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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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).
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\textsubscript{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\textsuperscript{2} although it allows for use in people with a BMI <35 kg/m\textsuperscript{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\textsubscript{1c}, Weight and Other Factors Through Intervention with Exenatide Once-Weeklyly) 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\textsuperscript{2}, exenatide once weekly (2 mg) lowered HbA\textsubscript{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\textsubscript{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 of exendin-4, a peptide discovered in the saliva of a lizard (Helloderma suspectum); it has 53% homology with human glucagon-like peptide-1 (GLP-1), is resistant to degradation by dipeptidyl peptidase-4 (DPP-4) and retains full GLP-1 receptor agonism.

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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*Neither of these agents are licensed for monotherapy in the UK.*
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 HbA1c 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.

DPP-4 inhibitors

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SGLT2 inhibitors

The kidney offers an opportunity to reduce hyperglycaemia and achieve calorie loss by increasing glucose elimination in the urine.
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 HbA1c 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 (HbA1c 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 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. Pramlintide is an injectable agent approved in the USA as an adjunct to insulin treatment in type 1 and type 2 diabetes. Pramlintide is an injectable agent approved in the USA as an adjunct to insulin treatment in type 1 and type 2 diabetes. 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.

Urinary cortisol and aldosterone are maintained independent of serum glucocorticoid concentrations. Since 11 beta hydroxysteroid dehydrogenase 1 (11 beta HSD 1) reduces the production of cortisol within these tissues without markedly altering the circulating cortisol concentrations, 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 decreased 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 would be expected to persist. Cessation of hypocaloric diet or bariatric surgery will result in relapse to a pre-existing level of (patho)glycaemic control and weight gain.

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 by 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).

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 HbA1c 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

| 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)** | **HbA1c (mmol/mol) [%]** |
| **Before** | **After** | **Before** | **After** | **Before** | **After** |
| **Bypass** | | | | | |
| Pories et al (1995) | IGT | 152 | T2D | 146 | 168 | 32.7 | N/G | 91% normal | N/G | 91% normal |
| MacDonald et al (1997) | T2D | 154 | 108 | 28 | 10.4 | <7.8 | N/G | N/G |
| Sugerman et al (2003) | T2D | 137 | 12–24 | 32 | N/G | 83% normal | N/G | 83% normal |
| **Restriction** | | | | | | | |
| | T2D | 19 | N/G | –9.7 | –6.4 | –66 [–8.2] | –40 [–5.8] |
| Sjöström et al (2004) | T2D | 82 | 24 | N/G | N/G | 72% normal | N/G | N/G |

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

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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.

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); obinpepitide (combined analogue of PYY and pancreatic polypeptide); combined topiramate and phentermine; vneluepert (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.

References


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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 glipitin.

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 and oral antidiabetic agents. 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, glimepiride 160 mg twice daily, amiodipine 10 mg once daily and atorvastatin 40 mg once daily. Her HbA₁c 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 HbA₁c 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 HbA₁c level has remained static over the past two clinic visits. What is the most appropriate management step? Select ONE option only.
   A. Increase the metformin dose to 3 g per day.
   B. Increase the metformin dose to 3 g per day.
   C. Add in a sulphonylurea.
   D. Offer lifestyle advice.
   E. None of the above.