Glycaemic management of type 2 diabetes

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Abstract

Type 2 diabetes mellitus (T2DM) is a chronic multifactorial disorder associated with hyperglycaemia and long-term end-organ damage. This end-organ damage is caused by hyperglycaemia and the accompanying risk factors such as hypertension, dyslipidaemia and obesity, leading to increased risk of cardiovascular disease and mortality. It is essential to adopt effective multifactorial risk reduction strategies. Pharmacological and non-pharmacological management aimed at improving glycaemic control in patients with T2DM is ever-evolving. Over the last decade, new anti-hyperglycaemic agents have been launched that act via non-traditional mechanisms, and drug development in this area remains very active.

Keywords DESMOND; glycaemic management; incretin therapy; insulin therapy; MRCP; oral anti-hyperglycaemic agents; type 2 diabetes mellitus

Key points

- Multifactorial treatment of type 2 diabetes mellitus (T2DM) results in a reduction of both macro- and microvascular complications of diabetes
- Intensive lifestyle changes in both exercise and diet form the mainstay of T2DM therapy at any stage, supporting patient self-empowerment and encouraging self-management
- Glycated haemoglobin targets should be individualized and discussed with patients, taking into account co-morbidities, age, duration of diabetes and the patient's social support system
- Hypoglycaemia and its resultant complications are the most important limiting factor in glycaemic treatment; hence the risk of hypoglycaemia should be taken into account when choosing medications
- Metformin is still the first-choice drug in treating T2DM
- Subsequent intensification can be performed using any of the available classes of agent
- Medications such as empagliflozin and liraglutide have demonstrated beneficial cardiovascular disease profiles in outcome studies

Introduction

The landmark UK Prospective Diabetes Study (UKPDS) clearly demonstrated the beneficial effects of intensive glycaemic management of type 2 diabetes mellitus (T2DM) on microvascular complications and, recently, a reduction in macrovascular complications, as well as all-cause mortality.[1,2] Epidemiological analysis of the UKPDS data shows impressive reductions in microvascular as well as macrovascular risk with each 1% reduction in glycated haemoglobin (HbA_{1c}; Table 1).[3]

The UK National Institute for Health and Care Excellence (NICE) has undertaken a comprehensive review of current evidence and issued national guidelines for the management of T2DM, including the use of newer anti-hyperglycaemic agents.[3] The last few years have also seen cardiovascular disease outcome data released for many hyperglycaemic agents, such as liraglutide and empagliflozin.

Patient education and new approaches to self-management

The DESMOND (Diabetes Education and Self-Management for Ongoing and Newly Diagnosed) Collaborative Project set out to develop an evidence-based structured education and self-management programme for people with T2DM. DESMOND is built on a clearly stated philosophy and explicit principles of care that are used to develop the individual's understanding of diabetes, the specific monitoring and goal-setting skills necessary for effective self-management, and the confidence necessary for a person to take charge of their own diabetes.

In a randomized controlled trial, 824 adults with T2DM recruited from 207 general practices were randomized to be given intervention with structured education or usual care. The intervention was a curriculum-based group education programme delivered by trained healthcare professionals and was quality-assured. HbA_{1c} after 1 year was lower in the intervention arm (−1.49% versus −1.21%), but this was non-significant after adjusting for baseline and clustering. The intervention group had a significantly greater weight loss ($p = 0.027$), along with a greater change in illness belief scores ($p < 0.001$) and lower depression scores ($p < 0.05$). The odds ratio in relation to giving up smoking was 3.56 in the intervention group ($p = 0.033$).[4] As a result, the 10-year modelled cardiovascular risks were significantly lower in the intervention arm. A subsequent cost-effectiveness analysis determined that the DESMOND programme was cost-effective even under modest conditions and the assumption that the benefits would be lost after the 1-year trial period.

Data from programmes in people with established diabetes have also demonstrated significant biomedical and psychosocial

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Beneficial effects of HbA_{1c} reduction on vascular complications

Effects of 1% reduction in updated mean HbA_{1c} on complications of type 2 diabetes

Complication	Risk reduction
Any diabetes-related complication	21%
Myocardial infarction	14%
Microvascular disease	37%
Death due to diabetes	21%

Source: UKPDS35. *Br Med J* 2010; **321**: 405–12.

Table 1

benefits. Structured education programmes fulfilling nationally agreed criteria should be offered to all people with T2DM from diagnosis.

