acting variant

Neither of these agents are licensed for monotherapy in the UK.

Page points

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2. Liraglutide is a human GLP-1 analogue with a single amino-acid substitution linked to a fatty acid; this aggregates the molecules into heptamers and binds them to albumin in the circulation, which gives protection from degradation by DPP-4.
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Page points

1. Dipeptidyl peptidase-4 (DPP-4) inhibitors slow the degradation of endogenous circulating incretin hormones, thereby enhancing the natural prandial incretin effect.
2. Extensive trials with currently marketed agents (sitagliptin, vildagliptin, saxagliptin and linagliptin) have shown similar efficacy, mostly achieving reductions in HbA_{1c} levels of 5.5–10.9 mmol/mol (0.5–1.0 percentage points) as monotherapy or in combination with other types of antidiabetes agents.
3. The incretin levels reached with DPP-4 inhibition do not appear to generate a significant satiety effect, although these agents are still typically weight neutral or may be associated with mild weight loss. However, the combination of convenient oral dosing, no titration or extra blood glucose monitoring, minimal risk of hypoglycaemic episodes, compatibility with other antidiabetes agents and minimal side-effects has encouraged their use, especially in combination with metformin.
4. The kidney offers an opportunity to reduce hyperglycaemia and achieve calorie loss by increasing glucose elimination in the urine.

of exenatide suited to once-daily injection in combination with insulin glargine (Ratner et al, 2010), and albiglutide (Ala8Gly), which is a longer-acting GLP-1 receptor agonist that provides activity for up to 2 weeks (Rosenstock et al, 2009). Other GLP-1 receptor agonists in development include CJC-1134, a variant of exenatide linked to albumin (Nauck et al, 2009; Conjuchem, 2012), and dulaglutide (LY-2189265), a long-acting GLP-1 receptor agonist linked to a fragment of immunoglobulin G4 (Barrington et al, 2011).

Delivery of GLP-1 receptor agonists by buccal, oral, inhaled and dermal patches is under consideration, and orally active non-peptide GLP-1 receptor agonists have shown proof of principle in animal studies (Knudsen et al, 2007).

DPP-4 inhibitors

DPP-4 inhibitors slow the degradation of endogenous circulating incretin hormones, thereby enhancing the natural prandial incretin effect (*Figure 2*). Extensive trials with currently marketed agents (sitagliptin, vildagliptin, saxagliptin and linagliptin) have shown similar efficacy, mostly achieving reductions in HbA_{1c} levels of 5.5–10.9 mmol/mol (0.5–1.0 percentage points) as monotherapy or in combination with other types of antidiabetes agents (Bailey et al, 2010a; Deacon, 2011).

In head-to-head trials the efficacy of DPP-4 inhibitors has been a little less than with injected GLP-1 receptor agonists (Bergenstal et al, 2010; Pratley et al, 2010). This probably reflects the capacity of DPP-4 inhibition to raise endogenous incretin levels two- to three-fold, whereas much higher levels of exogenous molecules are achieved by injection. The incretin levels reached with DPP-4 inhibition do not appear to generate a significant satiety effect, although these agents are still typically weight neutral or may be associated with mild weight loss (Bailey et al, 2010a). However, the combination of convenient oral dosing, no titration or extra blood glucose monitoring, minimal risk of hypoglycaemic episodes, compatibility with other antidiabetes agents and minimal side-effects has encouraged their use, especially in combination with metformin.

The different DPP-4 inhibitors offer different pharmacokinetic properties that may favour their use in different sub-populations of people with type 2 diabetes. For example, sitagliptin and saxagliptin are largely eliminated via the kidney (EMC, 2012a; 2012b) whereas linagliptin is almost entirely eliminated in faeces (EMC, 2011b). A fifth DPP-4 inhibitor, alogliptin, has been approved in Japan.

