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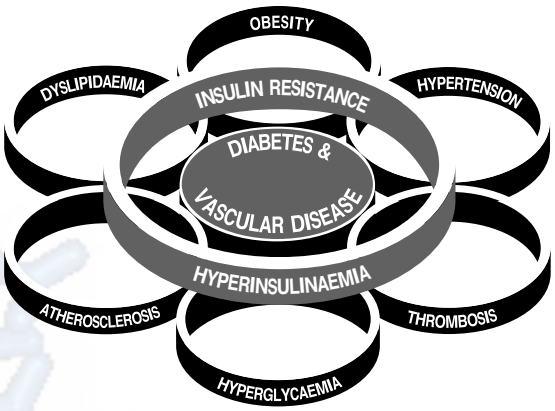

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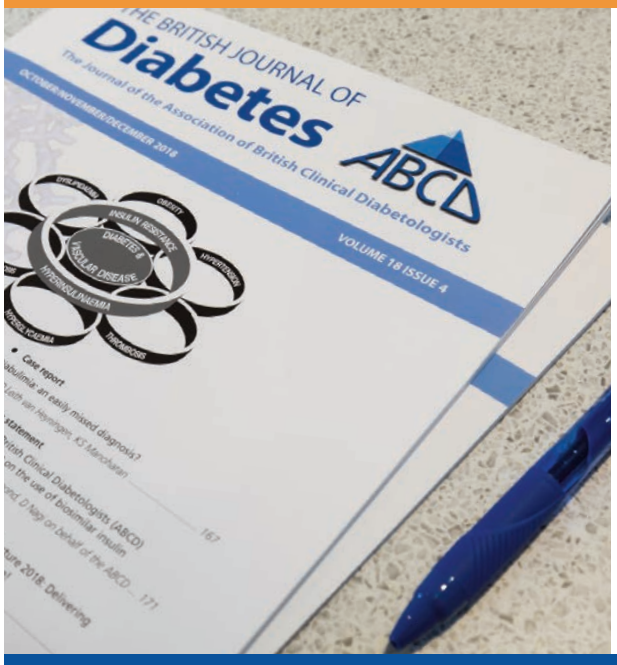

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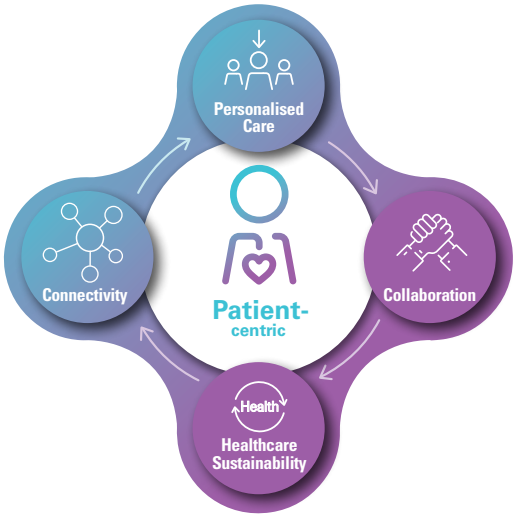

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4. Kulzer et al, 2018; Polonsky et al, 2011; Weissman et al, 2015; Mora et al, 2017
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'Real-world' clinical trials in diabetes care: meaningful or meaningless?

PHILIP HOME

Key words: clinical trials, real-world, diabetes

Abstract

So-called 'real-world' studies seem increasingly popular in diabetes care, as are the economic evaluations in secondary literature based upon them. The term is usually used for pharmacoepidemiological uncontrolled observational studies of different designs. Interpretation of the study findings is, however, badly undermined by the very reasons that the randomised controlled blinded study was invented – namely, non-medication study effects and biases in investigator selection and behaviour. In diabetes studies, glucose control seems particularly susceptible to such effects, perhaps through changes in patient motivation and education. Further, insulin studies are heavily influenced by baseline factors such as the site of starting insulin, the health circumstances of the patient at the time and the clinician involved. It is rare to see these issues adequately addressed or attempts made to understand their influence. In this article an attempt is made to discuss some of the issues further.

Background and need

Recent years have seen the development and introduction of a very welcome myriad of new therapies to aid the management of diabetes. These have included new classes of agents with unique properties (eg, sodium-glucose linked transporter type 2 blockers), derivatives within class with new properties (eg, insulin analogues) and 'me-too' additions within class. The early development pathway is often not well documented, but nearly always ends with published phase 2 and pivotal phase 3 randomised controlled trials (RCTs), sometimes placebo-controlled, sometimes active-controlled (with advantages and disadvantages to both). Where possible, these are double-blinded. The ideas behind the modern medication RCT can be traced back to many writings, amongst them Bernard who advocated blinding, Fisher who was strong on randomisation, and Bradford Hill, the last often credited with drawing together these ideas, and an author on the seminal MRC streptomycin tuberculosis study published in 1948.[1]

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RCTs are, however, not without problems, and the reader might like to reflect why there has never been such a study of stopping smoking for amelioration of heart disease risk (still an unknown) or, indeed, even for reducing lung cancer risk. Of these concerns, the most telling are narrow participant selection and, for safety outcomes, small study size. In many ways these problems come from the same source, namely cost, as providing blinded trial drugs across multiple centres with careful external monitoring and central assessment of outcome measures and central management is expensive. While the population willing to take part in studies may itself be a biased group, the requirements of statistical power with smaller numbers mean that population homogeneity is desirable at entry, a common example in insulin studies being that people with recurrent severe hypoglycaemia are excluded. While in recent years upper age restrictions have largely disappeared, numbers included tend to be relatively small and this approach has not resolved the difficulty in establishing efficacy and safety in, say, older people or some ethnic groups. These problems are often cited as the reason for doing 'real-world' studies, across broader populations unselected for willingness, or access, to join in RCTs.[2]

Terminology

The terminology used in publications of non-RCT studies of medications is often casual. The broad category of studies would be 'observational', but clearly observational studies extend to many areas of medicine beyond efficacy and safety of interventions. Smoking, air pollution, and COVID-19 severity studies are obvious examples. 'Real-world' studies in diabetes are for the most part pharmacoepidemiological (including pharmacoeconomic) studies, although the term is little used. Reference can also be found to 'real-world clinical trials', but the use of 'trials' here is a misnomer, used casually or to mislead the reader, as any kind of trial ('to try') has the requirement of use for the purposes of study, and not use in clinical practice (a 'trial of therapy' is legitimate in clinical practice but is not relevant here).

The term 'real-world' as used here is also misleading. In 'reality' all studies including RCTs exist, and are done in living humans! The impression that seems to be conveyed is that the study represents the use of the medication as it is really used in clinical practice, rather than the limited circumstance of the RCT. However, a reading of nearly all pharmacoepidemiological studies suggests that this is not usually the case. Perhaps coming closest are studies based on electronic clinical records of large swathes of people – for example, based on a large number of UK general practices. But even here the practices contributing

to such databases are not likely to be representative of prescriber or user populations. More commonly, in commercially supported studies there will be selection bias towards prescribers known to the sponsor, and of course then an unknown bias from the investigator/sponsor relationship. Sometimes retrospective criteria are used to try to ameliorate sponsor bias – for example, by stipulating that the participants have already been prescribed the medication in advance of recruitment[3] – but in practice that interval is often so short that the medication can be begun and then study entry delayed for that interval. Bias can then affect the way the medication is used over that time, or for any further duration of prospective data collection – for example, by increased monitoring and contact.

These problems may be partially ameliorated by introducing a random selection element into study centre recruitment, or using a database constructed for unrelated reasons. In one of my own insulin starter studies the sponsor's insulin (basal insulin alone) approach was used by 52% of the total study population, others using competing regimens,[3] but often the population is selected for the specific medication under study.

How do problems of interpretation arise?

Many of the difficulties are simply those which arise from the very reasons blinded, controlled, randomised studies were devised – namely, study effects contaminating the intervention effects. Study effects can be seen in RCTs, but here the effect by virtue of blinding and randomisation are equal (except by play of chance) in the control and active intervention study arms. Thus, statistical comparisons at endpoint, or change from randomisation to endpoint, should reflect the difference between active and control populations alone. It is useful to see here that such non-medication study effects are quite large, larger than any difference arising from the medication per se. Thus, in Figure 1 we see an improvement in HbA_{1c} to a very useful extent with a new insulin, but this is also seen with the control arm insulin.[4] What is telling here is that, prior to randomisation, both populations were being managed with the control arm insulin already (or with a therapy known to give similar HbA_{1c} levels), so the improvement in the control arm, and thus the new intervention arm, must be purely a study participation effect. In the Discussion section of similar studies it is often incorrectly said that glucose control improved with the intervention by n % – all that can really be said is that glucose control improved by n % in the intervention arm, with the emphasis on 'arm' rather than the intervention.

It is not possible to say precisely from these studies what drives the improvement in glucose control. It could, for example, be enhanced patient education, enhanced glucose monitoring or enhanced motivation from taking part in a clinical trial. In an early clinical trial of multiple injection therapy versus pump therapy,[5] the biggest improvement in glucose control came between people agreeing to take part in the study and a screening visit (ie, before any kind of intervention), indicating that even the idea of increased focus on someone's insulin therapy can influence the behaviours improving outcome.

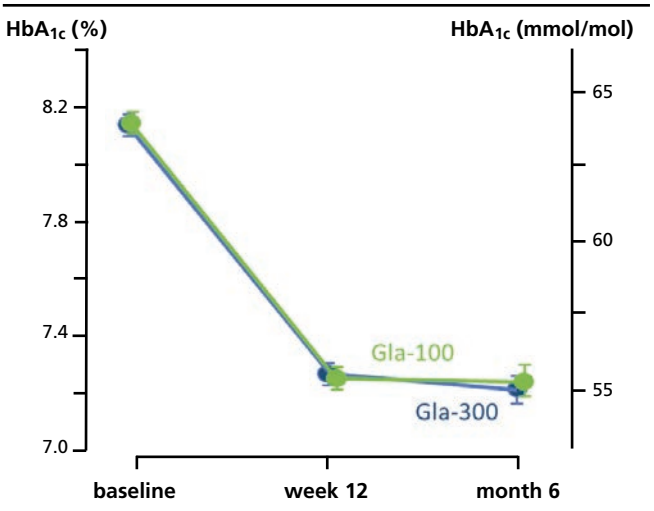

Figure 1. Change in HbA_{1c} in control (Gla-100) and new intervention (Gla-300) arms in people with type 2 diabetes entering a randomised controlled trial, having previously been using a basal plus meal-time insulin regimen. The prior basal insulin was dominantly the same as the basal insulin used in the control arm. After Riddle *et al*, 2014,[4] with permission

Whatever the causes of the effect of being included in any study, they can be large and, indeed, dwarf effects of the therapy itself. In the A1chieve study, of three different insulin analogue regimens, large improvements in glucose control from poor baseline levels in people not previously on insulin were not unexpected – the absolute improvement in control with a new medication is known to correlate with baseline levels.[6,7] But similarly large improvements were seen in people transferred from other insulins, despite controlled trial evidence that HbA_{1c} is difficult to improve with a new insulin regimen. A clue to what is going on was the evidence that body weight did not rise, something that, in the context of big changes in HbA_{1c} and thus marked improvement in glycosuria, strongly suggests positive lifestyle change. Indeed, other surrogate outcomes also improved, notably lipids and blood pressure, and these improvements cannot be attributed to the insulin. Clearly then it was the events surrounding starting the insulin analogue that improved glucose control, and not the analogue itself.

For insulin it is worth thinking about the circumstances under which insulin gets started in anyone with diabetes. Our default thinking is that an insulin starter is someone in our clinics with control above target, often for a little longer than is desirable. But in reality, and the proportions do vary globally, a large percentage of insulin starts occur in other circumstances, notably during hospital admissions when improved control is mandated by a concomitant illness or an imminent procedure, or in ambulatory care after a referral from a non-specialist because of control difficulties (Table 1). In both these scenarios the patient will often not be previously known to the insulin team, and then enhanced diabetes education, improved self-monitoring, and

Table 1 Some problems underlying interpretation and usefulness of pharmacoepidemiological studies in diabetes; these are rarely recorded, adjusted for, or discussed in diabetes real-world studies

Problem area	Examples
Study population biases	
Investigator-related	Prior relationship with sponsor, study funding relationship with sponsor
Study-related	Study halo effect
Patient-related	Activated interest in glucose control, patient education and lifestyle change, enhance self-monitoring
Confounding issues	
Circumstance of starting new therapy	Inpatient emergency, inpatient procedure, concomitant illness, continuing ambulatory care, referral for poor control, referral for injection therapy
Site of starting new therapy	Hospital inpatient, specialist diabetes service, office-based specialist, primary care
Practitioner advising start new therapy	Insulin specialist, diabetes specialist, endocrinologist, diabetes care team, primary health care team.
Outcome and monitoring issues	
Use of diverse laboratories and diverse assays	Biochemical analytes including HbA_{1c}
No adjudication of true health outcomes	Uncertainty over stroke, MI
Poorly recorded health outcomes	Hypoglycaemia in many clinical records and all coding databases
Missing data	True health outcomes (eg, MI) occurring in remote healthcare sites
Therapy-related biases	
Position in glucose-lowering algorithm	Metformin early, insulin late
Guideline use for specific populations	GLP-1RA use if prior CVD, SGLT2 blocker use if HF or CKD progression
Contraindications (actual and historic) and positive indications	Metformin with CKD, advanced HF, liver disease; insulin use in the presence of other complex conditions affecting glucose control

CKD, chronic kidney disease; CVD, cardiovascular disease; GLP-1RA, glucagon-like protein-1 receptor agonist; HF, heart failure; MI, myocardial infarction; SGLT2, sodium-glucose transporter-2.

reasons to self-motivate will be of significance. Accordingly, it would be surprising if there was not improvement in surrogate outcomes, independent of any therapy change. Curiously, in pharmacoepidemiological studies as a whole, and certainly in 'real-world' studies in diabetes, the circumstances under which a new medication is started are very rarely recorded.

Confounding

Confounding is a huge problem in epidemiological studies. Living in proximity to roads is associated with a number of adverse health risks, but of course associates with urban pollution as a whole, poor health education and the problems associated with health deprivation. Too often authors are allowed to get away with some brief statement about association and causation, with no attempt to identify or quantify potential issues. In diabetes pharmacoepidemiological studies other confounders are rife and too often ignored. Particular problems concern metformin, and separately insulin (Table 1).

Metformin has conventionally been used (since 1998) as first-line therapy in a stepped algorithm, and hence usually in people with the shortest diabetes duration. Furthermore, its contraindication to use with renal impairment or with more advanced heart failure and, in some minds, liver disease has meant that it will inevitably be associated with better health in terms of long-term outcomes than other glucose-lowering medications, as indeed is found for comparisons with sulfonylureas and insulin.[8] Insulin, by contrast, is enriched in use in people whose health is compromised by concomitant medical conditions, from myocardial infarction to chemotherapy. The bias effect here is very large; as severe adverse outcomes occur in only a small percent of our populations per year and are predominantly in those with prior health impairment. Accordingly, restricted or enhanced use markedly biases outcome rates even sometimes several-fold. Prescribing bias is obvious in other studies, none more so than a study of the incidence of pancreatitis with and without exposure to glucagon-like peptide-1 (GLP-1) based therapies.[9] In that study the GLP-1 therapy arm had a massively different baseline risk for pancreatitis across a wide range of known risk factors. The findings are uninterpretable.

Again, studies very rarely adequately assess these issues – often only going as far as adjusting by the Charleson Comorbidity Index at best. We know that the risk of severe hypoglycaemia (SH) is markedly increased in people with gastrointestinal, pulmonary and even skin disease.[10] If a study of SH fails to account for these, it is difficult to be confident in any conclusion.

Data quality and health economic analysis

Collection of outcome data, whether surrogate measures or health events, is usually rigorously standardised in RCTs. Thus, HbA_{1c} is measured in a central laboratory, hypoglycaemic events are recorded by electronic diary and confirmed by a standard meter, and true outcomes are adjudicated. In many 'real-world' studies the data are taken from the routine clinical record, with lack of standardisation and uncertainty over such things as to whether a myocardial infarction was robustly diagnosed. Indeed, because the site of diabetes care is often different geographically from the site of, say, a vascular event or an eye procedure, it may be unreliably captured.

Particular problems surround hypoglycaemia. General practice databases are generally of coded events and much outpatient

hypoglycaemia simply goes uncoded. Certainly there is no mapping of grades of hypoglycaemia or its confirmation status to most GP clinical records, and indeed this is poor even in specialist units. At best, all hypoglycaemia information in pharmacoepidemiological studies is to be viewed with caution.

Since health economic analysis depends on ascribing costs to health events (usually as health events saved being the offset for increased medication costs), it will be evident that cost-effectiveness calculations will also be unreliable. In short-term studies, changes in metabolic control (HbA_{1c} and sometimes other measures) have to be modelled to calculate the likely influence on true adverse outcomes over the years going forward – evidently, if the improvement in glucose control is overestimated, so will be the cost benefit. This was seen in a real-world-based analysis of Swedish data, where an HbA_{1c} gain was found in the context of starting insulin degludec and, although modest, would contribute to cost savings from a reduction in modelled long-term complications.[11] To a limited extent, such calculations will be able to estimate the cost-effectiveness of the intervention as a whole (the medication, the education, the self-monitoring, and the motivation) but will not be able to say what the benefit of the medication itself is, if indeed any.

Conclusion and way forward

Presently, it is difficult to see that 'real-world' studies of medications in diabetes care contribute anything usefully generalisable to our practice. Indeed, they are ignored by guideline developers and the health economists that advise them. In time there may be a way forward using true electronic health records given three conditions. Firstly, all the records for each person must be linked from all the different sites and practitioners delivering care; secondly, common definitions should be used for outcomes and measurements should be uniformly standardised; and, thirdly, the circumstances of care interventions (eg, outpatient or admission, professional affiliation of prescriber, referral or continuing care) need be recorded. But this is far from being realised currently. A problem here is that this approach will create a data monster, and it is unclear that statistical techniques yet exist to make all the appropriate adjustments, or whether – even if that is done – the findings will be applicable to the individual people with diabetes we serve.

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Care home diabetes: an important part of community diabetology where high standards of diabetes care are essential

Role of the National Advisory Panel on Care Home Diabetes (NAPCHD)

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Key words: care home, diabetes, quality

Diabetes mellitus affects between one in three and one in four residents of UK care homes and aged-care (long-term care) facilities globally and, apart from dementia, is the commonest disabling disorder in care homes.[1] The phenotype in residents is usually that of a person with type 2 diabetes (it is unclear what proportion of residents have type 1 diabetes) with an often complex co-morbid illness that leads to frailty, loss of independence, disability and reduced survival.[2] In addition, residents with diabetes have a high risk of hypoglycaemia and avoidable hospital admissions, and care homes – similar to the situation in other countries – have been seen as an epicentre of the pandemic in the UK.[3] Their susceptibility appears to be enhanced by a combination of advanced age, the presence of diabetes and the emergence of frailty representing a 'triple jeopardy' state.[4] As such, providing safe and effective care to residents with diabetes is a key challenge to the current care home workforce and, despite published comprehensive and well-received national guidance on care home diabetes more than a decade ago,[5] a large number of care staff have received little or no training and education in even minimal diabetes care. In our view this represents a failure in care provision to the most vulnerable diabetes population. This must be seen as a shared responsibility between all relevant stakeholders, including local authorities who have the legal responsibility for care provision and generally commission care services from external independent providers. However, we also see this as an opportunity for diabetes specialists (both medical and nursing) to take up the baton and make Care Home Diabetes part of their developing field of Community Diabetology, with a commitment to improve standards of diabetes care within institutional and long-term settings.

Whilst most clinical care should be based on the best available evidence, it is clear that, while descriptive and observational studies of residents with diabetes in care are available,[2,6] there is limited information on randomised clinical trials of interventions within care home settings[2] which should be a prompt to funding organisations, major pharma and researchers to take a greater interest in this sector of the diabetes population.[7] The lack of a robust evidence base creates uncertainty in clinical decision-making about what are the safest and most effective glucose-lowering therapies to use in residents with diabetes of varying grades of multi-morbidity and frailty, and what glycaemic targets are appropriate. As a consequence, clinical guidelines on diabetes in older people rely on applying expert advice only, which may be less than satisfactory.[8,9]

A recent review of this area[2] emphasised that the goals of caring for residents with diabetes should evolve around prevention of frailty and disability, risk management and optimising quality of life while preserving functional status with an overall consideration of life expectancy at all levels of intervention. This endorses the principles of the philosophical framework of the Australian McKellar Guidelines on managing diabetes in residential settings.[10] The review[2] concluded that additional resources are required (both public and private) to establish sustainable effective diabetes care within care homes and similar settings including training and upskilling care staff, providing modern equipment for diagnosis and point of care testing (POCT), the modification of facilities to allow for implementing new interventions and undertaking regular audit programmes. This represented a 'Call to Action' to bring about a global improvement in the care of residents with diabetes.

The establishment of the National Advisory Panel on Care Home Diabetes (NAPCHD) in July 2020 by a multi-stakeholder group of organisations (including all major diabetes organisations, Royal College of General Practitioners, Care England, Queen's Nursing Institute, Care Quality Commission, Directors

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of Adults Social Services and other key representatives) was driven by several forces including the need to produce a timely document that is a decade or so on from the 2010 national Diabetes UK care home diabetes guidance. Other drivers included the need for a document that requires a broader representation from all involved stakeholders that have an influence on the nature, quality and delivery of effective diabetes care in the care home sector. In addition, the recent COVID-19 and diabetes care guidance issued by the National Diabetes Stakeholders COVID-19 Response Group (April 2020)[11] revealed the high vulnerability of residents with diabetes, both to infection but also to developing serious acute medical illness. Thirteen key tasks were identified and eight subgroups among the panel members were set up. The work is due to finish in late Autumn 2021. Five key outcomes are hoped for:

1. To develop a national Strategic Document of Diabetes Care for Care Homes that will provide a set of recommendations which, if funded and implemented, will bring about worthwhile, sustainable and effective quality of diabetes care improvements that have a measurable effect on enhancing clinical outcomes, quality of life and wellbeing of all residents with diabetes. This, in principle, would represent a new model of health and social care for residents with diabetes in care homes
2. To bring about a culture change in all health and social care sectors that recognises the urgent need to fund and support the training and education of care staff to enhance their skills and abilities to deliver better quality diabetes care.
3. To bring about measurable but realistic improvements within the care home sector that will enhance the liaison with local laboratory services to enhance diagnosis, monitoring and management.
4. To create a preventative programme that minimises the risk of hospital admission of residents with diabetes.
5. To support a wider use of technology to support diagnosis, monitoring and liaison and networking between relevant community-based services, health and social care professionals and public health

At all times a caring and compassionate workforce supported by community-based health and social professionals will be needed, particularly for those residents with severe frailty and disability and those with diabetes at end of life. We feel it is also time to include Care Home Diabetes on the Specialist Training Curriculum in Diabetes & Endocrinology as part of Community Diabetology, which could be led by ABCD and JBDS-IP working in collaboration to define the learning objectives and training format. Better research, better joined-up thinking between stakeholders and implementation of the NAPCHD work should provide a sound basis for real and consistent improvements in diabetes care delivery within care homes.

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Diabetic kidney disease and pregnancy outcomes: a systematic review

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Abstract

Introduction: We systematically reviewed all relevant literature on diabetic kidney disease (DKD) and pregnancy published in the last 20 years to provide accurate and up-to-date information to inform family planning and maternal care.

Methods: A systematic review was completed in PubMed and Embase. Papers reporting maternal, fetal or renal outcomes of pregnant women with DKD published between 2001 and 2020 were included.

Results: 799 potentially relevant articles were identified, 731 of which were excluded on abstract alone. 68 full-text articles were reviewed and 15 papers were included as they met the selection criteria but were heterogeneous for size, study setting and years studied. The definition of DKD varied between papers and changed over time. 843 women with 873 pregnancies were included. There were high rates of pre-eclampsia and caesarean section, up to 64% and 100% respectively. Prematurity and neonatal intensive care admission were common, reported in up to 100% and 75%, respectively. Maternal and fetal complications were more common with more severe proteinuria and renal impairment. Pregnancy did not hasten progression of DKD.

Discussion: Adverse pregnancy outcomes are frequently encountered and correlate with degree of proteinuria and renal impairment. This information enables individualised risk stratification when a woman is considering pregnancy.

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Key words: diabetes mellitus, pregnancy, diabetic nephropathy, diabetic kidney disease

Introduction

Pre-existing diabetes is common, affecting one in every 250 pregnancies,[1] with diabetic kidney disease (DKD) affecting 2–8% of those.[2] Women with diabetes have poorer pregnancy outcomes compared with healthy women;[1,3] historically, those with DKD have had even worse outcomes, with fetal mortality rates up to 60%.[4] More recently, with advances in diabetes management, obstetric and neonatal care, these outcomes have improved, with fetal survival of 95–99%.[5,6]

Given this relatively high incidence of DKD and the rising prevalence of diabetes,[7] it is critical to have information on DKD in pregnancy. However, our knowledge of DKD and pregnancy is limited. Much of our information comes from case series and single-centre observational studies, often including small numbers of women, spanning many years. The definition of DKD has also evolved, with earlier studies only concerned with macroalbuminuria and more recent studies including microalbuminuria.[5,8]

We reviewed all relevant literature on DKD and pregnancy published in the last 20 years reporting on maternal, fetal and longer term renal outcomes. This systematic review in a modern timeframe aims to give women considering or entering pregnancy and their healthcare professionals the available information on renal, maternal and fetal risks, to allow them to make informed decisions when family planning and improve care during and after pregnancy.

Methods

This systematic review was completed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).[9]

Search strategy

We conducted electronic literature searches in PubMed and Embase. The initial search was carried out in August 2020 and repeated in October 2020.The databases were searched for 'diabetic nephropathy', 'diabetic kidney disease', 'microalbuminuria' AND 'pregnancy'. The search was deliberately broad to increase sensitivity. The reference lists of selected papers were searched for references missed by our search strategy.

Selection criteria

Papers reporting maternal, fetal and/or renal outcomes of pregnant women with DKD published between 2001 and 2020 were included. To reduce publication bias, case reports and series including ≤5 women were excluded. Other exclusion criteria included conference abstracts, papers in languages other than English and pregnancies in women with kidney transplants. If participants were included in more than one report, the larger study was included.

The search was completed in duplicate by SG and SS. They completed the searches independently and matched results. Titles and abstracts were screened by SG and SS. Full texts were assessed by SG. Discrepancies were resolved by discussion.

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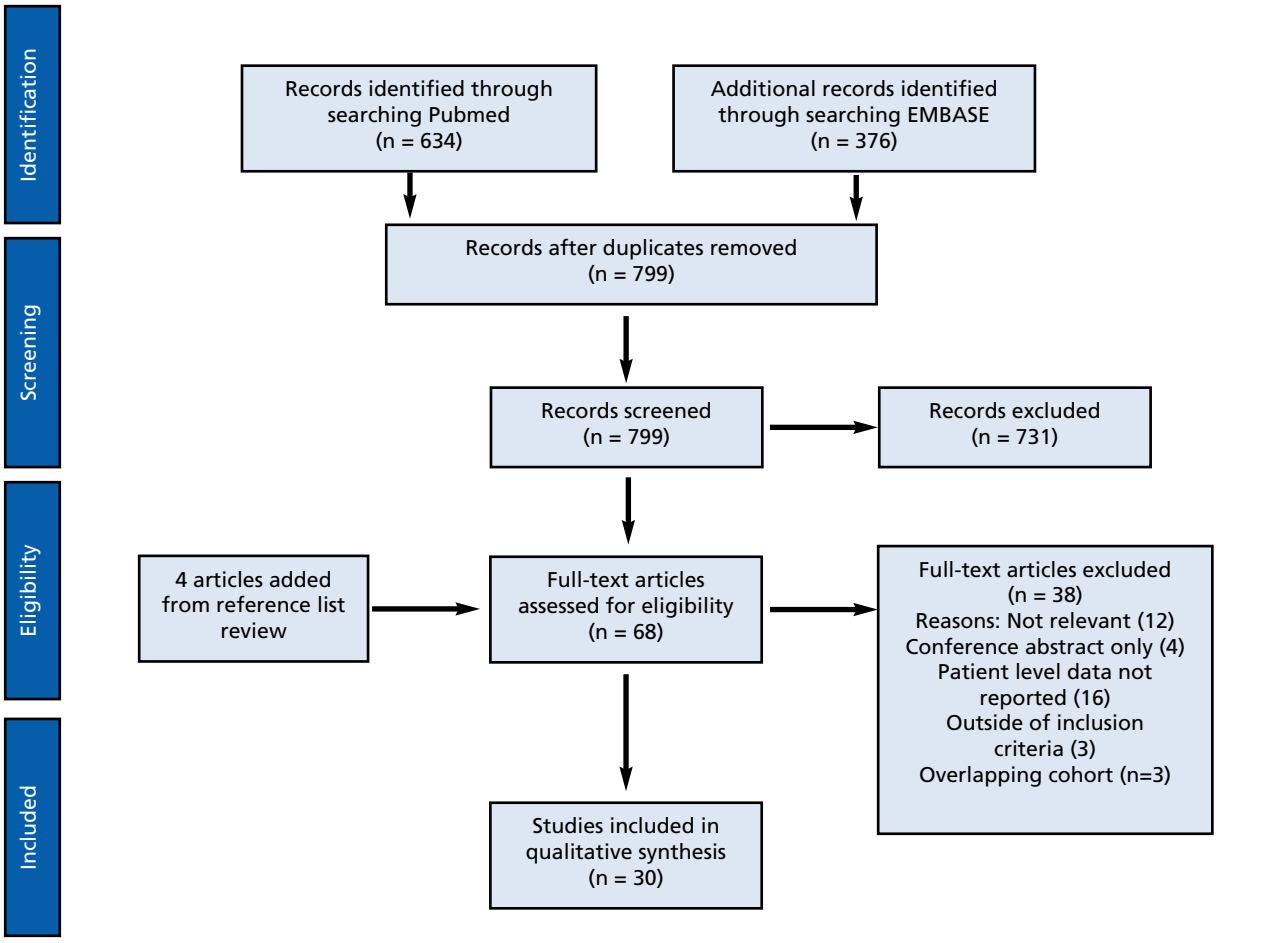
Figure 1. Study selection



Data collection and analysis

The data were analysed according to PICOS criteria as follows. The patients (P) were women with DKD. The intervention (I) was considered to be pregnancy, in the absence of an actual therapeutic intervention. The control (C) groups included healthy or women without DKD who were pregnant or women with DKD without pregnancy. The outcomes (O) studied were maternal, fetal and renal outcomes. The studies (S) were all studies reporting on pregnancy outcomes in women with DKD. As the data were expected to be heterogeneous, a narrative review of the results was planned.

Due to the lack of randomised controlled trials and the limited number and variability of control groups, no formal analysis of bias was performed.

Results

Study selection and general information (Table 1)

A total of 799 potentially relevant articles were identified after excluding duplicates. Of these, 731 were excluded after reviewing the abstract and 68 full-text articles were reviewed. Fifteen papers met the selection criteria and were included (Figure 1), 10 of which were retrospective studies and five were prospective. The studies were heterogeneous for size, study setting and years studied, ranging from 1988 to 2014. The majority were single-centre studies. Six studies included more than 50 women. The papers were from a range of countries including Denmark, Italy, UK, USA, Brazil, Israel and New Zealand. European countries, in particular Denmark, were the main source of data. Baseline characteristics were often inadequately described and varied between papers. The definitions of DKD varied widely and changed over time, with more recent studies including microalbuminuria (most commonly a urinary albumin of 30–299 mg/24 hours) and earlier studies including only 'overt' diabetic nephropathy: macroalbuminuria or macroproteinuria (typically more than 300–500 mg/24 hours proteinuria). One study divided participants into subgroups based on their renal function[10] and four divided them into subgroups based on micro- or macroalbuminuria.[11–14] Seven studies included controls, either diabetic or non-diabetic pregnant women or women with DKD who did not have a pregnancy. Study heterogeneity was significant, precluding the pooling of data and meta-analysis.

Baseline characteristics (Table 2)

Overall, this systematic review collected data on 843 women

Table 1. General information on studies

	Type	Years	Country	Aim	Definitions	Subgroups	Women	Pregnancies	Controls
Reece, 1990[19]	Retrospective	1970–1985	USA	To examine the effect of pregnancy on the rate of progression of DN	300 mg/day prior to 3rd trimester	NA	10	11	NA
Combs, 1993[20]	Retrospective	1982–1991	USA	To examine if pre-eclampsia in diabetic mothers is increased in incipient as well as overt nephropathy	>500 mg proteinuria/day	NA	62	62	No nephropathy Proteinuria 190–499 mg/24h
Hod, 1995[21]	Prospective	1990–1993	Israel	To examine whether treatment with ACE inhibitor pre-pregnancy improves pregnancy outcomes	>500 mg proteinuria/day	NA	8	8	NA
Kimmerle, 1995[4]	Retrospective	1982–1992	Germany	To study the effect of DKD on pregnancy and perinatal outcome, infant development and long-term function	>400 mg proteinuria/24h	Preserved renal function (CrCl >80 mL/min) Without preserved renal function (CrCl <80 mL/min)	Overall cohort 33	Overall cohort 40	110 in diabetic women without nephropathy
Gordon, 1996[22]	Retrospective	1988–1994	USA	To determine outcomes in pregnancies complicated by DN (white class F)	>400 mg/24h or CrCl <90 mL/min	NA	51	51	NA
Kaaja, 1996[23]	Prospective	1983–1985	Finland	To establish whether pregnancy affects long-term development and progression of retinopathy and nephropathy in diabetic women	White class F (CrCl >100 mL/min, creatinine <90 µmol/L	NA	6	9	4 women with DN without pregnancy
Mackie, 1996[10]	Retrospective	1985–1993	UK	To examine the effect of pregnancy on maternal renal function in women with DN	>500 mg/24h protein	Moderate renal impairment (serum creatinine >125 mmol/L) Mild renal impairment (serum creatinine <125 mmol/L)	6 12	11 13	NA
Miodovnik, 1996[24]	Prospective	1978–1991	USA	To examine whether pregnancy increases the risk of or accelerates the progression of DN	>500 mg/day proteinuria	NA	56	56	Diabetic pregnant women without nephropathy
Purdy, 1996[25]	Retrospective	1981–1993	USA	To determine whether pregnancy worsens renal function in women with DN and moderate-to-severe renal insufficiency	Serum creatinine >124 mmol/L	NA	11	11	11 women with similar renal function without pregnancy
Zhu, 1997[26]	Retrospective	1984–1996	Japan	To evaluate the outcomes of pregnancies complicated with diabetes mellitus	NR	NA	10	10	Pregnancies in women with diabetes without nephropathy
Reece, 1998[27]	Retrospective	1984–1990	USA	To report their 10-year experience in caring for patients with DN	>300 mg albumin or protein/24h	NA	27	27	NA
Bar, 1999[28]	Prospective	1990–1995	Israel	To examine the effect of pre-pregnancy captopril on renal function and on fetal-maternal outcome in DN	Proteinuria >500 mg/day	NA	24	24	NA
Biesenbach, 1999[11]	Retrospective	1982–1996	Austria	To evaluate the impact of pregnancy on the course of renal function in women with overt DN	Macroproteinuria >0.5 g protein-uria/24h	Increase in creatinine clearance during 1st two trimesters of pregnancy No increase in CrCl	12 5 7	14 6 8	NA
Dunne, 1999[29]	Retrospective	1990–1997	UK	To examine fetal/maternal outcomes in women with DN	>300 mg/24h or >1+ x 3	NA	18	21	NA
Biesenbach, 2000[30]	Retrospective	1985–1993	Austria	To evaluate perinatal complications and follow-up of infants of mothers with DN stage IV	500 mg/24h proteinuria	NA	10	10	NA
Ekbom, 2001[14]	Prospective	1996–2000	Denmark	Pregnancy outcome in T1 diabetic women with microalbuminuria	DKD >300 mg/24h Microalbuminuria 30–300 mg/24h	Microalbuminuria DN	26 11	26 11	Diabetic women with no microalbuminuria

Table 1. General information on studies (continued)

	Type	Years	Country	Aim	Definitions	Subgroups	Women	Pregnancies	Controls
Khoury, 2002[9]	Retrospective	NR	USA	To examine the association of renal function with maternal and fetal pregnancy outcome in women with DN	DN: proteinuria >500 mg/24h	Cr <1 mg/dL Cr 1–1.5 mg/dL Cr >1.5 mg/dL	58 (total cohort)	72 (total cohort) 49 13 10	NA
Rossing, 2002[18]	Retrospective	1970–1989	Denmark	To examine the long-term impact of pregnancy on the progression of DN	Albuminuria >300 mg/24h	NA	26	31	67 women without pregnancies
Bagg, 2003[31]	Prospective	1985–2000	New Zealand	To describe long-term maternal outcome after pregnancy in women with DN	>300 mg/24h albuminuria	NA	14	24	NA
Carr, 2006[7]	Retrospective	1986–2002	USA	To evaluate if hypertension in early pregnancy is associated with adverse perinatal outcome in women with DN	Proteinuria >0.3 g/24h	Above target BP (MAP >100 mmHg) Below target (MAP <100 mmHg)	43 22 21	43 22 21	NA
Nielson, 2006[32]	Retrospective	1995–2003	Denmark	To describe the impact of aggressive antihypertensive treatment in the prevalence of preterm delivery in women with DM	Albuminuria 30–300 mg/24h	1995–1999 2000–2003	26 20	26 20	NA
Nielsen, 2009[12]	Prospective	2004–2006	Denmark	To describe outcomes in microalbuminuria or DN after intensified anti-hypertensive therapy	DN: >300 mg albumin/24h Microalbuminuria: 30–299 mg albumin/24h	DN Microalbuminuria	7 10	7 10	100 women with normoalbuminuria 25 healthy pregnant women
Yogev, 2009[33]	Retrospective	2000–2007	Israel	To examine the factors associated with pregnancy complications in women with type 1 diabetes and DN	Protein 300 mg/24h pre or early pregnancy or serum creatinine >1.5	Non-complicated pregnancy Complicated pregnancy	15 31	15 31	NA
Jensen, 2010[34]	Prospective	1993–1999	Denmark	To describe microalbuminuria, pre-eclampsia, and preterm delivery in pregnant women with type 1 diabetes on a national level	Albuminuria 30–300 mg/24h	NA	84	84	Pregnant diabetic women without albuminuria
Bell, 2012[17]	Population-based cohort	1996–2008	UK	To quantify the risk of major congenital anomaly and to assess the influence of various risk factors including DN	Not reported	NA	60	60	Women with pregnancies complicated by congenital malformations without DN
Young, 2012[35]	Prospective	2010–2011	Brazil	To examine the effect of pregnancy on DN and the perinatal outcomes of diabetic pregnancies	Albuminuria >30 mg/24h	NA	11	11	32 pregnancies in diabetic women without DN
Damm, 2013[5]	Retrospective	2007–2012	Denmark	To evaluate the prevalence of DN and microalbuminuria in pregnant women with type 2 diabetes in comparison with type 1 diabetes and to describe pregnancy outcomes	Nephropathy: ACR >300 mg/g Microalbuminuria: ACR 30–299 mg/g	T2 nephropathy T1 nephropathy T2 microalbuminuria T1 microalbuminuria	5 11 10 15	5 11 10 15	NA
Piccoli, 2013[15]	Retrospective	2000–2012	Italy	To evaluate maternal and fetal outcomes in severe DN	Severe nephropathy: referred to nephrology clinic from diabetes in pregnancy clinic	NA	11	12	NA
Klemetti, 2015[16]	Retrospective	1988–2011	Finland	To analyse temporal changes in the glycaemic control, BP levels, markers of renal function as and perinatal outcomes of a population-based cohort of women with DN	Proteinuria >0.3 g/24h or dipstick 1+	1988–1999 2000–2011	65 43	65 43	NA
Seah, 2020[13]	Retrospective	2004–2014	Australia	Association between maternal renal function and pregnancy outcomes in type 1 and type 2 diabetes	Microalbuminuria: 3–300 mg/day or ACR of 3.4–35 Macroalbuminuria: >300 mg/day or ACR >35	Microalbuminuria Macroalbuminuria	198 with diabetes Number with nephropathy NR		119 pregnancies in healthy women