Dietary and lifestyle interventions

Dietary modification and lifestyle intervention remain the initial mainstays of T2DM treatment. Most patients with T2DM are overweight and have features of metabolic syndrome; weight reduction reduces insulin resistance and improves associated cardiovascular risk factors. Early and continued involvement of a dietitian with an interest in diabetes is important. It should be noted that dietary and lifestyle management are key components of the structured education programme referred to above.

General aims of dietary intervention

Energy intake and expenditure balance should be adjusted to achieve a body mass index of 20–25 kg/m^2. In clinical practice, however, realistic and individualized targets should be set for weight loss. With an exercise programme, weight loss of 1–2 kg/month can be achieved by reducing the caloric intake below that required for weight maintenance by at least 500 kcal/day.

Benefits of exercise

Regular physical activity increases muscle-related energy expenditure, improves insulin sensitivity, reduces blood pressure and improves lipid profile. Exercise improves glycaemic control in T2DM. Generally, any form of exercise with a duration of 30 minutes is recommended to aid weight loss, when accompanied by an appropriate diet. A recent study confirmed that 30 minutes of moderate-intensity exercise on most days was associated with a reduction in blood pressure and serum concentrations of total cholesterol and triglyceride (triacylglycerol). However, 60–75 minutes on most days was required to reduce weight, waist circumference, fasting glucose and low-density lipoprotein cholesterol, increase high-density lipoprotein and reduce overall 10-year cardiovascular risk.

Oral anti-hyperglycaemic agents (OAAs)

Whereas insulin resistance is a general feature of T2DM, hyperglycaemia results from significant β-cell depletion, suggesting that optimal glycaemic control requires glucose-lowering agents that act through both increased β-cell function and enhanced tissue responsiveness to insulin. The UKPDS demonstrated that >50% of the β-cells are lost by the time of diagnosis of T2DM.

Targets of therapy

As recent study data have suggested that targeting intensive glycaemic control can increase mortality, the current consensus is that HbA_{1c} targets should be individualized. The patient's age, duration of T2DM, co-morbidities, coexisting polypharmacy and social support are some factors that should be taken into consideration when glycaemic targets are set; these should be discussed with the patient and/or the key worker.[5] Insulin therapy is recommended if the HbA_{1c} remains >58 mmol/mol (>7.5%) despite use of appropriate and tolerated OAAs (Figure 1). Aggressive glycaemic therapy to achieve an HbA_{1c} <48 mmol/mmol (<6.5%) should be avoided in patients with longer duration of diabetes and in the presence of cardiovascular disease.

Data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study suggests that tight glycaemia is achievable with intensive therapy but is associated with increased risk of hypoglycaemia and mortality in patients with existing cardiovascular disease. Post hoc analysis of these data suggests that this risk is higher in patients with poor baseline glycaemic control in those who do not show improvement in HbA_{1c} despite intensification of anti-hyperglycaemic therapy. In this subgroup, attention should be directed towards patient education and adherence to treatment rather than intensifying glycaemic therapy.

Metformin

Biguanides have been the mainstay of OAA treatment since 1950, but metformin is the only one currently used in clinical practice. Its mechanism of action is unclear but probably involves reduction of hepatic gluconeogenesis through effects on mitochondrial function, thereby reducing insulin resistance. Metformin also has cardioprotective benefits, as shown in the UKPDS and other major studies. It is the first-line agent in overweight patients. It can be given as monotherapy or in combination with almost any other glucose-lowering agent.

The most common adverse effects are gastrointestinal, including diarrhoea, nausea, vomiting and flatulence; about 10% of patients stop taking it because of these effects. Tolerability can be improved by using a smaller initial dose, gradually titrating the dose, taking the drug with meals and using modified-release preparations. The dosage should be reviewed if the estimated glomerular filtration rate (eGFR) is <45 ml/minute or serum creatinine >130 mmol/litre. It should be discontinued if eGFR falls <30 ml/minute or serum creatinine rises >150 mmol/litre.

Metformin should also be avoided if there is clinical or laboratory evidence of liver dysfunction, and in patients with unstable or acute congestive heart failure, because of the rare possibility of lactic acidosis. It should be discontinued temporarily in the event of sepsis or dehydration, in association with use of radiographic contrast media, during the perioperative period and immediately after coronary events.