Other incretin-based therapies in development

The bile acid sequestrant colesevelam is licensed for the treatment of type 2 diabetes in the USA (Daiichi Sankyo, 2012). Although its blood glucose-lowering mechanism is uncertain, one possibility is that it defers glucose absorption more distally along the intestinal tract, thereby increasing the secretion of GLP-1 and possibly altering the release of other gastrointestinal hormones that could affect nutrient metabolism and satiety (Bays et al, 2008; Shang et al, 2010). Various G-protein coupled receptors for fatty acids are expressed on both pancreatic beta-cells and intestinal L-cells. Synthetic small-molecule agonists of these receptors have been shown to increase incretin activity and are under investigation for the treatment of type 2 diabetes (Ahrén, 2009).

SGLT2 inhibitors

The kidney offers an opportunity to reduce hyperglycaemia and achieve calorie loss by increasing glucose elimination in the urine. While this “glucuretic” effect does not directly address the endocrinopathic aspects of diabesity, it offers a potentially valuable mechanism to reduce both glucotoxicity and excess adiposity independently of either the secretion or the action of insulin, and reduce morbidity.

After renal filtration, most of the glucose entering the proximal tubules is reabsorbed by the sodium-glucose co-transporter 2 (SGLT2) during passage through the first segment, and any remaining glucose is reabsorbed in more distal regions of the proximal tubules by SGLT1. Thus, inhibition of these transporters provides an opportunity to reduce hyperglycaemia by elimination of excess glucose in the urine (Bailey and Day, 2010). However, SGLT1 is also responsible for glucose absorption by the intestine, and inhibition of this transporter would run the gauntlet of glucose malabsorption. Therefore, selective inhibition of SGLT2 is required.

Natural examples of reduced SGLT2 activity are mutations of the SGLT2 gene in cases of familial renal glucosuria in which there is lifelong elimination of glucose in the urine without evidence of detrimental effects. A herbal precedent for altered activity of sodium glucose transporters is provided by the presence of phlorizin from apple tree bark. Phlorizin exerts non-specific inhibition of both SGLT1 and SGLT2 and high doses have been shown to reduce hyperglycaemia in diabetic animal models, which may account for the use of apples among the traditional treatments for diabetes (Ehrenkranz et al, 2005).

The first highly selective SGLT2 inhibitor to receive extensive clinical investigation is dapagliflozin, which reduced HbA_{1c} levels by 5.5–10.9 mmol/mol (0.5–1.0 percentage points) and lowered body weight by 2–3 kg during trials lasting from 6 months to 2 years as monotherapy or add-on to other oral antidiabetes agents or insulin in overweight and obese people with type 2 diabetes (data from the placebo-controlled trials are summarised in *Table 1*). A 52-week study looking at dapagliflozin as add-on therapy to metformin compared with metformin plus glipizide in combination demonstrated similar glycaemic efficacy (HbA_{1c} reduction 5.7 mmol/mol [0.52 percentage points] versus 5.7 mmol/mol [0.52 percentage points]). However, a significant reduction in mean weight (–3.2 kg) was observed in those treated with metformin and dapagliflozin compared with weight gain of 1.2 kg in the comparator group (Nauck et al, 2011b). Similar efficacy of dapagliflozin was observed during continuation of the study to 2 years (Del Prato et al, 2011).

Dapagliflozin inhibition of SGLT2 eliminates 50–80 g of glucose per day in the

Page point

1. The first highly selective sodium-glucose co-transporter 2 inhibitor to receive extensive clinical investigation is dapagliflozin, which reduced HbA_{1c} levels by 5.5–10.9 mmol/mol (0.5–1.0 percentage points) and lowered body weight by 2–3 kg during trials lasting from 6 months to 2 years as monotherapy or add-on to other oral antidiabetes agents or insulin in overweight and obese people with type 2 diabetes.

Table 1. Effect of dapagliflozin on HbA_{1c} levels, fasting glucose, body weight and blood pressure in randomised, double-blind, placebo-controlled trials in people with type 2 diabetes.