DN, diabetic nephropathy; Cr, creatinine

Table 2 Baseline characteristics

	Age	Ethnicity	Duration of diabetes (years)	Hypertension (%)	Retinopathy (%)	Baseline creatinine	Type of diabetes	Baseline HbA_{1c} (%)	Baseline proteinuria	Baseline eGFR (ml/min) or CrCl (ml/min)	Nulliparity (%)
Reece, 1990[19]	30	NR	NR	91	100	1.3 mg/dL			2.5 g/24h	NR	NR
Combs, 1993[20]	27.3	NR	14.3	39	37	0.91	T1	9.0	NR	56	NR
Hod, 1995[21]	25.6	NR	15.6	NR	37.5	0.8 mg/dL	T1	7.9	273 mg/24h	114	NR
Kimmerle, 1995[4]	29	NR	20	61	65	NR	NR	NR	2.1 g/24h	NR	NR
Gordon, 1996[22]	25.5	76% white	15	27	53	0.8	T1	NR	1.74 g /24	120	64
Kaaja, 1996[23]	35.5		21.7	11%	NR	NR	NR	NR	NR	NR	NR
Mackie, 1996[10]		NR			NR		NR	NR		NR	NR
Moderate renal impairment	30.5		17	16.6		160			3.8 g/24h		
Mild renal impairment	NR		NR	NR		NR			NR		
Miodovnik, 1996[24]	25.5	NR	14.7	40.8	39.2	NR	NR	9.8%	NR	NR	32
Purdy, 1996[25]	29	Mainly white	20	NR	NR	159	NR	NR	2.4 g/24h	NR	NR
Zhu, 1997[26]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Reece, 1998[27]	27		16.4	77	89	NR	NR	NR	NR	NR	NR
Bar, 1999[28]	26	NR	NR	46	37.5	0.82 mg/dL	T1	7.9	202 mg/24h	NR	NR
Biesenbach, 1999[11]	29	NR	18	NR	NR	111	NR	8.0	1.7	69	NR
	28	NR	17			96		8			
	29		20			122		8	1.1 g/24h	80	
									2.2 g/24h	61	
Dunne, 1999[29]	26.5	NR	19.5	11	NR	88.3	T1	9.7	NR	NR	NR
Biesenbach, 2000[30]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ekbom, 2001[14]		NR		NR		NR	T1			NR	
DN	29		19		77			8.1	69 mg/24h		50
Microalbuminuria	30		16		100			8.8	1120		55
Khoury, 2002[9]						NR					
Cr <1 mg/dL	26.3	14.3% black	15.4	12.2	24.5		T1	9.9	800 mg/24h	87.8 mL/min	51
Cr 1–1.5 mg/dL	28.3	0% black	16.5	69.2	46.2		T1	9.5	1796	79.2	61.5
Cr >1.5 mg/dL	29.0	30% black	15.6	90	80		T1	8.9	1606	41.5	60
Rossing, 2002[18]	24	NR	14	NR	NR	79 mmol/L	T1	NR	534 mg/24h	NR	NR
Bagg, 2003[31]	30	NR	18.5	NR	NR	0.07 mmol/L	T1 and T2	NR	NR	NR	NR
Carr, 2006[7]							T1				NR
Above target BP (MAP >100 mmHg)	29.5		16	59.1	63.6	0.85 mg/dL		8.1	1.65 g/24h	135.9 mL/min	
Below target (MAP <100 mmHg)	27.2		17.5	85.7	85.7	1.23 mg/dL		8	4.69	90.2 mL/min	
Nielson, 2006[32]		NR		NR	NR	NR	T1	NR		NR	NR
1995–1999	19		6.7						69 mg/24h		
2000–2003	18		6.8						74		
Nielsen, 2009[12]		NR					T1			NR	NR
Diabetic nephropathy	30		20	100	100	57		6.5	690 mg/24h		
Microalbuminuria	31		14	50	50	51		6.9	91		
Yogev, 2009[33]		NR					T1			NR	NR
Non-complicated pregnancy	31.8		18	80	53	1.08		7.1	53% none, 47% <20 mg/24h		
Complicated pregnancy	31.2		19.7	89	32	1.11		7.5	74% none, 13% <20 mg/24h, 6.5% 20–300 mg/24h, 6.5% >300 mg/24h		
Jensen, 2010[34]	27	NR	15	13	11	NR	T1	7.6	NR	68	NR
Bell, 2012[17]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Young, 2012[35]	28.3	45% Caucasian	12	72.7	54.6	0.8 mg/dL	81.2% T1	8.5	119 mg/24h	81 mL/min	27%
Damm, 2013[5]		NR							ACR	NR	
Type 2 DN	31		2	0	75	52	T2	6.8	474 mg/mol		50
Type 1 DN	32		19	64	56	61	T1	7	712		45
T2 microalbuminuria	31		2	0	20	40	T2	6.8	110		30
T1 microalbuminuria	31		22	60	85	51	T1	7.1	84. 5		67
Piccoli, 2013[15]	34.3	NR	22.6	66%	100%	0.98 mg/dL	T1	8.01%	1.6 g/24h	67 mL/min	NR
Klemetti, 2015[16]		NR									
1988–1999 group	29		19	34.4	50.8	82 µmol/L	T1	66 mmol/mol	1.5 g/24h	1.12	46.2
2000–2011 group	31		24	65.1	65.1	68 µmol/L	T1	69	0.8	1.74	60.5
Seah, 2020[13]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

DN, diabetic nephropathy; Cr, creatinine; NR, not reported.

with DKD experiencing 873 pregnancies. The mean age ranged from 24 to 34 years and the mean duration of diabetes ranged from 2 years (in two subgroups with type 2 diabetes)[11] to 22.6 years.[15] Where reported, both pre-pregnancy hypertension and retinopathy ranged from 11% in a cohort with microalbuminuria to 100% in women with overt proteinuria. Across the studies, 27–67% of women were nulliparous. Values for baseline creatinine, estimated glomerular filtration rate (eGFR) or creatinine clearance, proteinuria or albuminuria and HBA_{1c} were given either pre-pregnancy or in early pregnancy. One paper[16] divided its study participants into subgroups based on whether they had a complicated or uncomplicated pregnancy. These results are included in Tables 1–5 but have been excluded from the analysis below.

Maternal outcomes (Table 3)

There were high rates of pre-eclampsia and caesarean section, especially in those with impaired renal function, more severe proteinuria or both. Pre-eclampsia was commonly reported, ranging from 0%[12] in one subgroup of 10 women with microalbuminuria to 64% (IQR 33.3–42.5%);[17] compared to healthy women, women with diabetic kidney disease were more likely to develop pre-eclampsia (OR 5.5 (2.5 to 11.8)).[13] One study which included diabetic women without albuminuria, with microalbuminuria and macroalbuminuria reported pre-eclampsia in 6%, 42% and 64%, respectively.[14] Caesarean section was the most common method of delivery, ranging from 20% to 100% (IQR 69.2–90.0). No papers reported maternal death. One paper reported requirement for renal replacement therapy in one of 108 pregnancies.[18]

Fetal outcomes (Table 4)

The mean gestational age ranged from 32.5 weeks in a cohort with heavy proteinuria and impaired renal function[15] to 37.7 weeks in a subgroup with microalbuminuria (IQR 35.6–37.0).[12] The majority of births reported were premature, ranging from 20% in a subgroup with microalbuminuria[12] to 100% in a cohort with heavy proteinuria and impaired renal function (IQR 43.5–73.9).[15] Compared with healthy women, DKD was associated with premature delivery (microalbuminuria OR 3.9 (1.5 to 9.90), macroalbuminuria OR 3.9 (1.5 to 9.9)).[13] One study which included diabetic women with no albuminuria, with microalbuminuria and macroalbuminuria reported premature delivery in 35%, 62% and 91%, respectively.[12] Very premature births, variably reported as before 32 or 34 weeks, occurred in 0–46% of births (IQR 9.4–38.6). Compared with healthy women, DKD was associated with very premature delivery (OR 4.2 (1.9 to 9.5)).[13] The mean birth weight reported ranged from 1880 g to 3430 g. The 1880 g occurred in a subgroup with moderately impaired renal function and significant proteinuria[5] and the 3430 g occurred in a subgroup with microalbuminuria only.[12] The ranges for small for gestational age (SGA), where the neonate weighed less than the 10th centile for gestation, and large for gestational age (LGA), where the neonate weighed more than the 90th centile corrected for gestation, varied widely between the studies and were inconsistently reported. The IQR for SGA was 7.7–30.1% and for LGA was 9.1–33%. One study which included diabetic women with no albuminuria, with microalbuminuria and macroalbuminuria reported rates of SGA in 2%, 4% and 45%, respectively.[12] Neonatal intensive care unit (NICU) admission was common, reported in 26.2–75% of births (IQR 41.3–66.8), increased compared with women without DKD (OR 2.4 (1.2 to 4.6)).[13] Congenital abnormalities and perinatal deaths were uncommon, reported in 0–14% (IQR 0–9.2) and 0–14.2% (IQR 0–9.6), respectively. One study found that diabetic nephropathy (not further characterised) was associated with congenital abnormalities with an adjusted OR of 2.45 (1.14 to 5.25).[19]

Overall higher rates of prematurity, SGA and NICU admissions were noted in the groups with overt proteinuria and impaired renal function than in those with microalbuminuria or normal renal function. Rates were highest where both severe proteinuria and impaired renal function were present.

Blood pressure control

A number of studies designed to assess the impact of blood pressure on pregnancy outcomes were included. One observational study divided their cohort into two subgroups; one group had a mean arterial blood pressure (MAP) below a target of 100 mmHg and the other had a MAP of >100 mmHg.[5] They reported better maternal outcomes (27.3% pre-eclampsia versus 42%) and fetal outcomes (mean gestation 35.1 weeks versus 32.1 weeks) in the target MAP group.[5] Two further studies[12,20] reported an improvement in maternal and fetal outcomes with more intensive control of hypertension.

Renal outcomes (Table 5)

Only two of the papers published in the last 20 years reported on longer term renal outcomes. One paper, which followed 14 women with albuminuria >300 mg at the time of pregnancy for a mean of 6 years, reported 36% reached end-stage renal failure in that time. There was no control group.[21] The other paper followed 26 women with diabetic nephropathy who had pregnancies and 67 women with diabetic nephropathy without pregnancies for 10 years. The outcomes were similar in both groups, with a slightly higher incidence of end-stage renal failure in the group without pregnancy.[22]

Discussion

This systematic review of pregnancy outcomes and DKD showed that most women were relatively young, nulliparous and had a long duration of diabetes, usually type 1. There were high rates of maternal and fetal complications and these were more common in women with macroalbuminuria or impaired renal function. For comparison, in the general population pre-eclampsia affects 5% of women, 7.3% of babies arrive preterm (prior to 37 weeks),[23] 77% of birth weights are >3000 g[24] and 10.9–14.5% of babies are admitted to the NICU.[25] This review highlights high rates of Caesarean section in women with DKD. Women with diabetes already have higher rates of Caesarean

Table 3 Maternal outcomes

	Pre-eclampsia (%)	Caesarean section (%)	Maternal deaths (%)	Dialysis during pregnancy (%)	Miscarriage (%)	Abortion (%)
Reece, 1990[19]	NR	NR	NR	NR	Ex	Ex
Combs, 1993[20]	47	NR	NR	NR	Ex	Ex
Hod, 1995[21]	38	75	0	0	Ex	Ex
Kimmerle, 1995[4]	NR		NR	NR	0	10
Preserved renal function		80				
Non–preserved renal function		100				
Gordon, 1996[22]	53	80	NR	NR	7.8	3.9
Kaaja, 1996[23]	NR	NR	NR	NR	NR	NR
Mackie, 1996[10]	NR		NR	NR		
Moderate renal impairment		100			27	9
Mild renal impairment		100			0	7
Miodovnik, 1996[24]	76	76	NR	NR	Ex	Ex
Purdy, 1996[25]	NR	NR	NR	NR	NR	NR
Zhu, 1997[26]	40	90	NR	NR	NR	NR
Reece, 1998[27]	53	63	NR	NR	NR	NR
Bar, 1999[28]	46	62.5	NR	NR	Ex	Ex
Biesenbach, 1999[11]	57.1	50	NR	NR	Ex	Ex
Dunne, 1999[29]	50	90.5	NR	NR	Ex	Ex
Biesenbach, 2000[30]	60	60	NR	NR	NR	NR
Ekbom, 2001[14]		NR	NR	NR	NR	NR
DN	42					
Microalbuminuria	64					
Khoury, 2002[9]			0	0		NR
Cr <1 mg/dL	41	76.9			49	
Cr 1–1.5 mg/dL	33.3	91.7			13	
Cr >1.5 mg/dL	44.4	88.9			10%	
Rossing, 2002[18]	41	38.7	0	0	Ex	Ex
Bagg, 2003[31]	NR	83	NR	NR	NR	NR
Carr, 2006[7]			0	0	Ex	Ex
Above target BP (MAP >100 mmHg)	27.3	63.4				
Below target (MAP <100 mmHg)	42.9	76.2				
Nielson, 2006[32]	42	20				
Nielsen, 2009[12]		NR	NR	NR	Ex	Ex
Diabetic nephropathy	43					
Microalbuminuria	0					
Yogev, 2009[33]	NR		NR	NR		0
Non-complicated pregnancy		67			0	
Complicated pregnancy		78			10	
Jensen, 2010[34]	41	NR	NR	NR	Ex	Ex
Bell, 2012[17]	NR	NR	NR	NR	x	NR
Young, 2012[35]	63.6	NR	0	NR	Ex	Ex
Damm, 2013[5]			NR		Ex	Ex
Type 2 DN	40	60		0		
Type 1 DN	36	91		0		
T2 microalbuminuria	10	80		0		
T1 microalbuminuria	20	80		0		
Piccoli, 2013[15]	NR	75%	0	0	Ex	Ex
Klemetti, 2015[16]			NR		Excluded	Excluded
1988–1999 group	52.3	100		1%		
2000–2011 group	41.9	92.9				
Seah, 2020[13]		NR	NR	NR	Ex	Ex
Microalbuminuria	OR 5.7 (1.8 to 17.8)					
Macroalbuminuria	OR 5.5 (2.5 to 11.8)					

Cr, creatinine; DN, diabetic nephropathy; Ex, excluded; NR, not reported.

Table 4. Fetal outcomes

	Mean gestation (weeks)	Preterm delivery (%)	Very preterm delivery <34 weeks (%)	Weight (g)	SGA (%)	LGA (%)	NICU admission (%)	RDS (%)	IUD/ perinatal mortality (%)	Congenital abnormality (%)
Reece, 1990[19]	36.3	NR	NR	2557	NR	NR	NR	NR	0	0
Combs, 1993[20]	35.2	60	23	2788	NR	NR	NR	NR	NR	NR
Hod, 1995[21]	37	13	NR	2998	21.5	25	Nr	NR	0	0
Kimmerle, 1995[4]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Gordon, 1996[22]	35.8	NR	15.5	2623	11	NR	89	NR	0	4
Kaaja, 1996[23]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mackie, 1996[19]		86	NR					NR	NR	
Moderate renal impairment	31			1970	14	14	100			14
Mild renal impairment	36			2600	8	8	42			0
Miodovnik, 1996[24]		57%	22	2745	9	22	NR	20	9	11
Purdy, 1996[25]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Zhu, 1997[26]	35.3	60	NR	2247	NR	NR	NR	NR	NR	NR
Reece, 1998[27]		26	NR	2687	9	NR	NR	NR	5	9
Bar, 1999[28]	NR	17	NR	2998	21	NR	4.2	NR	4.2	
Biesenbach, 1999[11]	34		64.2	1893	64.2	0	NR	21.4	14.2	7.1
Dunne, 1999[29]	NR	57.2	NR	2429	14	9.5	57.2	nr	9.5	4.7
Biesenbach, 2000[30]	36.3	NR	60	2250	50	0	NR	NR	10	NR
Ekbom, 2001[14]	NR					NR	NR	NR		
DN		62	23	3124	4				4	4
Microalbuminuria		91	45	2235	45				0	9
Khoury, 2002[9]		NR	<32 weeks	NR			NR			
Cr <1 mg/dL	35.7		7.7		7.7	12.8		15.4	5.1	12.9
Cr 1–1.5 mg/dL	34.3		16.7		8.3	0		41.7	0	0
Cr >1.5 mg/dL	33.3		44.4		33.3	33		33	11.1	0
Rossing, 2002[18]	37	NR	NR	2535	NR	NR	NR	NR	9.7	9.7
Bagg, 2003[31]	36		<35 weeks 46%	2950			75			12.5
Carr, 2006[7]			<32 weeks			NR	NR	NR		NR
Above target BP (MAP >100 mmHg)	35.1		4.6	2520	9.1				9.1	
Below target (MAP <100 mmHg)	32.8		38.1	1880	28.6				9.5	
Nielson, 2006[32]					NR	NR	NR	NR		
1995–1999	250 days	62	23	3124					4	4
2000–2003	259 days	40	0	3279					0	0
Nielsen, 2009[12]							NR	NR		
Diabetic nephropathy	258 days	71	14	2765	29	14			0	0
Microalbuminuria	264 days	20	0	3430	0	5			0	0
Yogev, 2009[33]			NR					NR		NR
Non-complicated pregnancy	37.8	0		3223	0	0	0		0	
Complicated pregnancy	32.4	32		3187	7	57	46		6	
Jensen, 2010[34]	260 days	36	16	3335	NR	50	NR	19	5	NR
Bell, 2012[17]	NR	NR	NR	NR	NR	NR	NR	NR	NR	Unadjusted OR 2.78 (1.37 to 5.64) Adjusted OR 2.45 (1.14 to 5.25)
Young, 2012[35]	36	63.6	NR	2710	40	9.1	NR	NR	0	20
Damm, 2013[5]								NR	NR	NR
Type 2 DN	250 days	60	40	2460	40	0	60			
Type 1 DN	249 days	82	27	2506	36	18	64			
T2 microalbuminuria	260 days	30	10	3355	20	30	44			
T1 microalbuminuria	259 days	47	7	3229	7	53	33			
Piccoli, 2013[15]	32.5	100	58	1919	7.6	NR	85	NR	20	0
Klemetti, 2015[16]			<32 weeks							
1988–1999 group	254 days	70.8	13.8	2978	15.4	35.4	26.2		4.6	9.5% of total cohort
2000–2011 group	246 days	76.7	20.9	2694	23.3	27.9	48.8		4.7	
Seah, 2020[13]	NR			NR	NR	NR	–	NR	NR	NR
Microalbuminuria group		OR 3.9 (1.5 to 9.9)								
Macroalbuminuria group		OR 3.5 (1.6 to 7.7)	OR 4.2 (1.9 to 9.5)				OR 2.4 (1.2 to 4.6)			

Cr, creatinine; DN, diabetic nephropathy; LGA, large for gestational age; NICU, neonatal intensive care unit; NR, not reported; RDS, respiratory distress syndrome; SGA, small for gestational age.

Table 5 Long-term renal outcomes

	Follow-up post delivery	Worsening proteinuria	Worsening renal function	Doubling creatinine	Mean eGFR decline/year	ESRF
Reece, 1990[19]	29 months	27%	27%	9%	0	0
Combs, 1993[20]	NR	NR	NR	NR	NR	NR
Hod, 1995[21]	NR	NR	NR	NR	NR	NR
Kimmerle, 1995[4]	NR	NR	NR	NR	NR	NR
Gordon, 1996[22] Subgroup <1 g proteinuria and CrCl >90 mL/min	2.8 years	No difference between groups	NR	NR	15.6 mL/min decline/year 6.6 mL/min vs 18.9 for rest of cohort	8.5%
Kaaja, 1996[23] With pregnancy Without pregnancy	5–9 years	 4/6 3/4	 2/6 1/4	NR	NR	 1/6 1/4
Mackie, 1996[10] Moderate renal impairment group (n=6) Preserved renal function (n=11)	6 months–8 years	NR	 50% (3) 9% (1)	NR	NR	 50% (3) 9% (1)
Miodovnik, 1996[24] Controls (diabetes and pregnancy, no DN)	9.5 years 9.1 years	NR	NR	NR	8–10 mL/year	26% 0.7%
Purdy, 1996[25]	35–138 months	82%	45%	NR	NR	6%
Zhu, 1997[26]	NR	NR	NR	NR	NR	NR
Reece, 1998[2]	NR	NR	NR	NR	NR	NR
Bar, 1999[28]	2 years	NR	0	0	NR	Nil
Biesenbach, 1999[11] Low clearance group Normal clearance group	6 months	 2.2 g/24 h to 2.8 g/24 h No change	 87% 0%	 61 mL/min to 38 mL/min 80 mL/min to 9 mL/min	 NR No change	 NR NR
Dunne, 1999[29]	2	NR	No difference	No difference	NR	5%
Biesenbach, 2000[30]	NR	NR	NR	NR	NR	NR
Ekbom, 2001[14]	NR	NR	NR	NR	NR	NR
Khoury, 2002[9]	NR	NR	NR	NR	NR	NR
Rossing, 2002[18] Women with DN and pregnancy Controls (women with DN without pregnancy)	10 years	 534 to 786 mg/24h 597 to 882 mg/24h	NR	 31% 33%	 2.2 mL/min 3.6 mL/min	 19% 24%
Bagg, 2003[31]	6 years	NR	NR	NR	NR	36%
Carr, 2006[7]	NR	NR	NR	NR	NR	NR
Nielson, 2006[32]	NR	NR	NR	NR	NR	NR
Nielsen, 2009[12]	NR	NR	NR	NR	NR	NR
Yogev, 2009[33]	NR	NR	NR	NR	NR	NR
Jensen, 2010[34]	NR	NR	NR	NR	NR	NR
Bell, 2012[17]	NR	NR	NR	NR	NR	NR
Young, 2012[35]	NR	NR	NR	NR	NR	NR
Damm, 2013[5]	NR	NR	NR	NR	NR	NR
Piccoli, 2013[15]	NR	NR	NR	NR	NR	NR
Klemetti, 2015[16]	NR	NR	NR	NR	NR	NR
Seah, 2020[13]	NR	NR	NR	NR	NR	NR

CrCl, creatinine clearance; DN, diabetic nephropathy; eGFR, estimated glomerular filtration rate; ESRF, end stage renal failure. NR, not reported.

Table 6 Management of diabetic kidney disease in pregnancy

Pre-pregnancy	• Women with diabetes should have an assessment of their renal function (including proteinuria) prior to stopping contraception • Women with a creatinine >120 mmol/L, albuminuria >30 mg/mmol or eGFR <45 mL/min should be referred to a nephrologist prior to pregnancy • Women with diabetic nephropathy should be offered pre-pregnancy counselling to inform them of potential adverse pregnancy outcomes and to allow optimisation of blood pressure, glycaemic control and proteinuria prior to pregnancy • They should remain on angiotensin converting enzyme inhibitors until conception, with regular pregnancy testing during attempts to conceive • The HbA_{1c} should be below 48 mmol/mol prior to conception (if achievable without causing problematic hypoglycaemia) • High dose folic acid 5 mg should be started 3 months prior to conception
During pregnancy	• Women with a creatinine >120 mmol/L, albuminuria >30 mg/mmol or PCR >50 mg/mmol should see a nephrologist during pregnancy (Note: eGFR should not be used during pregnancy) • They should have regular MDT visits throughout gestation (every 1–2 weeks) • They should be offered low-dose aspirin (75–150 mg) before 16 weeks of gestation as pre-eclampsia prophylaxis • Women with nephrotic range proteinuria (PCR >300 mg/mmol or ACR >250 mg/mmol should be offered prophylactic low molecular weight heparin during pregnancy and the postpartum period • Target blood pressure of 110–130 mmHg (systolic) and 70–90 mmHg (diastolic) should be used • The creatinine and ACR/PCR should be checked at least 4-weekly and at least fortnightly from 32 weeks of gestation
Post-partum	• Restart RAAS blockade post-partum as soon as renal function is stable. In breastfeeding, enalapril and captopril are the preferred ACE inhibitors, and angiotensin receptor blockade is not advised until breastfeeding cessation • Ensure follow-up with nephrologist post-partum (and with the diabetes services if not already engaged)

ACR, albumin:creatinine ratio; eGFR, estimated glomerular filtration rate; PCR, protein:creatinine ratio; RAAS, renin angiotensin aldosterone system.

section than the general population (46% versus 12%).[3] This risk is higher again in women with DKD. The additive risks of pre-eclampsia, growth restriction and concern over loss of kidney function likely contribute to the high rate of prematurity.

Historically, women with diabetic nephropathy had high rates of fetal loss, obstetric complications and progression to end-stage renal failure in pregnancy. In recent years, with improved diagnosis and management of DKD before and during pregnancy, outcomes have improved. However, the risk of complications is much higher than in healthy women and women with diabetes without kidney disease, as detailed above. The papers included in this review have informed our current knowledge and have been incorporated in a number of comprehensive guidelines including the National Institute for Health and Care Excellence and American Diabetes Association guidelines on management of diabetes in pregnancy and the Renal Association guidelines on Pregnancy and Renal Disease.[26–28] Important aspects of management include pre-pregnancy counselling, close multidisciplinary antenatal monitoring with strict blood pressure control, pre-eclampsia prophylaxis and consideration of thromboprophylaxis and early reintroduction of ACE inhibitors and ensuring appropriate follow-up postnatally. Key management points are summarised in Table 6.

This systematic review was limited by the quality of the studies included; they were most often retrospective, small and monocentric and may have been subject to selection or reporting biases. As a result of these very heterogeneous studies, the results reported varied widely between studies. The variations in the definition of DKD used, the evolving definition of pre-eclampsia and the notorious difficulty diagnosing pre-eclampsia in women with pre-existing hypertension and proteinuria are likely also to have affected the reported outcomes. As diabetes and DKD are common conditions, it is vital for women and their doctors from different disciplines, including obstetrics, endocrinology and nephrology, to be fully aware of the risks associated with pregnancy. This will empower women to make a fully informed decision when considering pregnancy and enable better obstetric and renal care, leading to a safer pregnancy with better outcomes.

Key messages

- The studies performed looking at diabetic kidney disease (DKD) and pregnancy are heterogenous and vary in the definitions used and the outcomes measured
- Adverse pregnancy outcomes are frequently encountered in women with DKD.
- Adverse pregnancy outcomes are more common in diabetic women with macroalbuminuria and impaired renal function
- Pregnancy outcomes in women with DKD have improved over the last few decades
- Important aspects of management include:
  - pre-pregnancy counselling
  - antenatal close multidisciplinary monitoring with strict blood pressure control, preeclampsia prophylaxis and consideration of thromboprophylaxis
  - postnatal - early reintroduction of ace-inhibitors and appropriate follow up postnatally

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Effect of sodium-glucose linked transporter-2 inhibitors on heart failure end points in people with type 2 diabetes mellitus: a systematic review and meta-analysis

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Abstract

Introduction: Type 2 diabetes is a condition which is frequently associated with macrovascular complications. Sodium-glucose linked transporter-2 inhibitors (SGLT2i) have been demonstrated to improve composite cardiovascular outcomes assessed via a 3-point Major Adverse Cardiovascular Events (MACE). Although they yield some benefit in reducing overall rates of cardiovascular death, stroke and myocardial infarction, it appears that the majority of the beneficial effects of SGLT2i drugs on composite outcomes are mediated by improvements in heart failure outcomes reducing cardiovascular death. This effect has been noted across multiple different drugs in the SGLT2i class. The aim of this review was to synthesise current evidence from randomised controlled trials (RCTs) comparing SGLT2i with placebo in adults with type 2 diabetes mellitus. The outcomes of interest were hazard ratios compared with placebo for hospitalisation due to heart failure (primary), death due to heart failure (secondary) and incidence rates of heart failure (secondary).

Methods: Searches were performed using recognised terms in MedLine, EMBASE, Pubmed, Cohrane CENTRAL and CINAHL. RCTs comparing SGLT2i with placebo were eligible for inclusion, providing they contained results for at least the outcome of interest. Studies were reviewed for inclusion by the two authors and data extraction and bias assessments were performed using a modified Cochrane's data extraction tool and bias assessment tool. Meta-analysis of hazard ratios (HRs) was performed in RevMan 5.4 using generic inverse variance and a fixed effects model.

Results: 3,212 records were identified of which 13 were eventually included, covering 11 clinical studies. The risk of hospitalisation for heart failure was significantly lower with SGLT2i compared to placebo (HR 0.69; 95% CI 0.64, 0.74). Inter-study heterogeneity was minimal (I^2=0%) Only one study contained outcomes for death due to heart failure, but its results were not significant. No current studies report hazard ratios for heart failure diagnoses with SGLT2i use compared with placebo.

Conclusion: SGLT2i drugs reduce the rates of hospitalisation due to heart failure in people with type 2 diabetes. This may help mediate the improvements seen in composite cardiovascular outcomes. More evidence is needed to support their use in reducing mortality due to heart failure and incidence rates of new heart failure in this high-risk cohort.

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Key words: diabetes, type 2, heart failure, SGLT-2, CVOT

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Introduction

Diabetes is a condition associated with significant macrovascular risk.[1] The incidence of heart failure among people with diabetes is significantly higher than in those without diabetes, especially at younger ages.[2] Approximately 12% of people with type 2 diabetes are estimated to have heart failure.[3] Although mortality due to heart failure has improved marginally, it remains poor compared with other life-limiting conditions such as cancer.[4] People with diabetes and heart failure with reduced or preserved ejection fraction have worse outcomes than those without diabetes.[5] Recent estimates place hospitalisation rates for heart failure in people with type 2 diabetes at 12.4 per 1,000 person/years compared with 2.4 per 1,000 person/years in those without diabetes.[6]

Until recently, diabetes therapies have shown limited efficacy in improving cardiovascular outcomes beyond any limited effect improvements in HbA_{1c} may yield. Furthermore, some drugs such as rosiglitazone were associated with increases in adverse cardiovascular outcomes, particularly heart failure.[7] Following the safety concerns surrounding rosiglitazone, new diabetes drugs were mandated to undergo robust trials to assess cardiovascular safety before approval,[8] and this requirement continues.[9]

Sodium-glucose linked transporter-2 inhibitors (SGLT2i) were first introduced in the 2010s for the management of type 2 diabetes mellitus. Given the new mandate for cardiovascular outcome data prior to approval, phase III trials were designed to assess these

outcomes using a 3-point Major Adverse Cardiovascular Events (MACE): a composite outcome of cardiovascular death, non-fatal myocardial infarction and stroke.[10] Although heart failure is not part of the MACE end point, it has been assessed separately and may contribute to improved MACE by reducing cardiovascular death. The EMPA-REG trial was the first of these to report in 2015 and demonstrated reductions in mortality due to cardiovascular causes as well as MACE.[11] Subsequent evidence has shown similar findings for other drugs in the class.[12,13] Most notably, SGLT2i drugs seem to be beneficial in heart failure, with more recent trials supporting their use in people with heart failure irrespective of co-morbid diabetes,[13–15] with improvements in cardiovascular mortality and heart failure hospitalisation rates. Early meta-analyses of five studies of SGLT2i showed improvements in rates of hospitalisation for heart failure with a pooled hazard ratio (HR) of 0.68 (05% CI 0.61 to 0.76).[16] Since this review, further studies have since been published. Given the significant benefits of SGLT2i on heart failure, it may be that reductions in cardiovascular death are mediated via improvements in heart failure outcomes. Some have suggested future assessments should include heart failure hospitalisation as a fourth point in the MACE outcome to better appreciate the benefit of these drugs on the condition.[17]

These data from randomised controlled trials (RCTs) are further supported by real-world evidence. One striking study compared SGLT2i with dipeptidylpeptidase-4 inhibitors and showed significant reductions in hospitalisation for heart failure and all-cause mortality with HRs of 0.69 (95% CI 0.61 to 0.77; p<0.0001) and 0.59 (95% CI 0.52 to 0.67; p<0.0001), respectively.[18]

The exact mechanism of action is not clear and there are many suggested possibilities but is thought to be independent of glycaemic outcomes and the osmotic diuretic effect of these drugs.[19] One suggested mechanism of action is attenuation of sodium-hydrogen exchanger activity, which is often increased in heart failure and contributes to diuretic resistance and fluid retention.[19,20] Other mechanisms of action have also been suggested including effects on cardiac remodelling, left ventricular hypertrophy and decreasing oxidative stress.[19,21]

It seems plausible that many of the beneficial effects of SGLT2i drugs may be mediated through improvements in heart failure outcomes, both in people with and without type 2 diabetes. The aim of this review was to assess current RCT evidence reporting heart failure outcomes in adults with type 2 diabetes to see whether this assumption may hold true.

Aims

The aim of this systematic review is to assess the effect of SGLT2i drugs on heart failure outcomes in adults with type 2 diabetes mellitus in RCTs. A summary of the population, intervention, comparison and outcomes (or PICO) model for this systematic review is shown in Table 1.

Methods

Protocol and registration

This systematic review and meta-analysis was prospectively registered with PROSPERO (registration number: CRD42020223256) and the reporting of this review has been undertaken in accordance with PRISMA guidelines.[22] The search was performed on 14 March 2021.

Table 1. Summary of the PICO (population, intervention, comparison and outcome) model used for this systematic review and meta-analysis

	Description
P (Population)	Adults aged ≥18 years
I (Intervention)	Treatment with any sodium-glucose linked transporter-2 inhibitor
C (Comparison)	Placebo
O (Outcomes)	**Primary**: Mortality due to heart failure **Secondary**: Admission to hospital due to heart failure Incident diagnosis of heart failure

Eligibility criteria

Randomised controlled trials comparing SGLT2i with placebo in adults (aged ≥18 years) with type 2 diabetes were eligible for inclusion. Relevant sub-analyses of studies containing a broader population were eligible. Other study designs were not considered. Included studies contained data for at least one of the outcomes of interest. Studies including those with other types of diabetes or including pregnant individuals or children were excluded. No exclusions were made on grounds of data or language.

The primary outcome of interest was hospitalisation due to heart failure. Death due to heart failure, and incident diagnosis of heart failure were both secondary outcomes.

Data sources and search strategy

EMBASE, MedLine, PubMed, Cochrane CENTRAL and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) were searched electronically. An example of the search terms used in OVID: Medline is shown in Table 2. These terms were adapted for each database as required. Language and date limits were not applied.

Study screening and selection

Identified studies were imported into EndNote v9.3 for reference management. Following the removal of duplicate manuscripts, titles and abstracts were screened for relevance. Potentially

Table 2. Example of search terms for retrieval of studies, in this case from Ovid: Medline electronic database at http://ovidsp.ovid.com/

1.	diabet*
2.	"heart failure" OR "cardiac failure" OR (("left ventricular" OR LV OR systolic OR diastolic) ADJ2 impairment) OR HFpEF OR HFrEH OR CCF OR HF
3.	("sodium-glucose" OR "sodium glucose") ADJ3 transport*
4.	SGLT2* OR "SGLT-2*" OR -gliflozin
5.	3 OR 4
6.	1 AND 3 AND 5

relevant manuscripts were then reviewed in full-text against the inclusion and exclusion criteria before a decision was made regarding final inclusion. Review articles identified by the search were cross-referenced to ensure no potentially relevant studies were missed. All identified full-text articles were readily accessible for inclusion; no data or manuscript requests to authors were required on this occasion.

All studies were reviewed independently by two reviewers (TSCJ and REJR). No disputes occurred in performing this review; a third reviewer was available to adjudicate the inclusion of manuscripts/studies if needed.

Data extraction

Data were extracted using a modified Cochrane's data collection form for RCTs specific to the needs of this review[23] and is included as an appendix to this manuscript (See Appendix 1 online at www.bjd-abcd.com). Key data to be extracted included the number of participants in each arm of the trial, the baseline characteristics of the study participants (weight, BMI, HbA_{1c}, age, ethnicity, duration of diabetes) and relevant co-morbidities including but not limited to pre-existing renal or cardiovascular disease. Outcomes were captured as the number of participants in each arm experiencing the outcome by the end of the study period. Bias assessment was performed using Cochrane's Collaboration bias assessment tool for RCTs.[24]

Synthesis of results

All data available for the primary outcome of hospitalisation due to heart failure in a suitable format, was incorporated into meta-analysis. Any studies which could not be included in meta-analysis have been synthesised narratively. Meta-analysis was conducted using generic inverse variance, log[hazard ratios] and standard error in RevMan 5.4 using a fixed-effects model and inter-study heterogeneity was assessed and reported using I^2 statistics. For the secondary outcomes of death due to heart failure or incident diagnosis of heart failure, a narrative synthesis was conducted due to limited avaialble data from the identified studies.