Sulfonylureas

Sulfonylureas are insulin secretagogues that bind to a pancreatic β-cell membrane receptor, promoting closure of

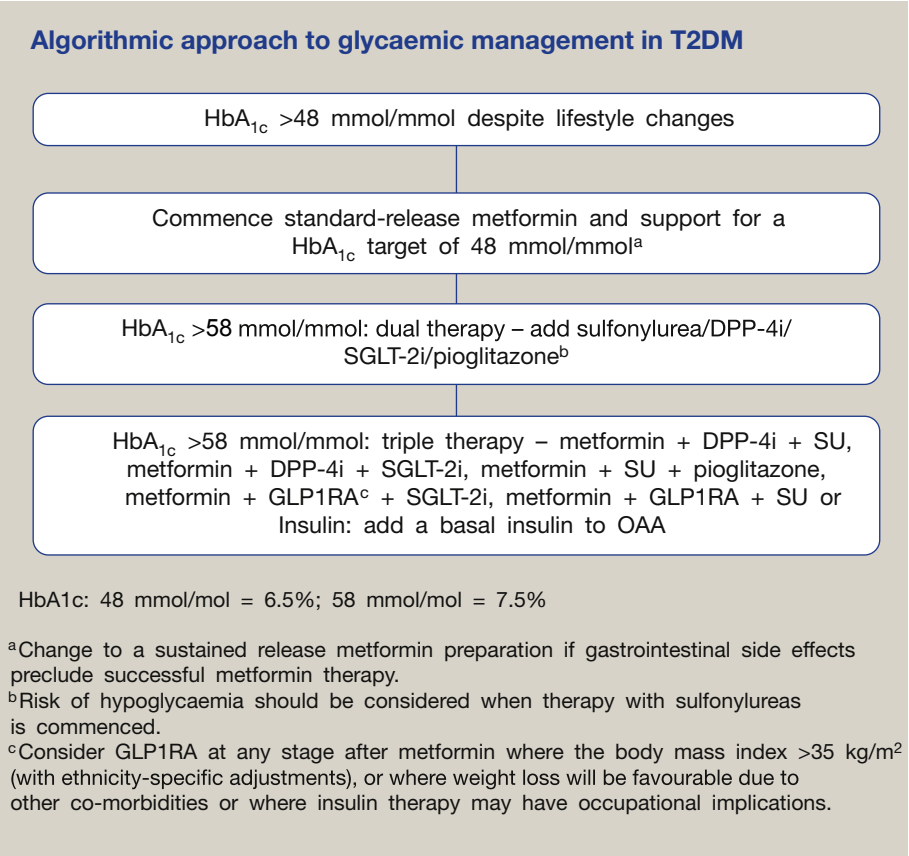

Figure 1 DPP-4i, dipeptidyl peptidase 4 inhibitor; GLP1RA, glucagon-like peptide 1 receptor agonist; OAA, oral anti-hyperglycaemic agent; SGLT-2i, sodium glucose co-transporter 2 inhibitor; SU, sulfonylurea. Adapted from NICE.[3]

hyperpolarizing adenosine triphosphate (ATP)-dependent potassium channels, cell membrane depolarization and exocytosis of insulin secretory vesicles. They are licensed for monotherapy or in combination with other OAAs except meglitinides. They are effective in reducing fasting plasma glucose, and in reducing HbA_{1c} by about 10–20 mmol/mmol (1.5–2.0%) but are associated with weight gain and an increased risk of hypoglycaemia.

Gliclazide is commenced at a dosage of 40–80 mg given once or twice a day and increased to a maximum of 160 mg twice a day. Gliclazide MR is a modified-release preparation given once a day at the starting dose of 30 mg/day (equivalent to 80 mg/day standard-release gliclazide).

Glimepiride is taken once a day up to a maximum dosage of 4 mg/day; this can be increased to 6 mg/day in exceptional circumstances. In the UKPDS, 7% of patients taking a sulfonylurea experienced at least one severe hypoglycaemic episode over 9–12 months. These episodes can be prolonged and potentially dangerous with long-acting agents such as glibenclamide. Predisposing factors for the development of hypoglycaemia are age, liver, renal and cognitive impairment, and other interacting medications (listed in Appendix 1 of the *British National Formulary* (BNF)). Patients presenting with hypoglycaemia secondary to sulfonylurea use should be hospitalized and their blood glucose monitored for 24–48 hours; this is particularly important in older patients with renal impairment.

Agents such as glibenclamide and tolbutamide are very rarely used in practice and have been replaced by newer agents such as gliclazide that are relatively short-acting.

Prandial glucose regulators (meglitinides)

Meglitinides have been developed to target early-phase insulin secretion, which is one of the earliest pathophysiological manifestations of T2DM. Repaglinide and nateglinide are currently available rapid-acting insulin secretagogues with a fast onset and short duration of action. Meglitinides act on a different β-cell membrane receptor from sulfonylureas, but also promote the closure of ATP-dependent potassium channels. However, this class of medicines still appears to be associated with weight gain and increased risk of hypoglycaemia, similar to sulfonylureas.