Author	*n*	Dapagliflozin (mg/day)	Duration (weeks)	Baseline HbA_{1c} (mmol/mol) [%]	↓HbA_{1c} range (mmol/mol) [%]	↓FPG range (mmol/L) [mg/dL]	↓Body weight range (kg)	↓SBP/↓DBP range (mmHg)
List et al (2009)	389	Monotherapy: 2.5–50	12	59–64 [7.6–8.0]	5.5–9.8 [0.55–0.90]	0.9–1.7 [16–31]	2.5–3.4*	2.6–6.4/ 0.1–2.6
		Placebo subtracted			~3.9–7.8 [~0.37–0.72]	0.6–1.4 [10–25]	1.3–2.2*	0.2–4.0/ ↑0.2–2.3
Ferrannini et al (2010)	485	Monotherapy: 2.5–10	24	63 [7.9]	~6.3–9.8 [~0.58–0.89]	0.8–1.6 [15–29]	3.3–3.8	2.3–4.6/ 1.7–2.8
		Placebo subtracted			~3.8–7.2 [~0.35–0.66]	0.61–1.39 [11–25]	1.1–1.6	1.4–3.7/ 1.0–2.1
Bailey et al (2010b)	546	Add-on to metformin: 2.5–10	24	64 [8.0]	7.3–9.2 [0.67–0.84]	0.99–1.30 [18–23]	2.2–2.9	2.1–5.1/ 1.8–2.5
		Placebo subtracted			~3.9–5.9 [~0.37–0.54]	0.66–0.97 [12–18]	1.3–2.0	1.9–4.9/ 1.7–2.4
Wilding et al (2009)	71	Add-on to 50% insulin dose: 10 or 20	12	68 [8.4]	~6.7–7.7 [~0.61–0.70]	0.83–1.5 [15–27]	4.3–4.5	–
		Placebo subtracted			~7.7–8.5 [~0.70–0.78]	0.86–1.52 [15.4–27.4]	2.4–2.6	–
Wilding et al (2010)	808	Add-on to insulin: 2.5–10	48	70 [8.5]	~7.9–10 [~0.74–0.93]	0.94–1.19 [17.0–21.5]	1.1–1.7	3.8–5.4/ 2.3–3.1
		Placebo subtracted			~3.6–5.5 [~0.31–0.50]	0.70–0.95 [12.6–17.1]	0.9–1.6	3.6–5.2/ 1.0–1.8

*Percentage decrease in body weight; ↓=decrease; ↑=increase; ~=approximately; DBP=diastolic blood pressure; FPG=fasting plasma glucose; SBP=systolic blood pressure.

Page points

1. Several further sodium-glucose co-transporter 2 inhibitors are being developed, including canagliflozin, empagliflozin, ASP1941 and LX4211. Preliminary data suggest similar efficacy for glycaemic and weight control.
2. Several recent proof-of-principle trials with 11 beta hydroxysteroid dehydrogenase 1 inhibitors have shown that they reduce hyperglycaemia and facilitate weight loss in people with diabesity.
3. The amylin analogue pramlintide is an injectable agent approved in the USA as an adjunct to insulin treatment in type 1 and type 2 diabetes.
4. The dopamine D2 receptor agonist bromocriptine, an established treatment for prolactinoma and Parkinson's disease, is also licensed for the treatment of type 2 diabetes in the USA.

urine, which equates to an energy deficit of 200–320 kcal/day (List et al, 2009). Since this is maintained independently of insulin status, it provides an opportunity for inclusion in the treatment regimen at any stage in the natural history of type 2 diabetes, provided there is adequate renal function. There is low risk of hypoglycaemia because SGLT1 can reabsorb almost all of the filtered glucose when blood glucose concentrations fall below normal.

Continual glycosuria increases the risk of infections in the urinary tract and urino-genital region. The trials with dapagliflozin indicated that such events were generally mild and either resolved naturally, were self-managed or responded to conventional medicines. Haematuria was routinely tested for in these trials and there was an increased ascertainment of bladder cancer in those treated with dapagliflozin, but the cancers appeared to have been sufficiently advanced to have been present prior to inclusion of the patients in the trials. A modest persistent osmotic diuresis was evident, which may have contributed to a consistent small reduction in blood pressure (reduced systolic blood pressure of 2–5 mmHg), but initial concerns about a risk of dehydration and electrolyte imbalance did not materialise (Bailey, 2011b).

