Management of type 2 diabetes: now and the future

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ABSTRACT

There are about 4.7 million people living with diabetes mellitus in the UK and 90% have type 2 diabetes mellitus (T2DM). This burden will only get worse as there are currently about 12.3 million more at risk of T2DM. Moreover, up to 30% of diagnosed patients already have eye, foot, kidney or nerve complications. This impacts the NHS considerably as it spends about £10 billion annually on diabetes (80% on complications alone). Atherosclerotic cardiovascular disease (ASCVD), the leading cause of death in diabetes, contributes significantly to this.

Therefore, there is significant emphasis on the prevention of T2DM especially in at-risk groups with the setting up of initiatives like the Diabetes Prevention Programme. When prevention fails, it is essential to commence glucose-lowering agents to reduce the burden of disease, prevent associated complications and improve quality of life.

A patient-centred approach is required to ensure efficacy of treatment strategies and the presence of co-morbidities such as cardiovascular and renal disease should be considered.

Introduction

There are about 4.7 million people living with diabetes mellitus in the UK and 90% have type 2 diabetes mellitus (T2DM).[1] This burden will only get worse as there are currently about 12.3 million more at risk of T2DM. Moreover, up to 30% of diagnosed patients already have eye, foot, kidney or nerve complications.[1] This impacts the NHS considerably as it spends about £10 billion annually on diabetes (80% on complications alone).[1] Atherosclerotic cardiovascular disease (ASCVD), the leading cause of death in diabetes, contributes significantly to this.[2]

Therefore, there is significant emphasis on the prevention of T2DM especially in at risk groups with the setting up of initiatives like the Diabetes Prevention Programme. When prevention fails, it is essential to commence glucose-lowering agents to reduce the burden of disease, prevent associated complications and improve quality of life.

A patient-centred approach is required to ensure efficacy of treatment strategies and the presence of co-morbidities such as cardiovascular and renal disease should be considered.[3]

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The goal of this article is to introduce the non-specialist clinician to the newer agents used in the management of T2DM and advise on drug choice based on clinical and cost effectiveness. This would be illustrated with a clinical case with reference made to the National Institute for Health and Care Excellence (NICE) and the American Diabetes Association (ADA) / European Association for the Study of Diabetes (EASD) guidelines. The focus will be on non-insulin and non-surgical treatment options.

Case illustration

A 60-year-old male with T2DM for 10 years who takes metformin, 1 g twice daily (other medications include aspirin 75 mg, ramipril 2.5 mg and atorvastatin 80 mg) was seen for his annual diabetes check.

He has a past medical history of ischaemic heart disease with a previous myocardial infarction and percutaneous coronary intervention with stenting.

Examination findings included a body mass index of 31 kg/m^2 and blood pressure of 128/78 mmHg with his most recent glycated haemoglobin (HbA1c) being 62 mmol/mol (target ≤53 mmol/L) and estimated glomerular filtration rate 65 mL/min/1.73m^2.

This man clearly needed optimisation of his glucose-lowering medication but would also benefit from an agent with

Key points

The UK prevalence of type 2 diabetes mellitus (T2DM) is rising and costing the NHS significantly.

Optimising glycaemic control promptly can confer long lasting protection from microvascular complications.

Metformin remains the first-line glucose-lowering agent in T2DM.

Sodium-glucose co-transporter-2 inhibitors and glucagon-like peptide-1 agonists have benefit in atherosclerotic cardiovascular disease and heart failure and confer renal protection.

These agents should be added to metformin promptly in at risk groups with patient-specific glycated haemoglobin targets set.

KEYWORDS: Type 2 diabetes mellitus, cardiovascular disease, chronic kidney disease, heart failure, glucose-lowering agents ■

cardiovascular and renal protection. We would suggest the addition of either a sodium-glucose co-transporter-2 inhibitor (SGLT-2i) or glucagon-like peptide-1 (GLP-1) receptor agonist with proven evidence of cardiovascular and renal benefit. These agents can also promote weight loss, which would also be beneficial.

However, patient preference and cost effectiveness of medication should be considered when choosing glucose-lowering agents.