Meglitinides are licensed for use as monotherapy, as an add-on to metformin when the latter alone is insufficient for glycaemic control, and in combination with insulin. Flexible dosing is possible, suiting shift-workers and individuals with a flexible lifestyle, although multiple doses must be taken. Repaglinide is started at a dose of 0.5 mg taken 15 minutes before meals and at least taken 30 minutes before the mealsmand adjusted to a maximum of 16 mg/day or a maximum single dose of 4 mg. Nateglinide is started at 60 mg taken three times daily with meals and adjusted to a maximum of 180 mg three times daily. Meglitinides are more expensive than sulfonylureas.

Thiazolidinediones

These are insulin sensitizers and act primarily by activating the peroxisome proliferator-activated receptor-γ (PPAR-γ), the key transcription factor in fat cell differentiation and function (but also present in liver, skeletal muscles and other tissues). This activation enhances the effects of endogenous insulin on target organs, reducing insulin resistance. Rosiglitazone and pioglitazone have been shown to reduce HbA_{1c} by up 15 mmol/mmol (1.5%). They do not generally cause hypoglycaemia.

One meta-analysis involving 42 studies concluded that rosiglitazone was associated with a significant increase in risk of myocardial infarction and a borderline significant finding for death from cardiovascular causes. An unplanned interim analysis of the RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes) study was inconclusive regarding the effect of rosiglitazone on overall risk of hospitalization or death from cardiovascular causes. More importantly, this analysis did not provide any reassurance regarding the safety of rosiglitazone in respect of the risk of myocardial infarction. The European Medicines Evaluation Agency suspended rosiglitazone from the European market in 2010, although it remains available in the USA. These agents are associated with fewer hypoglycaemic episodes than sulfonylureas, but lead to increased peripheral oedema, weight gain and an increased risk of distal fractures, especially in postmenopausal women.

Thiazolidinediones have been licensed for use as monotherapy and in combination with metformin, a sulfonylurea and insulin. NICE recommends their use in addition to a first-line agent (either metformin or a sulfonylurea) if another second-line agent (a sulfonylurea or metformin, respectively) is poorly tolerated or contraindicated. Thiazolidinediones are recommended as third-line agents in addition to metformin and a sulfonylurea for patients in whom insulin therapy is unacceptable. Pioglitazone can be combined with insulin, but the combined use is associated with significant weight gain. A recent meta-analysis has demonstrated an increased risk of bladder cancer in those taking pioglitazone (hazard ratio 1.23), the drug has been withdrawn from sale for this reason in France, Canada, Australia, New Zealand, India and Japan. Pioglitazone and rosiglitazone have also been shown to increase fracture risk in women, especially of the appendicular skeleton.

Pioglitazone has been shown to reduce the incidence of fatal and non-fatal myocardial infarction in individuals with T2DM.

Insulin therapy

In the UKPDS, >50% of patients required additional insulin therapy by 6 years; this was largely attributed to the fact that β-cell function worsened from about 53% at diagnosis to about 28% after 6 years of follow-up. General indications for insulin are shown in Table 2. The topic should be approached sensitively; the decision to start insulin should be made in partnership with the patient, and the choice of regimen tailored to the individual's needs. The patient should agree with the decision and understand the benefits of insulin and the implications of its use. Access to appropriate dietary and lifestyle advice is essential.

Potential barriers to insulin therapy: the main barriers to insulin therapy are hypoglycaemia, weight gain and fear of injections. Occupational factors can also be a barrier (e.g. in heavy goods vehicle drivers). Patients taking insulin generally gain weight, mainly because of improved glycaemic control. To limit this, one should determine the patient's appropriate weight and discuss the fact that additional 'snacks' are not automatically required; they should be tailored to the individual's needs and the type of insulin regimen.

Insulins

Porcine and bovine insulins were the first insulin preparations available before the advent of human and analogue insulins. They now account for only about 7% of insulin prescriptions in the UK and are predominantly used in patients with type 1 diabetes. Most insulin formulations are now produced at a concentration of 100 U/ml. Insulin has recently been marketed at both 200 U/ml (Humalog U-200, Tresiba) and 300 U/ml (Toujeo U300). These are considered as high-strength insulins and in most areas are for the use of or under the supervision of diabetes specialists only. For individual patients requiring higher doses, insulin can be procured on a named-patient basis at a