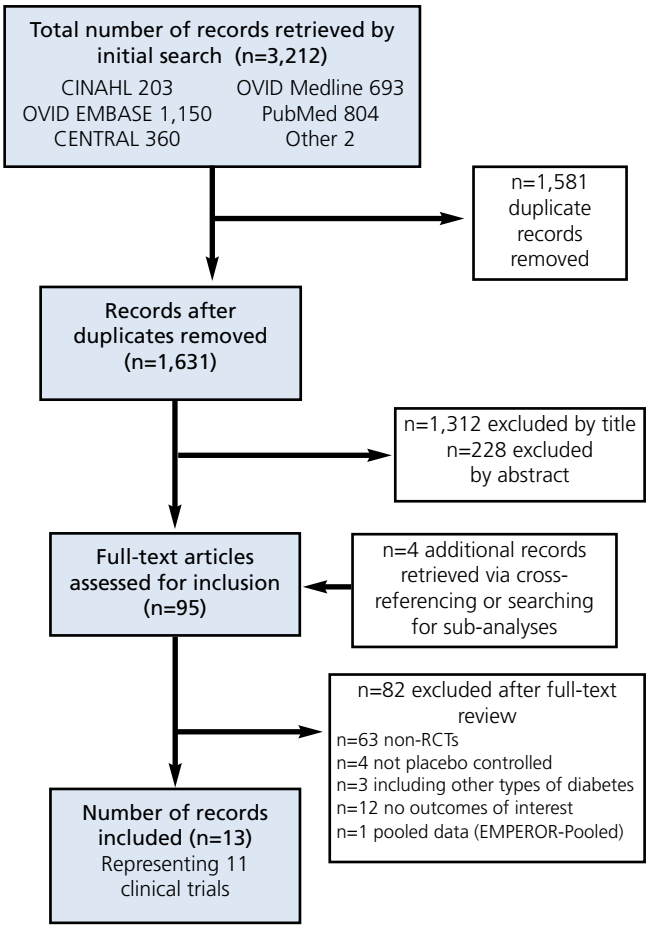
Results

A total of 3,210 records were identified, subsequently 1,581 duplicates immediately removed. The remaining 1,629 were screened, of which 89 were identified for full-text review following screening. Four additional studies of potential relevance were identified from cross-referencing pre-existing review articles. Eleven records covering nine clinical studies were eventually identified for inclusion in this review. Eight of these had data available in a format suitable for meta-analysis for hospitalisation due to heart failure; the other has been included in narrative form. At a later stage two further key studies were added following their presentation and publication (listed as other in the flow-chart). The review process is summarised in the flow chart shown in Figure 1. The characteristics of the identified studies are summarised in Table 3.

Risk of bias assessment

Bias assessment concluded potential sources of bias in most of the studies, although much of this was due to lack of clarity in the reviewed manuscripts. The effect of potential bias introduced by changes in protocol mid-way through many of the studies is uncertain. This was the case with multiple studies, where adaptations were made in light of new published outcome data from other drugs in the class. On assessment, these protocol amendments were done in a valid way without unblinding or affecting the outcomes. Included studies with major protocol revisions for this reason have therefore be highlighted as having an "unclear" risk of bias in the "other bias" domain. The risk of bias assessment for this systematic review is summarised in Table 4.

Figure 1. Flow chart showing the systematic review process and the numbers excluded at each stage



Primary outcome

All of the identified studies had outcome data for hospitalisation due to heart failure. Ten of the studies were included in meta-analysis. One study, DAPA-CKD,[25] did not report a HR for this outcome for the sub-group of people with type 2 diabetes and was therefore not included in the meta-analysis. However, data were available to calculate the number of events in the intervention and comparator arms during the follow-up period of the study, with 30 hospitalisations due to heart failure occurring in the intervention arm (n=1,455) compared with 63 in the control

Table 3. Summary of baseline characteristics and design of studies included in this review

Study name or reference	Drug	Study region	Number in intervention group, n/total, N†	Follow-up duration, median (weeks)	Age (years) mean±SD	Ethnicity (% white)	HbA_{1c} (%)* mean±SD	BMI (kg/m^2) mean±SD	Outcomes of interest (all due to heart failure)
CANVAS[25]	Canagliflozin	Global	5,795/10,142	126.1	63.3±8.3	78.3%	8.2±0.9	32.0±5.9	Hospitalisation Death
CREDENCE[26]	Canagliflozin	Global	2,202/4,401	136.8	63.0±9.2	66.6%	8.3±1.3	31.3±6.2	Hospitalisation
DAPA-CKD[27]‡	Dapagliflozin	Global	1,455/2,906	125.3	56.0±14.6	54%	5.6±0.4	n/a¶	Hospitalisation
DAPA-HF[28,29]*	Dapagliflozin	Global	1,075/2,139	79.2	66.3±9.9	69.2%	7.4±1.5	29.4±6.1	Hospitalisation
DECLARE-TIMI 58[30]*	Dapagliflozin	Global	8,582/17,160	219.2	63.9±6.8	79.7%	8.3±1.2	32.1±6.0	Hospitalisation
EMPA-REG[11]*	Empagliflozin	Global	4,687/7,020	161.8	63.1±8.6	72.6%	8.1±0.9	30.6±5.3	Hospitalisation
EMPEROR-Preserved[33]*∞	Empagliflozin	Global	1,466/2,938	113.4	71.8±9.3	76.3%	Not reported	29.8±5.8	Hospitalisation
EMPEROR-Reduced[14,15]*	Empagliflozin	Global	927/1,856	69.6	66.8±10.0	69.7%	7.4±1.6	28.8±5.5	Hospitalisation
SCORED*[34]	Sotagliflozin	Global	5,292/10,584	69.3	69 (63-74)3	83.2%	8.3 (7.6-9.3)	31.9 (28.1-36.2)§	Hospitalisation
SOLOIST[31]*	Sotagliflozin	Global	608/1,222	40	69 (63–76)§	93.2%	7.2 (6.4–8.2)§	30.4 (26.3–34.3)§	Hospitalisation
VERTIS-CV[32]	Ertugliflozin	Global	5,499/8,246	182.7	64.4±8.1	87.8%	8.2±1.0	31.9±5.4	Hospitalisation

*Combined placebo/intervention baseline data not available. Groups noted to be broadly similar, intervention group characteristics reported in table.
†Numbers for people with type 2 diabetes only in studies containing both people with and without diabetes.
‡Data not in a suitable format for meta-analysis therefore included in narrative review only.
¶Although BMI data were not available, baseline weight (kg) was reported as 78.3±19.9.
§Reported as median (interquartile range).
∞Baseline characteristics for only people with diabetes not yet reported, therefore available characteristics include the entire cohort

Table 4. Risk of bias assessment for included randomised controlled trials (RCTs) using the Cochrane Risk of Bias assessment tool for randomised controlled trials[24]

Bias Assessment - RCTs	CANVAS[25]	CREDENCE[26]	DAPA-CKD[27]	DAPA-HF[28,29]	DECLARE-TIMI 58[30]	EMPEROR-Reduced[14,15]	EMPA-REG[11]	SOLOIST[31]	VERTIS-CV[32]	SCORED[34]	EMPEROR-Preserved[33]
1. Random sequence generation	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
2. Allocation concealment	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
3. Blinding of participants and personnel	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
4. Blinding of outcome assessment	Unclear	Unclear	Low	Low	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Unclear
5. Incomplete outcome data	Low	Low	Unclear	Low	Low	Low	Low	Unclear	Low	Low	Low
6. Selective reporting	Low	Low	Low	Unclear	Low	Low	Low	Unclear	Low	Unclear	Low
7. Other sources of bias	Unclear	Low	Low	Low	Unclear	Low	Unclear	Unclear	Low	Unclear	Unclear

arm (n=1,451). The rate of hospitalisation due to heart failure with dapagliflozin was 2.1 per 100 person-years versus 3.8 per 100 person-years with placebo. One of the secondary outcomes for this study was a composite of cardiovascular mortality or hospitalisation due to heart failure and reported a HR of 0.7 (95% CI 0.52 to 0.92).

The meta-analysis of the results from the other 10 trials is shown in Figure 2. The studies included 65,708 patients of which 36,133 were taking an SGLT2i drug. The pooled hazard ratio for hospitalisation due to heart failure was 0.69 (95% CI 0.64, 0.74) significantly favouring SGLT2i to placebo. Inter-study heterogeneity was very low with an I^2 value of 0%. Of note, this is also comparable to the HRs for the composite outcome of hospitalisation due to heart failure or cardiac death in DAPA-CKD.

Secondary outcomes

Only one study reported mortality rates due specifically to heart failure. This study, the CANVAS study, reported a HR of 0.89 (95% CI 0.49 to 1.6) for canagliflozin compared with placebo. This fails to reach statistical significance. No studies reported the rates of incident new heart failure diagnoses with SGLT2i drugs compared with placebo.

Discussion

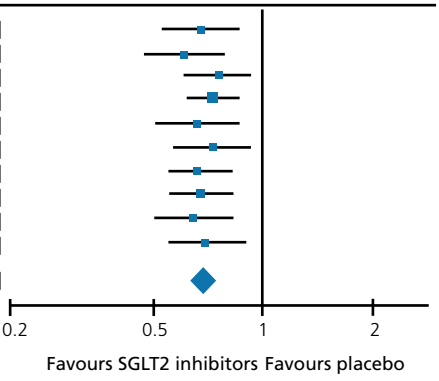
The cardiovascular outcome trials of SGLT2i drugs to date have provided robust and consistent evidence that their use in people with type 2 diabetes is associated with improved cardiac outcomes. In this systematic review looking specifically at heart failure outcomes, all identified studies favoured SGLT2i drugs to placebo (HR 0.69; 95% CI 0.64, 0.74) with very limited inter-study heterogeneity. This is comparable to the earlier meta-analysis of the five studies published at that point (HR 0.68; 0.61 to 0.76).[16] This is strong evidence that SGLT2i drugs reduce the risk of hospital admission due to heart failure and that this is likely to be a class effect. Several of the studies feature a composite outcome of death due to cardiovascular causes and hospitalisation due to heart failure – the significance of SGLT2i drugs in reducing this outcome may be primarily mediated by reductions in hospitalisation due to heart failure.

Unfortunately, the available studies did not consistently report mortality rates due to heart failure. The one study with this outcome demonstrated a trend towards reduced mortality, but failed to reach statistical significance. Further studies or sub-analysis of current works is needed to establish whether SGLT2i drugs improve heart failure-specific mortality.

Figure 2. Forrest plot showing meta-analysis of hazard ratios for hospitalisation due to heart failure for included studies

Study of subgroup	log (Hazard Ratio)	SE	SGLT2 Inhibitor Total	Placebo Total	Weight	Hazard Ratio IV, Fixed, 95% CI
CANVAS	-0.4004775	0.1312919	5795	4347	8.1%	0.67 [0.52, 0.87]
CREDENCE	-0.4942963	0.1356834	2202	2199	7.6%	0.61 [0.47, 0.80]
DAPA-HF	-0.2744369	0.113011	1075	1064	11.0%	0.76 [0.61, 0.95]
DECLARE-TIMI 58	-0.3147107	0.0934854	8582	8578	16.0%	0.73 [0.61, 0.88]
EMPA-REG	-0.4307829	0.1353644	4687	2333	7.6%	0.65 [0.50, 0.85]
EMPEROR-Preserved	-0.3147	0.1276	1466	1472	8.6%	0.73 [0.57, 0.94]
EMPEROR-Reduced	-0.4004775	0.1096573	927	929	11.6%	0.67 [0.54, 0.83]
SCORED	-0.4004775	0.10188	5292	5292	13.5%	0.67 [0.55, 0.82]
SOLOIST	-0.4462871	0.134444	608	614	7.7%	0.64 [0.49, 0.83]
VERTIS-CV	-0.356675	0.1303126	5499	2747	8.2%	0.70 [0.54, 0.90]
Total (95% CI)			**36133**	**29575**	**100.0%**	**0.69 [0.64, 0.74]**

Heterogeneity: Chi² = 2.83, df = 9 (p = 0.97); I^2 = 0%
Test for overall effect: Z = 10.02 (p < 0.00001)



No studies reported the incident rates of new heart failure diagnoses. Most studies to date have been in people with significant cardiovascular risk factors. Further work is needed to assess incident heart failure diagnosis rates in those with these significant risk factors but without heart failure at baseline.

The paucity of data from studies for two of the outcomes limits the conclusions we are able to draw at present from this review. SGLT2i drugs appear to be well tolerated by most, but potential side effects including ketoacidosis and urinary tract infection may limit their use in some people with diabetes.[35]

Both SGLT2i and long acting GLP1-receptor agonists improve cardiovascular outcomes and they appear to provide benefit by entirely different mechanisms.[19,36] Although SGLT2i drugs appear to reduce rates of cardiovascular disease and heart outcomes more than metformin,[37] the cost difference between these drugs makes cost-effectiveness less certain. Further health-economic analyses will be needed to establish this moving forwards. Cardiovascular benefit is also well established for pioglitazone[19] and it has been argued that SGLT2i, long-acting GLP-1 receptor agonists, pioglitazone and metformin could complement each other, if used in combination, to further improve cardiovascular outcomes.[19] Nevertheless, the benefits of SGLT2i drugs in improving cardiovascular outcomes are clear, and we welcome their inclusion in the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) joint type 2 diabetes treatment algorithm – especially their use as second-line therapy in those at increased risk.[38] Furthermore, we look forward to seeing their evolving role in the management of type 1 diabetes and future evidence that they improve cardiovascular outcomes beyond the positive glycaemic and weight outcomes demonstrated by the DEPICT trials.[39]

Conclusion

SGLT2i drugs significantly reduced heart failure hospitalisation rates in adults with type 2 diabetes in RCTs compared with placebo. This occurs, without any heterogeneity, in all drugs across the class in the studies identified for inclusion in this review. This may be the main mediator of improved composite cardiovascular outcomes reported in many of the trials. It is not clear whether SGLT2i drugs reduce mortality rates due to heart failure or incident diagnosis. We eagerly await further work to clarify the benefits of SGLT2i drugs in this regard.

Key messages

- SGLT2i are proven to reduce the rates of 3-point MACE (cardiovascular death, non-fatal myocardial infarction and non-fatal stroke)
- Reductions in cardiovascular death may be mediated by significant improvements in heart failure
- This meta-analysis provides additional evidence using all available studies to date for reductions in hospitalisation due to heart failure
- The reporting of death specifically due to heart failure is limited and should be considered as an outcome of interest for future sub-analyses or works. Where reported, reduction in mortality due to heart failure are clear

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Appendix 1. Data extraction form

Review Title/ID				
Study ID				
Link				
Ref				
Notes				
General information				
Date form completed				
Person ID/name				
Publication Type				
Study Eligibility				
RCT?				
Intervention?				
Comparator?				
Outcomes?		(one or more of interest as per protocol)		
INCLUDE				
Methods				
Aim of study				
Design				
Unit of allocation				
Start date				
End date				
Duration of participation				
Ethhics?				
Participants				
Population				
Setting				
Inclusion criteria				
Exclusion criteria				
Method of recruitment				
Consent?				
Number randomised				
Clusters				
Age				
Sex				
Race				
Co-mobiridty				
Diabetes duration				
Other drugs				
HbA1c				
Weight/BMI				
eGFR				
Subgroups measured?				
Subgroups reported?				
Group (intervention)				
Intervention randomised				
Co-interventions				
Group (comparator)				
Comparator randomised				
Co-interventions				
Outcomes		**Intervention**		**Comparator**
HF hospitalisation				
HF death				
Incident HF				
Bias		Hi	Unclear	Lo
Random seq?				
Allocation concealment?				
Blinding part and pers				
Blinding of outcome assessment				
Incomplete outcome data?				
Selective outcome reporting?				
Other Bias				

Previous structured education attendance and the relationship with HbA_{1c} and hypoglycaemia awareness in people living with type 1 diabetes mellitus using FreeStyle Libre: insights from the Association of British Clinical Diabetologists (ABCD) Nationwide Audit

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Abstract

Background: Dose Adjustment For Normal Eating (DAFNE) is the gold standard National Institute for Health and Care Excellence (NICE) recommended structured education programme that promotes self-management in people living with type 1 diabetes (T1D). We have recently shown that FreeStyle Libre (FSL) is associated with improved haemoglobin A1c (HbA_{1c}) and hypoglycaemia awareness.

Aims: To explore the effect of structured education including DAFNE on HbA_{1c} and GOLD score when combined with FSL use.

Methods: The ABCD national audit data on FSL users were used to conduct this prospective longitudinal study. The Student's t test was used to compare the baseline and follow-up HbA_{1c} and a change in the GOLD score for hypoglycaemia awareness. The baseline demographic and clinical characteristics of the study population were compared using ANOVA. Linear regression analysis identified predictors of change in HbA_{1c} with FSL use.

Results: The study consisted of 14,880 people living with insulin-dependent diabetes mellitus (IDDM), 97% of whom had T1D, of which 50% were female, with a mean±SD baseline HbA_{1c} of 70±18 mmol/mol and baseline body mass index (BMI) of 25.3±6.2 kg/m^2. Follow-up data for HbA_{1c} were available for 6,446 participants while data for GOLD score were available for 5,057 participants. The study population was divided into three groups: 6,701 people with no prior structured education (Group 1), 3,964 with other structured education (Group 2), and 4,215 had previously attended DAFNE structured education (Group 3). Groups 2 and 3 who had previously attended structured education had a lower initial HbA_{1c} than those in Group 1 ($p<0.0001$). However, there was a significant but similar magnitude of the fall in HbA_{1c} across all groups (–8.10 mmol/mol vs –6.61 mmol/mol vs –6.22 mmol/mol in Groups 1, 2 and 3, respectively), with p (ANOVA)=0.83. Similarly, the decline in GOLD score was comparable in Groups 1, 2 and 3 (–0.33 vs –0.30 vs –0.34, respectively), with p (ANOVA)=0.43. Linear regression analysis identified higher baseline HbA_{1c} ($\beta=0.585$, $p<0.0001$), number of FSL scans over 14 days ($\beta=–0.026$, $p=0.00135$) and other structured education ($\beta=–1.207$, $p=0.02483$) as predictors of HbA_{1c} reduction. Prior DAFNE training was not associated

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with improved HbA_{1c} reduction in the linear regression model.

Conclusions: **FSL use was associated with improvements in HbA_{1c} and GOLD score. Although DAFNE is an evidence-based intervention to improve outcomes in those with T1D, DAFNE attendance prior to commencing FSL did not influence HbA_{1c} or GOLD score outcomes when compared with FSL use alone. Other structured education was identified as a predictor of HbA_{1c} reduction when combined with FSL use.**

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Key words: type 1 diabetes mellitus, FreeStyle Libre monitoring, DAFNE structured education, structured education in diabetes, self-management in diabetes and improvement in HbA_{1c}

Introduction

Type 1 diabetes mellitus (T1D) is a challenging life-long condition requiring permanent insulin therapy, and suboptimal management can have catastrophic acute and chronic consequences. Regular multiple daily blood glucose measurements are required to inform insulin dosing with a view to achieving euglycaemia and thus reduce the risk of micro- and macrovascular complications.[1,2] Over the past few years, innovations in blood glucose monitoring have revolutionised care in people with T1D. FreeStyle Libre (FSL) monitoring is one such innovation, which became available on the UK National Health Services (NHS) drug tariff in November 2017 for people with T1D,[3] and can be described as intermittent or flash glucose monitoring. It has had a rapid uptake over the last few years and has now become standard of care for people with T1D receiving intensive insulin therapy.[4,5] By replacing self-monitoring of blood glucose (SMBG) using a glucometer, it eliminates lifestyle interference, inconvenience and discomfort/phobia from multiple daily finger pricks, which are limitations of SMBG.[6,7] FSL uses subcutaneous glucose-sensing technology to detect glucose levels in the interstitial fluid, automatically measuring glucose every minute while storing the readings at 15-minute intervals. To obtain a glucose reading, the Libre reader is held near the sensor and the device then displays glucose information over the preceding 8 hours, which includes current glucose and forecasts change in glucose levels thus allowing the operator to make necessary adjustments to diet and/or insulin dosing.[8] A lower cost, no calibration requirements (factory calibrated) and an infrequent sensor change (every 14 days) are seen as advantages over continuous glucose monitoring.[1] In a meta-analysis of clinical trials and real-world observational studies, Evans *et al* showed that, on commencing FSL, HbA_{1c} fell within the first 2 months and was sustained for 12 months, concluding that the use of FSL in the management of T1D and type 2 diabetes (T2D), both in adults and children alike, led to significant and sustained improvement in glycaemic control.[9] Randomised controlled trials have demonstrated that FSL use is associated with a significant reduction in the incidence of hypoglycaemia in people with T1D and T2D.[10,11]

Dose Adjustment For Normal Eating (DAFNE) is a national structured education programme for adults with T1D (adapted from the German Diabetes Teaching and Treatment Programme), which is taught over five days on an outpatient basis, Monday to Friday or one day a week for five consecutive weeks. It is a well-established, evidence-based and quality-assured programme, which promotes diabetes self-management with flexible insulin therapy and is delivered in over 70 centres across the UK and internationally in Ireland, Australia (Oz DAFNE), New Zealand, Kuwait and Singapore, serving as an important tool in the management of patients with T1D.[12]

In this study we explore the impact of attending a DAFNE or an alternate structured education programme prior to FSL initiation on glycaemic control and hypoglycaemia awareness.

Methods

Patient recruitment and data collection

The Association of British Clinical Diabetologists (ABCD) conducted a national audit on FSL use which began in November 2017.[13] Using data collected during this audit, we conducted a prospective longitudinal study. Data collected during routine clinical care were entered onto a secure online tool on the NHS IT network which allowed for anonymisation of the data. Baseline pre-FSL data included demographics, source of FSL funding, previous structured diabetes education completion, HbA_{1c} values from the previous 12 months, GOLD score[14] (to assess hypoglycaemia awareness), severe hypoglycaemia, paramedic callouts and hospital admissions due to hypoglycaemia, hyperglycaemia and diabetic ketoacidosis (DKA) over the previous 12 months. The GOLD score is a seven-point questionnaire validated for identifying impaired awareness of hypoglycaemia (IAH); a GOLD score ≥4 determines IAH. We used this FSL user database for our analysis.

Data analysis

The study population was divided into three groups based on their education category before commencing FSL. Group 1 had received no structured education, Group 2 had received other structured education while Group 3 attended the DAFNE structured education programme before FSL initiation. The Student's t test was used to compare the baseline and follow-up HbA_{1c} and change in the GOLD score for hypoglycaemia awareness. The baseline demographic and clinical characteristics of the study population were compared using ANOVA. To identify the effect of structured education on HbA_{1c} reduction in response to FSL use, change in the post-FSL HbA_{1c} (pre-FSL HbA_{1c} – post-FSL HbA_{1c}) was modelled as an independent variable with an average of the pre-FSL HbA_{1c}, age, sex, BMI, duration of diabetes, baseline BMI, number of FSL scans and structured diabetes education (entered as a dummy variable) as independent predictors. Data were collected at baseline and first follow-up visit following the initiation of FSL, which took place at a mean±SD of 7.2±6.3 months. Analysis was restricted to patients with complete information on the type of education, baseline and follow-up HbA_{1c} and GOLD score.

Ethical approval

The ABCD nationwide audit programme has Caldicott Guardian approval. The NHS encourages audit of clinical practice, and there are guidelines which were followed. Anonymisation of the

Table 1. Baseline demographic and clinical characteristics of the study population

	Group 1 (no prior structured education) (n=6,701)	Group 2 (other prior structured education) (n=3,964)	Group 3 (prior DAFNE structured education) (n=4,215)	P value*
Age (years)	40.6±18.3	33.5±19.7	45.2±14.9	<0.0001
Gender (% females)	2,999 (45%)	1,994 (50%)	2,383 (56%)	<0.0001
Baseline BMI (kg/m^2)	25.4±6.3	24.3±6.4	26.2±6.2	<0.0001
Duration of diabetes (years)	16±49.6	11±56.7	21±45.4	<0.0001
Type 1 diabetes (%)	6,290 (94%)	3,882 (98%)	4,100 (97%)	<0.0001
Insulin pump (%)	847 (13%)	1,039 (26%)	1,156 (27%)	<0.0001
Mean pre-FSL HbA_{1c} (mmol/mol)	72.3±20.8	68.4±16.9	69.3±16.1	<0.0001
Baseline GOLD score	2.7±1.8	2.5±1.6	2.7±1.7	<0.0001

Data are presented as mean±SD for continuous variables and N (%) for categorical variables.
*P values derived from Student's t test or χ^2 test.
BMI, body mass index; FSL, FreeStyle Libre.

collected data was ensured at the point of uploading to the central database, and the contributing centres were required to collect data from routine clinical practice only.

Results

The study consisted of 14,880 people with insulin-dependent diabetes mellitus (IDDM) (97% of whom had T1D), of which 6,701 received no structured education (Group 1), 3,694 had other structured education (Group 2) and 4,215 attended the DAFNE programme (Group 3) before initiation of FSL. Follow-up data for HbA_{1c} were available for 6,446 participants while data for GOLD score were available for 5,057 participants. In Group 1, FSL initiation resulted in a mean reduction in HbA_{1c} of 5.28±18.84) mmol/mol compared with 5.05±11.44 mmol/mol in Groups 2 and 3 (p=0.56). In Group 1, the mean reduction in GOLD score after FSL initiation was 0.33±1.57 compared with 0.32±1.50 in Groups 2 and 3 (p=0.92). The baseline demographic and clinical characteristics of the study population are shown in Table 1, which shows a statistically significant difference across all groups. DAFNE graduates were older with a longer duration of diabetes, were more likely to be female and on an insulin pump than the non-education group. There was a significant but similar reduction in HbA_{1c} in all groups after FSL initiation. In the unadjusted univariate analysis, HbA_{1c} fell by 8.10 mmol/mol in Group 1, 6.61 mmol/mol in Group 2 and 6.22 mmol/mol in Group 3 (Figure 1). The improvement in HbA_{1c} was statistically not significant when compared between the groups (p (ANOVA)=0.83). Table 2 shows the association of linear regression analysis with change in HbA_{1c} as a dependent variable. Predictors of HbA_{1c} reduction were higher baseline HbA_{1c} (β=0.585, p<0.0001), number of FSL scans over 14 days (β=–0.026, p=0.00135) and other structured education (β=–1.207, p=0.02483). Across the study population, with FSL use the GOLD score improved from 2.71±1.74 to 2.36±1.58 and was statistically significant (p<0.0001).

Table 2. Factors associated with HbA_{1c} response with use of FSL (n=6,446)

Variable	β	SE	P value
Age	0.019	0.012	0.13
Gender	0.118	0.437	0.78
Baseline BMI	–0.003	0.036	0.92
Duration of diabetes	0.006	0.003	0.06
Average pre-FSL HbA_{1c}	0.585	0.013	**<0.0001**
Insulin pump	0.401	0.530	0.44
Number of FSL scans over 14 days (monitoring)	–0.026	0.008	**0.001**
Other structured education	–1.207	0.537	**0.02**
DAFNE	–0.603	0.524	0.24

BMI, body mass index; DAFNE, Dose Adjustment For Normal Eating; FSL, FreeStyle Libre.

Figure 1. Reduction in HbA_{1c} post-FreeStyle Libre (FSL) by education category (no education n=2,714; other structured education n=1,757; Dose Adjustment For Normal Eating (DAFNE) n=1,975); p (ANOVA)=0.83 (no significant difference between the three groups)

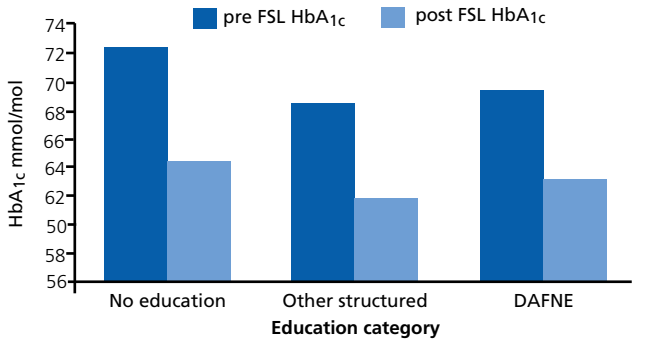
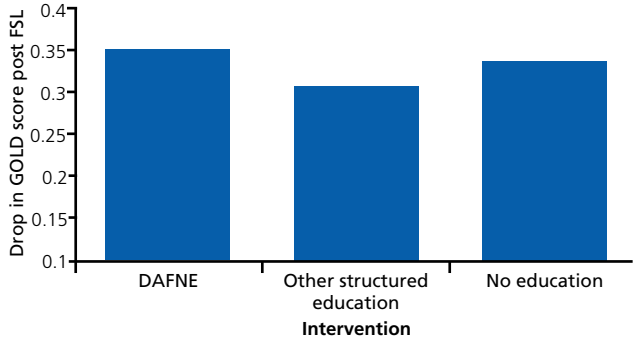


Figure 2. Fall in GOLD score by education category (no education n=2,034; other structured education n=1,446; Dose Adjustment For Normal Eating (DAFNE) n=1,577); p (ANOVA)=0.43 (no significant difference between the three groups)



The decline in GOLD score following FSL initiation was comparable in all three groups and was shown to improve by 0.33 in group 1, 0.30 in group 2 and 0.34 in group 3. p (ANOVA) was applied to assess the mean fall in GOLD score among the groups and no significant difference was found (p (ANOVA)=0.43). Figure 2 shows the change in GOLD score after FSL initiation.

Discussion

We report results of the largest real-world study investigating the interaction of previous structured education attendance and subsequent FSL initiation on glycaemic control in people living with T1D. We show that, although those who had previously attended any structured education had a lower initial HbA_{1c} and were more likely to be on an insulin pump, previous structured education did not demonstrate a significant difference in change in HbA_{1c} in response to FSL initiation. Interestingly, however, we show that other (non-DAFNE) structured education before FSL initiation was predictive of HbA_{1c} reduction post FSL compared with those without structured education or those who had attended DAFNE. From our analysis, pre-FSL HbA_{1c}, number of FSL scans over 14 days and other structured education were identified as predictors of HbA_{1c} reduction.

Several studies have demonstrated improved glycaemic control with FSL use, which was reported to be greater in people with higher pre-FSL HbA_{1c} levels and the number of FSL scans over 14 days.[15–20] In a large observational study, we have previously shown that FSL use is associated with improved glycaemic control and hypoglycaemia awareness among other clinically beneficial outcomes. However, on linear regression modelling, structured education was not a significant factor in the reduction of HbA_{1c} (β=0.82, p=0.090).[20] In a prospective observational study of 900 individuals with T1D, Tyndall *et al* showed that FSL use was associated with a reduction in HbA_{1c} of ≥5 mmol/mol in 48.1% of individuals. Interestingly, DAFNE attendance was amongst other variables (age, sex, diabetes duration, etc) which were not associated with a greater likelihood of achieving a 5 mmol/mol fall in HbA_{1c} with FSL use.[19] These results support our findings of improvement in HbA_{1c} with FSL use, which is independent of previous DAFNE education. Stimson et al explored the change in HbA_{1c} and the rates of hospital admission following FSL monitoring in people with T1DM and reported a median fall in HbA_{1c} of 1 mmol/mol over a median duration of 38 weeks while observing no change in overall hospital admissions.[18] In this study, DAFNE attendance was among the factors associated with a greater fall in HbA_{1c}. However, as this was a univariate analysis and was not adjusted for other variables (baseline HbA_{1c}, age, gender, etc), it should be interpreted with caution.

There are several possible reasons as to why DAFNE structured education prior to FSL use was not found to have an additional advantage in improving glycaemic control and hypoglycaemia awareness. The first is the timing of the completion of structured education. DAFNE courses have been running for 21 years, and many participants in the cohort may have completed DAFNE several years ago, possibly without recent re-enforcement of core DAFNE principles. Second, the HbA_{1c} prior to FSL initiation was lower in the education groups (although this was controlled for in the multivariate analysis). Another possibility could be that DAFNE is not tailored to FSL use, although neither are other available structured education courses. Nevertheless, DAFNE is NICE recommended,[21] has been shown to improve glycaemic control[22–26] and hypoglycaemia awareness,[24] reduces severe hypoglycaemia episodes,[24,27] reduces diabetes-related distress,[24,27] improves the quality of life (QoL),[22,25,27] is cost-effective[28] and so remains integral to the management of T1D. A possible reason for a significant improvement in HbA_{1c} in the other (non-DAFNE) structured education group could be an over-representation of the paediatric population in this subgroup. The paediatric population are more likely to have other structured education (as DAFNE is not available in this age group) and are also more likely to have a close follow-up and monitoring of their HbA_{1c}. Therefore, a specific analysis of the children and young people (CYP) network programmes, such as SEREN, among others, might reveal a synergy with FSL use.

Very recently, Garden *et al* combined FSL initiation with a locally developed and accredited 1-day structured education programme (Cedric) for people with T1D and demonstrated improved glycaemic control in all the participants together with a reduction in the time spent in the hypoglycaemic range and number of hypoglycaemic episodes.[29] It is likely that the combination of the two intervention modalities resulted in a cumulative effect. A small sample size (n=213) and lack of a comparator arm (FSL alone) were limitations of this analysis. Nevertheless, these are encouraging results and support the findings of our analysis, where we have shown other structured education prior to FSL use to be a predictor of HbA_{1c} reduction.

In the regression analysis, we show that other (non-DAFNE) structured education was associated with an approximate 1 mmol/mol (β=1.16) fall in HbA_{1c} after adjustments for all covariates. We have previously shown that, in the whole population, FSL use resulted in a 5.2 mmol/mol fall in HbA_{1c} ,[20] and therefore it could be argued that FSL is valuable irrespective of previous education status.

There are numerous reasons as to why FSL use alone led to a significant HbA_{1c} reduction and improvement of hypoglycaemia awareness, one of which is the alleviation of previously described limitations to conventional SMBG.[6,7] Using state of the art technology, FSL provides on-demand, real-time record and trend of the glucose level, placing the users in a position of strength as they can make prompt adjustments to insulin doses in relation to diet/activity, which facilitates time spent in the glucose target range.[1] Furthermore, it has been observed that FSL users were more likely to administer prandial insulin 15–20 min before a meal,[15,17] a practice that has been shown to improve postprandial glucose control.[30,31]

It is also worth noting that, on commencing FSL monitoring, people are provided with a brief face-to-face tutorial surrounding its use and provided access to online educational resources including the Diabetes Technology Network (DTN) (https://abcd.care/dtn-education/flash-glucose-monitoring). It is likely that these measures maximise the benefits from FSL monitoring for people with T1D.

In terms of limitations, as this was an observational study, causality cannot be inferred and the effect of structured education programmes prior to initiation of FSL can be more effectively stud-

Key messages

- Introduction of FreeStyle Libre monitoring improves glycaemic control irrespective of prior completion of structured education
- Higher baseline HbA_{1c}, number of FreeStyle Libre scans over 14 days and other (non-DAFNE) structured education were predictors of HbA_{1c} reduction

ied with a randomised controlled trial. Furthermore, we did not have information about the exact nature of the other (non-DAFNE) structured education programmes, which can vary in different hospitals across the UK. However, we provide the largest real-world data to date investigating the effect of structured education prior to FSL on glycaemic control.

Considering the results presented from our analysis, we show that FSL monitoring improves glycaemic control irrespective of previous structured education status. It is likely related to the increase in glucose monitoring frequency, a conclusion supported by the results of our analysis and several previous studies where the number of FSL scans over 14 days was a predictor of improvement in HbA_{1c}.[15–20] Perhaps attendance at a targeted, intensive and flexible education programme combined with FSL initiation may be a helpful approach in securing optimum benefit in terms of glycaemic control in people living with T1D who are started on FSL. However, well-designed randomised controlled trials will be needed to establish this conclusively.

Conclusion

In this large cohort of people with IDDM (97% T1D), those who had completed structured education before FSL initiation had lower HbA_{1c} values than those who had not. However, the subsequent change in HbA_{1c} and GOLD score associated with FSL use did not differ between those who had completed education and those who had not. In addition to this, our multivariate analysis showed that other (non-DAFNE) structured education was a predictor of HbA_{1c} reduction even after adjusting for glucose monitoring (number of FSL scans over 14 days) and other covariates. Our findings add to the growing evidence of the effectiveness and utility of FSL monitoring; however, large-scale randomised controlled trials are needed to conclusively underline the clinical efficacy of FSL monitoring in clinical practice.

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Conflict of interest EGW serves on the advisory panel for Abbott Diabetes Care, Dexcom and Eli Lilly and Company; has received research support from Diabetes UK; and is on the speakers' bureau for Abbott Diabetes Care, Dexcom, Eli Lilly and Company, Insulet Corporation, Novo Nordisk and Sanofi. PC had recommended fees from Abbott, Dexcom, Medtronic, Novo Nordisk, Lily, Sanofi and Insulet. CW has a spouse/partner serving on the advisory panel for Celgene and on the speakers' bureau for LEO Pharma and Novartis. REJR serves on the advisory panel for Novo Nordisk A/S and is on the speakers' bureau for BioQuest. TS serves on the speakers' bureau for Novo Nordisk Foundation and reports a relationship with Bristol-Myers Squibb, Eli Lilly and Company, and Sanofi. The other authors have no conflicts of interest in relation to this article.

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* Average additional time in range per day for study participants who used Control-IQ Technology. Brown SA, Kovatchev BP, Raghinaru D, et al. Six-month randomised, multicenter trial of closed-loop control in type 1 diabetes. N Eng J Med. 2019;381(18):1701-1717.

A secondary qualitative analysis exploring the emotional and physical challenges of living with type 2 diabetes

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Abstract

Background: Many feel that their new identity as 'someone living with diabetes' does not fit with their biography. Some individuals may be able to re-assess life goals, adapt their identity and adjust to living with type 2 diabetes mellitus (T2DM). For others, the biographical disruption experienced with their condition may negatively affect their emotional well-being and identity.

Aim: To conceptualise and explore the emotional challenges experienced living with T2DM, using biographical disruption as analytical references.

Design and setting: Secondary qualitative analysis of data collected from 31 semi-structured interviews.

Method: Semi-structured interviews were conducted with people with T2DM in England. Data analysis was informed by constant comparative techniques.

Results: People with T2DM undergo a cognitive process when their biography suddenly becomes interrupted. Suboptimal T2DM can bring a feeling of loss of control over one's future, and loss of independence. What used to be perceived as 'normal' is now perceived as something that requires regular management, negatively impacting their daily routine and ability to carry out activities that once used to be effortless.

Conclusions: Living with T2DM that is socially stigmatised can lead to poor well-being and may disturb one's life biography. Strategies must take place to bring awareness to healthcare professionals of the impact and disruption that T2DM can have on an individual's biography, identity and diabetes management.