We would therefore suggest introducing empagliflozin 10 mg or dapagliflozin 10 mg once daily to his medication and he should have a repeat HbA1c in 3 months to assess the efficacy of treatment as well as monitoring of his renal function.

Discussion: glucose-lowering agents

The level of HbA1c is an estimate of mean blood glucose over a 3 month period.[4] HbA1c targets have been set by different national and international guidelines to determine when to optimise treatment. These targets should be patient centred and treatment individualised to ensure success. This is important because there is evidence showing that if glycaemic control is optimised especially around the time of diagnosis, the effects in preventing microvascular complications can be long lasting.[5]

The choice of glucose-lowering agent used in T2DM is dependent on a number of factors including patient preference, drug efficacy, presence of co-morbidities and side effect profile (eg weight gain or hypoglycaemia).[6] Traditionally, due to the close association of T2DM and obesity, medication that are either weight neutral or those that promote weight loss are preferred (see Table 1 for commonly used glucose-lowering agents).

Reviewing the case illustration, the patient is obese with ASCVD, early stage renal impairment and sub-optimal glycaemic control. Optimising his glucose-lowering medication should factor all these and the most clinical and cost-effective agent should be selected using evidence based medicine.

There is now evidence showing that certain SGLT-2i and GLP-1 receptor agonists have beneficial cardiovascular protection in ASCVD and heart failure (HF) and can reduce the progression of chronic kidney disease (CKD).

Empagliflozin has shown a 38% risk reduction in cardiovascular deaths (reduced hazard ratio (HR) 0.62; 95% confidence interval (CI) 0.49–0.77; p<0.001) in people with T2DM and established ASCVD.[7] Also, canagliflozin demonstrated a reduction in three-point major adverse cardiovascular events (MACE; HR 0.86; 95% CI 0.75–0.99; p=0.02).[8] Furthermore, dapagliflozin was proven to reduce cardiovascular death and hospitalisation due to heart failure (HR 0.83; 95% CI 0.73–0.95; p=0.005).[9] This effect might be related to blood pressure lowering or effects on vascular endothelium as it occurred irrespective of improvement in HbA1c.

It should be noted that there was no significant reduction in cardiovascular death or hospitalisation due to heart failure in patients without established ASCVD. One could argue that if the patient in the illustrated case did not have ASCVD, then a dipeptidyl peptidase-4 inhibitor (DPP-4i) may have been an appropriate addition to his medication.

Furthermore, liraglutide and semaglutide have both shown statistically significant reduction in three-point MACE with the former reducing CV death and the latter reducing non-fatal strokes, respectively.[10,11] Canagliflozin and semaglutide reduce the

Table 1. Common glucose-lowering agents. Data derived from meta-analyses and British National Formulary

Drug class (example)	Glycated haemoglobin reduction	Effect on weight	Side effects	Cardiovascular benefit	Renal benefit	Monthly cost
Biguanide (metformin[a])	0.8–1.0% (9–12 mmol/mol)	Neutral	Gastrointestinal	Yes	N/A	£3.20 or £4.26 modified release
Sulphonylurea (gliclazide, glibenclamide)	0.8–1.1% (9–22 mmol/mol)	Weight gain	Hypoglycaemia	N/A	N/A	£1.63 or £3.27 modified release
Thiazolidinedione (pioglitazone)	0.5–0.7% (6–8 mmol/mol)	Weight gain	Fluid retention Osteoporosis Bladder cancer	No	N/A	£1.84
Dipeptidyl peptidase-4 inhibitors (vildagliptin, sitagliptin, saxagliptin, linagliptin)	0.4% (5 mmol/mol)	Neutral	Cough Nasopharyngitis Pancreatitis	N/A	No	£26.60–£33.26
Sodium-glucose co-transporter-2 inhibitor (canagliflozin,[a] dapagliflozin,[a] empagliflozin,[a] ertugliflozin)	0.4% (5 mmol/mol)	Loss	Urinary tract infections Genital candidiasis	Yes	Yes	£36.59–£39.20
Glucagon-like peptide-1 receptor agonists (dulaglutide,[a] exenatide, liraglutide,[ab] lixisenatide, semaglutide[ab])	0.5–0.7% (6–8 mmol/mol)	Loss	Gastrointestinal Pancreatitis	Yes	Yes	£73.25

[a] = evidence of cardiovascular benefit; [b] = evidence of renal benefit.

development and progression of albuminuria thereby preventing the progression of CKD.[9,11]

However, despite the efficacy of these agents, metformin remains the first-line drug for the management of T2DM. It has been shown to reduce diabetes related deaths; all-cause mortality and the development of myocardial infarction.[12] It is relatively well tolerated, weight neutral and is unlikely to cause hypoglycaemia.