Indications for insulin and early insulin use in T2DM

- Failure of all previous attempts to achieve desired target (lifestyle measures, maximal oral therapy)
- Persistent failure to achieve optimal HbA_{1c}
- Symptomatic patient (weight loss, lethargy)
- Corticosteroid-induced diabetes
- Gestational diabetes; women with T2DM who become pregnant or are planning pregnancy
- Post-acute myocardial infarction
- Intolerance to oral agents
- More suited to the patient's lifestyle
- Acute neuropathy (e.g. proximal amyotrophy)

In the following clinical scenarios, insulin is considered at presentation:

- Patients with newly diagnosed diabetes, with random plasma glucose >11.1 mmol/litre presenting with myocardial infarction, severe intercurrent illness (e.g. sepsis), ketonaemia/ketonuria or hyperosmolar non-ketotic state
- Patients with fasting plasma glucose >15 mmol/litre and/or random glucose >24 mmol/litre who are increasingly symptomatic

Table 2

concentration of 500 U/ml (Humulin R). The rate of insulin absorption differs between sites, being fastest in the abdomen and slowest in the thigh and buttocks. The site of insulin injection should be varied to prevent lipo-hypertrophy. Patients should be educated on site and technique hygiene, and this should be reviewed at every review.

Insulin regimens in T2DM: the individual insulin regimen (Table 3) should be tailored to address both fasting and post-prandial glycaemic excursions. Fasting hyperglycaemia is addressed by isophane (medium-acting) insulin given twice daily or by one of the long-acting analogues — glargine, detemir or degludec. Post-meal glucose excursions can be targeted using short-acting insulins either alone or as mixed insulin. A reasonable starting dose of insulin is 10 U twice daily for twice-daily mixtures and 10–12 units daily for once-daily NPH (neutral protamine Hagedorn) and insulin analogues.

The Treating to Target in Type 2 Diabetes (4-T) study was designed to compare three types of insulin regimen (basal, prandial, biphasic) in addition to OAA in patients with T2DM. Although the risk of hypoglycaemia and weight gain was greater in patients using biphasic or prandial insulins, by 3 years most patients required a 'complex' insulin regimen. This study supports the initial use of basal insulin, followed by intensification with a basal–prandial regimen. The 4-T study also demonstrated that was no increased risk of hypoglycaemia when initiating insulin using a proactive regimen.

Incretin-based therapy

An oral glucose load stimulates increased insulin release from pancreatic β-cells, whereas a glucose load administered intravenously has an isoglycaemic effect. This is known as the incretin effect. Two main gut hormones — glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1 (GLP-1), known as incretins — are released from intestinal cells in response to food. GLP-1 is a potent incretin and has a variety of favourable metabolic effects. It inhibits glucagon secretion, delays gastric emptying and reduces food intake, leading to weight loss. It has also been shown to increase β-cell proliferation. Because its release is glucose-dependent, it is unlikely to be associated with hypoglycaemia.

The discovery of these favourable effects of GLP-1 led to the development of new therapeutic agents targeted to mimic or augment the action of this important molecule; unfortunately, the half-life of endogenous GLP-1 is about 2 minutes, as it is rapidly degraded by the enzyme dipeptidyl peptidase 4 (DPP-4). Incretin-based therapy is thus broadly divided into two groups. The agents targeted towards inhibition of DPP-4, leading to increased activity of endogenous GLP-1, are called DPP-4 inhibitors (incretin enhancers) and are taken orally. Agents that are analogous to GLP-1 but partially resistant to degradation by endogenous DPP-4 are called GLP-1 receptor agonists (GLP1RA) and are administered as subcutaneous injections.

DPP-4 inhibitors: sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin are currently licensed for the treatment of T2DM in the UK. Although there are subtle licensing differences between these agents, broadly speaking, NICE recommends their use in addition to a first-line agent (either metformin or a sulfonylurea) when sulfonylureas are contraindicated owing to the risk of hypoglycaemia, or when metformin has been poorly tolerated. Sitagliptin is recommended as a third-line agent in addition to metformin and a sulfonylurea for patients in whom insulin therapy is unacceptable (Figure 1). DPP-4 inhibitors may be preferred to a thiazolidinedione if the latter is contraindicated, or has led to weight gain or peripheral oedema.

Sitagliptin is licensed for use along with metformin and/or a sulfonylurea at a dose of 100 mg orally once a day. Vildagliptin is given in a dosage of 50 mg orally twice daily in combination with metformin or thiazolidinedione, or 50 mg once daily with concurrent sulfonylurea therapy. Saxagliptin is given in a dosage of 5 mg orally once a day. The dosage of all three of these agents should be reduced in patients with moderate to severe renal impairment (see BNF section 6.1.3). Linagliptin is not excreted via the renal route, and its dosage (5 mg orally once a day) need not be adjusted if renal function is impaired.