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Key words: qualitative, type 2 diabetes, biographical disruption, emotional wellbeing

Introduction

Type 2 diabetes (T2DM) is a progressive lifelong condition affecting over three million people in the UK and is associated with a number of severe complications,[1] including stroke, kidney and coronary heart disease. When diagnosed with a long-term condition such as T2DM, many people experience significant hiatus in their lives[2] that can impact on both their physical and emotional well-being. This hiatus is conceptualised as 'biographical disruption',[3] in which an individual's expectations and plans about their future and self-concept are disrupted by their diagnosis.[3,4] This intrusion can alter one's identity and self-worth,[5] leading to a sense of 'loss of self'.[3,6,7] Their diagnosis can "throw people out of ordinary life, order becomes disorder, the controllable becomes uncontrollable, the understandable becomes unfathomable".[8]

Biographical disruption is a concept that has been applied in other long-term conditions such as cancer and chronic obstructive pulmonary disease.[9–13] A recent study used this framework to examine the experiences of young people living with type 1 diabetes.[14] Their findings indicated that people hide their illness in public spaces to maintain a normal illness biography[14] and present themselves as what would be 'normal' to others. They negotiate between their normal and disrupted biographies to cope with the expectations of society. Although the literature explores chronic illness and the cognitive and material processes that help individuals conceptualise the sudden change in life, some qualitative studies appear to present findings based on a range of health conditions clustered together. One study, for example, explored the experience of people with both hypertension and diabetes[15] whilst another study explored the hidden disruptive experiences of those living with non-visible diseases including stroke, diabetes and cancer.[16] Further studies should focus on each condition individually to grasp their true impact on one's biography.

Despite the wide range of research in this area, the lack of attention to the disruption that T2DM can bring to one's biography still remains overlooked. One of the few qualitative studies that explored biographical disruption and reinvention in T2DM found that the diagnosis of this condition was regarded as a major life event that had a knock-on effect on people's identity.[17] It was concluded that many people respond to their T2DM with fear or confusion, with many not feeling that their new identity as 'someone

living with diabetes' fits with their biography.[17] Some individuals may be able to re-assess life goals, adapt their identity and adjust to living with T2DM.[7,18] For others, however, the onset of their condition is experienced as very demanding which can change the narrative of what life once used to be.[19]

The aim of this study was to conceptualise and explore the emotional and practical challenges experienced by people living with T2DM using the biographical framework as our analytical reference.

Methods

Participants and recruitment

Our secondary analysis was based on 21 qualitative semi-structured interviews, which were conducted with people with T2DM who had attended at least one session of a structured education programme. This was part of the DESMOND (Diabetes Education and Self-Management for Ongoing and Newly Diagnosed) Ongoing Study, a randomised controlled trial of an integrated approach for providing self-management to people with established T2DM.[20] This trial was funded by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research (CLAHRC) Leicestershire, Northamptonshire and Rutland, now reconvened as NIHR Applied Research Collaboration (ARC) East Midlands. Ethics approval was obtained from the Leicestershire Northampton and Rutland Committee (ref: 10/H0406/54) and it was prospectively registered.[20] When providing written informed consent, participants optionally agreed to be approached at the end of the study to take part in a qualitative study to discuss their experience of the education programme. Participants invited to take part in an interview were purposively sampled to achieve a range in terms of age, gender and duration of T2DM. This sampling method was carried out by inviting participants in small batches and reviewing the data.

Data collection

Interviews were conducted in participants' homes. Informed consent was taken immediately prior to the interview and interviews were audio-recorded and fully transcribed. A flexible topic guide aimed to explore participants' views and experiences of the different types of care and the potential support and education received for T2DM management from the particular trial. Questions also explored their views and reflections on their own management of diabetes, and their views and understanding of diabetes and its implications. The qualitative researcher involved in this primary qualitative study also acted as the second coder of the secondary analysis study (HE).

In order to carry out secondary analysis on the primary data, ethical approval was obtained from the University of Leicester to ensure that any ethical issues were considered in this secondary analysis study. Inbuilt safeguards were placed to prevent identification of subjects on whom the original study was based. Personal details of the participants were not included in the documents shared from the original dataset. Demographic information was shared by the primary team, which was anonymised. Furthermore, any identifiable information that may have been mentioned throughout the interviews was removed during the transcription process in the primary study. For the purpose of the secondary qualitative analysis, we only had access to the anonymised transcripts and the anonymised demographic table.

Data analysis

The qualitative researcher involved in the primary qualitative study alerted us of potential data relating to the emotional and practical impact of T2DM. We thus set out to conduct secondary analysis and explore the emotional and practical challenges of living with T2DM in more detail. Originally, we adopted an inductive approach with the data analysis; however, when we began interrogating the data, we noticed patterns emerging that were common to the biographical disruption concept. With this in mind, we used biographical disruption as our analytical frame to present our themes.

Transcripts were read and coded by an experienced qualitative researcher (MH), and most of the transcripts were read and coded by a second coder (HE) to ensure consistency with the coding and analysis. The two coders retrieved and organised the data into framework charts (using Microsoft Excel) to identify patterns in the data. Use of NVivo qualitative data indexing software allowed us to organise and compare codes systematically. Discrepancies were resolved through discussion among the two coders (MH and HE).

Results

Sample characteristics

The sample comprised 31 individuals with T2DM aged between 29 and 87 years, with 68% aged over 60 years; 45% were female (see Table 1). Five participants had lived with T2DM for 1–3 years, 11 participants for 3–10 years, and 11 participants had lived with T2DM for >10 years. Four did not provide this information.

Themes

The findings are presented based on our own perception of the biographical disruption and the emotional and physical challenges faced when living with T2DM. These themes are: disruption of daily activities; self-identity; concerns about the future; shame and blame; and lack of support from healthcare professionals.

Table 1. Participant characteristics

Characteristics	Total (n=31)
Gender, n (%)	
Female	14 (45)
Male	17 (55)
Distribution within age range, n (%)	
20–39 years	1 (3)
40–59 years	9 (29)
60–75 years	14 (45)
>76 years	7 (23)
Duration of T2DM, n (%)	
1–3 years	5 (17)
3–10 years	11 (35)
>10 years	11 (35)
Not known	4 (13)

T2DM, type 2 diabetes mellitus.

Disruption of daily activities

It was reported that T2DM was in the back of participants' minds. Whilst one participant indicated that T2DM did not affect their daily living, the remainder expressed concerns and frustrations of living with T2DM. These concerns varied from having sub-optimal blood readings to experiencing hypoglycaemia. In addition to feeling frustrated and confused, participants also reported feeling scared with the fluctuation of their glucose.

> *Sometimes I have two little wafer table water biscuits before I go to bed because often my sugar drops and I daren't go to bed with it as low as that or I might have a wobbly during the night. I have had two during the night and they scared me to death*. (Participant 4, male, 51)

One participant described the impact that sub-optimal glucose levels had on their daily living and shared feelings of distress whilst having a hypo in public:

> *I went down to the supermarket and I only wanted the paper and a bottle of milk. I was in there with them in my hand and I could not find a check out. I was going round and round in circles. In the end I put them down and found my way out and got on my bike and went home and checked my blood and it was 2.2 … that was very scary.* (Participant 3, female, 80)

Participants also reported feeling 'restricted' and frustrated with their diet, particularly in social situations.

> *I feel frustrated when I am going out to a restaurant and you don't know what they make it out off. You can't choose a meal … so it is very difficult to cope with type 2 specifically because I have found that some days my sugars are reasonable and other days it is sky rocket so it depends on what I eat as to what the results are. If I test during the day, it seems to be average through the day but if I test in the morning it is high*. (Participant 12, male, 60)

Difficulties living with T2DM were expressed throughout the interviews. Experiences around loss of control seemed to centre around the fluctuation of glucose levels, which for some had a potential impact on their social and daily life. Reports were also raised on the emotional impact of living with such a demanding condition; raising feelings of distress, confusion, frustration and fear.

Self-identity

Adverse impacts on identity were expressed unequivocally with many participants feeling overwhelmed by diabetes and feeling antagonistic to the condition defining and dominating their life. One participant was vehement that diabetes was not part of who they were.

> *I think about it all the time, but I don't go around saying I am Rose the diabetic (not real name).* (Participant 7, female, 68)

Resistance to diabetes 'taking over your life' was clear in some participants' accounts.

> *I want to live with diabetes and not have diabetes drive my life because it can. So I am a person with diabetes and not a diabetic trying to stagger through life.* (Participant 11, female, 48)

> *I can't, I won't let it (diabetes) run my life.* (Participant 5, female, 68)

Many participants sought to retain their pre-diagnosis identity, viewing the label of a 'diabetic' patient negatively.

Concerns about the future

In addition to sharing concerns about the day-to-day struggles, worries were also raised around the unpredictability and potential development of future complications. For some participants, the possibility of severe complications led to fear of the unknown and fear of losing independence.

> *The fear of blindness, when I started to get these problems with my eyes and I thought, "Oh, heck! What is going wrong?" So the last [appointment] I had, they scared me because they said "We see something at the back of your eyes", so I have a fear of going blind. I think a lot of it is fear in my case so not being able to understand what is causing it. Is it the diabetes or is it something else?* (Participant 3, female, 80)

The impact on their own future health was a big concern for many participants, but for some, the negative impact of diabetes on their loved ones was a greater issue. Their identity as a family member and as a grandparent was also 'disrupted' by physical challenges and complications of diabetes.

> *I want to be here for when my grandchildren grow up*. (Participant 5, female, 68)

> *The little one (grandchild) wanted to go out and I wanted to go out but I couldn't as I did not feel well. My health was bad so the quality of my day suffered and other people suffered because of it as well. If I don't have good quality of life, then my little one doesn't have either because I can't do what he wants. His quality of life suffers because of mine.* (Participant 4, male, 51)

For some participants, the possibility of severe complications led to fear of loss of physical independence and fear of affecting their quality of life.

> *… that is what I am worrying about, the consequences, but also people looking after me as well if I had my leg off or something like that, so it affects other people as well.* (Participant 10, female, 69)

> *If I do lose my leg, how am I going to drive? Somebody is going to have to drive for me … You can still have a quality of life but it drops and your expectations shrink because you know you can't go outside of the front door and get in your car, drive to see a friend, have a cup of tea, moan about the world, put it right, come back and get on with your life. If you are indoors, you are dependent on people coming to see you.* (Participant 1, female, 55)

As demonstrated, numerous concerns featured severe complications of T2DM such as loss of eyesight and limb amputation. The physical impact of T2DM, current or future, appeared to be a basis for people's sense of independence and good quality of life. Some were not ready to face the reality of the negative consequences of severe T2DM complications and did not know how to address the

'disruption' emerging from their condition. Fear of future and potential loss of independence lead to feelings of distress.

Shame and blame

Many felt judged by others about their diagnosis, by being told that diabetes was their own 'fault'. Participants were blamed for not being responsible for their own health, with many being criticised by others.

> *She (the nurse) was telling me that it was my fault because I drank so much fizzy pop and that basically I had done it to myself so that psychological bullying did not help.* (Participant 6, female, 29)

> *… well it's like it was our fault that we started eating out and gaining weight …* (Participant 8, female, 65)

Other participants expressed self-blame and self-judgment particularly around the cause of their diabetes. These concepts were reported mainly for their 'unhealthy' lifestyle and for their inability to make effective lifestyle changes.

> *I am a fatty who has got diabetes.* (Participant 1, female, 55)

> *It can be a genetic thing or it can be you are a greedy pig and you are eating too much and look what has happened to you now. I think I have done a bit of both.* (Participant 1, female, 55)

This expression of self-blame was evident across all interviews, with a focus on past behaviours to explain culpability.

> *I wish I had done something when I was younger. I just wish I had known what it entailed, […], because, like I said, that doctor used to say, "If you don't lose weight …" but it did not mean anything to me … I think that if I had known more I might have done something about it.* (Participant 10, female, 69)

The same participant who blamed themselves for their diagnosis expressed feelings of anger, regret and guilt for their previous lifestyle at the time of diagnosis.

> *I cried my eyes out and I thought, "bugger!" And I was very, very, very cross and I did believe some of it was my fault, because I knew I had been taking too much sugar and so I did feel guilty about it, but I can't change that.* (Participant 1, female, 55)

Overall, there were strong signs of self-blame for their diagnosis, particularly blame on themselves for living an unhealthy lifestyle and for being the cause of their condition. Due to the negative image that accompanies T2DM, feelings of shame also emerged for not preventing their diabetes, a feeling that was partly amplified by their social interactions with healthcare professionals.

Lack of support from healthcare professionals

For the participants who reported that their diabetes was 'getting them really down', provision of emotional support was highly valued.

> *[The nurse] knows that sometimes I feel a bit depressed. She has said that if I want to talk, to come up.* (Participant 10, female, 69)

Indeed, emotional support was articulated as essential, not just for depressive symptoms but for those who struggle with the day-to-day stresses of the condition.

> *You don't have to live with it just on your own. As I say, you can get a lot of help from all the different people like the diabetic nurses. They are only a phone call away. You can get help from your doctor or anybody if you need help. If you are worried about anything like your limbs or your feet or your eyesight.* (Participant 3, female, 80)

However, participants highlighted that accessing emotional support though primary care was challenging.

> *… even with the doctors here, you know, you battle, you phone at eight o'clock in the morning, you can stand here until half past eight and you still don't get through, and then when you get through, "I'm sorry, he's booked up, and he won't be here again until next week" …* (Participant 13, female, 87)

Others reported that their diabetes consultations did not offer the emotional support they required; some expressed frustration at not being listened to, feeling judged and/or dismissed by their doctor.

> *… one of the comments [the doctor] came up with was – "That's life". You don't want that type of statement.* (Participant 12, male, 60)

> *It is very clear that [the doctor] was going through a set process of questions, answers and processes rather than listening to answers and tailoring the care or tailoring it to what I was saying. You can tell when somebody is going through a process and that is what is happening.* (Participant 2, male, 45)

Despite participants believing that support from their healthcare professional was fundamental for their diabetes management, empathy and overall emotional support from healthcare professionals was in fact lacking, which led participants feeling frustrated and uncertain about their condition.

Discussion

Summary

Our secondary qualitative analysis explored the emotional and physical challenges experienced by people living with T2DM. The analysis of the data aligned with the biographical framework. The process of our data analysis was not guided by this concept, but rather these became our analytical reference to better understand the emotional and physical impact of living with T2DM. With these in mind, we concluded that people with T2DM undergo a cognitive process when their lives suddenly become interrupted.[15] Suboptimal T2DM can bring a feeling of loss of control over one's future, and loss of independence. What used to be perceived as 'normal' is now perceived as something that requires regular management, negatively impacting their daily routine and ability to carry out activities that once used to be effortless.

Strengths and limitations

We aimed to summarise the study's strengths and limitations based on the four suggested criteria for qualitative research (credibility, transferability, dependability and confirmability).[21] To ensure credibility, we used a strategy known as investigator triangulation, whereby two independent researchers coded and analysed the data. The two researchers held regular meetings during the data analysis process and their interpretations were compared and discussed until agreement was made. The involvement of a second coder allowed for reflective thoughts and note-taking to ensure some level of dependability and confirmability. As a multidisciplinary team consisting of academics, behavioural scientists, dietitians and primary care clinicians, we sought to explore the concept of biographical disruption in T2DM based on our diverse experiences and positions in academia and primary care.

As this study is based on secondary analysis, we are aware that there may be limitations in the description of the research process. However, we attempted to provide a rich account of data including the setting, sample size and demographics of the participants to enhance transferability and allow the reader to assess whether our findings are transferable to their own setting.

The primary dataset is not yet published; however, we provided detailed information of the methodology rigour of the parent study and its relationship with our secondary data analysis. Although data are based on secondary analysis and thus may be limited, the secondary analysis method is a valid and credible research methodology and we ensured that the data were analysed in a robust manner by two independent researchers using principles of the constant comparative approach. Even though the topic guide questions which guided the primary analysis were not directly related to our research question, they nonetheless proved to provide sufficient data on the emotional and practical challenges, recognising the association between biographical disruption and T2DM. The input of a qualitative researcher who was heavily involved in and familiar with the primary dataset was considered as a major strength during the secondary data analysis, a measure that is also highly recommended for robust secondary data analyses.[22]

Comparison with existing literature

Many people with T2DM were concerned about depending on others as a consequence of losing their independence from T2DM. This supports the concept of biographical disruption, that chronic conditions such as T2DM can interrupt the 'normal rules of reciprocity', which in turn may disturb one's life biography.[5] Many people with T2DM adjust well to this biographical disruption and re-establish normality within their new lifestyles. Others, however, as described in this paper, may show signs of resistance to their new identity.

In addition to the emotional impact of living with T2DM, our findings also highlighted the overlap between biographical disruption and one's psychological state. For example, episodes of hypoglycaemia experienced by a person with diabetes can reinforce negative risk perceptions preventing them from returning to what is perceived as 'normal' life. We present this disruption through quotes shared by our participants – for example, the impact that suboptimal glucose levels had on their daily living, and feeling 'restricted' and frustrated in social situations. In this case, our findings consider the detrimental impact that the disruption caused by T2DM may have had on their quality of life. This perhaps suggests that biographical disruption not only disrupts the sense of 'self' and breaks normality down within a social context (ie, work and family life), but that it also breaks normality down within their own psychological well-being.

Shame is represented as both pre-existing vulnerability and 'acquired' behaviour, with some reports supporting that people hold internal negative attributes towards their identity. As feelings of shame may come from within, they may also be triggered externally through social interactions and may thus become a learned behaviour.[23] Our findings echo existing qualitative findings that T2DM-related shame can be triggered by self-stigmatisation and the internalisation and acceptance of the stigmatising beliefs.[24,25] Our work proposes that these feelings of shame can be triggered by stigmatising beliefs and attitudes from healthcare professionals.

People diagnosed with T2DM, a condition that is considered as self-inflicted by society, may begin to feel stigmatised. Acts of being judged and discriminated against, as demonstrated in our findings, have been shown to provoke emotional responses including poor psychological well-being and overall poor self-care. This relationship between stigma, self-blame and poor well-being was also illustrated in a cross-sectional study of people with diabetes.[26] A recent qualitative study exploring the reflections of physicians and patients with T2DM highlighted that the latter target group expressed self-blame for failure to follow a self-care regimen, and for the lack of progress with their diabetes management.[27]

As reported in recent findings, people value the supportive relationship with healthcare professionals.[28] Respondents in this study, however, reported that this emotional support was lacking, reiterating previous surveys that the emotional support provided by healthcare professionals is minimum.[29] In order to cope emotionally with the intrusion of a life-changing chronic condition, receiving medical as well as emotional support from healthcare professionals is fundamental for the person's emotional well-being and diabetes management. In addition to understanding the causes of T2DM, it is also important to understand the physical and emotional consequences of living with such a demanding condition.

Implications for research and practice

This study illustrates that concerns about the future and the consequences of long-term complications can have negative effects on the emotional well-being and identity of people living with T2DM. Many people were able to cope with the biographical disruption caused by their condition, whereas others struggled to deal with the emotional and physical challenges faced with the day-to-day management of their condition.

Biographical disruption is a concept that has mainly been applied in long-term conditions like cancer. As a concept, our study has shown that it may also be used and adapted in T2DM. This exploratory study was based on secondary analysis data, and thus it was not feasible to explore biographical disruption in detail.

Key messages

- Biographical disruption is a concept mainly applied in long-term conditions like cancer, this concept should be considered in diabetes management consultations
- Strategies must be implemented to bring awareness to healthcare professionals of the biographical disruption associated with T2DM
- Our findings suggest that the diagnosis of T2DM may have a negative impact on one's identity and wellbeing
- Feelings of shame may be triggered by stigmatising beliefs and attitudes from healthcare professionals

We can, however, suggest that more aspects deserve fuller investigation in future research to better understand the impact of T2DM on people's biography and life narrative and, more so, to better understand what is needed to strengthen diabetes care delivery. Our findings concur with recommendations published in the Diabetes UK positive statement, that healthcare professionals must be provided with adequate training to identify well-being problems and deliver appropriate support as part of the ongoing diabetes care.[30]

We propose that these findings are followed up by future research to investigate the impact of diabetes at different life stages. It would also be worthwhile to implement robust strategies in diabetes consultations and diabetes care to acknowledge and address the biographical disruption associated with T2DM.

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Impact of socioeconomic geography on outcomes following hospital discharge for people with diabetes

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Abstract

Background: **Socioeconomic factors drive poor diabetes outcomes. Little research has assessed the impact of socioeconomic factors on outcomes when people with diabetes are discharged from hospital. We evaluate the impact of socioeconomic factors on readmission and mortality.**

Methods: **We performed a retrospective evaluation of data extracted from an electronic health record of a large UK hospital for all patients discharged with a diabetes diagnosis over 3 years. Data were extracted for 46,357 distinct discharges and matched at patient level to postcode sector socioeconomic data. Outcomes were evaluated against prespecified diabetes cohorts. Standardised effect sizes were calculated.**

Results: **Socioeconomic status was statistically significantly associated with 14 of 19 socioeconomic variables in relation to 180-day mortality for a type 2 diabetes mellitus (T2DM) patient cohort; no statistically significant association between mortality and socioeconomic variables in a type 1 diabetes mellitus (T1DM) cohort was noted. Socioeconomic status was significantly associated with one of 19 variables for 28-day readmission in T2DM patient cohorts compared with nine statistically significant variables for T1DM cohorts. Effect sizes were strongest for deprivation indices (Cohen's D=0.29) and health-related activity impairment (Cohen's D=0.15).**

Conclusion: **There is a strong association between geographical socioeconomic status and readmission outcomes for patients with T1DM but only a limited association with mortality. In contrast, mortality for T2DM cohorts is strongly associated with socioeconomic status whilst readmission is not.**

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Key words: diabetes, socioeconomic, readmission, hospital discharge

Introduction

The proportion of people in hospital with a diagnosis of diabetes continues to grow at a rapid rate.[1] It is well established that people with a diagnosis of diabetes are at increased risk of longer hospital stays, increased rates of complications and increased inpatient mortality.[2,3] There has been less work on the impact of diabetes on outcomes following hospital discharge.[4] There is, however, increasing evidence that people with diabetes are at an increased risk of poorer outcomes including readmission[5] and mortality[6,7] following discharge from an inpatient hospital admission.

Avoiding excess readmissions is a particular priority for healthcare services, based on an underlying belief that readmission rates reflect the quality of care provided and the potential financial savings associated with reduced readmission rates.[4] Sonmez *et al* showed that, in an urban teaching hospital, the 30-day adjusted readmission rate for patients with diabetes was 15.3% versus 8.4% for patients without diabetes.[8] Excess readmissions for diabetes are estimated to cost the NHS over £99 million annually.[9] Whilst research considering the impact of diabetes on mortality rates following hospital discharge is relatively scarce and typically focused on particular conditions, there is also good evidence that patients with diabetes are at an increased risk of mortality following discharge from hospital compared with those without diabetes.[10,11]

The increased risk of poor outcomes when people are discharged from hospital with diabetes has driven searches to understand both the drivers for these poor outcomes and potential methods to mitigate against them. A recent systematic review acknowledged 48 studies identifying risk factors of readmission when people with diabetes are discharged from hospital.[12] These studies reported 76 distinct statistically significant risk factors for readmission. The most commonly reported risk factors were comorbidity burden, age, race and insurance type.

A relatively small number of studies considered the impact of socioeconomic status on readmission rate, particularly outside small subsets of patients with type 1 diabetes (T1DM).[13] There are no studies within the current research literature assessing the impact of socioeconomic status on mortality following hospital discharge for patients with diabetes. This paucity of research on

the impact of socioeconomic status on patients with diabetes following hospital discharge comes despite there being well-known associations between lower socioeconomic status and diabetes outcomes in general. Lower markers of socioeconomic status have been associated with an increased prevalence of type 2 diabetes mellitus (T2DM),[14] lesser attainment of diabetes treatment goals[15] and increased mortality.[16] The contrast between socioeconomic research for diabetes in general and research considering risk factors at hospital discharge may reflect the data interoperability challenges associated with matching diverse inpatient electronic health record (EHR), primary care and socioeconomic datasets at the individual patient level.

We present the first assessment of the impact of socioeconomic status on the risk of readmission and mortality at the point of discharge from hospital for people with diabetes. This research is essential if we are to personalise healthcare services to meet the needs of individual patients and appropriately design strategies to reduce the excess readmission and mortality risks seen for patients with diabetes when discharged from hospital.

Methods

We performed a retrospective evaluation of data extracted from an EHR of a large tertiary referral centre in the Coventry and Warwickshire region of the UK for all patients discharged with a diagnosis of diabetes over a 3-year period. Outcome variable data were extracted for hospital readmission within 30 days and mortality within 180 days of hospital discharge.

The diagnosis of diabetes was taken from the coding of patients at discharge and, thus, if there was discrepancy in the diagnosis within the record, the latest diagnosis of diabetes at discharge was used. Maternity patients were excluded from the study due to the differing nature of maternity care and readmission patterns. Patients discharged within the last 6 months of the study period were not evaluated as index patients to ensure that all patients had a full period of 6 months follow-up on the EHR, in order to assess for the outcome measures of interest. Patients with a postcode outside the Coventry & Warwickshire region were excluded to ensure accurate capture of readmission rates to the hospital.

Socioeconomic data were extracted from the latest UK Census performed by the Office for National Statistics. The last UK Census was performed in 2011 and published in July 2012. It represents a 'detailed snapshot of the population and its characteristics, and underpins funding allocation to provide public services'; with a 93% coverage rate, it is a unique and invaluable resource considering the characteristics of the UK population.

Socioeconomic data were extracted from the Office of Statistics Nomis Portal relating to the following pre-specified variables: indices of multiple deprivation, adults in employment, ethnicity, language, housing density, activity limitation and provision of unpaid care. Socioeconomic data were extracted and matched to patient postcodes within the EHR at postcode sector level. The 5-digit postcode sector (eg, 'SW1A 2' from the full postcode 'SW1A 2AA') represents the smallest area level within the Census dataset.[17] There are 89 postcode sectors within the Coventry and Warwickshire region, with approximately 9,000 people living in each postcode sector.

The association between socioeconomic status and outcomes of interest was assessed using the Student's t-test for continuous variables, following adequate assessment for skew and kurtosis to ensure normality. Outcomes of interest were readmission and mortality. An absolute skew value larger than 2 or an absolute kurtosis (proper) larger than 7 was used as a reference value for determining substantial non-normality.[18]

A p value of <0.05 was considered significant. Standardised size was evaluated using Cohen's D for continuous variables. Standardised effect size measures offer an important statistical choice for this research question, as outlined by Robbins et al.[19] Effect size statistics are also particularly valuable when looking to make comparisons – for example, between different predictors, cohorts or variables –,and it is primarily in this context that standardised effect sizes have utility in considering risk predictors for negative outcomes.

All statistical testing was performed using Microsoft Excel 2016 (Redmond, WA, USA) and IBM SPSS Version 24 (Armonk, NY, USA).

Ethical approval was granted by the local NHS Trust Research Ethics Committee at University Hospitals Coventry & Warwickshire NHS Trust through the Governance arrangements for Research Ethics Committee Process (study reference: GF0220). Approval was also granted through the University of Warwick's Biomedical & Scientific Research Ethics Committee (study reference: REGO-2017-2114).

The research topic, strategy and approach were informed by direct patient public involvement (PPI). The research topic was identified following engagement with patient representatives through the Diabetes UK 'Diabetes Voices programme' who were sent free-text questionnaires enquiring about their experiences of inpatient hospital stays. The research approach was developed and adapted by working with two PPI ambassadors, who were recruited through the National Institute of Health Research (NIHR) People in Research (https://www.peopleinresearch.org/)

Results

Data were extracted for 24,108 hospital discharges with a diagnosis of diabetes recorded, 2,538 for patients with T1DM and 21,048 for patients with T2DM. Twenty-four percent (N=5,741) of emergency hospital admissions were identified as being readmitted within 30 days for the generalised population of diabetes, 26.7% (n=678) of emergency admissions with T1DM and 23.4% (n=4,981) of emergency admissions with T2DM. Fifteen percent of patients (n=3,718) died within 180 days of hospital discharge in the generalised population of patients with diabetes, 6.9% (n=175) of patients with T1DM and 16% (n=3,460) of patients with T2DM.

Socioeconomic status was significantly associated with one of 19 variables for readmission at 30 days in T2DM patient cohorts compared with nine statistically significant variables for T1DM cohorts ($p<0.05$, Student's t-test). Standardised size mea-

Table 1 Association between socioeconomic status and readmission risk at 30 days

	Readmission all diabetes		Readmission T1DM		Readmission T2DM	
	P value	Cohen's D	P value	Cohen's D	P value	Cohen's D
% not deprived	0.75		0.00*	0.14*	0.25	
% deprived in 1 dimension	0.16		0.00*	–0.29*	0.33	
% deprived in 2 dimensions	0.72		0.09		0.20	
% deprived in 3 dimensions	0.54		0.01*	–0.12*	0.41	
% deprived in 4 dimensions	0.50		0.03*	–0.10*	0.51	
% Adults in employment	0.71		0.11		0.19	
% Ethnic minority race (not English)	0.05*	0.03*	0.01*	0.13*	0.17	
Day-to-day activities limited a little, %	0.01*	0.04*	0.00*	0.16*	0.12	
Day-to-day activities limited a lot, %	0.03*	0.03*	0.05*	0.09*	0.10	
Day-to-day activities not limited, %	0.01*	–0.04*	0.00*	–0.14*	0.08	
Day-to-day activities limited a lot: age 16–64, %	0.04*	0.03*	0.14		0.08	
Day-to-day activities limited a little: age 16–64, %	0.18		0.95		0.11	
Day-to-day activities not limited: age 16–64, %	0.04*	–0.03*	0.63		0.05	
Provides no unpaid care, %	0.49		0.36		0.44	
Provides 1–19 hours unpaid care a week, %	0.86		0.28		0.92	
Provides 20–49 hours unpaid care a week, %	0.27		0.46		0.13	
Provides ≥50 hours unpaid care a week, %	0.06		0.41		0.09	
Main language is not English	0.00*	0.05*	0.02*	0.11*	0.00*	0.05*
Density (number of persons per hectare)	0.93		0.14		0.43	

*p<0.05.

sures were relatively large and strongest for deprivation indices (Cohen's D=0.29) and health-related activity impairment (Cohen's D=0.15).

Socioeconomic status was statistically significantly associated with 14 of 19 socioeconomic variables in relation to 180-day mortality for the T2DM patient cohort (p<0.05, Student's t-test). Standardised effect sizes were relatively small; however, they were strongest for language and activity limitation (both 0.09). There was no statistically significant association between mortality and socioeconomic variables in the T1DM cohort.

Tables 1 and 2 show the association between socioeconomic factors and readmission at 30 days or mortality at 30 days for generalised populations of people with diabetes, T2DM populations and T1DM populations at discharge from hospital. A standardised effect size measure (Cohen's D) is presented for statistically significant associations.[19]

Discussion

There is a strong association between geographical socioeconomic status and readmission outcomes for patients with T1DM. However, there is very limited association between socioeconomic status and mortality outcomes for the T1DM cohort. In direct contrast, socioeconomic status is strongly associated with mortality outcomes following hospital discharge for patients with T2DM, whilst there is very little association with readmission.

This is an important finding as it will help guide and understand how to most appropriately risk stratify these different patient cohorts at discharge from hospital, as well as make suggestions as to the potential design of interventions to reduce readmission or mortality following discharge. The results also go some way to explaining variations in outcomes when patients are discharged from hospital with diabetes, as they suggest that both the geographical socioeconomic status and the type of diabetes may be of significant relevance.

These results clearly demonstrate an association between geographical socioeconomic status and outcomes following hospital discharge; however, they do not provide any information on causation. Further work is clearly needed to understand the possible mechanisms and causes for the findings reported here. There are a wide range of possible explanations for these findings. One may include drivers of readmission related to socioeconomic status in T1DM cohorts being both compliance with treatment and health-seeking behaviour. Drivers of mortality related to socioeconomic status in T2DM cohorts may be related to wider lifestyle choices and cardio-metabolic risk. There are, however, a range of possible hypotheses that would merit further investigation. It is important to note that we have not attempted to control the populations for factors such as age, sex or diabetes control. Whilst we have not controlled for such variables, the results remain useful, in particular for the development of risk stratification tools.

There are a number of strengths and weaknesses with the study described. Foremost among the strengths is that we have used a large sample size over a prolonged period of time (3 years). This is important as previously very few studies, which have looked at the association between socioeconomic status

Table 2 Association between socioeconomic status and mortality risk at 180 days

	Readmission all diabetes		Readmission T1DM		Readmission T2DM	
	P value	Cohen's D	P value	Cohen's D	P value	Cohen's D
% not deprived	0.17		0.49		0.00*	-0.08*
% deprived in 1 dimension	0.12		0.24		0.01*	0.05*
% deprived in 2 dimensions	0.14		0.84		0.00*	0.07*
% deprived in 3 dimensions	0.03*	0.04*	0.36		0.00*	0.08*
% deprived in 4 dimensions	0.02*	0.04*	0.25		0.00*	0.08*
% Adults in employment	0.50		0.74		0.02*	0.04*
% Ethnic minority race (not English)	0.00*	0.05*	0.07		0.00*	0.09*
Day-to-day activities limited a little, %	0.29		0.57		0.95	
Day-to-day activities limited a lot, %	0.00*	–0.08*	0.69		0.01*	-0.05*
Day-to-day activities not limited, %	0.01*	0.05*	0.61		0.25	
Day-to-day activities limited a lot: age 16–64, %	0.04*	0.04*	0.38		0.00*	0.05*
Day-to-day activities limited a little: age 16–64, %	0.23		0.80		0.01*	0.05*
Day-to-day activities not limited: age 16–64, %	0.00*	0.06*	0.72		0.15	
Provides no unpaid care, %	0.01*	0.05*	0.37		0.03*	0.04*
Provides 1–19 hours unpaid care a week, %	0.02*	–0.04*	0.34		0.01*	-0.05*
Provides 20–49 hours unpaid care a week, %	0.78		0.76		0.01*	0.05*
Provides ≥50 hours unpaid care a week, %	0.23		0.76		0.96	
Main language is not English	0.01*	0.04*	0.05		0.00*	0.09*
Density (number of persons per hectare)	0.19		0.87		0.12	

*p<0.05.

and diabetes outcomes, have used sufficiently large sample sizes.[20] Weaknesses of the study include its nature as a retrospective study and that we have only considered a single centre. This was, however, a large tertiary referral centre set within a diverse population representing a mix of affluence, ethnicity and urbanisation. It should be noted that this study is the first of its kind. There are limitations in the statistical methods presented here, with the results not adjusted for factors such as age and co-morbidities, the latter of which is not well recorded within the electronic record system used. Furthermore, the article does not present a Bonferroni correction with respect to the multiple t-tests performed. Such a statistical approach is beyond the initial remit of this work, however, it would be an important element of future larger multicentre studies looking to understand this area in more detail.

The use of postcode sectors, as opposed to full postcodes, also merits discussion. This was necessitated both by the availability of census data provided within the Office of National Statistics datasets and also the need to ensure that patient identity was not inadvertently compromised. From a research perspective, it would of course be interesting to repeat the study with identifiable patients' datasets and full postcodes with an individual assessment of socioeconomic status. However, from a practical perspective, the benefits of such an approach would be limited. The use of postcode sectors and publicly available socioeconomic datasets allows ready and rapid incorporation of such data into risk stratification tools, which could be implemented within hospital discharge processes without significant disruption to the clinical teams and yet provide valuable information. An individual assessment of socioeconomic status at discharge would, of course, be laborious and impractical.

Key messages

- There is a potentially important association between socioeconomic geography and hospital discharge outcomes for people with diabetes
- There may be a different association depending on whether a person has type 1 or type 2 diabetes
- Further work is needed to better understand the impact of socioeconomic geography and work towards risk stratification tools

In summary, we present here the first large-scale assessment of the impact of geographical socioeconomic status collected from publicly available data sources on outcomes for cohorts of patients discharged from hospital with diabetes. We demonstrate clear associations between socioeconomic status and readmission for patients with T1DM and socioeconomic status and mortality for patients with T2DM. These findings can – and we believe should – be readily incorporated into risk stratification tools applied at the point of discharge and thus supporting evidence-based individualised care for patients leaving hospital with diabetes.

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Conflict of interest Nothing to declare.

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Quality of life in people with Type 2 diabetes; a study in a multi-ethnic clinical trial population

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Abstract

Background: The long-term burden of self-management in type 2 diabetes can impact quality of life.

Aims: To examine associations between demographic and clinical factors, anxiety/depression and perception of health in people with type 2 diabetes.

Methods: Retrospective analyses of anonymised data from completed clinical trials provided by the diabetes subsection of Virtual International Cardiovascular and Cognitive Trials Archive (VICCTA). Data on demographics, polypharmacy, HbA_{1c}, anxiety/depression (EQ-5D-3L) and perception of health (EQ-5D-3L VAS) were extracted. Regression analyses explored associations amongst polypharmacy, HbA_{1c} and quality of life (anxiety/depression and health perception) at baseline.

Results: In 2783 participants with type 2 diabetes (median age 66 years (IQR 61–70), n=1,595 (57%) male), female sex and Caucasian/European ethnicity were each associated with increased anxiety/depression and lower EQ-5D-3L VAS scores. Following adjustment for covariates, each additional prescribed medication was associated with increased anxiety/depression: OR 1.09 (95% CI 1.04 to 1.14; p<0.001) and lower VAS scores: B= –1.06 (95% CI –1.37 to –0.75, p<0.001)).

Conclusion: Demographic factors and polypharmacy are associated with anxiety/depression and lower health perception.

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Key words: anxiety, depression, diabetes, quality of life

Introduction

Type 2 diabetes comprises 90% of diabetes cases worldwide.[1] People with type 2 diabetes experience a high burden of self-management of their condition and are at an increased risk of depression and lower quality of life.[2,3] Given the impact on quality of life and the high prevalence of mental health conditions in people with type 2 diabetes, there is a need to better understand these associations.[4]

Several demographic and clinical factors may affect quality of life and prevalence of anxiety/depression in people with type 2 diabetes: for example, depression is more likely to occur in younger women with diabetes.[5] There is conflicting evidence regarding the role of ethnicity, with one study showing that African Americans with type 2 diabetes were less likely to report depressive symptoms compared with other ethnicities, while another showed no link.[6,7] Another study of men with type 2 diabetes aged 70–89 years found that the risk of depression was greatest immediately after diagnosis and towards the end of life.[8] A previous meta-analysis also reported a link between obesity, depression and type 2 diabetes.[9]

Type 2 diabetes is a challenging condition due to associations with other morbidities and complications; this often results in polypharmacy, defined as taking five or more medications.[10,11] A higher medication burden is twice as likely in people with diabetes and co-existing mental health conditions, including anxiety/depression.[12] While an increased medication burden has been shown to adversely affect quality of life, the potential link between anxiety/depression and polypharmacy is under-researched.[13]

Evidence is somewhat conflicting on the association between glycaemic control and anxiety/depression. However, lower HbA_{1c} levels, reflecting better metabolic control, have been associated with higher quality of life.[14]

Validated predictors that can be used in the clinic to identify people with type 2 diabetes at risk of anxiety/depression are lacking. One study found that mental health conditions in people with diabetes were only identified by health professionals when symptoms were severe.[15] For the present analysis, access to archived data from existing high-quality studies provided an opportunity to further explore these associations. We sought to identify demographic and clinical risk factors, including polypharmacy, associated with a higher risk of anxiety/depression and lower quality of life to inform the management and support of people with type 2 diabetes.