Although there are some instances when its use is not appropriate such as in advanced CKD or intolerance due to gastrointestinal side effects. NICE guidelines then recommend either a DPP-4i, pioglitazone or a sulphonylurea (SU) instead.[13] SGLT-2is are only to be considered if a SU is not tolerated or otherwise inappropriate for the patient and the other option would have been a DPP-4i.

The Scottish Intercollegiate Guidelines Network (SIGN) also have similar recommendations; if metformin is contraindicated they suggest an SU instead.[14] SGLT-2is are only commenced when an SU is not tolerated, this could be a potentially missed opportunity to appropriately commence patients with ASCVD on an SGLT-2i or GLP-1 agonist. They recommend an SGLT-2i as second-line treatment if metformin does not achieve target HbA1c and a GLP-1 agonist as third-line. GLP-1 agonist use may be limited because they are given via subcutaneous injections and cost more than standard oral treatment.

In contrast to NICE and SIGN, ADA and EASD recommend starting treatments with proven efficacy in ASCVD, CKD and HF in at-risk groups sooner.[15] The ADA/EASD guidelines advice metformin as first-line but suggest including an SGLT-2i or GLP-1 even if patients are at HbA1c target. This would involve reviewing patient specific targets to ensure they receive the added cardiovascular and/or renoprotective benefits without compromising their glycaemic control.

Therefore, it may be appropriate to add an SGLT-2i to the case patient's medication even if his HbA1c was 51 mmol/mol (6.8%) due to the cardiovascular and renal benefits conferred. These agents have been shown to be cost effective and would help lessen the economic burden on the NHS in the long term.[16]

We suggest that NICE consider implementing ADA/EASD recommendations to introduce SGLT-2i and GLP-1 agonists sooner in patients with T2DM and ASCVD, CKD or HF when it is appropriate. Rather than focusing on HbA1c targets and optimising treatment only when glycaemic control is above target, patient-specific treatment plans should involve their cardiovascular and renal co-morbidities.

Conclusion

Type 2 diabetes is a complex entity that can be associated with multiple end-organ complications if not adequately managed. Lifestyle modification in the form of reduced carbohydrate intake and increased physical activity is fundamental. However, if glucose-lowering treatment is required, metformin remains the first-line treatment but SGLT-2i or GLP-1 agonists should be instituted early in patients with ASCVD, HF or CKD with patient-specific HbA1c targets set. Using these agents appropriately has been shown to be both clinically and cost effective. ■

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Royal College of Physicians

Complex regional pain syndrome in adults

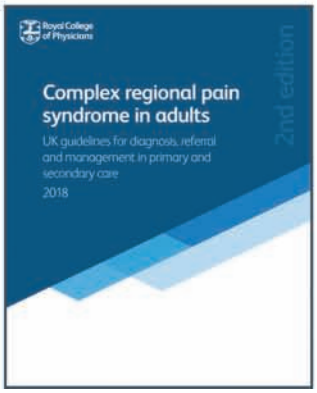
UK guidelines for diagnosis, referral and management in primary and secondary care

Published by the Royal College of Physicians, these guidelines concern the diagnosis and management of patients with complex regional pain syndrome (CRPS). They are designed for professionals working in the different health specialties who care for these patients.

Updated in 2018, and published in partnership with over 20 other medical organisations, the guidelines provide information on diagnosis, treatment, management and support for patients in a wide variety of clinical settings.

The report underlines the need for multidisciplinary support to manage CRPS and outlines the four pillars of care that underpin management:

> education
> pain relief
> physical rehabilitation
> psychological intervention.



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