Common insulin regimens in type 2 diabetes mellitis (T2DM)

- **Twice-daily pre-mixed insulin** includes conventional mixtures of short-acting and isophane insulins (e.g. Humulin M3, Insuman Comb 15,25). The percentage of short-acting insulin ranges from 10% to 50%, the most commonly used ratio being 30:70. Short-acting insulin analogue mixtures such as Novomix 30, Humalog Mix25 and Humalog Mix50 have become available and may have advantages in terms of patient convenience (no need to wait before eating). They are widely used in the UK, particularly because of their ease of use. However, a fixed combination is not 'physiological', and achieving optimal glycaemic control in some patients can be difficult with this relatively rigid regimen
- **Once-daily basal insulin** in combination with an oral anti-hyperglycaemic agent includes a sulfonylurea or a prandial glucose regulator, with metformin if tolerated. Evidence suggests that conventional isophane insulin, when used in this regimen, is best administered in the evening or before bedtime. Basal insulin analogues have been suggested for once-daily use in combination with oral agents, because they have advantages in terms of nocturnal hypoglycaemia
- **Twice-daily isophane insulin** can be used as basal insulin therapy. Although data suggest that once-daily basal insulin analogues are effective in lowering HbA_{1c} and carry a reduced risk of hypoglycaemia, other factors such as cost and choice of insulin device can lead to continued use of twice-daily isophane insulin (human Insulatard or Humulin I)
- **Formal basal–bolus** regimens comprise four injections of insulin per day. Short-acting insulin or short-acting analogues are taken before each main meal, together with basal insulin (once-daily or twice-daily isophane insulin, or once-daily long-acting insulin analogue (glargine or detemir)). This regimen is often used in type 1 diabetes, but is seldom the first choice in patients with T2DM

Table 3

These agents are generally well tolerated, with occasional gastrointestinal effects and peripheral oedema. Liver function should be monitored before treatment and every 3 months for the first year (and periodically thereafter during vildagliptin therapy) owing to the rare incidence of liver toxicity. DPP-4 inhibitors are generally weight neutral and less likely to be associated with hypoglycaemia than sulfonylureas. The risk of hypoglycaemia is increased in patients taking a concomitant sulfonylurea or insulin, the dose of which should be reduced if necessary.

GLP-1 receptor agonists (GLP1RAs): exenatide is the first incretin mimetic licensed to be used in patients with T2DM. It shares 53% amino acid identity with endogenous GLP-1. The initial dosage is 5 micrograms twice daily, increased to a maximum dose of 10 micrograms twice daily after 1 month if tolerated. Exenatide should be used with caution when the eGFR is 30–50 ml/minute and should be avoided if the eGFR is <30 ml/minute. In clinical practice, more frequent monitoring of renal function may be needed, particularly when GLP1RAs are used in combination with other agents that can cause a fall in eGFR (e.g. angiotensin-converting enzyme inhibitors). Improvements in glycaemic control can be sustained over a period of 3 years with continued exenatide therapy.

Liraglutide is a once-daily preparation with 97% amino acid sequence identity with endogenous GLP-1. Its prolonged half-life results from the formation of heptamers at the injection site, leading to slow absorption and reversible binding to albumin; this results in delayed renal clearance as well as degradation by DDP-4, so this drug requires only once a day administration. It is licensed for use along with metformin, with a sulfonylurea or in combination with insulin detemir. It is available in 0.6 mg, 1.2 mg and 1.8 mg doses given by subcutaneous injection. Liraglutide can be used in patients with renal impairment. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) study has demonstrated a 13% reduction in major adverse cardiovascular events and a 15% reduction in all-cause mortality in patients with T2DM and a high cardiovascular risk.

A long-acting once-weekly formulation of exenatide (exenatide LAR) is also available and well tolerated. It is associated with a greater reduction of HbA_{1c} (1.9% versus 1.5%) than twice-daily exenatide over a 30-week period, an effect that is sustained after 52 weeks. It is used as a 2 mg once-weekly dose. This preparation is also licensed to be used with a sodium glucose co-transporter 2 (SGLT-2) inhibitor (discussed below).

GLP-1 receptor agonists are increasingly being used in combination with basal insulin to optimize glycaemia, reduce weight and optimize insulin dose requirements. Lixisenatide is an agent in this series to be licensed for use in combination with OAAs, and is also licensed for use in combination with basal insulin glargine.