Methods

Transparency and openness

In this article we report how we determined all data exclusions and measures included in the study. Data can be made available

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by contacting viccta@glasgow.ac.uk. We analysed data using IBM SPSS Statistics version 26.

Design

We conducted retrospective analyses of fully anonymised, placebo group, randomised controlled trial data from the diabetes subsection of VICCTA (www.virtualtrialsarchives.org/viccta). VICCTA is a collaborative venture that coordinates access to datasets from trials and registries to allow further clinical research.

Data extraction

VICCTA-Diabetes typically contains people with diabetes, a glycated haemoglobin level of 7.5% or more, or an admission blood glucose >11.0 mmol/L, aged 18–79 years, and can include people with cardiovascular disease or risk factors for cardiovascular disease; selected body mass index (BMI) criteria include BMI ≥25 kg/m^2 (>23 kg/m^2 for Asians) and ≤45 kg/m^2 (with stable body weight (±5%) for 3 months), and receiving a stable dose of antihyperglycaemic medication for ≥3 months prior to screening, maintenance of prior diet and exercise habits during the study, and women of child-bearing potential using two medically approved methods of contraception and continued use during the course of the trial.

Data access and ethical approval

The Steering Committee governing VICCTA-Diabetes approved the project proposal and granted access to the dataset. VICCTA holds institutional ethical approval (University of Glasgow, MVLS Ethics).

Data extraction

We selected key demographic variables considered to be associated with anxiety/depression and overall health perception following a review of the literature. We extracted data on age, sex, BMI, ethnicity, duration of type 2 diabetes, age at onset, self-reported data on dependency for activities of daily living (ADLs) and medical history. The number of prescribed medications, HbA_{1c} measures, anxiety/depression and overall perception of health at baseline were also extracted.

The self-reported European Quality of Life (EQ-5D-3L) domain score was used to define the presence or absence of anxiety/depression. We defined "no anxiety/depression" as a score of 1 (not anxious/depressed) and "anxiety/depression" as a score of 2 or 3 on the EQ-5D-3L anxiety/depression domain.

We defined the individual perception of health using the self-reported Visual Analogue Scale (VAS) score. A score of 100 translated to the "best health you can imagine" and a score of 0 translated to the "worst health you can imagine".

Statistical analysis

We described the population using summary statistics; continuous variables using medians and IQRs and categorical variables using frequencies and percentages (%). We examined univariable associations among age, sex, ethnicity, BMI, type 2 diabetes duration, polypharmacy, HbA_{1c}, anxiety/depression and VAS scores in regression analyses. In multivariable analyses we included the variables found to be statistically significant in univariable analyses ($p<0.05$). Models were checked for approximate linearity and adjusted for age, sex, ethnicity, BMI and diabetes duration. Logistic regression analyses were reported as odds ratios (OR) and 95% confidence intervals (95% CI) while linear regression models were reported using unstandardised beta coefficients (B) and standardised beta coefficients (β). We excluded participants with missing data from the relevant analyses.

Results

Study population characteristics

The analysis population comprised people with a diagnosis of type 2 diabetes mellitus at 30 years of age or older, an age of at least 55 years at the time of study entry and a history of major macrovascular or microvascular disease or at least one other risk factor for vascular disease.

Data were available from 2,783 people with type 2 diabetes (57% male, median age 66 years, median duration of diabetes

Table 1 Characteristics of the study population

Variable	Number	%
Sex		
Men	1,595	57
Women	1,188	43
Ethnicity		
Caucasian/European	1,667	60
Chinese	842	30
South Asian or South-East Asian	217	7.8
Others	57	2.0
Number of concurrent medications		
0	44	1.6
1–3	1,240	45
4–6	1,198	43
7–10	300	11
>10	1	0
Smoking status		
Current smokers	169	6.1
Ex-smokers	758	27
Non-smokers	1,856	67
Presence of comorbidities		
Prior stroke	259	9.3
Myocardial infarction	327	12
Chronic ischaemic heart disease	174	3.7
Transient ischaemic attack	115	4.1
Heart failure	78	2.8
Atrial fibrillation	151	5.4
Hypertension	1,946	70
Leg ulcers	41	1.5
Retinopathy	606	21.8
EQ-5D-3L anxiety/depression score		
1 (not anxious/depressed)	1,988	72
2 (moderately anxious /depressed)	745	27
3 (extremely anxious/depressed)	37	1.3
	Median	**IQR**
Age (years)	66	61–70
Diabetes duration (years)	7	3–11
Age of T2D onset (years)	58	52–64
BMI (kg/m^2)	27.6	24.7–31.1
HbA_{1c} (mmol/mol)	55	48–66
VAS score according to EQ-5D-3L	80	70–90

BMI, body mass index; EQ-5D-3L, European Quality of Life Score; HbA_{1c}, glycated haemoglobin A1c; IQR, interquartile range; T2D, type 2 diabetes; VAS, Visual Analogue Scale.

7 years and median BMI 27.6 kg/m^2). Caucasian/European ethnicity was most prevalent (60%). The prevalence of current smoking was 6.1% and median HbA_{1C} level was 55 mmol/mol. 28% of participants had anxiety/depression (defined as some or extreme problems on the EQ-5D-3L) and the median VAS score was 80 (Table 1).

Factors associated with anxiety/depression

In univariable analysis, female sex was significantly associated with an increased prevalence of anxiety/depression (p<0.001). Chinese ethnicity (p=0.046), older age (p=0.007) and a lower BMI (p=0.040) were each significantly associated with lower odds of anxiety/depression (Figure 1).

In multivariable analysis, South/South-East Asian versus Caucasian/European ethnicity (OR, 0.67; 95% CI 0.47 to 0.95; p=0.026), Chinese versus Caucasian/European ethnicity (OR 0.75; 95% CI 0.61 to 0.93; p=0.009) and older age (OR 0.98; 95% CI 0.97 to 0.99; p=0.004) were each significantly associated with lower odds of anxiety/depression. Female sex was significantly associated with increased odds of anxiety/depression (OR 2.03; 95% CI 1.71 to 2.41; p<0.001).

We then examined polypharmacy. In univariable analysis (n=2,770), polypharmacy was significantly associated with increased anxiety/depression (OR 1.09; 95% CI 1.04 to 1.13; p<0.001) (Table 2).

Multivariable analyses (n=2,713), adjusting for covariates, revealed that polypharmacy remained significantly associated with increased anxiety/depression (OR 1.09; 95% CI 1.04 to 1.14; p<0.001). Within this model, older age (OR 0.98; 95% CI 0.97 to 0.99; p=0.003), Chinese versus Caucasian/European ethnicity (OR 0.79; 95% CI 0.64 to 0.99; p=0.037) and South/South-East Asian versus Caucasian/European ethnicity (OR 0.67; 95% CI 0.47 to 0.95; p=0.024) were each significantly associated with decreased anxiety/depression. Female sex was significantly associated with increased anxiety/depression (OR 2.05; 95% CI 1.72 to 2.43; p<0.001) (Table 3).

There was no association between dependency for ADLs or HbA_{1C} levels (n=2,761) with anxiety/depression (Figure 1, Table 2).

Factors associated with overall perception of health

In univariable analysis (n=2,770), polypharmacy was significantly associated with lower VAS scores (B= –1.40; 95% CI –1.70 to –1.10, p<0.001) (Table 2). In multivariable analyses (n=2,713), following adjustment for covariates, polypharmacy remained significantly associated with lower VAS scores (B= –1.06, 95% CI –1.37 to –0.75, p<0.001). Within this model, Chinese versus Caucasian/European ethnicity (B=3.73, 95% CI 2.30 to 5.16, p<0.001) and South/South-East Asian versus Caucasian/European ethnicity (B=3.77, 95% CI 1.52 to 6.02, p=0.001) were each

Table 2 Summary of baseline characteristics and design of studies included in this review

Independent variable	Anxiety/depression					VAS score					
	N	OR	95% CI		P value	N	B	95% CI		β	P value
			LL	UL				LL	UL		
No of medications (+1)	2,770	1.09	1.04	1.13	<0.001	2,771	–1.40	–1.70	–1.10	–0.17	<0.001
HbA_{1C} (+1 percentage point)	2,761	1.00	0.94	1.05	0.924	2,762	0.10	–0.28	0.48	0.01	0.616

Odds ratios (OR), 95% confidence intervals (CI) and P values were obtained by logistic regression. Unstandardised beta coefficients (B), 95% confidence intervals (CI), standardised beta coefficients (β) and P values were obtained by linear regression.

HbA_{1C}, glycated haemoglobin A_{1C}; LL, lower limit; ULL, upper limit; VAS, Visual Analogue Scale.

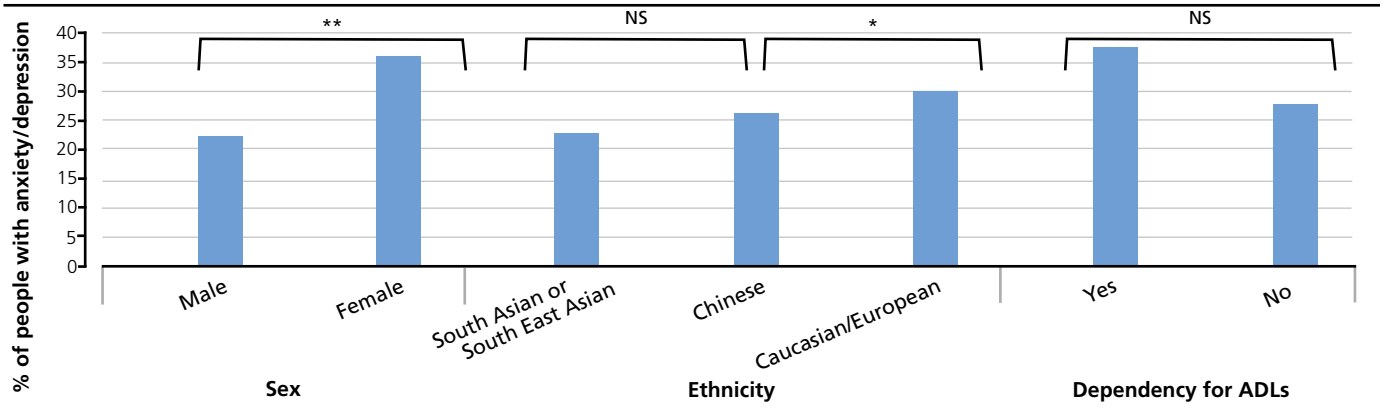
Table 3 Summary of baseline characteristics and design of studies included in this review

Independent variable	Anxiety/depression					VAS score					
	N	OR	95% CI		P value	N	B	95% CI		β	P value
			LL	UL				LL	UL		
Medications	2,713	1.09	1.04	1.14	<0.001	2,714	–1.06	–1.37	–0.75	–0.13	<0.001
Age		0.98	0.97	0.99	0.003		–0.06	–0.15	0.03	–0.03	0.181
BMI		0.99	0.97	1.01	0.412		–0.33	–0.46	–0.20	–0.11	<0.001
Diabetes duration		1.01	0.99	1.02	0.856		–0.04	–0.13	0.05	–0.02	0.410
Female vs male		2.05	1.72	2.43	<0.001		–1.35	–2.50	–0.20	–0.04	0.021
Ethnicity											
Caucasian/ European			Ref					Ref			
Chinese		0.79	0.64	0.99	0.037		3.73	2.30	5.16	0.11	<0.001
South Asian or South-East Asian		0.67	0.47	0.95	0.024		3.77	1.52	6.02	0.07	0.001

Odds ratios (OR), 95% confidence intervals (CI) and P values were obtained by logistic regression. Unstandardised beta coefficients (B), 95% confidence intervals (CI), standardised beta coefficients (β) and P values were obtained by linear regression.

BMI, body mass index; HbA_{1C}, glycated haemoglobin A_{1C}; LL, lower limit; UL, upper limit; VAS, Visual Analogue Scale.

Figure 1. Proportion of people with anxiety/depression according to sex, ethnicity and dependency for activities of daily living



Note: n=2,770 for sex; n=2,713 for ethnicity; n=2,770 for dependency for ADLs.
P values for sex and dependency for ADLs derived from $\chi 2$ test of association. P values for ethnicity derived from logistic regression. *p<0.05; **p<0.001.

ADLs, activities of daily living; NS, not significant.

significantly associated with higher VAS scores. A higher BMI (B= –0.33, 95% CI –0.46 to –0.20, p <0.001) and female sex (B= –1.35, 95% CI –2.50 to –0.20, p=0.021) were each significantly associated with lower VAS scores (Table 3).

HbA_{1c} levels were not associated with VAS scores in univariable analysis (n=2,761) (Table 2).

Discussion

Main findings

In this analysis of pooled data from the placebo groups of diabetes clinical trials, female sex and Caucasian/European ethnicity were each associated with increased anxiety/depression and a lower perception of health. Increased medication burden was also associated with increased anxiety/depression and lower perception of health.

Strengths and limitations of this study

Strengths of this study include a moderate sample size and a multi-ethnic population; although derived from participants in clinical trials, many characteristics were similar to those of people with type 2 diabetes seen in clinical practice.[16] Anonymised clinical trial data were of high quality, near complete and standardised according to operational definitions. Moreover, the 3-point EQ-5D-3L score is a convenient method of detecting anxiety/depression and has been used in other studies including participants with type 2 diabetes.[17–19] One study, albeit from participants without diabetes, found that respondents with diagnosed depression reported more problems on all components of the EQ-5D score than participants with no medical conditions.[20]

In terms of limitations, average glycaemic control was closer to target than in most clinic populations. While the EQ-5D-3L score has its benefits, it only has moderate sensitivity, a "ceiling effect"[17] and may introduce self-reporting bias.

Nevertheless, the associations we observed with anxiety/depression aligned with our findings on quality of life.

Our retrospective analysis of an existing dataset meant we were unable to examine the impact of variables such as stressful life events, fear of hypoglycaemia, health literacy and diabetes distress. Finally, we did not adjust for multiplicity in these exploratory analyses.[21]

Interpretation of findings in relation to previously published work

Our study showed that 28% of participants reported having anxiety/depression using the EQ-5D-3L scale. Studies using other self-reporting measures[22,23] and clinician-led measures[24–26] show similar figures.

Our observation of sex differences in anxiety/depression supports findings in previous studies.[5,27] Lower EQ-5D scores both in women with type 2 diabetes and in the general population have also been previously reported.[28,29]

In addition, there have been previous reports that Caucasian participants with type 2 diabetes are at increased risk of depressive symptoms.[30] Moreover, there is evidence, albeit from populations without diabetes, that people of non-Caucasian ethnicities are less likely to seek help regarding mental health than Caucasians.[31] Non-Caucasian/European participants may therefore have been less likely to self-report anxiety/depression.

We observed that, for each additional prescribed medication, the risk of anxiety/depression increased by approximately 9%. This is in keeping with results from previous research from other populations.[12] Number of prescribed medications may be an indicator of disease severity (ie, a marker of more severe/advanced type 2 diabetes with associated anxiety/depression and lower quality of life). However, clinicians should be aware of the negative impacts of polypharmacy and, where possible, review and/or minimise the number of prescribed medications as this may reduce anxiety/depression and improve quality of life.

Our observation of a lack of association between HbA_{1c} and anxiety/depression differs from previous research.[27,32] Although

Key messages

- In a multi-ethnic clinical trial population with type 2 diabetes, female sex, Caucasian/European and polypharmacy were each associated with increased anxiety/depression and lower health perception.
- These findings could contribute to development of future interventions to better manage and support people with type 2 diabetes.

our sample size was moderate, we acknowledge that there may not have been sufficient statistical power given the relative insensitivity of the anxiety/depression scoring on the EQ-5D-3L (a 3-point ordinal scale).

Implications for future research, policy and practice

Our findings have clinical relevance: anxiety and depression can be a barrier to self-management for people with type 2 diabetes and heighten the risk of severe and life-changing microvascular and macrovascular complications. In addition, diabetes distress (defined as unease occurring due to the self-managing nature of diabetes and the future possibility of complications) is associated with higher HbA_{1c} .[27,33,34] Increased awareness of mental health conditions among specific high-risk subpopulations of people with type 2 diabetes, such as women and Caucasians, may contribute to improving outcomes.[35]

Conclusion

Female sex, Caucasian ethnicity and polypharmacy are associated with increased anxiety/depression in people with type 2 diabetes. These findings could contribute to development of future targeted interventions to better manage and support mental health and quality of life in people with type 2 diabetes.

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Very low-calorie diet in patients with longstanding type 2 diabetes mellitus: a study of real-world outcomes

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Abstract

Introduction: There is a paucity of evidence regarding the efficacy of a very low-calorie diet (VLCD) in the real-world setting. We evaluated outcomes in patients with type 2 diabetes mellitus (T2DM) who underwent VLCD.

Methods: This retrospective observational study included all patients who had undergone VLCD from 2014 to 2017 (n=61). The VLCD consisted of an eight-week 800 kcal/day dietary restriction. Metabolic parameters and medications were recorded at baseline, immediately post-VLCD and at 6 and 12 months.

Results: There was a significant reduction in weight of 9.96 kg ($p<0.001$) immediately post-VLCD, with net weight loss sustained to 12 months ($p<0.05$). There was a significant reduction in body mass index (BMI) sustained to 12 months ($p<0.05$). Paired HbA_{1c} data were available for 38 patients. There was a significant reduction in HbA_{1c} of 13.29 mmol/mol immediately post-VLCD ($p<0.001$), however no significant reduction was observed at 12 months ($p>0.05$). 78.7% patients had a reduction in T2DM medication burden post-VLCD, sustained in 44.3% of patients at 12 months. Analysis of patients with T2DM diagnosis duration >6 years demonstrated statistically significant weight loss sustained to 12 months ($p<0.001$).

Conclusion: Our results demonstrate sustained reduction in BMI and weight, reduction in medication burden and temporary reduction in HbA_{1c} in patients with T2DM undertaking a VLCD in the real-world setting

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Key words: very low-calorie diet (VLCD), obesity, type 2 diabetes mellitus (T2DM), weight, glycosylated haemoglobin (HbA_{1c})

Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterised by peripheral insulin resistance and/or insulin deficiency.[1] It is rapidly becoming an epidemic, with the global prevalence of diabetes amongst adults aged over 18 years rising from 4.7% in 1980 to 8.5% in 2014.[2] Diabetes mellitus (DM) carries a significant risk of morbidity and mortality, currently representing the fifth largest cause of death globally.[3]

A study from the UK published in 2012 predicted that the annual cost of direct patient care for people with diabetes (treatment, intervention and management of complications) will increase from £9.8 billion to £16.9 billion in the next 25 years.4 A significant proportion of this cost is attributed to T2DM, which accounts for 90% of all DM.

The relationship between T2DM and obesity is well established. For every 1 kg of weight gain there is a 9% increase in the relative risk of developing T2DM.[5] Weight reduction is the principal management strategy for the prevention and management of T2DM as it reduces insulin resistance, improves glycaemic control and reduces cardiovascular risk and mortality.[2]

T2DM has historically been considered a progressive and irreversible condition with a high prevalence of microvascular complications and loss of beta cell function frequently present at diagnosis, thus treatment was aimed at slowing the progression of such complications.[6] In the last two decades, however, it has been observed that patients with T2DM may go into remission following bariatric surgery.[7-8] Diabetes remission, as defined by the Association of British Clinical Diabetologists (ABCD) and the Primary Care Diabetes Society (PCDS) in a recent consensus statement, is the "achievement of glycaemia below the threshold currently used for the diagnosis of T2DM, which is sustained for at least 6 months off glucose lowering therapy".[9] Results of studies investigating the role of bariatric surgery in T2DM remission have been remarkable and this link is now considered well-established.

More recently, the feasibility of achieving remission through methods other than surgery has been demonstrated, most notably with the use of a low-calorie diet (LCD) or very low-calorie diet (VLCD).[10–13] VLCD is defined as a diet of less than 800 kcal per day.[14] The percentage energy derived from protein compared with car-

bohydrate and fat is increased, enhancing lipolysis and ketosis while preventing a negative nitrogen balance, thus sparing lean body mass.[15] In principle, the visceral fat reduction triggered by this acute calorie deficit may result in improved hepatic insulin sensitivity and pancreatic beta-cell function, which in turn delivers improvement in glycaemic control that is comparative with bariatric surgery.[16–19] Recent clinical trials have provided firm evidence for the efficacy of VLCD in a controlled setting with carefully selected patients;[10,11] however, to date there is a paucity in real-world evidence of VLCD programme use in patients with a wide spectrum of T2DM disease severity and duration. Moreover, there are limited data regarding long-term outcomes following VLCD. In this study we aim to evaluate metabolic and glycaemic outcomes for patients with T2DM who had undertaken a VLCD in our secondary care institution.

Methods

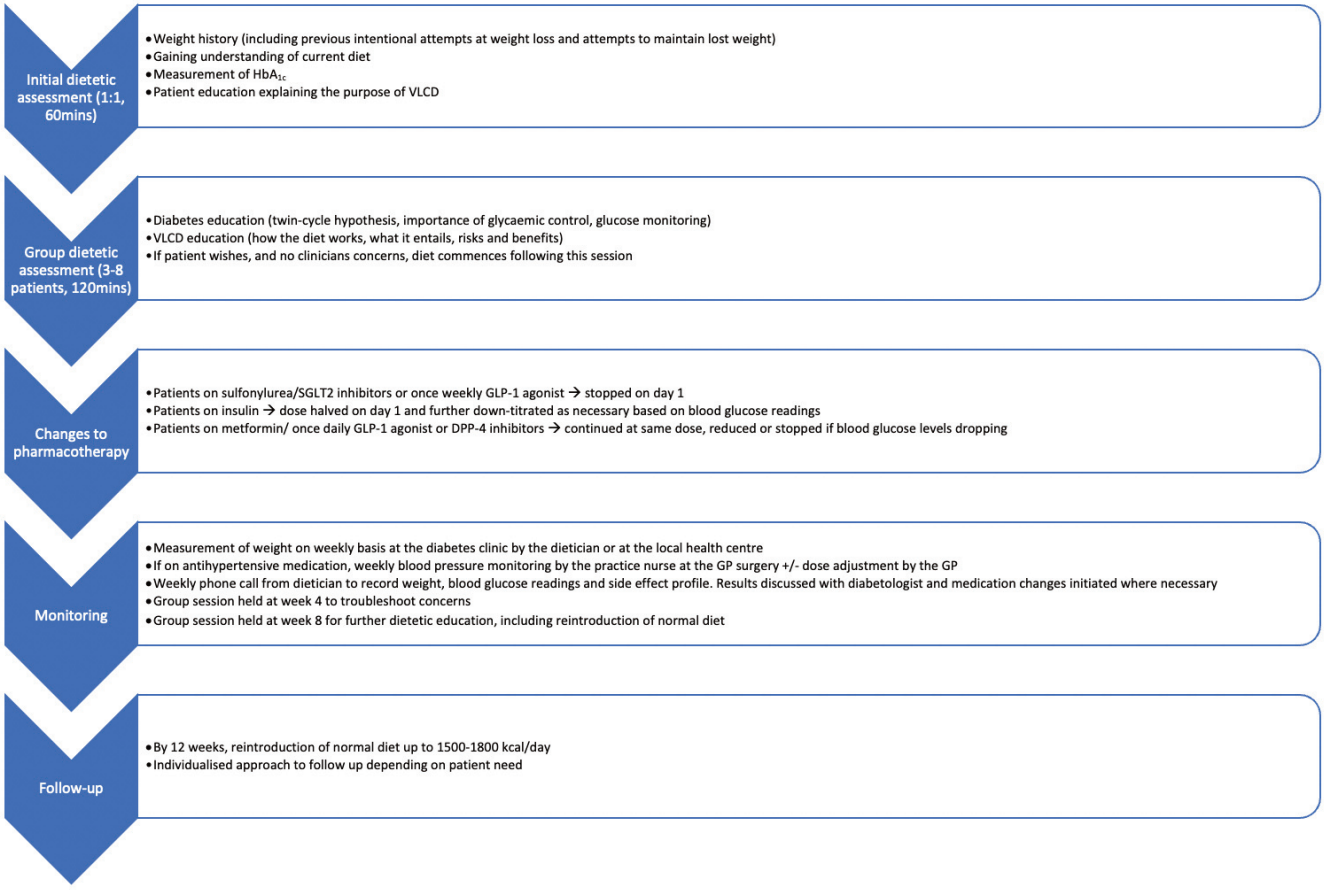
A service which supported patients undertaking a VLCD was introduced in our centre in 2014. The service was dietetics-led; however, there was substantial diabetologist involvement due to the broad selection criteria. In contrast to published literature, patients were not excluded on the basis of their duration of diabetes or degree of polypharmacy and patients taking insulin therapy were eligible for inclusion.

The service model is outlined in Figure 1. Our programme involved the use of 600 kcal of meal replacement products per day with up to 200 kcal ring-fenced to allow the patient to choose and make a vegetable or salad-based meal. Weight was measured weekly. Support was provided in the form of weekly dietitian-led telephone calls with group meetings at weeks 4 and 8 to provide ongoing education and facilitate troubleshooting.

Data collection

Following local institutional approval (registration no. 18/412), all patients who had undertaken a VLCD programme between the inception of the service (August 2014) and December 2017 were retrospectively identified (n=61). Only patients who had completed the full VLCD course were included. Electronic patient records were accessed with clinic letters, investigation results and dietetic notes reviewed. Data were collated onto a secure electronic database containing categories encompassing patient demographics, weight change, glycaemic and metabolic parameters. In addition, the documented medications of patients were recorded at each time point. The medication burden was assessed between time points and deemed to have decreased if the overall number or dose of diabetes-related medications (metformin, sulfonylurea, sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP1) agonists, dipeptidyl peptidase-4 (DPP4) inhibitors,

Figure 1. The VLCD model used at our institution



thiazolidinediones, insulin) had decreased between the two time points.

The primary outcome measure was change in weight between pre-VLCD and time points of immediately post-diet, 6 months post-diet and 12 months post-diet. Key secondary outcomes included changes in HbA_{1c} and medication burden at equivalent time points. Sub-group analysis assessed these outcomes with patients according to duration of diabetes and duration of their follow-up post-VLCD.

Data analysis

Statistical analysis was undertaken in SPSS version 25.0 for Windows (IBM corporation). The Shapiro–Wilk test (if n <50) or Kolmogorov–Smirnov test (if n >50) was performed to assess for normality of distribution, defined as p>0.05. Parametric data were analysed using paired-samples t-test for pre- and post-VLCD values and independent samples t-test for non-paired data. Non-parametric data were analysed using Mann–Whitney U test and $\chi 2$ test as appropriate. Parametric data are presented as mean±standard deviation unless otherwise stated. Non-parametric data are presented as median±range/interquartile range unless otherwise stated. Statistical significance was defined as per the standard value of p<0.05.

Results

Baseline characteristics

Sixty-one patients commenced on VLCD between August 2014 and December 2017. The mean age of patients was 55.20 years (range 36–75 years). There were 34 males and 27 females (M:F=1.26:1). The mean number of weeks on the diet was 7.97 weeks (±0.26 weeks); while most patients completed 8 weeks, a small number of patients completed just over 7 weeks but were deemed to have completed the course by the service clinicians. The mean starting weight for patients was 108.16 kg (±19.08 kg). Mean baseline BMI was 38.21 kg/m^2 (±6.25 kg/m^2). The mean starting HbA_{1c} was 79.60 mmol/mol (±16.99 mmol/mol). The mean length of follow-up post-completion was 23.93 months (±16.86 months). There were no documented adverse events.

Impact of VLCD on metabolic parameters

Weight measurements were obtained for pre-VLCD, immediately post-VLCD, 6 months post-VLCD and 12 months post-VLCD. The mean starting weight for patients was 108.16 kg (±19.08 kg). There was a significant reduction in mean weight post-VLCD of 9.96 kg (±6.02 kg, 95% CI 8.32 to 11.61; p<0.001), equating to a 9.3% loss in total body weight. This significant reduction was maintained to 6 months post-VLCD with a mean weight loss compared with baseline of 10.93 kg (±8.27 kg, 95% CI 8.09 to 13.77; p<0.001), equating to a 10.1% loss in total body weight. Despite moderate weight gain between 6 and 12 months post-VLCD, there was still a significant net reduction in body weight of 5.67 kg (±11.64 kg) at 12 months compared with pre-VLCD (95% CI 1.16 to 10.19; p=0.016), equating to an overall weight loss of 5.2% at 12 months compared with baseline.

Paired BMI data were available for 27 patients at the baseline and 12 month time points. Mean baseline BMI was 38.21 kg/m^2 (±6.25 kg/m^2). Mean BMI at 12 months was 36.01 kg/m^2 (±7.28 kg/m^2), equating to a significant mean reduction in BMI of 2.20 kg/m^2 (95% CI 0.53 to 3.84; p=0.01).

Paired sample HbA_{1c} readings were available for 38 patients for pre-VLCD, post-VLCD, 6 months post-VLCD and 12 months post-VLCD. The mean starting HbA_{1c} was 79.60±16.99 mmol/mol (9.4±3.7%). There was a significant reduction in HbA_{1c} of 13.29±17.65 mmol/mol (3.4±3.8%) between pre-VLCD and immediately post-VLCD time points (95% CI 7.49 to 19.09; p<0.001). However, a significant overall net reduction in HbA_{1c} was not sustained to 6 months or 12 months (p>0.05).

Impact of VLCD on medication burden

The results are shown in Table 1. Of note, 78.7% of patients were prescribed fewer diabetes-related medications after completing VLCD, with 57.4% of patients continuing to have a reduced medication burden at 6 months and 44.3% of patients at 12 months.

Twenty-three of the 61 patients (37.7%) were prescribed insulin prior to commencing VLCD. Data were obtained for changes in insulin dosage immediately post-VLCD, at 6 months and at 12 months. The results are shown in Table 2. 95.7% of patients were using less insulin after completing VLCD, with 65.2% of patients maintaining this reduction to 6 months and 52.1% to 12 months. Additionally, 6/23 (26.1%) patients no longer required any insulin at all 12 months post-VLCD.

The cost of diabetic medications (not including insulin) was approximated using National Health Service (NHS) pricing guidelines. The mean cost of diabetic medications per patient per month prior to undertaking VLCD was £56.29. The mean cost of diabetic medication per patient per month at 12 months post-VLCD

Table 1 Medication changes in patients on a very low-calorie diet

	Post-VLCD	6 months	12 months
Lower net medication burden	48 (78.7)	35 (57.4)	27 (44.3)
Same net medication burden	5 (8.2)	10 (16.4)	11 (18.0)
Higher net medication burden	0 (0)	1 (1.6)	4 (6.6)
N/A	8 (13.1)	15 (24.6)	19 (31.1)

Data are presented as n (%).
N/A denotes data not available or applicable and includes both patients for whom there was a lack of documentation of medication changes or who had not been on any diabetes-related medication at any time.

Table 2 Insulin dose changes in patients on a very low-calorie diet

	Post-VLCD	6 months	12 months
Lower net insulin prescription	22 (95.7)	15 (65.2)	12 (52.1)
Same net insulin prescription	0 (0)	2 (8.7)	1 (4.3)
Higher net insulin prescription	1 (4.3)	2 (8.7)	2 (8.7)
N/A	0	4 (17.4)	8 (34.9)

Data are presented as n (%). N/A denotes data not available

completion was £40.40. This equates to an estimated mean cost saving of £15.89 per patient per month (28.23% estimated cost saving, p=0.024).

VLCD in patients with a diagnosis of T2DM for over five years

Patients were stratified according to duration of diagnosis of T2DM. Nine of 61 (14.8%) patients had received a diagnosis of T2DM ≤5 years of starting VLCD, 10/61 (16.4%) patients had been diagnosed for 6–10 years, 14/61 (23.0%) had been diagnosed for 11–15 years and 15/61 (24.6%) patients had been diagnosed for ≥16 years (24.6%). Data on duration of diagnosis were unobtainable for 13 (21.3%) patients.

Patients with a T2DM diagnosis for >5 years (n=39) had a significant reduction in weight at post-VLCD and 6 months (p<0.001) and 12 months (p=0.013). There was also a significant reduction in HbA1c (p=0.001) in this cohort immediately post-VLCD, but this was not sustained to 6 or 12 months.

Patients with a T2DM diagnosis for >10 years (n=29) had a significant reduction in weight at post-VLCD and 6 months (p<0.001), which was not sustained at 12 months (p=0.137). A significant reduction in HbA_{1c} (p=0.007) was noted post-VLCD in this cohort, not sustained to 6 or 12 months.

Patients with a T2DM diagnosis for >15 years (n=15) demonstrated a significant reduction in weight at post-VLCD and at 6 months (p<0.001), which was not sustained at 12 months (p=0.532). No significant reduction in HbA_{1c} was noted at any time point in this cohort.

Discussion

This retrospective observational study provides valuable real-world outcomes of VLCD utilisation in patients with a spectrum of T2DM duration and severity. Notably, our results demonstrate significant weight loss in the overall cohort, sustained to 6 and 12 months post completion of the diet, that support the conclusions of tightly managed randomised controlled trials (RCTs).[10,11]

The eligibility criteria for patients undertaking VLCD at our institution were broad; patients were not excluded on the basis of their age, duration of T2DM or medication regimen. In contrast, much of the evidence surrounding VLCD in T2DM comes from interventional trials with strict inclusion and exclusion criteria; the Counterpoint study restricted inclusion to patients aged 35–65 years with an HbA_{1c} of 48–75 mmol/mol, BMI 25–45 kg/m^2 and diabetes duration <4 years, while the DiRECT trial included patients aged 20–65 years with an HbA_{1c} <108 mmol/mol, BMI 27–45 kg/m^2 and diabetes duration <6 years.[10,11,20,21] While the breadth of disease severity and baseline characteristics have the potential to confound outcomes in our study, the significant weight loss we demonstrate in our overall cohort supports the assertion that VLCD can be effective, at least in the short to medium term, regardless of T2DM disease duration or severity.

Indeed, significant weight loss was seen in the whole cohort with a net reduction of 5.2% (5.67 kg) sustained at 12 months follow-up. While this percentage is lower than the 12-month results in the DiRECT trial (which may be the result of a less intensive follow-up regime in the real-world setting), it nonetheless represents clinically significant weight loss. Previous studies of VLCD in T2DM have demonstrated the benefits of weight loss following acute calorie deficit on pericardial fat and on markers of renal and hepatic health.[22,23] Information on lipid profiles and measures of hepatic function were limited in our cohort of patients and were therefore not available for analysis, a limitation of this retrospective approach to this study. Nonetheless, it is likely that an initial mean weight loss of approximately 10% and sustained weight loss of approximately 5% will have clinically relevant benefits for a number of obesity- related co-morbidities.[24] Meanwhile, our subgroup analysis seems to suggest that there is little sustained benefit in terms of weight loss and HbA_{1c} following VLCD in patients with a diabetes duration >10 years (although their medication burden may be reduced).

Despite initial significant reduction in HbA_{1c} in our cohort, this was not sustained to 6 or 12 months. This is in contrast to the DiRECT trial, where there was an overall significant reduction in HbA_{1c} of 0.9% at 12 months.[11] Notably, in DiRECT, HbA_{1c} reduction was proportionate to weight loss; 7% patients who lost 0–5 kg at 12 months achieved remission of T2DM, with this rising to 34% in patients who lost 5–10 kg. Given the mean weight loss at 12 months in our study was approximately 5 kg and paired HbA_{1c} readings were only available for 38 patients, this may help to explain the lack of statistical significance in HbA_{1c} improvement at 12 months.

As an evaluation of standard care, our study did not have the intensive follow-up from which patients in a trial setting would benefit; while in DiRECT patients received a review at the end of week 1, then a face-to-face review every other week until week 18, and then a face-to-face monthly review thereafter. In our centre, patients received telephone contact from dietetic staff during weeks 1–3 and 5–7, with a face-to-face group session at weeks 4 and 8 of the intervention period. Subsequently, patients returned to normal standard of care (for most, 6-monthly secondary care appointments). It is likely that intensive contact may have contributed to the improved HbA_{1c} and weight loss outcomes seen in DiRECT along with DiRECT patients having shorter duration of T2DM (<6 years), which would mean that they had higher chances of reinstituting intrinsic insulin production. However, this has to be balanced against the resource implications of a high number of face-to-face appointments in a publicly-funded healthcare system. In future, it may be beneficial to have regular (3-monthly) HbA_{1c} checks with telephone follow-up to identify and address worsening glycaemic control at an early enough stage to facilitate intervention and ultimately maintain the post-VLCD HbA_{1c} improvement seen in our study. Additionally, due to the retrospective nature of our study and the lack of structured follow-up, HbA_{1c} values were often missing at the 6 and 12 month time points, and it may be that a more structured approach to follow-up would enable patients to achieve positive outcomes in HbA_{1c}.

Our results demonstrate a significant reduction in diabetes medication burden post VLCD, sustained in almost half of patients to 6 and 12 months. Medication burden was also assessed in DiRECT; patients in the intervention group had a mean reduction of 0.8 oral

Key messages

- VLCD can be an effective treatment in T2DM population up to 10 years from diagnosis
- An element of patient food choices can be safely incorporated within a VLCD programme without compromising efficacy
- Re-introduction of medications post-VLCD is a critical balance between minimising medication burden and optimising HbA_{1c}

antidiabetic medications per patient at 12 months.[11] While improvement in HbA_{1c} remained significant at 12 months alongside the medication reduction in DiRECT, in our study a significant reduction in HbA_{1c} was not maintained in line with reduction in medication burden. Notably, the number of medications at baseline was greater per patient in our study, indicating greater medication burden and thus posing a different challenge in managing medications during and post-VLCD. Additionally, approximately one in four patients who were prescribed insulin pre-VLCD in our study were no longer requiring insulin at 12 months, and in those originally prescribed insulin who had an improvement in HbA_{1c}, 80% also saw a concomitant reduction in insulin burden. Being on insulin was an exclusion criterion for DiRECT, thus limiting the ability to draw comparisons between trial and real-world evidence, but the reduction in insulin burden seen in this study is promising.

Re-introduction of medications post-VLCD is a critical balance between minimising medication burden and optimising HbA_{1c}. There is a lack of evidence base informing this balance, and thus reintroduction of medications is often managed on a patient-by-patient and clinician-by-clinician basis. Given the more intensive follow-up regimen in DiRECT, it is possible that reintroduction of medication was managed more closely and that, with more structured follow-up post-VLCD, a reduction in medication burden can be achieved alongside improvement in HbA_{1c} in the real-world setting. Further work is needed to establish the optimal pathway for reintroduction of medications post-VLCD. Additionally, whilst we have noted a cost saving associated with the reduction in medication burden, this is offset to some degree by the lack of improvement in HbA_{1c} and the long-term complications associated with worsening glycaemic control.