Several further SGLT2 inhibitors are being developed, including canagliflozin, empagliflozin, ASP1941 and LX4211. Preliminary data suggest similar efficacy for glycaemic and weight control (Tahrani et al, 2011).

11 beta HSD 1 inhibitors

Since truncal obesity, hyperglycaemia and insulin resistance are commonly associated with raised glucocorticoid concentrations, strategies are being developed to reduce the activity of cortisol in selected tissues, notably liver and adipose tissue. A substantial amount of cortisol secreted by the adrenal cortex is converted to relatively inactive cortisone, largely by the kidney. Cortisone is then converted back to cortisol by the enzyme 11 beta hydroxysteroid dehydrogenase 1 (11 beta HSD 1), which is expressed most strongly in the liver and adipose tissue (*Figure 3*). Selective inhibition of 11 beta HSD 1 reduces the production of cortisol in these tissues without markedly altering the circulating cortisol concentrations. Several recent proof-of-principle trials with such inhibitors have shown that they reduce hyperglycaemia and facilitate weight loss in people with diabesity (Tomlinson and Stewart, 2007; Rosenstock et al, 2010).

Other primarily blood glucose-lowering agents

The amylin analogue pramlintide is an injectable agent approved in the USA as an adjunct to insulin treatment in type 1 and type 2 diabetes (Amylin Pharmaceuticals Inc., 2008). It acts mainly via central effects (area postrema) resulting in deceased glucagon secretion, slowing of gastric emptying and a satiety effect. It improves glycaemic control and is typically associated with modest weight loss. Nausea and risk of hypoglycaemia necessitate careful dose titration (Day, 2005).

The dopamine D2 receptor agonist bromocriptine, an established treatment for prolactinoma and Parkinson's disease, is also licensed for the treatment of type 2 diabetes in the USA (VeroScience, 2010). A low-dose quick-release formulation has been shown to reduce hyperglycaemia without weight gain, possibly acting via the hypothalamus to reduce hepatic gluconeogenesis and reinstate the diurnal rhythm of glucose homeostasis (Holt et al, 2010).

Antiobesity agents

A very substantial reduction in energy intake, as achieved with a hypocaloric diet or bariatric surgery, will rapidly improve glycaemic control before reducing adiposity (Henry et al, 1986; Flatt et al, 2009b). Sustaining caloric deficit will reduce adiposity and, if maintained, the improvement in glycaemic control

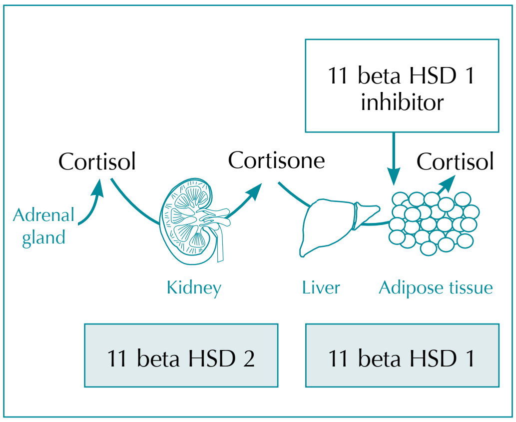

Figure 3. The enzyme 11 beta hydroxysteroid dehydrogenase 1 (11 beta HSD 1), which is expressed mostly in liver and adipose tissue, converts relatively inactive cortisone into active cortisol within these tissues. Selective inhibitors of 11 beta HSD 1 can reduce the availability of cortisol within liver and adipose tissue.

will also be maintained. Weight loss is particularly difficult in type 2 diabetes, because as glycaemic control improves, fewer calories are lost as glucose in the urine; at the same time insulin sensitivity will be improved, enhancing the anabolic actions of insulin to increase nutrient storage. Additionally, cellular adaptations to reduced energy intake will increase metabolic efficiency, which undermines efforts to lose more weight (Bailey, 2011a).

Indeed, any agent that reduces adiposity should benefit glycaemic control and several studies have confirmed that interventions causing even modest weight loss lead to improved glycaemia in diabesity (Colagiuri, 2010).