Dulaglutide is a once-weekly GLP1RA that is licensed for use as monotherapy (where metformin is not tolerated) or in combination with other anti-hyperglycaemic agents and insulin. The preparation is not recommended in individuals with severe renal impairment (glomerular filtration rate <15 ml/minute). Semaglutide is the latest weekly preparation in this series.

NICE recommends the use of GLP1RAs in addition to metformin and or a sulfonylurea in patients with a BMI >35 kg/m^2 whose glycaemic control is inadequate (HbA_{1c} >58 mmol/mol (>7.5%)). It should be continued only if HbA_{1c} is reduced by 10 mmol/mmol (1%) and a weight loss of 3% is achieved at 6 months. In comparison to orally available DPP-4 inhibitors, GLP-1RA are associated with more weight loss and a greater reduction in HbA1c.

All incretin mimetics should be used with caution in patients with a predisposition to pancreatitis and avoided in those with a previous history of this.

SGLT-2 inhibitors: SGLT-2 is present in the proximal renal tubules and plays a major role in reabsorbing glucose from the tubular fluid. Inhibition of this co-transporter leads to calorie loss by increasing urinary glucose excretion. As a result, glycaemic control is improved without risk of weight gain or hypoglycaemia as this approach is independent of insulin. Increased glycosuria leads to increased diuresis and urogenital infections. This class of agents, which currently comprises dapagliflozin, canagliflozin and empagliflozin, have an insulin-independent mode of action and therefore the potential to confer a lesser risk of hypoglycaemia. Head-to-head trials comparing SGLT-2 inhibitors and DPP-4 inhibitors have shown an equivalent reduction in HbA_{1c}, with the added benefit of weight loss in the case of SGLT-2 inhibitors.

Broadly speaking, NICE recommends SGLT-2 inhibitors for use in T2DM in combination with metformin in the same way as DPP-4 inhibitors. There are minor licensing differences between the available agents. Dapagliflozin results in a significant and sustained reduction in HbA_{1c} with an added benefit of weight loss when added to existing treatment with metformin. These effects appear to be sustained when compared with those of a sulfonylurea at 4 years. Canagliflozin, the second agent in this class, has a similar marketing authorization but, along with the third agent empagliflozin, is available to be used at a lower dose up to a glomerular filtration rate of 45 ml/minute.

Empagliflozin has also shown a significant reduction in death from cardiovascular disease (38% RR), hospitalization from heart failure (35%) and all-cause mortality (32%) in those with T2DM and a high risk of cardiovascular disease.

Data from outcome trials using canagliflozin have shown an increased risk of minor amputations in predisposed patients. Hence all SGLT-2 inhibitors should be discontinued in patients with active foot ulcers or untreated peripheral vascular disease. A small increase in the risk of euglycaemic diabetic ketoacidosis has also been reported in patients with T2DM taking SGLT-2 inhibitors. Patients appear to be at higher risk if they have an intercurrent illness such as infective illness and dehydration, and when there is a rapid reduction in insulin dosage in those treated with insulin. Patients should be counselled on this risk at the time these agents are started.

The future

Several other incretin-based agents and SGLT-2 inhibitors are at different stages of drug development.

Dual PPAR-α and PPAR-γ agonists – agents activating both PPAR-α receptors (improving dyslipidaemia) and PPAR-γ receptors (reducing insulin resistance) are on the horizon. One of these, aleglitazar, has been shown to improve HbA_{1c} by 0.36

−1.35% in a dose-dependent manner during a placebo-controlled trial over 16 weeks. Phase III trials and longer pre-clinical studies are needed to confirm the safety of these agents.

Glucokinase activators − these molecules activate the glucokinase enzyme, present in hepatic cells and pancreatic β-cells, leading to increased glycogen synthesis and glucose release. This effect has proved beneficial in reducing plasma glucose in animal models, and the role of these drugs in humans is currently being tested.

SGLT-1 inhibitors − SGLT-1 receptors are located predominantly in the small intestine. They contribute to intestinal glucose absorption but to <10% of renal reabsorption of glucose. Receptor blockade presents a novel way of improving glucose tolerance and provides exciting avenues for the treatment of T2DM. Molecules that exhibit selective and variable SGLT-1 and SGLT-2 affinity are in various trial stages. Some of these agents are also bring trialled in type 1 diabetes.