The 8-week diet programme (Figure 1) was tailored to patient need, with 200 kcal per day for patients to choose a vegetable-based meal to cook themselves from recipes provided by the department. While this pragmatic approach does reduce the controlled nature of the VLCD regime, it also offers some notable advantages; encouraging cooking, particularly vegetable-based cooking, may help facilitate long-term behaviour change for the better and thus maintenance of weight loss.[25–27] Additionally, qualitative analysis of patient satisfaction with VLCD in T2DM has revealed that lack of variation in the diet is a risk factor for poor compliance;[28] introducing this element of choice may facilitate improved satisfaction and thus potentially improve concordance with the regimen. Our results show that an element of patient choice can be safely incorporated within a VLCD programme without compromising efficacy.

The VLCD programme at our institution incorporates a significant amount of patient education, both in groups and on a one-to-one basis, centring around improving patient understanding of T2DM. It is well acknowledged that multimodal patient education plays a pivotal role in promoting health behaviour change and reducing long-term complications associated with T2DM through improved self-care.[25,27,29] Empowering patients with the knowledge to understand their glycaemic control and the mechanism by which VLCD might improve their T2DM in turn may well support long-term results beyond the VLCD follow-up.[30] Further work is needed to evaluate the effect of VLCD education (including different educational tools) on long-term glycaemic and metabolic outcomes, as well as qualitative analysis of patient experience and the effect of socio-demographics on outcomes. In future, the ongoing NHS England Low Calorie Diet pilot may shed light on some of these outcomes; individuals undertaking a low-calorie diet will be supported to achieve their goals via either group, one-to-one or digital/app-based support, and comparison of outcomes between these methods as well as patient experience may facilitate more tailored support for individuals undertaking low-calorie/VLCD in future.[31]

Despite our study providing important real-world outcomes to support RCT data, we acknowledge there are a number of limitations to our work. Firstly, retrospective data collection raises the possibility of a greater degree of influence due to unmeasured confounders, and also to selection and misclassification bias although every effort was made to minimise these by having two data collectors corroborate entries whenever unclear. In addition, there is a lack of control arm in our study. Our data do not include information on baseline socio-demographic difference, lipid profiles, blood pressure or markers of liver dysfunction; heterogeneity in reporting and timing of measurements introduced a large degree of confounding into these data and thus the results were not analysed. Further prospective work will ensure standardisation in such data collection. Furthermore, data are not available for the referral rate to the service nor the dropout rate amongst participants who did not complete the course. Due to the retrospective nature of the study and the changes in provision as the service developed, accurate data surrounding the cost implications of running a VLCD service have not been accurately captured; further prospective work should aim to undertake formal cost analyses.

Conclusion

Our study demonstrates a significant reduction in weight to 12 months post-VLCD in a heterogeneous group of patients with T2DM. Additionally, our work shows that a VLCD programme can be safely and successfully delivered with modifications from clinical trial protocols that allow for a more pragmatic approach in the real-world clinical setting. Further prospective studies assessing long-term efficacy in multiple metabolic parameters are required to validate the findings of this study.

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Contributorship MN and SM contributed to the study design, data collection, data analysis, writing and revision of the manuscript. RL and VW contributed to data collection and writing and revision of the manuscript. MR, EJ and AD contributed to study design, writing and revision of the manuscript. LNRB was responsible for the study concept and contributed to study design, writing and revision of the manuscript.

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COVID-19 outcomes in people with diabetes in Wales: a secondary analysis of the ABCD audit

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Abstract

Background: **People with diabetes and coronavirus disease 2019 (COVID-19) have a significantly greater risk of death and/or intensive care unit (ICU) admission. The Association of British Clinical Diabetologists (ABCD) recently audited outcomes for people hospitalised in the UK with diabetes and COVID-19.**

Methods: **The ABCD COVID-19 and diabetes audit was a retrospective audit of patients admitted to UK hospitals with diabetes and COVID-19 between March and December 2020. Data related to patients admitted in Wales were compared with patients admitted in England and Scotland.**

Results: **In Wales, 40/82 (48.7%) patients with diabetes had COVID-19-related mortality compared with 1,149/2,916 (39.1%) in the UK group (p=0.08). The Welsh cohort were more likely to be Caucasian, have a higher body mass index and HbA1c, be diagnosed with diabetic retinopathy and prescribed a sodium-glucose co-transporter 2 inhibitor or insulin than those in England and Scotland. Patients admitted to the ICU in Wales were more likely to be male and have type 2 diabetes.**

Conclusions: **Patients admitted to hospital with diabetes and COVID-19 in Wales had a poorer outcome compared with England and Scotland. This disparity may reflect social inequality, differences in cardiovascular risk factors and/or differences in diabetes medications between hospitalised patients in Wales and the UK.**

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Key words: COVID-19, diabetes, Wales, United Kingdom

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Background

The extraordinary impact of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) on health systems, global economics and everyday life is unprecedented. At the time of writing, around 187 million cases of coronavirus disease 2019 (COVID-19) have been confirmed worldwide, associated with over 4 million deaths.[1] Epidemiological studies have found that the risk of death or admission to an intensive care unit (ICU) with COVID-19 is much greater in people with increasing age, significant medical comorbidity (diabetes, cardiovascular disease, renal disease), non-white ethnicity, male gender or social deprivation.[2–5]

Indeed, a third of people who died in the UK during the first wave of COVID-19 in England had underlying diabetes. People with type 1 diabetes (T1D) and type 2 diabetes (T2D) had an odds ratio for in-hospital death of 3.51 (95% CI 3.16 to 3.90) and 2.03 (95%

CI 1.97 to 2.09), respectively, relative to people without diabetes.[6] Mortality rates in people with diabetes and COVID-19 in the UK were greater in older people and in those of male gender, non-white ethnicity, socioeconomic deprivation, poorer glycaemic control, obesity and previous renal or cerebrovascular disease and cardiac failure.[3] Several biological interactions have been suggested to explain the excess risk of poor COVID-19 outcomes in people with diabetes. These include increased angiotensin-converting enzyme-2 receptor glycosylation, dipeptidyl peptidase-4 (DPP4) receptor expression, the association between diabetes and obesity, cardiovascular and/or renal disease and possibly an interaction with some pharmacotherapies used to treat diabetes.[7]

In view of the increased risk reported in people with diabetes and COVID-19, the Association of British Clinical Diabetologists (ABCD) recently undertook a UK-wide audit of outcomes in people with diabetes and COVID-19. In this paper we aim to determine the relative outcomes and characteristics of the patients in Wales and compare these with the UK results.

Methods

The ABCD audit primarily aimed to determine the characteristics and outcomes of people with T1D and T2D admitted to hospital with COVID-19. Secondary aims were to determine whether any patient factors such as ethnicity, obesity, medical comorbidity, glycaemic control or diabetes treatments were associated with the observed health outcomes. Data were collected by clinical teams across the UK and submitted centrally using a specific data collection tool registered to each centre.[8]

Patient data were collected retrospectively for demographics, patient outcomes, body mass index (BMI), glycaemic control, renal function, diabetes complications, medical comorbidities and diabetes treatments across the UK by individual clinical sites. Complete data were collected for 3,413 inpatients admitted to UK hospitals between March and December 2020.[8] Data for patients in Wales were extracted from the complete dataset and compared with data from patients in England and Scotland.

Ethical approval

The audit was registered with Oxford University Hospitals NHS Foundation Trust (OUH) and a data protection impact assessment carried out by the steering group was reviewed by the OUH Caldicott Guardian for use in England and Wales, and by the Public Benefit and Privacy Panel for use in Scotland (reference 2021-0111).[8] Data collected as part of this audit included routinely collected clinical data only, communicated in pseudonymised form via the secure NHS network. Therefore, this audit did not require research ethics committee approval.[9]

Outcomes

The primary outcome of this analysis was to determine mortality and ICU admission outcomes of patients admitted to hospitals in Wales with COVID-19 and diabetes. Secondary outcomes were to determine the characteristics of patients admitted to hospitals in Wales, clinical features associated with greater risk of ICU admission and to compare outcomes and clinical characteristics of patients admitted with COVID-19 and diabetes in Wales with the rest of the UK.

Statistical analysis

Continuous variables are presented as mean (SD) and statistical significance was determined using a paired t-test. Categorical data are presented as the absolute number (%) and statistical significance determined using a χ^2 test. Statistical significance was considered at $p<0.05$.

Results

Clinical characteristics and outcomes of Welsh population

Clinical characteristics of the 104 patients with diabetes and COVID-19 in Wales are presented in Table 1. Some data are missing and the data available are presented. Patients had a mean age of 72 years and 55.7% were male with a mean BMI of 33.5 kg/m^2 and mean HbA_{1c} of 67 mmol/mol (8.3%). Table 2 summarises the pre-existing diabetes-associated complications and diabetes pharmacotherapy prescribed for these patients. At presentation to hospital services, 5.8% of patients admitted in Wales were in diabetic ketoacidosis (DKA).

During admission to hospital with COVID-19, 45/104 (43.2%) patients in Wales died and/or were admitted to the adult intensive care unit (AICU) and 40/82 (48.7%) of the patients died (missing data for 22 patients). Greater mortality was observed with increasing age in these patients: <55 years, 3/11 (27.3%); 55–74 years, 15/34 (44.1%) and ≥75 years, 22/37 (59.5%) patients died. In the Welsh cohort, death and/or admission to AICU were significantly more likely in males and in patients with T2D rather than T1D, as shown in Table 3. There was no statistically significant association between death and/or admission to AICU with ethnicity, age, BMI, admission blood glucose, HbA1c, creatinine, medical comorbidity or diabetes pharmacotherapy in the Welsh cohort.

Comparing Welsh and UK outcomes and population characteristics

As shown in Table 1, people in Wales admitted with diabetes and COVID-19 had a non-significant trend for increased mortality compared with those admitted in the rest of the UK (40/82 (48.7%) vs 1,149/2,916 (39.1%), p=0.08) and a similar rate of death and/or admission to AICU. Patients admitted in Wales were significantly more likely to be Caucasian, have a greater BMI or HbA1c and had a comparable rate of medical comorbidities compared with patients admitted across the rest of the UK.

Patients with COVID-19 and diabetes admitted to hospital in Wales were significantly more likely to have diabetic retinopathy and be prescribed a sodium-glucose co-transporter 2 (SGLT-2) inhibitor or insulin than patients admitted across the rest of the UK. There were no significant differences in the rates of other diabetes complications including DKA or medication prescriptions between the groups (Table 2).

Discussion

In this secondary analysis of the ABCD audit we aimed to determine the outcomes of the 104 patients admitted with diabetes and

Table 1 Comparison of the major outcomes of death or AICU admission, patient demographics and comorbidity between patients with diabetes and COVID-19 in Wales and the UK

Clinical features	Wales (n=104)	UK (n=3309)	Hazard ratio	P value
Death	40/82 (48.7%)	1109/2834 (39.1%)	1.24	0.08
Death and/or AICU	45/104 (43.2%)	1319/2976 (44.3%)	0.98	0.83
Male/total patients (%)	58/104 (55.7%)	1950/3129 (62.3%)	0.89	0.18
Mean (SD) age (years)	72 (13)	72 (14)	–	1.00
Ethnicity	White (71/80, 88.8%) Asian (1/80, 1.2%) Black (2/80, 2.5%) Other (6/80, 7.5%)	White (1839/2836, 64.8%) Asian (472/2836, 16.6%) Black (218/2836, 7.7%) Other (317/2836, 11.1%)	–	<0.01 <0.01 0.08 0.30
BMI (kg/m^2)	33.5 (7.7)	29.3 (7.1)	–	<0.01
Admission blood glucose (mmol/L)	11.8 (7.4)	11.1 (6.8)	–	0.34
HbA_{1c} (mmol/mol)	67 (24)	57 (26)	–	<0.01
Creatinine (µmol/L)	144 (110)	153 (162)	–	0.42
Hypertension	70/96 (72.9%)	2045/2943 (69.5%)	1.05	0.47
Dementia	15/92 (16.3%)	400/2693 (14.9%)	1.10	0.70
Asthma	18/97 (18.6%)	395/2757 (14.3%)	1.30	0.25
COPD	18/97 (18.6%)	365/2568 (14.2%)	1.31	0.23
Malignant neoplasm	14/94 (14.9%)	436/2819 (15.5%)	0.88	0.88
Smoker	6/78 (7.7%)	123/1575 (7.8%)	0.98	0.97

The significance of differences in categorical data was determined by χ^2 test and significance of differences in continuous data by paired t-test.
AICU, adult intensive care unit; BMI, body mass index; COPD, chronic obstructive pulmonary disease; HbA_{1c}, glycated haemoglobin; SD, standard deviation.

Table 2 Comparison of the rates of diabetes complications and diabetes pharmacotherapy prescription between patients with COVID-19 and diabetes in Wales and the UK

Clinical features	Wales (n=104)	UK (n=3309)	Hazard ratio	P value
DKA on admission	6/103 (5.8%)	101/2815 (3.6%)	1.62	0.24
Diabetic foot ulcer	11/94 (11.7%)	174/2157 (8.1%)	1.44	0.21
Nephropathy	19/95 (20.0%)	554/2215 (25.0%)	0.80	0.27
Peripheral neuropathy	18/92 (19.6%)	294/2224 (13.2%)	1.48	0.08
Diabetic retinopathy	35/90 (38.9%)	516/2159 (23.9%)	1.63	<0.01
Microvascular disease	45/101 (44.6%)	1011/2458 (41.1%)	1.08	0.49
Macrovascular disease	48/102 (47.1%)	1119/2753 (40.6%)	1.16	0.20
Metformin	40/91 (44.0%)	1472/2950 (49.9%)	0.88	0.26
Sulfonylurea	16/78 (20.5%)	582/2907 (20.0%)	1.03	0.92
DPP-4 inhibitor	20/82 (24.4%)	669/2900 (23.1%)	1.06	0.78
GLP-1 analogue	3/73 (4.1%)	96/2880 (3.3%)	1.23	0.75
SGLT-2 inhibitor	17/93 (18.3%)	185/2736 (6.8%)	2.70	<0.01
Insulin	39/84 (46.4%)	971/2753 (35.3%)	1.32	0.04

Significance of differences in categorical data was determined by χ^2 test.
DKA, diabetic ketoacidosis; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT-2, sodium-glucose co-transporter-2.

COVID-19 in Wales and compare these outcomes to those in the rest of the UK. We observed that 48.7% of the patients with diabetes and COVID-19 admitted in Wales died, around 10% more than that observed in England and Scotland. We also observed that patients admitted in Wales were more likely to be Caucasian, have a greater BMI, HbA_{1c} and have co-morbid retinopathy compared with the rest of the UK. Of the patients in Wales who died and/or were admitted to AICU, there was a significantly greater male prevalence and number of patients with T2D compared with T1D. However, we did not observe any significant difference in anthropometric measures, medical comorbidities or diabetes-related complications associated with an increased risk of death and/or AICU admission in the Wales cohort. Similarly, we did not find an association between any diabetes treatments with death and/or AICU admission.

Table 3 Comparison of demographic data, diabetes complications and diabetes treatment between patients with diabetes and COVID-19 who died and/or were admitted to the AICU against patients who survived COVID-19 and were not admitted to the AICU in Wales

Clinical features	Death and/or AICU			P value
	Yes (n=45)	No (n=59)	Hazard ratio	
Male/total patients (%)	30/45 (67%)	28/59 (47%)	1.41	0.05
Mean (SD) age (years)	73 (12)	71 (14)	–	0.44
Ethnicity	White (30/36, 83%) Asian (1/36, 3%) Black (2/36, 6%) Other (3/36, 8%)	White (41/44, 93%) Asian (0/44, 0%) Black (0/44, 0%) Other (3/44,7%)	–	0.17 0.27 0.11 0.80
Type of diabetes	T1D 0/45 (0%) T2D 45/45 (100%)	T1D 8/59 (14%) T2D 51/59 (86%)	–	<0.01 <0.01
BMI (kg/m^2)	34.7 (7.4)	32.5 (7.9)	–	0.15
Admission blood glucose (mmol/L)	11.3 (6.7)	12.2 (7.9)	–	0.53
HbA_{1c} (mmol/mol)	68 (26)	66 (23)	–	0.68
Creatinine(μmol/L)	156 (121)	135 (101)	–	0.35
DKA on admission	3/44 (7%)	3/59 (5%)	1.34	0.71
Diabetic foot ulcer	4/39 (10%)	7/55 (13%)	0.81	0.71
Diabetic nephropathy	10/43 (24%)	9/53 (17%)	1.37	0.44
Diabetic peripheral neuropathy	8/39 (21%)	10/53 (19%)	1.09	0.84
Diabetic retinopathy	16/39 (41%)	19/51 (37%)	1.10	0.72
Microvascular disease	21/43 (49%)	24/58 (41%)	1.18	0.46
Macrovascular disease	24/44 (55%)	24/58 (41%)	1.32	0.19
Hypertension	33/40 (83%)	37/56 (66%)	1.25	0.07
Dementia	8/36 (22%)	7/56 (13%)	1.78	0.22
Asthma	6/41 (15%)	12/56 (21%)	0.68	0.40
COPD	9/41 (22%)	9/56 (16%)	1.37	0.46
Malignant neoplasm	8/40 (20%)	6/54 (11%)	1.80	0.23
Smoker	3/33 (9%)	3/45 (7%)	1.36	0.69
Metformin	19/37 (51%)	21/54 (39%)	1.32	0.24
Sulfonylurea	10/34 (29%)	6/44 (14%)	2.16	0.09
DPP-4	8/34 (24%)	12/48 (25%)	0.94	0.88
GLP-1	1/31 (3%)	2/42 (5%)	0.68	0.74
SGLT-2	8/39 (21%)	9/54 (17%)	1.23	0.64
Insulin	18/35 (51%)	21/49 (43%)	1.20	0.44

The significance of differences in categorical data was determined by $\chi 2$ test and significance of differences in continuous data by paired t test.
AICU, adult intensive care unit admission; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DKA, diabetic ketoacidosis; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; SD, standard deviation; SGLT-2, sodium-glucose co-transporter-2; T1D, type 1 diabetes; T2D, type 2 diabetes.

Given that patients in the Welsh cohort were significantly more likely to be Caucasian and trended to a lower proportion of male patients, it may seem surprising that these patients demonstrated a higher mortality considering previous UK COVID-19 epidemiological observations.[3] There are several possibilities which may explain the poorer outcomes observed in the Welsh population. The first is that of social deprivation, and its impact upon health behaviours and outcomes is well known.[10] Indeed, greater social deprivation has been previously associated with higher morbidity and mortality in patients with COVID-19 in populations in both Wales and the UK generally.[2,5] In one study 42.3% of patients admitted to the ICU with COVID-19 resided in geographical areas representing the 20% most deprived in Wales and were therefore greatly over-represented in the ICU cohort.[2] Whilst the relative social deprivation of our cohort compared with the rest of the UK is unknown from the limited data related to social deprivation available, previous studies have observed that people in Wales are significantly more deprived than those in England or Scotland.[11]

Patients in the Welsh cohort were observed to demonstrate a greater prevalence of risk factors associated with poorer health outcomes such as greater HbA_{1c} and BMI. Indeed, in the national diabetes audit 2018–2019, patients with either T1D or T2D in Wales were less likely to attain a target HbA_{1c} <48 mmol/mol (6.5%), <58 mmol/mol (7.5%) or <86 mmol/mol (10.0%) than patients in England.[12] Moreover, the obesity rate in adults in Wales is increasing and the rate of obesity in 15-year-olds is one of the highest in Europe.[13,14] This may reflect poorer health behaviours associated with greater social deprivation in the Welsh cohort compared with that of the rest of the UK. Irrespective of their relative social deprivation, these greater risk factors will have contributed to the greater mor-

tality observed in the Welsh group compared with the rest of the UK. Furthermore, in the Welsh cohort there was a trend to greater BMI in those who died and/or were admitted to AICU compared with those who were not (BMI 34.7 vs. 32.5 kg/m^2, p=0.15). The influence of obesity on patient outcomes is stressed by epidemiological studies observing greater COVID-19 mortality in patients with increasing BMI.[15,16]

Multiple factors may explain the greater risk of death in people with obesity, including a pro-inflammatory state, insulin resistance, ACE2 receptor expression in adipocytes and greater difficulties associated with intubation. Nevertheless, this association is confounded by the complex inter-relationship between obesity, medical comorbidity and social deprivation.[10] A further possibility is that differences in the medications prescribed for diabetes between the two groups affected patient outcomes. There had been major concerns at the start of the pandemic around the prescription of diabetes medications such as SGLT-2 inhibitors for people with diabetes during the pandemic, due to a potentially greater risk of diabetic ketoacidosis (DKA) associated with their use which may be exacerbated by SARS-CoV-2.[17] Patients admitted in Wales were significantly more likely to be prescribed SGLT-2 inhibitors or insulin compared with patients admitted in the rest of the UK. Similarly, patients admitted to hospitals in Wales had a numerically – though not statistically significant – greater risk of presentation with DKA compared with the rest of the UK (5.8% vs 3.6%, p=0.24). However, as shown in Table 3, there was no statistically significant difference in the prevalence of SGLT-2 inhibitor prescription between patients who died and/or those admitted to AICU in Wales. The increased rate of insulin prescription in patients admitted to hospital in Wales compared with the UK likely reflects the poorer glycaemic control in this cohort and therefore their more advanced pharmacotherapy for diabetes. Nevertheless, previous analyses have observed that insulin prescription is associated with a greater risk of COVID-19-related death in people with T2D,[18] although this is likely an association observed in a cohort with more complicated diabetes and/or comorbidity rather than a causative relationship.

To mitigate the difference in mortality, efforts to address modifiable risk factors for poorer outcomes in this cohort are essential. To achieve this, improving the national attainment of the NICE recommended eight care processes and three treatment targets is important. Indeed, Wales had a poorer performance than England with respect to completion of these targets in the national diabetes audit 2017–18. Moreover, patients had less time on average with specialist diabetes nurses, specialist dieticians and podiatrists in Wales compared with England.[19] Addressing such inequalities between the delivery of diabetes care in Wales and the rest of the UK will likely reduce the prevalence of the risk factors presented in this analysis. This may lessen the observed difference in outcomes associated with severe illness such as COVID-19 in the future.

Limitations

There are some important limitations to this analysis. Importantly, the sample number of the patients admitted to hospitals in Wales (n=104) was relatively much smaller than the total number included in the UK (England and Scotland) dataset (n=3,309). Given the retrospective nature of the data collected, these data are disposed to the usual biases affecting this type of study and there may be incomplete case ascertainment and reporting of patients with diabetes and COVID-19. Particularly within the Wales dataset, there were missing data with respect to death outcomes in 22 patients (21.1% of the patients in Wales included in this analysis). Unfortunately, there was insufficient data related to social deprivation to allow comparison between patients in Wales and the rest of the UK including multivariate analysis for independent risk factors for death and/or AICU admission. These data are also limited by the lack of a control group of people with COVID-19 without diabetes.

Key messages

- People with diabetes are at greater risk of poorer COVID-19 outcomes, demonstrated in several previous epidemiological studies
- The ABCD COVID-19 and diabetes audit represents the largest cohort of patients with diabetes admitted to UK hospitals with COVID-19
- In this analysis, patients with COVID-19 and diabetes admitted in Wales were observed to have poorer outcomes compared with similar patients admitted in the rest of the UK
- This difference may reflect social inequalities between these populations with associated differences in cardiovascular risk factors between patients hospitalised in Wales and the UK

Conclusion

The impact of COVID-19 in the UK and worldwide has been unprecedented, and the impact felt by people with diabetes has been even greater. This audit undertaken by the ABCD represents the largest cohort of people with diabetes admitted to NHS hospitals in the UK with COVID-19. This analysis highlights important differences in the clinical outcomes and characteristics of patients with diabetes in Wales compared with rest of the UK. These differences may result from several possibilities including social deprivation, medication prescription and control of the underlying cardiovascular risk factors observed in these populations.

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Antidiabetic medication-induced acute interstitial nephritis: case report and literature search

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Key words: GLP-1 receptor agonists, liraglutide, renal impairment, acute kidney injury, nephrology, renal, diabetes

Introduction

Liraglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, is a recognised treatment for type 2 diabetes mellitus (T2DM). It mimics human GLP-1 and works by augmenting insulin secretion, inhibiting glucagon secretion and inhibiting gastric acid secretion.[1] It has been shown to not only improve glycaemic control in people with diabetes, but also result in weight loss, reduced hypoglycaemic episodes, reduced albuminuria, reduced progression to macroalbuminuria and reduced incidence of myocardial infarction and stroke events.[2–5] Gastrointestinal upset is the commonest reported side effect, which occurs in up to 56% of patients in clinical trials. Furthermore, BNF recommends avoiding liraglutide treatment in end-stage renal disease/estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2 (depending on brand), due to the increased risk of adverse events.

We present a rare case of a female with chronic kidney disease (CKD), whose treatment with liraglutide was associated with rapid deterioration of renal function and tubulointerstitial nephritis. Our literature search highlighted one previous case, thus we would like to raise awareness of this potential rare side effect of liraglutide treatment.[6] We have further conducted a literature search of all case reports noting associations of glucose-lowering therapies with acute interstitial nephritis to raise awareness of this potential complication.

Case history

A 59-year-old woman with T2DM and CKD stage 3 (G3b A1), maintained stable glycaemic control with HbA_{1c} 58 on linagliptin 5 mg once daily and reduced carbohydrate diet. Medication history also included amlodipine 5 mg and atorvastatin 20 mg. She was started on liraglutide in January 2019 to improve her metabolic control further. Linagliptin treatment was discontinued, given that the combination of linagliptin and liraglutide is unlikely to provide synergistic effects and is not cost effective. Despite improvement in glycaemia, rapid deterioration in renal function was noted subsequent to starting liraglutide (Table 1 and Figure 1).

Table 1 Renal function and glycaemic control pre- and post-liraglutide treatment

	Liraglutide started	Liraglutide stopped
Creatinine	136	248
eGFR	35	17
HbA_{1c}	58	55

*eGFR, estimated glomerular filtration rate; HbA_{1c}, haemoglobin A_{1c}.

There was no other explanation for the drop in eGFR: she did not experience diarrhoea, nausea or vomiting. Weight and BMI had remained stable throughout liraglutide treatment at 70 kg and 24.3 kg/m^2, respectively. Furthermore, blood pressure remained stable at around 120/70 mm Hg. She had remained euvolaemic whilst on liraglutide treatment. She had not taken NSAIDs. Urinalysis was bland. Complement C3 and C4, double-stranded DNA 1 (dsDNA1), anti-neutrophil cytoplasm antibodies (ANCA), myeloperoxidase (MPO) and anti-proteinase 3 antibody (PR3) were all negative. Ultrasound of the kidney showed normal kidneys bilaterally (right 10.7 cm, left 10.4 cm) and no evidence of obstruction. Moreover, there was no family history of renal disease.

As the rapid drop in eGFR was only noted after commencing liraglutide, it was postulated that the loss in renal function may be due to liraglutide initiation. Unfortunately, due to a delay in the medical appointments, the only available eGFR results were prior to and at 5 months after start of treatment, thus complicating matters further. The eGFR was 35 mL/min/1.73 m^2 prior to starting liraglutide and dropped rapidly to 17 mL/min/1.73 m^2 when measured five months later – a significant fall of 51%. It was therefore decided to stop liraglutide treatment in May 2019 and her linagliptin was restarted.

Renal biopsy was performed in July 2019 (Figure 2). Significant interstitial fibrosis and tubular atrophy (IFTA) were present, with

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Figure 1. Change in estimated glomerular filtration rate (eGFR) with time. Our case showed rapid deterioration in renal function on initiation of liraglutide treatment. This unfortunately did not improve once liraglutide was stopped.

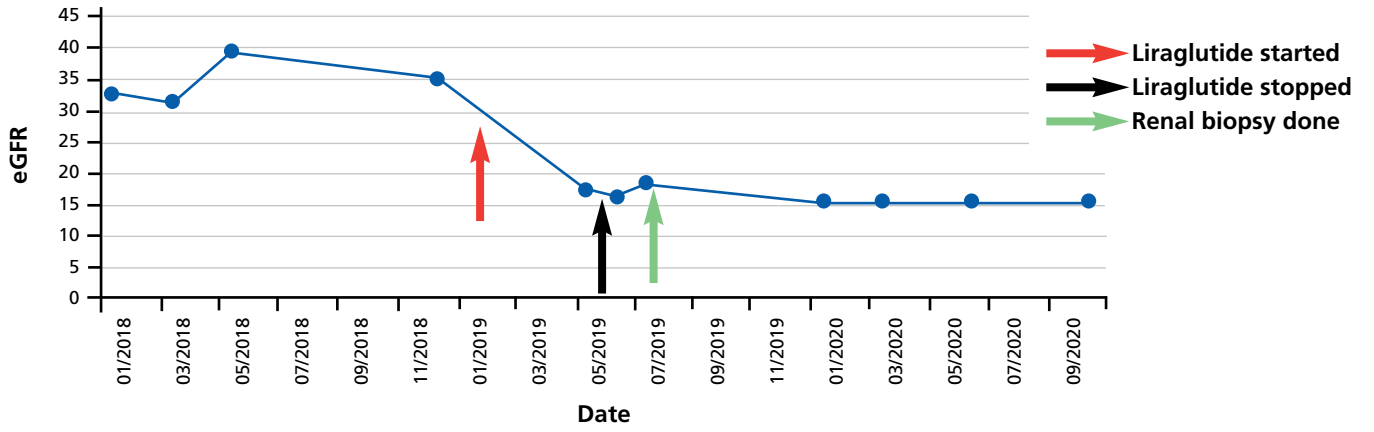
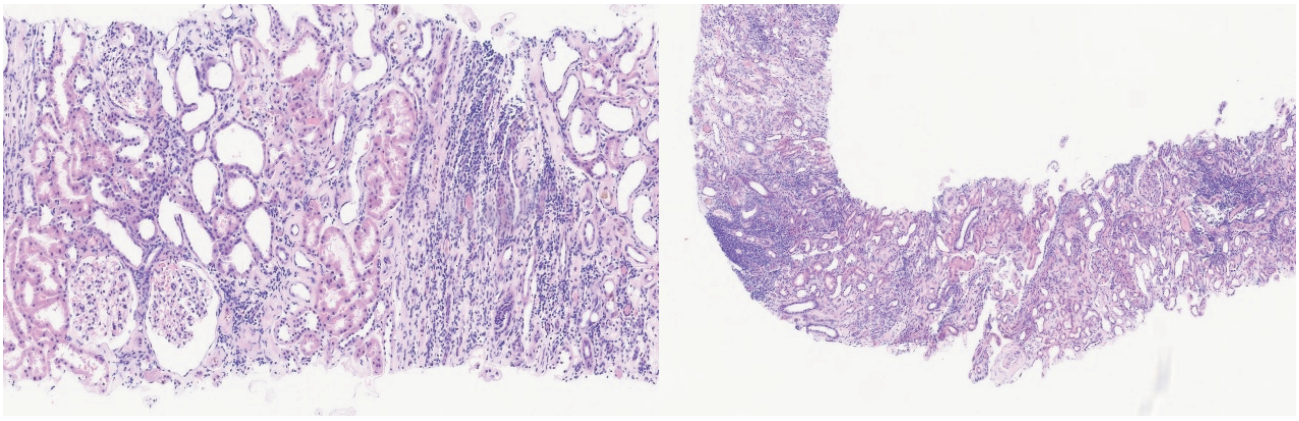


Figure 2. Renal biopsy showing marked interstitial fibrosis and tubular atrophy involving two-thirds of the cortical tissue. There is prominent interstitial infiltrate, including substantial numbers of eosinophils suggestive of tubulointerstitial nephritis. Mild focal tubulitis is evident.



profound interstitial inflammatory infiltrate and mild focal tubulitis. All these findings heavily supported the diagnosis of acute interstitial nephritis. Furthermore, mild glomerular mesangial expansion and arteriolar hyalinosis was seen, suggestive but not specific for a diagnosis of diabetic nephropathy. We therefore concluded that the kidney biopsy showed significant acute interstitial nephritis with mild diabetic nephropathy.

Despite stopping liraglutide, her renal function did not improve (Figure 1). She progressed to end stage renal disease. Steroid treatment was considered but not deemed beneficial due to severe IFTA and her diabetes. She has started peritoneal dialysis and is awaiting renal transplant.

Discussion

Acute interstitial nephritis is a common cause of acute kidney injury (AKI), and has been identified in the diagnosis of 12.9% of kidney biopsies from patients with AKI.[7] The main cause of acute interstitial nephritis in the developed world is medications, which contribute to >70% of cases.[8] Antibiotics, NSAIDs, anti-inflammatory agents, anticonvulsants, diuretics and proton pump inhibitors are the most common culprits.[9,10] Other causes of interstitial nephritis include infections, autoimmune disorders, systemic diseases, metabolic causes and environmental exposure.[11] The presentation of drug-induced acute interstitial nephritis is highly variable.[12] The classic triad of symptoms of rash, fever and eosinophilia are only witnessed in <10% of patients.[9] Laboratory tests and imaging are usually unhelpful in the diagnosis of drug-induced acute interstitial nephritis as they lack both sensitivity and specificity.[9,12] Renal biopsy is the gold standard investigation to make a definitive diagnosis. Main histological findings include interstitial inflammation, comprising primarily of lymphocytes and monocytes, and tubulitis is evident. If the nephritis continues to deteriorate, chronic appearances of interstitial fibrosis and tubular atrophy may be present.[9]

Our case highlights a person with stable diabetes and established CKD whose kidney function rapidly deteriorated further after liraglutide initiation. People with diabetes and CKD3 are expected

Table 2 Cases of antidiabetic medication-induced acute interstitial nephritis to date

Class of Drug	Drug name	Author	Patient	Initial renal function	Time to presentation at hospital	Renal function post GLP-1 introduction	Renal	Treatment biopsy	Recovery
GLP 1 RA	Liraglutide	Gariani *et al* 2014[1]	83M	Creatinine 2.14 mg/dL eGFR 32 mL/min/1.73m^2	–	Creatinine 9.3 mg/dL eGFR 6 mL/min/1.73 m^2	Confirmed	Stopped liraglutide. Steroids and transient dialysis	Partial recovery
	Exenatide	Dubois – Laforgue *et al* 2014[2]	75M	Creatinine 130 µmol/L	5 days	Creatinine 1148 µmol/L	Not done	Stopped exenatide. Haemodialysis for 48h insulin therapy	Full recovery – 9 days
	Exenatide	Bhatti *et al* 2010[3]	65F	Creatinine 77 µmol/L eGFR 66 mL/ min/m^2	9 weeks	Creatinine 393 µmol/L eGFR 10 mL/min/m^2	Not done	Liraglutide stopped. Prednisolone	Partial recovery – 6 weeks
	Exenatide	Nandokaban *et al* 2013[4]	58M	Creatinine 120 µmol/L eGFR 59 mL/min/1.73m^2	2 months	Serum creatinine 209 µmol/L eGFR 39 mL/min/1.73m^2	Confirmed	Stopped exenatide. Prednisolone	Partial recovery – 4 months
	Semaglutide	Leehey *et al* 2021[5]	~80F	Creatinine 1.59 mg/dL eGFR 30 mL/min/1.73m^2	5 months	Creatinine 3.50 mg/dL eGFR 11 mL/min/1.73m^2	Confirmed	Discontinued semaglutide	No recovery
	Dulaglutide	Taylor *et al* 2018[6]	63F	Creatinine 1.6mg/dL eGFR 34 mL/min/1.73m^2	1 month	Creatinine 3.4 mg/dL eGFR 13.7 mL/ min/1.73m^2	Not done	Discontinued dulaglutide	Full recovery – 4 weeks
SGLT2 inhibitors	Empagliflozin	Ryan *et al* 2021[7]	63F	Creatinine 60 µmol /L	6 weeks	Creatinine 381 µmol/L	Confirmed	Discontinued empagliflozin. Prednisolone	Partial recovery – 8 weeks
	Empagliflozin	Bnaya *et al* 2020[8]	67F	Creatinine 0.9 mg/dL eGFR 66 mL/min/1.73m^2	1 week	Creatinine 3.19 mg/dL eGFR 15 mL/min/1.73m^2	Confirmed	Haemodialysis, prednisolone	Partial recovery - 3 months.
	Canagliflozin	Gribben *et al* 2021[9]	51M	Creatinine 1.5 mg/dL eGFR 63 mL/min/1.73m^2	2 weeks	Creatinine 11.6 mg/dL eGFR 6 mL/min/1.73m^2	Not diagnostic – not enough tissue obtained	Discontinued canagliflozin. IV fluids. Haemodialysis	Deterioration of kidney function
DPP4 Inhibitors	Sitagliptin	Lin *et al* 2014[10]	69M	Creatinine 1.07 mg/dL eGFR 69 mL/min/1.73m^2	4 weeks	Creatinine 4.95 mg/dL eGFR 12 mL/min/1.73m^2	Confirmed	Discontinued sitagliptin. Haemodialysis. Prednisolone	Partial recovery – 3 weeks
	Sitagliptin	Alsaad *et al* 2016[11]	56M	Creatinine 1.5 mg/dL eGFR 51 mL/min/1.73m^2	2 weeks	Creatinine 2.2mg/dL eGFR 33 mL/min/1.73m^2	Confirmed	Discontinued sitagliptin. Prednisolone	Full recovery – 6 weeks
	Alogliptin	Shima *et al* 2019[12]	68M	Creatinine 0.75mg/dL eGFR 110 mL/ min/1.73m^2	14 months	Creatinine 1.55mg/dL eGFR 48 mL/ min/1.73m^2	Confirmed	Discontinued alogliptin	Partial recovery – 3 weeks
Sulfonylureas	Gliclazide	Oyama *et al* 2018[13]	Retrospective study using spontaneous reporting system databased. Based on 5,195,890 reports of all adverse drug reactions, 3,088 reports of drug-induced tubulointerstitial nephritis were evaluated. Results suggested that gliclazide had the highest reporting odds ratio of tubulointerstitial nephritis						
	Glimepiride	Akbar *et al* 2010[14]	50M	Unreported	Unreported	Creatinine 2.72 mg/dL eGFR 32 mL/min/1.73m^2	Confirmed	Discontinued glimepiride. Prednisolone	Partial recovery – few weeks
Thiazolidinediones	Rosiglitazone	Castledine *et al* 2006[15]	55M	Creatinine 97 µmol/L eGFR 97 mL/min/1.73m^2	3 weeks	Creatinine 458 µmol /L eGFR 12 mL/min/1.73m^2	Confirmed	Discontinued rosiglitazone. Prednisolone	Partial recovery – 6 months
	Rosiglitazone	Ghani *et al* 2009[16]	65M	Creatinine 150 µmol/L eGFR 43 mL/min/1.73m^2	2 weeks	Creatinine 1474 µmol /L eGFR 3 mL/min/1.73m^2	Confirmed	Discontinued rosiglitazone. Haemodialysis. Mycophenolate mofetil.	Partial recovery – 6 weeks

GLP1RA, glucagon-like peptide 1 receptor agonist; SGLT2 inhibitors, sodium-glucose co-transporter-2 inhibitors; DPP4 inhibitors, dipeptidyl-peptidase 4 inhibitors; F, female; M, male.