In the UK, orlistat, which inhibits intestinal lipase activity and thereby reduces lipid intake, is the only antiobesity agent available on prescription. Orlistat may owe its efficacy in diabesity more to self-enforcement of dietary circumspection than to maldigestion of lipids, and it has typically reduced HbA_{1c} in the order of 5.5 mmol/mol (0.5 percentage points), alongside weight reductions of 2–4 kg (Day and Bailey, 2006; Henness and Perry, 2006). Other intestinal lipase inhibitors such as cetilistat (ATL-962) and GT389-255 are in development, and lipid-binding fibre supplements such as chitosan and litramine are available via retail outlets (Grube et al, 2011).

The pharmacological treatment of obesity has a history of agents that have been discontinued (Day and Bailey, 2006) due to their side-effect profile and inappropriate use. Recent casualties are rimonabant and sibutramine, which were both effective in the treatment of diabesity (Anon, 2010).

Bariatric lessons

Although the success of bariatric surgery in the treatment of diabesity (*Table 2*) is beyond the remit of this review, it is likely that lessons can be learnt from the alterations in intestinal endocrine

Page points

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Table 2. Studies in which long-term glycaemic control has been recorded after bariatric surgery in obese people with type 2 diabetes, impaired glucose tolerance or impaired fasting glucose levels.

	Patient number	Duration (months)	Weight loss (%)	Plasma glucose (mmol/L)		HbA_{1c} (mmol/mol) [%]	
				Before	After	Before	After
Bypass							
Herbst et al (1984)	23 T2D	20	26	17.8	6.4	105 [11.8]	63 [7.9]
Pories et al (1992)	52 T2D	12	31	11.8	6.5	95 [10.8]	46 [6.4]
Pories et al (1995)	152 IGT 146 T2D	168	32.7	N/G	91% normal	N/G	91% normal
MacDonald et al (1997)	154 T2D	108	28	10.4	<7.8	N/G	N/G
Schauer et al (2003)	14 IFG 177 T2D	24	N/G	10.4	5.6	66 [8.2]	38 [5.6]
Sugerman et al (2003)	137	12–24	32	N/G	83% normal	N/G	83% normal
Restriction							
Scheen (1998)	24 T2D	28	23	8.6	5.8	67 [8.3]	38 [5.6]
Dixon and O'Brien (2002)	50 T2D	12	20	9.4	6.2	62 [7.8]	44 [6.2]
Pontiroli et al (2002)	47 IGT 19 T2D	36	N/G	~6.1 ~9.7	~5.3 ~6.4	~48 [~6.5] ~66 [~8.2]	~36 [~5.4] ~40 [~5.8]
Sjöström et al (2004)	82 T2D	24	N/G	N/G	72% normal	N/G	N/G
Ponce et al (2004)	53 T2D	24	N/G	N/G	80% normal	56 [7.25]	41 [5.58]
Dixon et al (2008)	30 T2D	24	20	8.7	5.9	62 [7.8]	42 [6.0]

IFG=impaired fasting glucose; IGT=impaired glucose tolerance; T2D=type 2 diabetes; N/G=no given value for T2D participants.

Reproduced from Flatt et al (2009b). The final definitive version of this table was originally published in *Br J Diabetes Vasc Dis* **9**: 103–7 by SAGE Publications Ltd.,

Page points

1. Therapeutic use of the adipocyte hormone leptin, either alone or in combination with other antiobesity agents, remains under consideration for its weight loss and blood glucose-lowering actions.
2. Development of leptin antibodies and leptin resistance have been problematic during leptin administration, and current research is focused on leptin analogues and non-peptide leptin receptor agonists.
3. The adipocyte hormone adiponectin has been shown to improve insulin sensitivity, reduce blood glucose levels and body weight, improve vascular reactivity and decrease inflammation in animal models of diabesity, and remains a possible basis for therapeutic innovation.

function that accompany these procedures (Flatt et al, 2009b; Pournaras and le Roux, 2009). In addition to GLP-1, several other agents of intestinal origin are being considered for the treatment of obesity due to their satiety inducing actions, notably peptide PYY3-36 and oxyntomodulin (Field et al, 2010). Ghrelin antagonism might provide appetite suppression and GIP antagonists have shown weight loss effects and await detailed investigation in diabesity (Field et al, 2010; Flatt et al, 2009b; Pournaras and le Roux, 2009).