Glucagon receptor antagonists − glucagon is secreted by pancreatic α-cells and plays a vital role in maintaining glucose homeostasis. It prevents hypoglycaemia and counteracts the effects of insulin by stimulating hepatic glucose synthesis and mobilization. In patients with T2DM, the glucagon-to-insulin ratio is increased, leading to gluconeogenesis and glycogenolysis. Experimental studies have shown a state of hyperglucagonaemia in patients with T2DM, and suppression of the excess glucagon levels or activity resulted in improved glycaemic control. One such agent, Bay 27-9955, has been shown to reduce glucagon-induced hyperglycaemia in adults. Various peptide- and non-peptide-based glucagon receptor antagonists are currently being tested in animals and humans.

Imiglimin − this novel type of oral hypoglycaemic agent has been shown to reduce hepatic gluconeogenesis and improve muscle glucose uptake. Favourable effects have been demonstrated in trials using it as monotherapy and combination therapy. ◆

KEY REFERENCES

1 Intensive blood glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 2007; **352:** 837−53.

2 Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; **359:** 1577−89.

3 National Institute for Health and Care Excellence. Type 2 diabetes: management in adults. London: Department of Health, 2017.

4 Davies MJ, Heller S, Skinner TC, et al. Effectiveness of the diabetes education and self management for ongoing and newly diagnosed (DESMOND) programme for people with newly diagnosed type 2 diabetes: cluster randomised controlled trial. *Br Med J* 2008; **336:** 491−5.

5 Inzucchi SE, Bergenstal RM, Buse JB, et al. American diabetes association (ADA); European association for the study of diabetes (EASD). Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American diabetes association (ADA) and the European association for the study of diabetes (EASD). *Diabetes Care* 2012; **35:** 1364−79.

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To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 74-year-old woman was seen for annual review. She had type 2 diabetes. She had a past history of ischaemic heart disease, Parkinson's disease and hypertension. She was the main carer for her husband, who had vascular dementia, and she had failed to attend multiple reviews. She was taking metformin 500 mg 12-hourly, co-beneldopa 125 mg 8-hourly, perindopril 4 mg daily, atorvastatin 40 mg at night, bisoprolol 5 mg daily and nicorandil 20 mg 12-hourly.

On clinical examination, her blood pressure was 142/80 mmHg, and body mass index 27 kg/m^2.

Investigations

- Urea 7.2 mmol/litre (2.5−7.0)
- Creatinine 140 micromol/litre (60−110)
- Estimated glomerular filtration rate 40 ml/minute (>60)
- HbA_{1c} 64 mmol/mmol (20−42); 8%

Which of the following is the next most appropriate escalation step for glycaemic management?

A. Increase metformin to 1 g twice daily
B. Commence a basal insulin
C. Commence dapagliflozin 5 mg once a day
D. Add in sitagliptin 100 mg once a day
E. Add linagliptin 5 mg once a day

Question 2

A 40-year-old woman with a 2-year history of type 2 diabetes was seen. She was self-empowered, had attended the local NICE approved self-management and education programme, and had lost 7 kg in weight. She was taking metformin 1 g 12-hourly, atorvastatin 20 mg at night and ramipril 1.25 mg daily.

On clinical examination, her blood pressure was 136/72 mmHg, and body mass index was 34 kg/m^2.

Investigations

Investigations and the annual review biochemistry revealed:

- Urea 3.2 mmol/litre (2.5−7.0)
- Creatinine 86 micromol/litre (60−110)
- Estimated glomerular filtration rate >90 ml/minute (>60)
- HbA_{1c} 62 mmol/mmol (20−42); 7.8%

Which of the following is the next most appropriate escalation step for glycaemic management?

A. Add gliclazide 40 mg 12-hourly
B. Commence dapagliflozin 10 mg daily
C. Commence a glucagon-like peptide 1 (GLP-1) receptor agonist
D. Commence linagliptin 5 mg daily
E. Commence pioglitazone 30 mg 12-hourly

Question 3

A 48-year-old man was due for a urethral dilatation for stenosis. He had a 5-year history of type 2 diabetes mellitus. He had a history of obstructive jaundice of unknown cause (he was awaiting endoscopic retrograde cholangiopancreatography) and hypertension. He was taking metformin 1 g 12-hourly, pioglitazone 45 mg daily and perindopril 6 mg daily.

On clinical examination, his blood pressure was 146/80 mmHg, and body mass index was 30 kg/m^2.

Investigations

- Urea 3.2 mmol/litre (2.5–7.0)
- Creatinine 86 micromol/litre (60–110)
- Estimated glomerular filtration rate >90 ml/minute (>60)
- HbA_{1c} 102 mmol/mmol (20–42) (11.5%);

Which of the following is the next most appropriate escalation step for glycaemic management?

A. Gliclazide
B. Pre mix insulin 12-hourly
C. Dapagliflozin
D. A GLP-1 receptor agonist
E. Pioglitazone