NOTE: References for the above table can be found at the end of the article before the main article references

to experience a progressive decline in eGFR of 1.9–3.3 mL/min/1.73 m^2 per year.[13] In contrast, our case experienced a decline in eGFR of 18 mL/min/1.73 m^2 within 5 months. Due to the time correlation between eGFR decline and initiation of liraglutide, it was highly suggestive that this decline was due to liraglutide therapy; we could not determine any other reason for such a rapid decline in eGFR.

There have been similar case reports to ours in the literature where use of liraglutide (and other antidiabetic medications) resulted in acute interstitial nephritis (Table 2). These cases, like ours, experienced no gastrointestinal symptoms thus no dehydration, yet deterioration in kidney function was evident. Renal biopsy supported the diagnosis.

It is speculated whether this injury results from an immunological response. Pathogenesis of drug-induced acute interstitial nephritis is thought to occur from type IV delayed hypersensitivity reaction to the offending medication. This can happen within days or months of exposure to the medication in question. It is unclear exactly how this process occurs, however suspected mechanisms include molecular mimicry or direct binding of hapten drug to tubular membrane, resulting in an immunogenic response.[12] Furthermore, antibody production has been shown to occur after liraglutide introduction (~8.5% of cases).[14]

Current standard of care for treatment of drug-induced acute interstitial nephritis involves early recognition of the culprit drug and discontinuation of the medication. Late recognition of kidney damage and continued drug use may result in kidney fibrosis, with 40–60% of people with acute tubulointerstitial nephritis ultimately developing chronic kidney disease.[8] Corticosteroid therapy is controversial in the treatment of drug-induced acute interstitial nephritis. Some studies report rapid and complete recovery of baseline renal function in those treated with steroids,[15,16] whilst others have failed to confirm these findings.[17,18] No prospective randomised controlled trials investigating corticosteroid treatment in acute interstitial nephritis have been conducted as yet. Multicentre prospective randomised controlled trials are needed to study the effect of corticosteroid therapy on interstitial nephritis. Nevertheless, the main conclusion from all studies investigating steroid treatment is that the earlier steroid treatment was initiated, the better the prognosis.[19]

The situation is further complicated when using steroids to treat acute interstitial nephritis in people with diabetes due to glucocorticoid-induced hyperglycaemia.[20] Furthermore, it has been noted in the literature that people with diabetes are less likely to respond to steroid treatment. In addition, interstitial fibrosis in renal biopsy is associated with poor response to steroids.[21] This may be due to fibrosis indicating irreversible damage of renal tissue. In our case, as significant interstitial fibrosis and tubular atrophy was noted on renal biopsy, it was deemed that steroid therapy would not be beneficial. Furthermore, with our patient's diabetes under stable control, steroid therapy was avoided to ensure HbA_{1c} did not deteriorate.

Of interest, liraglutide and other GLP-1 agonists have been reported to cause acute kidney injury via a different pathogenesis. Those affected severely by the gastrointestinal side effect of liraglutide treatment may experience dehydration and progress to acute kidney injury. In these patients, renal biopsy confirms acute tubular necrosis. Careful fluid balance and examination is necessary to determine intravascular volume depletion. Fluid rehydration is essential in the treatment of these patients.[22,23] This represents a diagnostic challenge for physicians, whereby clinical and laboratory features are comparable for both acute tubulointerstitial nephritis due to medication and acute tubular injury due to dehydration.[24] Especially in people with diabetes, the complexity for diagnosis of renal disease is challenging. However, as our case experienced no gastrointestinal side effects, had stable weight and blood pressure and was clinically euvolaemic throughout liraglutide treatment, it was unlikely she had kidney function deterioration via this mechanism. Histological investigation further confirmed our suspicions, and excluded volume depletion as a cause of her eGFR deterioration.

Despite our case report, we would like to highlight the multiple studies reporting the benefit of liraglutide on metabolic, cardiovascular and renal outcomes.[2–4] Furthermore, post hoc analysis of people with CKD have further shown the safety and efficacy of liraglutide treatment, and its benefits in reducing all-cause mortality in this patient subtype.[25,26] We therefore conclude that liraglutide has a positive impact on renal function. However, physicians should be aware of acute interstitial nephritis as a possible rare side effect.

Key messages

- Despite its multiple benefits, liraglutide on rare occasions can possibly induce a rapid deterioration in renal function. This may occur via two mechanisms: acute interstitial nephritis (represented in our case report) and acute tubular necrosis (as reviewed in the literature)
- Acute interstitial nephritis should be suspected in patients with deterioration of renal function along with absence of gastrointestinal symptoms and lack of improvement of renal function to fluid rehydration treatment
- In people with bland urinalysis and negative immunology, once volume depletion is excluded as the source of renal deterioration, renal biopsy is recommended to confirm diagnosis
- We suggest physicians should monitor renal function in people initiating liraglutide treatment (and other antidiabetic medications)

Conclusion

Despite the multiple cardiovascular and renal benefits of liraglutide therapy, our case highlights a rare side effect – acute interstitial nephritis. Few cases have been reported in the literature, thus high clinical suspicion needs to be maintained in those with rapid renal deterioration after liraglutide (and other antidiabetic medication) initiation. If interstitial nephritis is suspected and volume depletion has been excluded as a differential diagnosis, the gold standard in-

vestigation is renal biopsy. Definitive management of antidiabetic medication-induced acute interstitial nephritis involves identification and removal of the offending medication. Steroid therapy is controversial, with a limited effect noted in those with diabetes. From our case we thus aim to raise awareness to clinicians about a rare possible side effect of liraglutide (and other antidiabetic medication) therapy and highlight its investigation and management.

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Review of microbiological sampling in diabetic foot disease

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Abstract

Introduction: Diabetes mellitus is a significant cause of morbidity and mortality. Foot-related complications affect 2–2.5% of people with diabetes. There is significant variation in outcomes for patients with diabetic foot disease within the UK. The multidisciplinary approach to diabetic foot disease is well publicised and protocols, guidance and consensus approaches exist for most components of the management of diabetic foot disease. Antimicrobial therapy to treat diabetic foot infections based on microbiological sampling and culture is well documented, but no consensus exists on how these samples should be obtained, processed and reported.

Methods: A literature review was undertaken to establish the reporting of techniques used in obtaining and processing microbiological samples in diabetic foot disease to establish if consensus exists in the methodologies used with a view to develop best practice guidelines.

Results: Six out of 102 papers reported all processes in obtaining and processing microbiological samples.

Conclusion: No gold standard consensus exists for microbiological sampling of diabetic foot infections, preventing optimisation of this aspect of management of diabetic foot disease and ultimately potentially adversely affecting the outcomes of this growing patient cohort.

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Key words: diabetic foot; microbiology sampling; osteomyelitis

Introduction

Diabetes mellitus is a significant cause of morbidity and mortality.[1] Foot-related complications affect 2–2.5% of people with diabetes, equating to a point prevalence of approximately 58,000 people in England alone.[2]

There is significant regional variation in outcomes for patients with diabetic foot disease within the UK.[3] The National Diabetes Foot Care Audit aims to quantify these variations at an organisational level so that markers of an effective service can be identified. However, low levels of participation have so far made it difficult to draw any consensus on this.[4]

The management of diabetic foot disease is complex, involving input from a multidisciplinary team of professionals.[5] The mainstays of treatment in these challenging cases are off-loading of pressure areas and appropriate footwear, surgical debridement of infected and necrotic tissue, revascularisation if required, appropriate wound care and dressings, and antimicrobial therapy. Healthcare institutions managing diabetic foot disease should have clear pathways and guidance for management of these patients with alignment of services and processes to ensure the best patient outcomes and reduce major limb amputation rates and the associated morbidity and mortality.[4]

Each facet of the management of diabetic foot disease has been subject to review in the medical literature with consensus documents produced advising on the best practice for the treatment. The use of antimicrobial therapy and prolonged courses to treat osteomyelitis is well documented[6] and should be based on tissue or bone sampling, culture and appropriate sensitivity testing cultures.[5] However, how these samples should be obtained, processed and reported is poorly documented, making alignment of services difficult. Targeted antimicrobial therapy relies on certain steps to be completed, as demonstrated in Figure 1. Each of the steps shown has the potential to affect the subsequent accuracy of results and must be clearly described so accurate comparison can be made between techniques and results.

A literature review was undertaken to clarify the practice for reporting of tissue sampling techniques in the diabetic foot population and to determine if consensus exists in the literature for sampling techniques and processing, with the aim of developing best practice guidelines particularly in relation to the intraoperative bone sampling techniques used.

Methods

The NICE Healthcare Databases Advanced Search (https://hdas.nice.org.uk) was used to search EMBASE and Medline databases in September 2020. The search strategy is detailed in Appendix 1. Studies were restricted to human subjects, in the English language, published between 2010 and 2020 with an abstract available.

A total of 707 papers were identified. Duplicates, case reports and conference abstracts were removed and abstracts were screened by HT and JD for relevance and any conflicts were resolved by the senior author (MW). One hundred and forty-nine full-text articles were deemed relevant for review and 102 were included in the analysis. Figure 2 shows the PRISMA flow diagram.

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Figure 1. The journey of the bone/deep tissue specimen

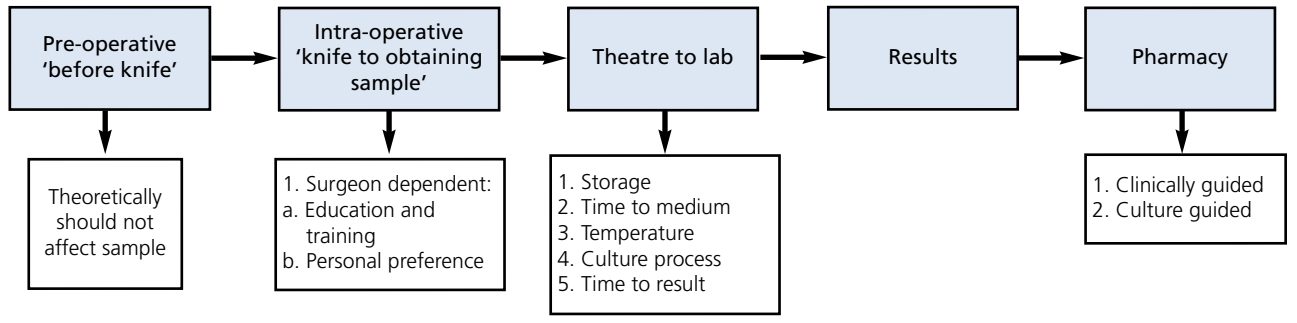
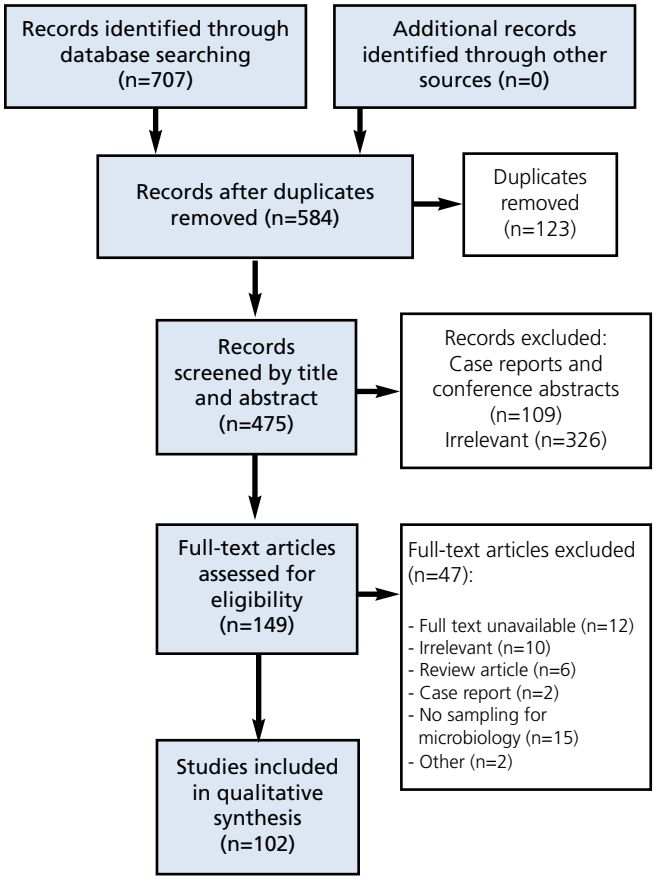


Figure 2. Prisma Flow Diagram



Studies were reviewed by the authors and basic information was collected on the study type and population. The papers were reviewed for the following aspects of their methodology with a view to whether the study would be reproducible: what was sampled, how it was sampled, whether the wound was cleaned prior to sampling and how, how the specimen was transported for processing and what processing occurred. This information was compiled and analysed using Microsoft Excel (Windows 10).

Results

Of the 707 papers identified through database searching, 123 duplicates and 109 case reports and conference abstracts were removed; 475 were screened by title and abstract and 326 were deemed irrelevant and excluded. Of the 149 full-text articles assessed for eligibility, a further 47 were excluded (reasons detailed in Figure 2). One hundred and two papers were included in qualitative analysis (see Appendix 2), of which 45 were prospective studies, 25 were retrospective studies and in 32 the time frame was unclear. There were 16 observational studies, 1 case series, 3 case–control studies, 55 cohort studies, 22 cross-sectional studies, 4 randomised controlled trials and 1 pilot study.

Eighty (78%) studies described the sampling technique used, 58 (57%) described how the wound was cleaned prior to sampling, 50 (49%) described how the specimen was kept prior to processing and 80 (78%) described the processing techniques used.

Samples taken

Wound or ulcer swabs only were performed in 26 of the papers and pus cultures in five. Bone sampling alone was used in 17 papers, tissue including skin in 17 and other samples in one paper. Thirty-one papers described more than one specimen type being taken.

Sampling technique

The percentage of papers reporting the use of different techniques for obtaining samples in the systematic review is shown in Table 1.

Wound cleaning

The percentage of papers reporting how the wound was cleaned prior to microbiology sampling is shown in Table 2.

Specimen transport

All three variables (time, medium, temperature) of transportation of specimens were reported in 6.9% of papers, 50% of papers detailed no information about how the specimen was kept or transported prior to processing, 22.5% of papers reported only one of the three transport variables (medium 15.7%, time frame 4.9%, temperature 2.0%) and 19% reported on two of the

Table 1. Percentage of papers reporting the use of different techniques for obtaining samples in the systematic review

Sample Type	Technique	Percentage of papers reporting
Wound swab	Levine's	8.8%
	Other	5.9%
	Insufficient description/ no comment	22.5%
Tissue	Described	6.9%
	Insufficient description/ no comment	14.7%
Bone	Described	6.9%
	Insufficient description/ no comment	9.8%
Multiple sample types	Technique specified	1.0%
	Samples taken using "established method" referencing another paper	2.9%
	Insufficient description/ no comment	13.7%
Other samples (pus/ fluid/ulcer)	Insufficient description/ no comment	6.9%

three variables. One paper stated that the specimens were transported by "conventional methods".

Specimen processing

Detailed processing methods were described in 23.5% of papers, 30.4% stated "conventional methods" or "culture and sensitivity" were used, 18.6% made no comment about the processing techniques, 11.8% were sent for aerobic and anaerobic culture and 3.9% for aerobic culture only, and 11.8% of papers described molecular microbiological techniques.

Complete sampling protocols

Thirty-five papers (34%) described all four stages of microbiological sampling and processing and six papers (6%) sampled bone and described all four stages. These papers were all studies in patients with diabetic foot disease. The techniques described in these six papers are summarised in Appendix 3.

Discussion

Diabetic foot disease is an international pandemic with a large socioeconomic burden on people and healthcare systems worldwide. Attempts to improve the treatment of diabetic foot disease have been ongoing throughout the medical community with identification of trends in microbiology and the best sampling techniques. Duration of antimicrobial therapy is guided by the culture and sensitivity of samples taken from active diabetic foot infections. Positive bone cultures attract a prolonged (6-week) course of antimicrobial therapy.[7,8] Inappropriate use of antimicrobials is not without its morbidity and therefore accurate culture and sensitivity is imperative to optimise management.

Table 2. Percentage of papers reporting how the wound was cleaned prior to microbiology sampling

Method of cleaning	Percentage of papers reporting
No comment	42.2%
"Asepsis/ Conventional methods"	5.9%
Cleaning/ Irrigation - solution specified	22.5%
Cleaned/ Irrigation - solution not specified	5.9%
"Cleaned (solution specified) and debrided"	7.8%
"Cleaned (solution not specified) and debrided"	3.9%
Debridement	6.9%
Multiple steps, well described	4.9%

The management of diabetic foot infection requires a multidisciplinary approach and it is the links between specialities that improve patient care. The authors, as surgeons, were concerned that the process by which specimens are sampled and transported to the laboratory for microbiological processing may well be impacting upon the reliability of results. Having standard operating procedures and protocols is well documented in healthcare to improve outcomes; however, there is no gold standard for microbiology sampling and processing to guide antimicrobial therapy in the management of diabetic foot disease. A standardised approach to the sampling process will reduce variation in technique and may help avoid inaccurate results, therefore leading to greater reliability and reproducibility.

There are some limitations to this study. It is a qualitative literature review rather than a systematic review due to the fact that the authors are examining methodology and reporting rather than study results. Non-English language studies were excluded and 12 studies were not available as full-text articles. This may have led to exemplary studies being excluded from this literature review but, if they are not readily available to clinicians treating diabetic foot disease internationally, it is difficult for their results to influence practice.

This literature review clearly demonstrates that there is no standardised methodology for reporting of specimen type, sampling method or processing methods for microbiological culture for the diagnosis and treatment of diabetic foot infection in the medical literature. This heterogeneous reporting means that it is difficult for readers and practitioners to draw accurate conclusions from the published literature in order to improve their own practice or to train the future generation of the multidisciplinary team managing this disease. A recent survey conducted by the author showed a lack of consistency in the sampling techniques in the trainee surgical community.[9] It also demonstrated a lack of understanding of the processing techniques, procedural reporting and a lack of ongoing training in the surgical debridement of diabetic foot disease, specifically toe amputations.

The authors feel that a consensus must be sought for the sam-

Key messages

- Gold standard consensus in microbiology sampling techniques and reporting in diabetic foot management is lacking
- Optimal sampling techniques need to be established to increase specimen yield and allow targeted antimicrobial therapy
- Optimisation and standardisation of all aspects of management is key to reduce morbidity and mortality of diabetic foot disease

pling and processing of diabetic foot samples. The publication of papers in relation to microbiology sampling in diabetic foot disease must clearly delineate the steps in sampling, transportation and processing, making the studies transparent and reproducible. This will allow the reader to interpret the results and optimise all aspects of management of diabetic foot disease, allow for further studies into techniques, allow rationalisation of antimicrobial therapy and ultimately reduce the long-term sequelae, morbidity and mortality of diabetic foot disease.

Conflict of interest All authors have non to declare.
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Appendix 1. Search strategy

Search	Search Term
1	exp DIABETES MELLITUS/
2	(Diabet*).ti,ab
3	1 or 2
4	FOOT DISEASES/
5	ULCER/
6	GANGRENE/
7	OSTEOMYELITIS/
9	"SOFT TISSUE INFECTION"/ OR "wound infections/"
10	((foot* OR feet* OR toe* OR tissue* OR wound*) ADJ4 (infect* OR disease*)).ti,ab
11	(4 OR 5 OR 6 OR 7 OR 9 OR 10)
12	(3 AND 11)
13	(diabetic foot).ti,ab
14	(diabet* ADJ4 (foot* OR feet* OR toe* OR ulcer* OR gangrene* OR osteomyelit*)).ti,ab
15	(12 OR 13 OR 14)
16	(micro*).ti,ab
17	(culture).ti,ab
18	(organis*).ti,ab
19	(sampl*).ti,ab
20	(16 OR 17 OR 18)
21	(20 ADJ4 samp*).ti,ab
22	(19 AND 20)
23	(21 OR 22)
24	(15 AND 23)
25	(15 AND 23) [English language] [Humans]

Appendix 2. All papers included in the qualitative review

Year	Authors	Title
2020	Macdonald KE et al	A retrospective analysis of the microbiology of diabetic foot infections at a Scottish tertiary hospital
2010	Nagoba BS et al	A simple and effective approach for the treatment of diabetic foot ulcers with different Wagner grades
2019	Thanganadar AS et al	A Study on isolation, characterization, and exploration of multiantibiotic-resistant bacteria in the wound site of diabetic foot ulcer patients
2019	Niazi NS et al	Adjuvant antibiotic loaded bio composite in the management of diabetic foot osteomyelitis - a multicentre study
2020	Manas AB et al	Admission time deep swab specimens compared with surgical bone sampling in hospitalized individuals with diabetic foot osteomyelitis and soft tissue infection
2011	Landsman A et al	An open-label, three-arm pilot study of the safety and efficacy of topical Microcyn Rx wound care versus oral levofloxacin versus combined therapy for mild diabetic foot infections
2019	Malone M et al	Analysis of proximal bone margins in diabetic foot osteomyelitis by conventional culture, DNA sequencing and microscopy
2016	Wolcott RD et al	Analysis of the chronic wound microbiota of 2,963 patients by 16S rDNA pyrosequencing
2020	Monami M et al	Antimicrobial photodynamic therapy in infected diabetic foot ulcers: a multicenter preliminary experience
2018	Pugazhendhi S and Dorairaj AP	Appraisal of biofilm formation in diabetic foot infections by comparing phenotypic methods with the ultrastructural analysis
2019	Lavery LA et al	Are we misdiagnosing diabetic foot osteomyelitis? Is the gold standard gold?
2020	Min KR et al	Association between baseline abundance of Peptoniphilus, a Gram-positive anaerobic coccus, and wound healing outcomes of DFUs
2018	Vatan A et al	Association between biofilm and multi/extensive drug resistance in diabetic foot infection
2016	Karmaker M et al	Association of bacteria in diabetic and non-diabetic foot infection - an investigation in patients from Bangladesh
2017	Sanchez-Sanchez M et al	Bacterial prevalence and antibiotic resistance in clinical isolates of diabetic foot ulcers in the Northeast of Tamaulipas, Mexico
2020	Ullah I et al	Bacteriological profile and antibiotic susceptibility patterns In diabetic foot infections at Lady Reading Hospital, Peshawar
2017	Amjad SS et al	Bacteriology of diabetic foot in tertiary care hospital; frequency, antibiotic susceptibility and risk factors
2018	Yasin M et al	Baseline characteristics of infected foot ulcers in patients with diabetes at a tertiary care hospital in Pakistan
2010	Sotto A et al	Beneficial effects of implementing guidelines on microbiology and costs of infected diabetic foot ulcers
2015	Lipsky BA et al	Ceftaroline fosamil for treatment of diabetic foot infections: the CAPTURE study experience.
2014	Murali TS et al	Characteristics of microbial drug resistance and its correlates in chronic diabetic foot ulcer infections.
2020	Goh TC et al	Clinical and bacteriological profile of diabetic foot infections in a tertiary care
2012	Mendes JJ et al	Clinical and bacteriological survey of diabetic foot infections in Lisbon
2018	Kim PJ et al	Clinic-based debridement of chronic ulcers has minimal impact on bacteria
2011	Zubair M et al	Clinico-microbiological study and antimicrobial drug resistance profile of diabetic foot infections in North India
2018	Nelson A et al	CODIFI (Concordance in Diabetic Foot Ulcer Infection): a cross-sectional study of wound swab versus tissue sampling in infected diabetic foot ulcers in England
2016	Nelson EA et al	Concordance in diabetic foot ulceration: A cross-sectional study of agreement between wound swabbing and tissue sampling in infected ulcers
2019	Bellazreg F et al	Correlation between superficial and intra-operative specimens in diabetic foot infections: Results of a cross-sectional Tunisian study
2011	Lesens O et al	Culture of per-wound bone specimens: A simplified approach for the medical management of diabetic foot osteomyelitis
2013	Aslangul E et al	Diagnosing diabetic foot osteomyelitis in patients without signs of soft tissue infection by coupling hybrid 67Ga SPECT/CT with bedside percutaneous bone puncture.
2012	Sotto A et al	Distinguishing colonization from infection with Staphylococcus aureus in diabetic foot ulcers with miniaturized oligonucleotide arrays: a French multicenter study
2018	Wu M et al	Distribution of microbes and drug susceptibility in patients with diabetic foot infections in Southwest China
2017	Malone M et al	Effect of Cadexomer iodine on the microbial load and diversity of chronic non-healing diabetic foot ulcers complicated by biofilm in vivo
2019	Malone M et al	Effect on total microbial load and community composition with two vs six-week topical Cadexomer iodine for treating chronic biofilm infections in diabetic foot ulcers
2018	Saseedharan S et al	Epidemiology of diabetic foot infections in a reference tertiary hospital in India
2016	Reveles KR et al	Epidemiology of methicillin-resistant Staphylococcus aureus diabetic foot infections in a large academic hospital: implications for antimicrobial stewardship
2019	MacDonald A et al	Evidence of differential microbiomes in healing versus non-healing diabetic foot ulcers prior to and following foot salvage therapy
2019	Couturier A et al	Comparison of microbiological results obtained from per-wound bone biopsies versus transcutaneous bone biopsies in diabetic foot osteomyelitis: a prospective cohort study

continued...

Year	Authors	Title
2018	Elmarsafi T et al	Concordance between bone pathology and bone culture for the diagnosis of osteomyelitis in the presence of Charcot neuro-osteoarthropathy
2017	Esposito S et al	Deep tissue biopsy vs. superficial swab culture, including microbial loading determination, in the microbiological assessment of skin and soft tissue infections (SSTIs)
2013	Malone M et al	Deep wound cultures correlate well with bone biopsy culture in diabetic foot osteomyelitis
2011	Tascini C et al	Microbiology at first visit of moderate-to-severe diabetic foot infection with antimicrobial activity and a survey of quinolone monotherapy
2018	Noor S et al	Molecular and culture based assessment of bacterial pathogens in subjects with diabetic foot ulcer
2013	Djahmi N et al	Molecular epidemiology of staphylococcus aureus strains isolated from inpatients with infected diabetic foot ulcers in an Algerian University Hospital
2017	Oli AN et al	Multi-antibiotic resistant extended-spectrum beta-lactamase producing bacteria pose a challenge to the effective treatment of wound and skin infections
2016	Smith K et al	One step closer to understanding the role of bacteria in diabetic foot ulcers: Characterising the microbiome of ulcers
2014	Mannucci E et al	Photodynamic topical antimicrobial therapy for infected foot ulcers in patients with diabetes: A randomized, double-blind, placebo-controlled study - The D.A.N.T.E (Diabetic ulcer Antimicrobial New Topical treatment Evaluation) study
2010	Saltoglu N et al	Piperacillin/tazobactam versus imipenem/cilastatin for severe diabetic foot infections: A prospective, randomized clinical trial in a university hospital
2015	DaCosta RS et al	Point-of-care autofluorescence imaging for real-time sampling and treatment guidance of bioburden in chronic wounds: first-in-human results
2014	Dunyach-Remy C et al	Polymerase chain reaction-denaturing gradient gel electrophoresis (PCR-DGGE): A promising tool to diagnose bacterial infections in diabetic foot ulcers
2011	Bernard L et al	Predicting the pathogen of diabetic toe osteomyelitis by two consecutive ulcer cultures with bone contact
2017	Chisman R et al	Prescribing antibiotics in diabetic foot infection: what is the role of initial microscopy and culture of tissue samples?
2019	Jaju K et al	Profile and antibiotic susceptibility of bacterial pathogens associated with diabetic foot ulcers from a rural area
2014	Merlet A et al	Prognostic factors of calcaneal osteomyelitis
2013	Redel H et al	Quantitation and composition of cutaneous microbiota in diabetic and nondiabetic men
2012	Atway S et al	Rate of residual osteomyelitis after partial foot amputation in diabetic patients: a standardized method for evaluating bone margins with intraoperative culture.
2011	Elamurugan TP et al	Role of bone biopsy specimen culture in the management of diabetic foot osteomyelitis
2019	Sloan TJ et al	Examining diabetic heel ulcers through an ecological lens: Microbial community dynamics associated with healing and infection
2018	Jneid J et al	Exploring the microbiota of diabetic foot infections with culturomics
2019	Beroukhim G et al	Factors predicting positive culture in CT-guided bone biopsy performed for suspected osteomyelitis
2020	Kosmopoulou OA et al	Feasibility of percutaneous bone biopsy as part of the management of diabetic foot osteomyelitis in a 100% neuropathic, grade 3 IDSA/IWGDF population on an outpatient basis
2013	Aragon-Sanchez J et al	Gram-negative diabetic foot osteomyelitis: Risk factors and clinical presentation
2011	Weiner RD et al	Histology versus microbiology for accuracy in identification of osteomyelitis in the diabetic foot
2016	Kumar D et al	Identification, antifungal resistance profile, in vitro biofilm formation and ultrastructural characteristics of Candida species isolated from diabetic foot patients in Northern India
2017	Ottolino-Perry K et al	Improved detection of clinically relevant wound bacteria using autofluorescence image-guided sampling in diabetic foot ulcers
2013	Ray GT et al	Incidence, microbiology, and patient characteristics of skin and soft-tissue infections in a U.S. population: a retrospective population-based study.
2013	Turhan V et al	Increasing incidence of Gram-negative organisms in bacterial agents isolated from diabetic foot ulcers
2015	Cervantes-García E et al	Infections of diabetic foot ulcers with methicillin-resistant Staphylococcus aureus
2017	Noor S et al	Inflammatory markers as risk factors for infection with multidrug-resistant microbes in diabetic foot subjects
2019	Park J et al	Influence of microbiota on diabetic foot wound in comparison with adjacent normal skin based on the clinical features
2018	Saltoglu N et al	Influence of multidrug resistant organisms on the outcome of diabetic foot infection
2014	Boffeli TJ et al	In-office distal Symes lesser toe amputation: a safe, reliable, and cost-effective treatment of diabetes-related tip of toe ulcers complicated by osteomyelitis
2018	Makki D et al	Is it necessary to change instruments between sampling sites when taking multiple tissue specimens in musculoskeletal infections?
2011	Vinodkumar CS et al	Isolation of bacteriophages to multi-drug resistant Enterococci obtained from diabetic foot: a novel antimicrobial agent waiting in the shelf?
2018	Meyr AJ et al	Level of agreement with a multi-test approach to the diagnosis of diabetic foot osteomyelitis
2017	Dunyach-Remy C et al	Link between nasal carriage of Staphylococcus aureus and infected diabetic foot ulcers

continued...

Year	Authors	Title
2018	Ramanujam CL et al	Medical imaging and laboratory analysis of diagnostic accuracy in 107 consecutive hospitalized patients with diabetic foot osteomyelitis and partial foot amputations
2018	Suryaletha K et al	Metataxonomic approach to decipher the polymicrobial burden in diabetic foot ulcer and its biofilm mode of infection
2012	Parvez N et al	Microbial profile and utility of soft tissue, pus, and bone cultures in diagnosing diabetic foot infections
2013	Islam S et al	Microbial profile of diabetic foot infections in Trinidad and Tobago
2020	Pontes DG et al	Microbiologic characteristics and antibiotic resistance rates of diabetic foot infections
2012	Tiwari S et al	Microbiological and clinical characteristics of diabetic foot infections in northern India.
2015	Parsa H et al	Microbiological features and risk factors in patients with diabetic foot ulcers
2017	Miyan Z et al	Microbiological pattern of diabetic foot infections at a tertiary care center in a developing country
2014	Sugandhi P et al	Microbiological profile of bacterial pathogens from diabetic foot infections in tertiary care hospitals, Salem
2018	Shettigar K et al	Severity of drug resistance and co-existence of Enterococcus faecalis in diabetic foot ulcer infections
2018	Drampalos E et al	Single stage treatment of diabetic calcaneal osteomyelitis with an absorbable gentamicin-loaded calcium sulphate/hydroxyapatite biocomposite: The Silo technique
2017	Kassam NA et al	Spectrum and antibiogram of bacteria isolated from patients presenting with infected wounds in a tertiary hospital, northern Tanzania.
2016	Fujii M et al	Surgical treatment strategy for diabetic forefoot osteomyelitis
2018	Chang JW et al	The appropriate management algorithm for diabetic foot: A single-center retrospective study over 12 years
2013	Malik A et al	The diabetic foot infections: Biofilms and antimicrobial resistance
2020	Crisologo PA et al	The infected diabetic foot: Can serum biomarkers predict osteomyelitis after hospital discharge for diabetic foot infections?
2017	Rastogi A et al	The microbiology of diabetic foot infections in patients recently treated with antibiotic therapy: A prospective study from India
2019	Banerjee T et al	The microflora of chronic diabetic foot ulcers based on culture and molecular examination: a descriptive study
2016	Nageen A	The most prevalent organism in diabetic foot ulcers and its drug sensitivity and resistance to different standard antibiotics
2013	Gardner SE et al	The neuropathic diabetic foot ulcer microbiome is associated with clinical factors
2012	Abbas Z et al	The utility of Gram stains and culture in the management of limb ulcers in persons with diabetes
2020	Hunter P et al	Topical oxygen therapy shifts microbiome dynamics in chronic diabetic foot ulcers
2012	Pinzur MS et al	Treatment of osteomyelitis in charcot foot with single-stage resection of infection, correction of deformity, and maintenance with ring fixation
2019	Johani K et al	Understanding the microbiome of diabetic foot osteomyelitis: insights from molecular and microscopic approaches
2016	Shettigar K et al	Virulence determinants in clinical Staphylococcus aureus from monomicrobial and polymicrobial infections of diabetic foot ulcers
2018	Haalboom M et al	Wound swab and wound biopsy yield similar culture results

Appendix 3. Summary of papers reporting all aspects of bone sampling techniques and processing in diabetic foot patients

Year	Authors	Title	Study type	What was sampled	How they sampled it	Was the wound cleaned prior to sampling and how	How was the specimen kept prior to processing	What processing occurred
2020	Macdonald K.E. et al	A retrospective analysis of the microbiology of diabetic foot infections at a Scottish tertiary hospital	Retrospective cohort study	Diabetic foot infections, ulcers and suspected osteomyelitis	Deep wound swab from ulcer base. If suspected osteomyelitis, bone biopsy	Yes, cleaned and debrided, no more detail given	Deep tissue swab: Amies transport medium with charcoal. Bone biopsies: sterile universal container	Cultured for aerobic and anaerobic organisms, pure cultures obtained and subjected to antibiotic sensitivity testing.
2011	Lesens O et al	Culture of per-wound bone specimens: A simplified approach for the medical management of diabetic foot osteomyelitis	retrospective cohort review	Bone	All samples taken by the same operator sterile gloves and a gown worn disposable needle holder used to harvest the fragment of infected bone.	careful debridement, wound cleaned with polyvidone iodine, then washed with sterile saline solution	Bone samples were sent to the microbiology laboratory within 2 h in a sterile tube with a few drops of sterile saline solution	Aerobic and anaerobic cultures were performed for each sample for 6 days
2019	Couturier A. et al	Comparison of microbiological results obtained from per-wound bone biopsies versus transcutaneous bone biopsies in diabetic foot osteomyelitis: a prospective cohort study	prospective cohort	Per bone biopsy and Transcutaneous bone biopsy	All samples taken at the bedside by the same operator Sterile gloves, gown, mask worn Bone biopsies: through healthy skin, performed by introducing a 13-gauge pediatric osteo-medullary biopsy trocar through a 3-mm incision made approximately 10 mm from the margins of the wound. For per-wound biopsies: bone sample was taken using metal forceps.	Debridement of the necrotic and fibrinous tissues was performed using a scalpel or curette before a bone sample was taken	Bone samples were sent to the microbiology laboratory in a sterile tube with a few drops of sterile saline solution within 2 h of sampling. All samples were transferred to, and processed by, the center's local clinical microbiology laboratory.	The laboratory identified bacteria by MALDI MS technology using a VITEK MS system (Biomérieux, La Balme, France) and determined antibiotic susceptibility using the VITEK2 system or the disk diffusion method. Susceptibility results were interpreted according to the recommendations of the Antibiogram Committee of the French Microbiology Society
2020	Kosmopoulou O.A.; Dumont I.J.	Feasibility of Percutaneous Bone Biopsy as Part of the Management of Diabetic Foot Osteomyelitis in a 100% Neuropathic, Grade 3 IDSA/IWGDF Population on an Outpatient Basis	Retrospective, Observational	Bone from foot with osteomyelitis (metatarsals or toes), away from open wound or through dorsum	Biopsy using a bone biospy needle - T shaped Jamshedi needle. No anaesthesia due to neuropathy	Cleaned with povidone iodine, sterile drape.	Sent directly to lab in 0.9% saline. If possible specimen divided into and second sample sent for histology(only 7 samples of 23)	Culture and sensitivity and histology in 7 samples.
2011	Weiner R.D. et al	Histology versus Microbiology for Accuracy in Identification of Osteomyelitis in the Diabetic Foot	Prospective	Bone from surgical field taken during other surgery	During surgical procedure, piece of suspected osteomyelitis bone was sampled and split into two	Sterile technique, no further details mentioned	Microbiology specimen transported in dry sterile container. Histology specimen transported in 10% buffered formalin	Aerobic, anaerobic and fungal cultures + histology
2012	Parvez N. et al	Microbial profile and utility of soft tissue, pus, and bone cultures in diagnosing diabetic foot infections	Prospective	Soft tissue specimens - scraping and bone specimens	During surgical debridement: with scalpel for soft tissue and bone nibbler or bone curette or ultrasound guided transcutaneous biopsies with 18 G needle	Soft tissue specimens: after washing with saline and surface debridement Bone specimen: - aseptic precautions and sterile nibbler used. Transcutaneous biopsy - detergent and antiseptic on normal skin .	Sent directly to lab in sterile saline	Aerobic and anaerobic cultures and sensitivity.