Adipokines

Several hormones from adipose tissue exert blood glucose-regulating or weight-regulating effects that might offer templates for the treatment of diabesity (Billyard et al, 2007). Therapeutic use of the adipocyte hormone leptin, either alone or in combination with other antiobesity agents, remains under consideration for its weight loss and blood glucose-lowering actions. Beyond its centrally-mediated satiety and thermogenic effects, leptin can reduce glucagon secretion and may have direct effects on cellular nutrient metabolism (Wang et al, 2010). However, development of leptin antibodies and leptin resistance have been problematic during leptin administration, and current research is focused on leptin analogues and non-peptide leptin receptor agonists.

The adipocyte hormone adiponectin has been shown to improve insulin sensitivity, reduce blood glucose levels and body weight, improve vascular reactivity and decrease inflammation in animal models of diabesity, and remains a possible basis for therapeutic innovation (Billyard et al, 2007; Qi et al, 2004). Another adipokine, zinc-2-glycoprotein (ZAG), which is associated with fat loss in cancer cachexia, induced weight loss and improved glycaemic control in animal models of diabesity and may provide a further therapeutic lead (Russell and Tisdale, 2010).

Other antiobesity agents

The weight-lowering efficacy of various potential antiobesity agents has been demonstrated in non-diabetic states, and the results of studies in diabesity are awaited. These include combined bupropion and naltrexone; combined bupropion and zonisamide; lorcaserin (serotonin 5HT2c receptor agonist); obinepitide (combined analogue of PYY and pancreatic polypeptide); combined topiramate and phentermine; velneperit (neuropeptide Y Y5 receptor antagonist) and ZGN-433 (methionine aminopeptidase-2 inhibitor).

Conclusion

Lifestyle measures alone appear unable to address the diabesity epidemic, thus pharmacotherapy needs to be added to these initiatives. Metformin, DPP-4 inhibitors, GLP-1 receptor agonists and orlistat are helpful in the treatment of diabesity. However, diabesity is highly heterogeneous and a variety of differently acting agents – of which there are several in development – would be a welcome boost to the therapeutic armamentarium in the recognised battle to target concurrent control of hyperglycaemia and excess adiposity. ■

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"Lifestyle measures alone appear unable to address the diabesity epidemic, thus pharmacotherapy needs to be added to these initiatives."

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Online CPD activity

Visit www.diabetesonthenet.com/cpd to record your answers and gain a certificate of participation

Participants should read the preceding article before answering the multiple choice questions below. There is ONE correct answer to each question. After submitting your answers online, you will be immediately notified of your score. A pass mark of 70% is required to obtain a certificate of successful participation; however, it is possible to take the test a maximum of three times. A short explanation of the correct answer is provided. Before accessing your certificate, you will be given the opportunity to evaluate the activity and reflect on the module, stating how you will use what you have learnt in practice. The CPD centre keeps a record of your CPD activities and provides the option to add items to an action plan, which will help you to collate evidence for your annual appraisal.

1. Which of these statements regarding the enzyme dipeptidyl peptidase-4 (DPP-4) is correct? Select ONE option only.

A. DPP-4 enhances incretin action.
B. DPP-4 inhibits intestinal lipase activity.
C. DPP-4 enhances the action of endogenous GLP-1 (glucagon-like peptide-1).
D. DPP-4 degrades endogenous circulating GLP-1.
E. DPP-4 is a gliptin.

2. Which of these statements regarding the incretin hormone GLP-1 is correct? Select ONE option only.

A. GLP-1 is secreted by K cells.
B. GLP-1 is secreted by parietal cells.
C. GLP-1 potentiates nutrient-induced insulin secretion.
D. GLP-1 enhances glucagon secretion.
E. GLP-1 inhibits insulin secretion.

3. Which of these statements is INCORRECT? Select ONE option only.

A. Fibre supplements reduce postprandial peaks in blood glucose levels.
B. Alpha-glucosidase inhibitors reduce the rate of carbohydrate digestion.
C. Reducing adiposity is associated with improved glycaemic control.
D. Visceral adiposity is not associated with insulin resistance.
E. Diabesity is the coexistence of excess adiposity with type 2 diabetes.

4. In animal models of diabesity, which of the following statements about adiponectin is INCORRECT? Select ONE option only.

A. It improves insulin sensitivity.
B. It reduces blood glucose levels.
C. It reduces body weight.
D. It improves vascular reactivity.
E. It increases inflammation.

5. Which of the following statements is INCORRECT? Select ONE option only.

A. Calorie loss can be achieved by increasing glucose elimination in the urine.
B. Following filtration most of the glucose entering the proximal tubules is reabsorbed by sodium-glucose co-transporter 2 (SGLT2).
C. SGLT1 is located in more distal regions of the proximal tubule and in the small intestine.
D. Stimulation of SGLT1 and SGLT2 reduces glucose absorption.
E. Inhibition of SGLT1 and SGLT2 is not insulin dependent.

6. Which of the following effects is NOT observed with dapagliflozin? Select ONE option only.

A. Selective inhibition of SGLT1.
B. Selective inhibition of SGLT2.
C. Decreased body weight.
D. Decreased hyperglycaemia independently of insulin.
E. Glycosuria.

7. Which of the following statements is INCORRECT? Select ONE option only.

A. Empagliflozin and canagliflozin are SGLT2 inhibitors in late-stage development.
B. Linagliptin, saxagliptin, sitagliptin and vildagliptin are DPP-4 inhibitors.
C. The GLP-1 receptor agonists albiglutide and dulaglutide are available in the UK.
D. The amylin analogue pramlintide, available in the USA, improves glycaemic control and aids weight loss.
E. Agents to treat diabesity need to improve glycaemic control and facilitate a reduction in adiposity.

8. A 46-year-old man who has had type 2 diabetes for 3 years attends for annual review. He works shifts in a manufacturing factory and operates heavy machinery on a daily basis. He is currently treated with metformin 850 mg three times daily, simvastatin 40 mg once daily and ramipril 5 mg once daily. His most recent HbA_{1c} level is 57 mmol/mol (7.4%) and his BMI is 32 kg/m². What is the most appropriate management step? Select ONE option only.

A. Increase metformin to 3 g per day.
B. Add in acarbose as a second-line treatment.
C. Add in a sulphonylurea as a second-line treatment.
D. Add one of the DPP-4 inhibitors.
E. Answers A and C.

9. A 63-year-old woman with a BMI of 37 kg/m² has type 2 diabetes, hypertension and hyperlipidaemia and attends for annual review for her diabetes. She is on metformin 1 g twice daily, exenatide 10 µg twice daily, gliclazide 160 mg twice daily, amlodipine 10 mg once daily and atorvastatin 40 mg once daily. Her HbA_{1c} level is 86 mmol/mol (10%) and her blood pressure is 152/86 mmHg. What is the most appropriate management step? Select ONE option only.

A. Consider commencing insulin therapy.
B. Change from exenatide twice-daily to the newer once-weekly formulation.
C. Add a DPP-4 inhibitor to optimise the duration of action of exenatide.
D. Add pioglitazone.
E. Add acarbose.

10. A 49-year-old man with type 2 diabetes diagnosed 5 years ago on metformin 850 mg three times daily attends for annual review. His most recent HbA_{1c} level is 50 mmol/mol (6.7%). His BMI is 36 kg/m² and he does not perform self-monitoring of blood glucose regularly. In addition to metformin, he takes simvastatin 40 mg once daily and ramipril 5 mg once daily. He was commenced on exenatide at the previous visit, but he stopped taking it after 2 weeks due to severe nausea. His HbA_{1c} level has remained static over the past two clinic visits. What is the most appropriate management step? Select ONE option only.

A. Consider a trial of another GLP-1 receptor agonist or a DPP-4 inhibitor.
B. Increase the metformin dose to 3 g per day.
C. Add in a sulphonylurea.
D. Offer lifestyle advice.
E. None of the above.