Hyperglycaemia in COVID-19: improving recognition and management in a single centre

JORDAN WARDROPE,[1] IONA E MCKENZIE,[1] NICHOLAS D BARWELL[2]

Abstract

Background**: Hyperglycaemia is a recognised complication of COVID-19 disease and is associated with increased morbidity and mortality. Effects are noted in individuals with and without diabetes and potentiated by the use of recognised COVID-19 treatments such as corticosteroids. Early glycaemic control in the inpatient with COVID-19 disease impacts significantly on outcomes.**

Methods**: A three-phase improvement project evaluated the recognition and management of hyperglycaemia in 120 adult inpatients with COVID-19 disease over a 4-month period. A local guideline and a separate acute care 'bundle' were implemented to improve performance. The main outcomes of the project were evaluated in a repeated cross-sectional design; assessing the performance of regular capillary blood glucose monitoring and appropriate treatment of hyperglycaemia where indicated.**

Results**: Prior to intervention, 78.6% of patients had appropriate capillary blood glucose monitoring and no patients were deemed to receive appropriate treatment. Following interventions, 83–100% of patients had appropriate monitoring and 75–100% received appropriate treatment.**

Conclusions**: In this setting, implementation of a guideline and a care bundle contributed towards improved recognition and management of hyperglycaemia in patients with COVID-19 disease. Future study could assess the impact of interventions on a larger scale whilst investigating variation in the subtype of diabetes, patient sex and other demographics on outcomes such as length of stay, morbidity and mortality.**

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Key words: COVID-19; diabetes mellitus; hyperglycaemia; glycaemic control; quality improvement

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Background

There is increasing recognition of the morbidity and mortality associated with the secondary sequelae of COVID-19 disease. In people with and without diabetes, hyperglycaemia is a recognised complication and may have clinically significant effects including diabetic ketoacidosis and hyperosmolar hyperglycaemic state.[1] The mechanism for COVID-19-associated hyperglycaemia is not yet clear, although likely implicates increased reactive oxygen species production and circulating interleukin-6, along with a state of increased insulin resistance.[2] There is perhaps a direct link between hyperglycaemia and the physiological response to the stressor of an acute severe viral syndrome – so-called stress hyperglycaemia. Furthermore, the development of hyperglycaemia may be exacerbated or precipitated by some therapies approved for COVID-19 disease, in particular dexamethasone.

It is estimated that hyperglycaemia occurs in around 50% of patients with COVID-19 during the acute phase of illness.[3] Hyperglycaemia and/or diabetes in COVID-19 patients are independent risk factors for prolonged hospital stay, critical illness and mortality.[4] Additionally, it has been reported that controlled blood glucose levels during the first 24 hours of disease correlate with a lower risk of severe disease progression and lower mortality by day 20 of illness in both subjects with and without diabetes.[3] This highlights the importance of early recognition and intervention in hyperglycaemia.

The pathophysiological response to COVID-19 disease has an impact on which therapies can be used in the acute phase of illness and makes selection of a specific agent more challenging. Current evidence recommends use of insulin therapy in hospitalised and critically unwell patients;[2] advantages include relatively easy dose titration and the option of an insulin infusion for more challenging cases. Less favourable options include glucagon-like peptide 1 (GLP-1) analogues,[2] sodium-glucose co-transporter 2 (SGLT-2) inhibitors,[2] thiazolidinediones[2] and sulfonylureas.[1,2] Evidence is limited for dipeptidyl peptidase-4 (DPP-4) inhibitors.[5] Metformin has been associated with a lower risk of death in hospitalised COVID-19 patients[6] and should be continued in individuals already established on the drug; however, other studies discourage its use in patients with critical disease severity[2] due to association with lactic acidosis in such disease states. The pharmacological management of hyperglycaemia in COVID-19 is complex and clinicians must adapt their approach accordingly – hence the importance for guidelines and protocols in this relatively novel patient group.

During the emergence of COVID-19 in early 2020, a number of cases of hyperglycaemia in patients with the disease were noted

by the authors; in particular, in patients with co-existing diabetes and/or those who were receiving dexamethasone therapy. This observation encouraged a search of the relevant literature and guidance available at the time, which was found to be relatively scarce. Given the recognised complications of hyperglycaemia in unwell patients and the associated morbidity and mortality of it alongside COVID-19, the topic was studied further at a local level. This project aimed to evaluate and improve the quality of monitoring and management of hyperglycaemia for hospitalised patients with COVID-19 disease.

Methods

Population

This project collected data relevant to medical inpatients with a laboratory-confirmed diagnosis of COVID-19 disease within Forth Valley Royal Hospital between November 2020 and March 2021. The population group included adult inpatients within the acute medicine and general medicine wards of the hospital (age range 19–92). Children, obstetric and critical care unit patients were not included in this study.

Data collection

This study consisted of three periods of data collection by means of a repeated cross-sectional design. Data were collected by two of the authors by examining patient notes, inpatient prescriptions and capillary blood glucose (CBG) monitoring charts. The main outcomes evaluated in the project were performance of regular CBG monitoring and appropriate treatment for hyperglycaemia where indicated.

During each phase of data collection, patients were initially identified as having a confirmed diagnosis of COVID-19 disease. The authors then evaluated the proportion of the patient group with pre-existing diabetes mellitus and the proportion of total patients receiving dexamethasone therapy. Performance of regular CBG monitoring was assessed, with particular attention to patients with a recorded CBG >12 mmol/L triggering initiation of insulin treatment, as adapted from national guidance[1] and taking into account the risks and benefits of various antidiabetic medications.[1,2,6] The proportion of patients who warranted such treatment, and received it appropriately, was also assessed.

Interventions

Data were collected at regular intervals throughout the study: baseline data prior to any intervention; over the course of 2 months following a 1-week run-in from the implementation of a local 'Hyperglycaemia in COVID-19' guideline; and again, over 1 month following a 1-week run-in from the implementation of a local 'COVID-19 Acute Care Bundle'.

The initial guideline was developed by a multidisciplinary team (MDT) of the project authors, Diabetes Consultant Physicians and an inpatient Diabetes Specialist Nurse, with subsequent publication on the local clinical guidelines intranet page. Awareness of the guideline was disseminated to staff by email.

The subsequent intervention, a 'COVID-19 Acute Care Bundle', was developed later in the project by the authors in conjunction with the medical leads of the acute medical unit (AMU). Taking the form of a two-page checklist/guideline, this was part of a wider project to optimise the overall acute medical management of COVID-19 patients (including basic investigation, prescribing and escalation decisions) and included a prompt for implementing a CBG chart for a COVID-19-positive patient. Infographics regarding the management of hyperglycaemia in COVID-19 were included on the reverse of the document. The bundle was introduced at an AMU safety brief before being made available on the local intranet page and in hard copy in the AMU MDT office.

Results

One hundred and twenty hospitalised adults with COVID-19 disease were evaluated in this project over a 4-month period (12% in phase 1, 56% in phase 2, 32% in phase 3). Of all patients studied, 24 (20%) had a pre-existing diagnosis of diabetes mellitus and 74 (61.7%) patients received dexamethasone treatment for COVID-19 disease. A total of 26 (21.7%) patients had a CBG of >12 mmol/L that would merit insulin treatment.

Prior to any intervention, 78.6% of patients received regular CBG monitoring; however, no patients studied received appropriate treatment for hyperglycaemia. Following the first intervention, in cycle 1, 54–88% of patients had regular CBG monitoring and 71–100% of patients received appropriate treatment for hyperglycaemia. Following implementation of the second intervention, in cycle 2, 83–100% of patients received regular monitoring and 75–100% received appropriate treatment. The overall results throughout the duration of the project are shown in Figure 1.

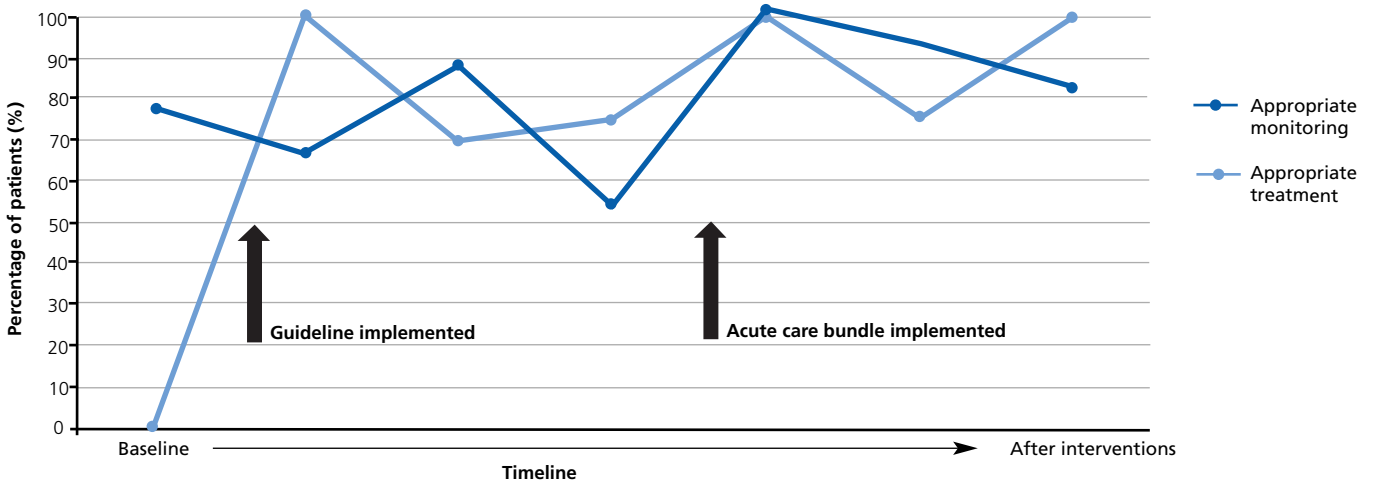
Discussion

The prevalence of co-existing diabetes mellitus in COVID-19 disease in other studies is 17–28.3%,[3,7,8] correlating with the findings of this project. Conversely, a British multicentre prospective cohort study by Närhi *et al* found that only 33.5% of hospitalised COVID-19 patients received steroid therapy (with missing data from 18.3% of total patients).[9] This figure is significantly less than demonstrated for the population in the current study. Smaller sample size may explain some of this effect; however, given that the current study was undertaken from November 2020, considerable impact is likely due to the widely recognised findings of the RECOVERY trial,[10] encouraging use of dexamethasone in COVID-19 patients. The study by Närhi *et al* assessed data from June to September 2020,[9] when the use of dexamethasone therapy in COVID-19 was just gaining popularity.

Our study suggests that 21.7% of patients warranted management of hyperglycaemia for CBG >12 mmol/L. This compares to an American multicentre study of a patient group with diabetes and/or uncontrolled hyperglycaemia where 37.8% of patient days were spent with a mean blood glucose level >180 mg/dL[11] (equivalent to 10 mmol/L). Given the morbidity associated with hyperglycaemia in COVID-19 disease, both the study by Bode *et al* and the current study demonstrate a significant proportion of patients requiring intervention for above-threshold hyperglycaemia.

During this study, performance with CBG recording was consistently high, even prior to intervention. This may reflect general good

Figure 1. Monitoring and management of hyperglycaemia in patients with COVID-19 disease over time.



practice within the hospital and is likely supported by the proportion of people with diabetes and/or patients on dexamethasone where regular monitoring of CBG levels is already common practice. Performance with CBG monitoring over time increased following interventions. The primary outcome of this study – appropriate treatment of hyperglycaemia – also improved over time. These data demonstrated a clear improvement in appropriate therapy following the implementation of a local guideline and care bundle for COVID-19 patients. There may also be an experience effect contributing to improved performance as clinicians become more familiar with appropriate glycaemic management over time.

At the time of publication, the authors were aware of few other single-centre quality improvement projects addressing dysglycaemia in patients with COVID-19 disease. As such, this project demonstrates novel methods of tackling the issue at a local level through sustainable practical solutions. The current guideline and care bundle have since been approved at a hospital clinical governance meeting to ensure ongoing use for possible future waves of COVID-19 presentations. Although the current study has differentiated patients by presence of diabetes and/or steroid therapy, future study would benefit from a larger sample size to corroborate findings within each study phase. Similarly, future study would benefit from implementation within other hospital settings, and investigation of the differences on outcomes between male and female patients, age brackets, diabetes subtypes and in those with stress glycaemia or in other acute causes of hyperglycaemia (such as pancreatic insult, intravenous fluid therapy, concurrent illness). Examination of additional outcomes such as length of stay, incidence of critical care admission, incidence of dysglycaemic complications and mortality may enhance future practice with prognostic relevance.

Conclusion

Hyperglycaemia is an important complication of COVID-19 disease, associated with increased morbidity and mortality. The presence of co-existing diabetes mellitus and/or steroid therapy in such patients are recognised as exacerbators of this effect, and it has been previously described that early glycaemic control in the inpatient with COVID-19 disease impacts significantly on outcomes. Until further research demonstrates otherwise, there are limited safe treatment options for hyperglycaemia in patients with COVID-19 disease beyond that of insulin therapy. This quality improvement project investigated the monitoring and management of glycaemic control in 120 inpatients with COVID-19 disease in one hospital setting – before, during and following two changes of practice. The implementation of a COVID-19 specific hyperglycaemia guideline and a subsequent acute care 'bundle' have contributed towards improved blood glucose monitoring and hyperglycaemia management for this patient group, although there would be much to gain from more detailed study within patient subgroups and on longer-term outcomes for future work in this area.

Key messages

- Hyperglycaemia is a recognised complication of COVID-19 disease and has an impact on subsequent morbidity and mortality
- The management of hyperglycaemia in the context of COVID-19 disease differs from the management in patients without
- The implementation of local guidelines and pathways can contribute to improved glycaemic monitoring and control in patients with COVID-19 disease

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Series: Cardiovascular outcome trials for diabetes drugs
Canagliflozin and the CANVAS Program, dapagliflozin and DECLARE-TIMI 58, ertugliflozin and VERTIS CV

MILES FISHER

Abstract
EMPA-REG OUTCOME was a landmark trial with the sodium-glucose co-transporter-2 (SGLT2) inhibitor empagliflozin, which demonstrated significant reductions in major adverse cardiovascular events (MACE, a composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) driven by reductions in cardiovascular deaths and accompanied by an early reduction in hospitalisation for heart failure. This was followed by cardiovascular outcome trials with canagliflozin, dapagliflozin and ertugliflozin. The CANVAS Program was an integrated analysis of the CANVAS and CANVAS-R trials with canagliflozin. It demonstrated a significant reduction in MACE, but not in any of the components, and there was an unexpected increase in amputations and fractures with canagliflozin. The DECLARE-TIMI 58 trial with dapagliflozin had two co-primary endpoints. A composite endpoint of cardiovascular death or hospitalisation for heart failure was significantly reduced, but there was no significant difference in MACE comparing dapagliflozin with placebo. Analysis of patients with a prior myocardial infarction, however, demonstrated significant reductions in MACE. The VERTIS CV trial with ertugliflozin was disappointing as there was no difference in MACE comparing ertugliflozin and placebo. In all four trials a reduction in hospitalisation for heart failure was observed in patients with type 2 diabetes, regardless of whether they had existing atherosclerotic cardiovascular disease or increased cardiovascular risk. Prespecified renal outcomes were reduced with empagliflozin, canagliflozin and dapagliflozin, and these drugs are now commonly used in the management of people with type 2 diabetes. It is hard to envisage an ongoing role for ertugliflozin in routine clinical management as the evidence for its cardiovascular benefit is not convincing.
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Key words: diabetes, cardiovascular outcome trial, canagliflozin, dapagliflozin, ertugliflozin

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Introduction

Licensing requirements for new antidiabetic drugs changed in the USA and EU following the rosiglitazone controversy and there was a much greater requirement to demonstrate cardiovascular safety. Between 2015 and 2020 four dedicated cardiovascular outcome trials were completed with sodium-glucose co-transporter-2 (SGLT2) inhibitors in patients with type 2 diabetes.[1–4] EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) was the first of these,[1] and was reviewed earlier in this series.[5] EMPA-REG OUTCOME can truly be described as a landmark trial as not only did it satisfy the safety requirements for empagliflozin, but it demonstrated remarkable cardiovascular benefits, including significant reductions in major adverse cardiovascular events (MACE, a composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) powered by an early reduction in cardiovascular deaths. Secondary outcomes of hospitalisation for heart failure and a renal composite outcome were also significantly reduced.[1]

This review describes results from the other three cardiovascular safety trials with SGLT2 inhibitors in patients with type 2 diabetes; the CANVAS Program with canagliflozin,[2] DECLARE-TIMI 58 with dapagliflozin[3] and VERTIS CV with ertugliflozin.[4] The review describes the primary endpoint and important secondary outcomes from the principal publications, making comparisons with the results of EMPA-REG OUTCOME, and directs attention to important subsequent publications of data from subgroups and/or post hoc analyses.

The CANVAS Program

The CANVAS Program comprised two sister trials and data from the two trials were integrated to assess cardiovascular safety and

efficacy. The rationale, design and baseline characteristics from CANVAS (Canagliflozin Cardiovascular Assessment Study) was published in 2013,[6] and the rationale, design, and baseline characteristics of CANVAS-R (Canagliflozin Cardiovascular Assessment Study-Renal) was published in 2017.[7] Prior to the completion of the trials, the CANVAS Program collaborative group described how the integrated statistical analysis would be performed to optimise the analysis strategy.[8]

The principal results from the CANVAS Program were presented in 2017 at the meeting of the American Diabetes Association (ADA) and published simultaneously in the *New England Journal of Medicine*.[2] The key features of the trial and baseline characteristics of subjects are described in Table 1. The CANVAS Program recruited a mixture of subjects with established atherosclerotic cardiovascular disease (66%) and subjects over 50 years of age with two or more risk factors for cardiovascular disease (34%), whereas EMPA-REG OUTCOME recruited only patients with established atherosclerotic cardiovascular disease. Two doses of canagliflozin were included (100 mg and 300 mg) and the results of both doses of canagliflozin and both CANVAS trials were pooled for analysis.

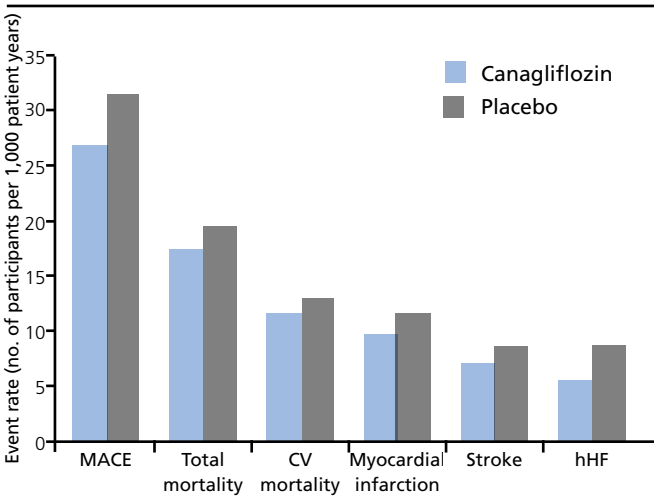
In the CANVAS Program there was a significant reduction in MACE with canagliflozin, demonstrating superiority versus placebo (Figure 1, Box 1). Statistical hypothesis testing was scheduled to proceed sequentially, and there was no significant difference in the next sequential outcome which was all-cause mortality. Any further statistical analysis of CANVAS is therefore deemed to be exploratory. There were no nominal differences in any of the components of the composite MACE outcome, but there were reductions in hospitalisation for heart failure, the progression of albuminuria and a renal composite outcome (40% reduction in estimated glomerular filtration rate (eGFR), the need for renal replacement therapy or death from renal causes).

Unexpectedly, there was a significantly increased rate of amputation of the toes, feet or legs with canagliflozin, which was particularly seen in subjects with a history of amputation or peripheral vascular disease. The rate of all fractures was also significantly higher with canagliflozin than placebo, and this appeared to be higher with canagliflozin than placebo in the CANVAS trial but not in CANVAS-R. As might be anticipated, rates of genital fungal infections with canagliflozin were significantly increased in women and men. Diabetic ketoacidosis was rare with only 18 episodes, and although it was twice as common in the canagliflozin group, this was not statistically significant.

Other results from the CANVAS Program

The effect of canagliflozin on amputation risk in the CANVAS Program was calculated for amputations of different types and aetiologies and different canagliflozin doses.[9] The increased risk of amputation was similar for ischaemic and infective aetiologies and for 100 mg and 300 mg doses. The risk of amputation was associated with a baseline history of previous amputation and other established risk factors for amputation. Disappointingly, no specific aetiological mechanism or at-risk subgroup for canagliflozin was identified.

Figure 1. Event rates (number of participants/1,000 patient-years) comparing canagliflozin and placebo for major adverse cardiovascular events (MACE), total mortality, cardiovascular mortality (CV mortality), non-fatal myocardial infarction, non-fatal stroke and hospitalisation for heart failure (hHF).



Box 1 Results of the CANVAS Program[2]

Principal result
- Significant reduction in MACE and hospitalisation for heart failure[2]

Other results from the CANVAS Program
- The increased risk of amputation was similar for ischaemic and infective causes, and was associated with a history of previous amputation and other established risk factors for amputation.[9]
- The increase in fracture risk was not explained by interactions with participant characteristics, dose effects, duration of follow-up, metabolic effects, adverse events related to falls or adverse events possibly causing falls.[10]
- In a pre-specified exploratory analysis, canagliflozin treatment was associated with a reduced risk of sustained loss of kidney function, attenuated eGFR decline and a reduction in albuminuria,[25] supporting a possible renoprotective effect of this drug that was later confirmed in CREDENCE.[11]
- Canagliflozin reduced the risk of cardiovascular death or hospitalisation for heart failure across a broad range of different patient subgroups, but benefits appeared greater in those with a history of heart failure at baseline.[26]

Further analysis of fractures in the CANVAS Program was also disappointing as the differences in fracture risk between CANVAS and CANVAS-R was not explained by differences in baseline characteristics, interactions of randomised treatment with participant characteristics, dose effects, duration of follow-up, metabolic effects, adverse events related to falls or adverse events possibly causing falls.[10] The investigators concluded that this was a chance finding without providing any evidence for this conclusion, other than the fact that there was no increase in fractures (or amputations) in the CREDENCE renal outcome trial with canagliflozin.[11] They conceded that an unidentified mechanism related to falls remained a possibility. The results of

CREDENCE were not available when the post hoc analysis of amputations was performed, but it would have stretched credibility to suggest that the increase in amputations and fractures were both chance findings!

DECLARE-TIMI 58

Papers on the design and rationale for DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58) and on the baseline patient characteristics were published in 2018.[12,13] Key features of the trial and baseline characteristics of subjects are described in Table 1. Like the CANVAS Program, DECLARE-TIMI 58 recruited a mixture of subjects with established atherosclerotic cardiovascular disease (41%) and subjects over 55 years of age with one or more risk factors for cardiovascular disease (59%). For the statistical analysis, the first analysis was for non-inferiority of dapagliflozin to placebo for MACE. If non-inferiority was confirmed, then two co-primary outcomes were tested for superiority, which were MACE and a composite of cardiovascular death or hospitalisation for heart failure. MACE is the primary endpoint in cardiovascular trials when studying drugs that reduce events in patients with atherosclerosis (eg, statins), and the composite of cardiovascular death or hospitalisation for heart failure is the preferred primary endpoint when studying drugs that reduce events in patients with heart failure (eg, ACE inhibitors, beta blockers, etc).

The principal results from DECLARE-TIMI 58 were presented in 2018 at the meeting of the American Heart Association (AHA) and published simultaneously in the *New England Journal of Medicine*.[3] In DECLARE-TIMI 58 there was a significant reduction in the co-primary composite endpoint of cardiovascular death or hospitalisation for heart failure with dapagliflozin, but no significant reduction in the co-primary MACE endpoint (Figure 2, Box 2). There were no significant differences in death from any cause, death from cardiovascular causes, myocardial infarction or stroke. There were statistically significant differences in the rate of hospitalisation for heart failure and in the pre-defined renal composite outcome which in DECLARE-TIMI 58 was a ≥40% reduction in eGFR to <60 mL/min/1.73 m^2, new end-stage renal disease or death from renal or cardiovascular causes.

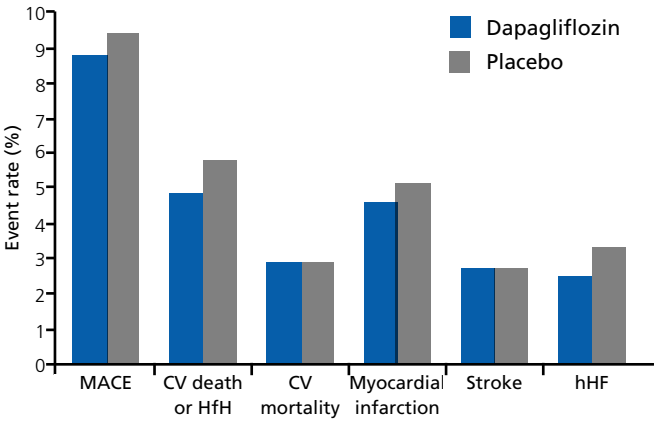
Again, as expected there was a significant increase in genital infections with dapagliflozin, and rates of diabetic ketoacidosis were doubled, which in DECLARE-TIMI 58 was a statistically significant difference. There was no difference in the rates of amputation or fracture.

Other results from DECLARE-TIMI 58

The biggest differences between DECLARE-TIMI 58 and EMPA-REG OUTCOME were the inclusion of a large number of patients without established atherosclerotic cardiovascular disease in DECLARE-TIMI 58, and the absence of a reduction in MACE in the results. Perhaps anticipating these findings, the DECLARE-TIMI 58 investigators pre-specified subjects with a prior myocardial infarction as a subgroup of interest.[14]

A statistically significant reduction in MACE was observed comparing dapagliflozin and placebo in the 3,584 subjects with a previous myocardial infarction, but there was no difference in subjects without a previous myocardial infarction, including in patients with established atherosclerotic disease but without a prior myocardial infarction.

Figure 2. Event rates (%) comparing dapagliflozin and placebo for major adverse cardiovascular events (MACE), cardiovascular death or hospitalisation for heart failure (CV death or HFH), cardiovascular mortality (CV mortality), myocardial infarction, stroke and hospitalisation for heart failure (hHF)



Box 2 Results of the DECLARE-TIMI 58 trial[3]

Principal result
- Significant reduction in the composite of cardiovascular death and hospitalisation for heart failure[3]
- No significant difference in MACE[3]

Other results from DECLARE-TIMI 58
- A statistically significant reduction in MACE was observed comparing dapagliflozin and placebo in the 3,584 subjects with a previous myocardial infarction, but there was no difference in subjects without a previous myocardial infarction.[14]
- Of 17,160 patients, 671 (3.9%) had heart failure with a reduced ejection fraction (HFrEF), 1,316 (7.7%) had heart failure without known reduced ejection fraction and 15,173 (88.4%) had no history of heart failure at baseline. Dapagliflozin reduced cardiovascular death/hospitalisation for heart failure more in patients with HFrEF than in those without HFrEF.[27]
- A pre-specified secondary cardiorenal composite defined as a sustained decline of at least 40% in estimated glomerular filtration rate (eGFR) to <60 mL/min/1.73 m^2, end-stage renal disease (defined as dialysis for at least 90 days, kidney transplantation or confirmed sustained eGFR <15 mL/min/1.73 m^2) or death from renal or cardiovascular causes was reduced, as was a pre-specified renal specific composite outcome which was the same but excluded death from cardiovascular causes.[28]
- Acute kidney injury was less common with dapagliflozin, and there was no increase in adverse events suggestive of volume depletion irrespective of blood pressure or diuretic use including the use of loop diuretics.[29]

VERTIS CV

A paper describing the design and baseline characteristics of VERTIS CV (Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular

Outcomes Trial) was published in 2018.[15] This explained that, following the publication of the results of EMPA-REG OUTCOME, it was decided to double the number of subjects in VERTIS CV with the aim of testing for superiority for cardiovascular and renal outcomes. The principal VERTIS CV results were presented in 2020 at the virtual meeting of the ADA and the results were accompanied with an updated systematic review and meta-analysis of cardiovascular and renal outcomes of SGLT2 inhibitors in patients with type 2 diabetes. The print publication of VERTIS CV in the *New England Journal of Medicine* followed later in 2020[4] and the meta-analysis was published soon after in *JAMA Cardiology*.[16] Key features of the trial and baseline characteristics of subjects are described in Table 1. Like EMPA-REG OUTCOME, all the subjects in VERTIS CV had established atherosclerotic heart disease, and the main difference in VERTIS CV was a higher rate of investigator reported heart failure at baseline (24% in VERTIS CV versus 10% in EMPA-REG OUTCOME).

Surprisingly, in VERTIS CV there was no significant difference in MACE, so non-inferiority was established but not superiority (Figure 3, Box 3). There was also no difference in the composite of death from cardiovascular causes or hospitalisation for heart failure, no difference in death from cardiovascular causes, and no difference in the pre-specified renal composite outcome, which for VERTIS CV was doubling of serum creatinine levels, the need for renal replacement therapy or death from renal causes. A reduction was observed in the rate of hospitalisation for heart failure with ertugliflozin, which again can be considered exploratory because of the hierarchal statistical testing sequence.

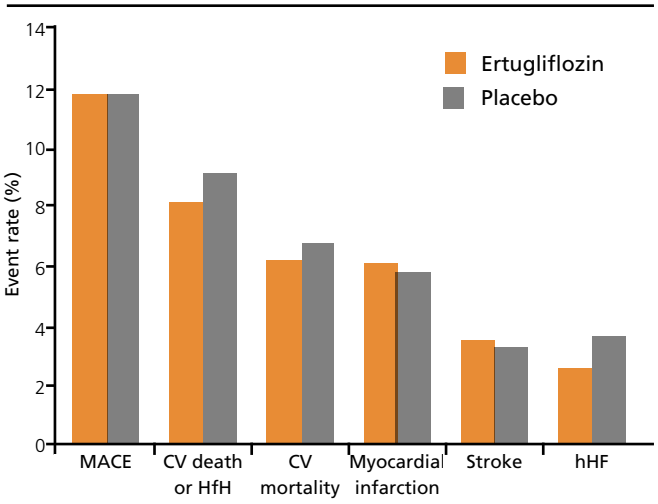
In VERTIS CV genital mycotic infections were significantly increased in women and men in the ertugliflozin group. Numerical increases were seen in diabetic ketoacidosis and amputations, but these were not statistically significant.

Results of the meta-analysis and other results from VERTIS CV

VERTIS CV failed to demonstrate reductions in MACE or the secondary renal composite outcome, and an early publication after the principal publication reported the results of a pre-specified exploratory analysis of renal outcomes.[17] The analysis replaced doubling of serum creatinine with a sustained 40% decrease from baseline in eGFR, and on this analysis a significant reduction in the renal composite outcome was observed. As had been seen in other SGLT2 inhibitor outcome trials, there was an attenuation of the decline in eGFR with ertugliflozin, and there was a decrease in the albumin to creatinine ratio.

The meta-analysis included data from the four cardiovascular outcome trials plus CREDENCE.[16] The authors reported that there was no significant heterogeneity across the trials in the reduction in MACE or the reduction in kidney outcomes, and that the risk reduction for hospitalisation for heart failure was consistent across the trials. Regardless of the statistical analysis, it is striking that there was absolutely no effect of ertugliflozin on MACE (hazard ratio 0.99, 95% confidence intervals 0.88 to 1.12). Significant heterogeneity of associations with outcomes was noted for cardiovascular death, and only EMPA-REG OUTCOME was associated with a reduction in cardiovascular death.

Figure 3. Event rates (%) comparing ertugliflozin and placebo for major adverse cardiovascular events (MACE), cardiovascular death or hospitalisation for heart failure (CV death or HFH), cardiovascular mortality (CV mortality), fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, and hospitalisation for heart failure (hHF)



Box 3 Results of the VERTIS CV trial

Principal result
- No significant difference in MACE

Other results from VERTIS CV
- An analysis replacing doubling of serum creatinine with a sustained 40% decrease from baseline in estimated glomerular filtration rate (eGFR) showed a statistically significant reduction in the renal composite outcome, with an attenuation of the decline in eGFR, and a decrease in the albumin to creatinine ratio.[17]
- Ertugliflozin reduced the risk for first and total hospitalisation for heart failure (HHF) and total HHF/cardiovascular death, adding further support for the use of SGLT2 inhibitors in primary and secondary prevention of HHF.[30]

Discussion

EMPA-REG OUTCOME was a landmark study which rapidly increased the use of empagliflozin in diabetic patients with established atherosclerotic cardiovascular disease. By comparison, the results of the CANVAS Program were less dramatic. Although the pattern of benefit was broadly similar to EMPA-REG OUTCOME, several individual outcomes were not significantly reduced. Part of this difference can be explained by the inclusion of lower risk subjects who did not have established atherosclerotic cardiovascular disease, and the CANVAS Program may have been statistically underpowered for some of the comparisons. Renal benefits of canagliflozin were demonstrated in the CANVAS Program and subsequently confirmed in the dedicated CREDENCE trial of people with diabetic kidney disease. Reductions in hospitalisation for heart failure were also seen as a secondary outcome in the CANVAS Program, but to date there are no plans for a dedicated heart failure outcome trial with

Table 1 Key features of EMPA-REG OUTCOME,[1] the CANVAS Program,[2,6,7] DECLARE-TIMI 58[3,12,13] and VERTIS CV[4]

	EMPA-REG OUTCOME[1]	CANVAS Program[2,6,7]	DECLARE-TIMI 58[3,12,13]	VERTIS CV[4,15]
SGLT2 inhibitor	Empagliflozin 10 mg and 25 mg	Canagliflozin 100 mg to 300 mg	Dapagliflozin 10 mg	Ertugliflozin 5 mg and 15 mg
Subjects	7,020	10,142	17,160	8,246
Follow-up	Median observation 3.1 years	Mean 3.6 years	Median 4.2 years	Mean 3.5 years
Age	63 years	63 years	64 years	64 years
Duration of diabetes	57% duration over 10 years	14 years	11 years	13 years
Baseline HbA_{1c}	8.1% (65 mmol/mol)	8.2% (66 mmol/mol)	8.3% (67 mmol/mol)	8.2% (66 mmol/mol)
Baseline CVD	99% ASCVD 76% CAD 46% prior MI 23% stroke 10% HF	66% ASCVD 56% CAD 19% stroke/cvd 14% HF 34% CV risk	40% ASCVD 33% CAD 21% prior MI 7% stroke/cvd 10% HF 60% CV risk	100% ASCVD 76% CAD 48% Prior MI 23% stroke/cvd 24% HF
Baseline diabetes treatments	74% metformin 42% sulfonylurea 48% insulin 11% DPP-4 inhibitor 3% GLP-1 RA	77% metformin 43% sulfonylurea 50% insulin 12% DPP-4 inhibitor 4% GLP-1 RA	82% metformin 43% sulfonylurea 40% insulin 17% DPP-4 inhibitor 4% GLP-1 RA	77% metformin 41% sulfonylurea 47% insulin 11% DPP-4 inhibitor 3% GLP-1 RA

ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CV risk, subjects without established cardiovascular disease but at increased risk of developing cardiovascular disease; HF, heart failure; MI, myocardial infarction; stroke/CVD, stroke or cerebrovascular disease.

canagliflozin. Although not replicated in CREDENCE or in several real-world databases, the increase in amputations and fractures is worrying and lacks a credible explanation.

As the third published cardiovascular trial with an SGLT2 inhibitor trial, the results of DECLARE-TIMI 58 were also broadly similar to EMPA-REG OUTCOME. A reduction in heart failure events was seen in a wider population of people with type 2 diabetes in DECLARE-TIM 58, with reductions in patients who were at increased cardiovascular risk but did not have established cardiovascular disease. A dedicated outcome trial of dapagliflozin in patients with well characterised heart failure with a reduced left ventricular ejection fraction (DAPA-HF) subsequently demonstrated clear benefits with reductions in heart failure events in subjects with and without diabetes.[18] Trials with empagliflozin have shown reductions in heart failure events in patients with and without diabetes who have heart failure with a reduced ejection fraction (EMPEROR-Reduced)[19] and patients with a preserved ejection fraction (EMPEROR-Preserved).[20] A trial of dapagliflozin in patients with heart failure and a preserved ejection fraction (DELIVER) is expected to complete in 2022.[21] The licences of dapagliflozin and empagliflozin have been updated to allow prescribing in patients with heart failure in addition to use in patients with diabetes.

In DECLARE-TIMI 58 reductions in the renal composite outcome were also seen in a wider group of patients than in EMPA-REG OUTCOME. A subsequent dedicated outcome trial of dapagliflozin in patient with chronic kidney disease with and without diabetes (DAPA-CKD) demonstrated clear reductions in renal outcomes.[22] Another change in the licence for dapagliflozin broadens the indication for use in this group of patients, and canagliflozin has a similar licence for use in patients with kidney disease, but only for diabetic patients. A dedicated renal trial with empagliflozin (EMPA-KIDNEY) including patients with and without diabetes is expected to complete in 2022.[23]

There was general expectation that the results of VERTIS CV would be broadly similar to the results of EMPA-REG OUTCOME as the study population was very similar. The lack of a clear benefit in reducing the major study endpoints was a surprise, with only reductions in hospitalisation for heart failure and a revised renal composite outcome. There are no current plans for dedicated trails of ertugliflozin in patients with heart failure or chronic kidney disease. None of the four dedicated cardiovascular trials studied possible mechanisms of benefit, and there are many possible explanations for the reductions in cardiovascular and renal outcomes that are observed with SGLT2 inhibitors. As ertugliflozin has similar effects to dapagliflozin and empagliflozin on HbA_{1c}, body weight and blood pressure, as presented by the VERTIS CV investigators at the virtual ADA meeting, the benefits are unlikely to be mediated by changes in HbA_{1c}, body weight or blood pressure.[24] For diabetic patients with established atherosclerosis, empagliflozin is a better treatment option than ertugliflozin based on the results of EMPA-REG OUTCOME and, for patients who are at increased cardiovascular risk, dapagliflozin is a better treatment option based on the results of DECLARE-TIMI 58.

Conflict of interest The author has received personal fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Lexicon, MSD, NAPP, Novo Nordisk and Sanofi outside the submitted work

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Key messages

- In the CANVAS Program, canagliflozin reduced major adverse cardiovascular events in patients with type 2 diabetes but at the expense of an increase in amputations and fractures
- In DECLARE-TIMI 58 there was a reduction in heart failure events in a broad spectrum of patients with type 2 diabetes, but reductions in major adverse cardiovascular events were only observed in patients with a previous myocardial infarction
- The results of the VERTIS CV cardiovascular outcome trial with ertugliflozin were disappointing as there was no significant reduction in major adverse cardiovascular events or the chosen renal composite outcome

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Diabetic myonecrosis: challenges in diagnosis and management

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Key words: diabetic myonecrosis; diabetic muscle infarction; diabetic nephropathy

Introduction

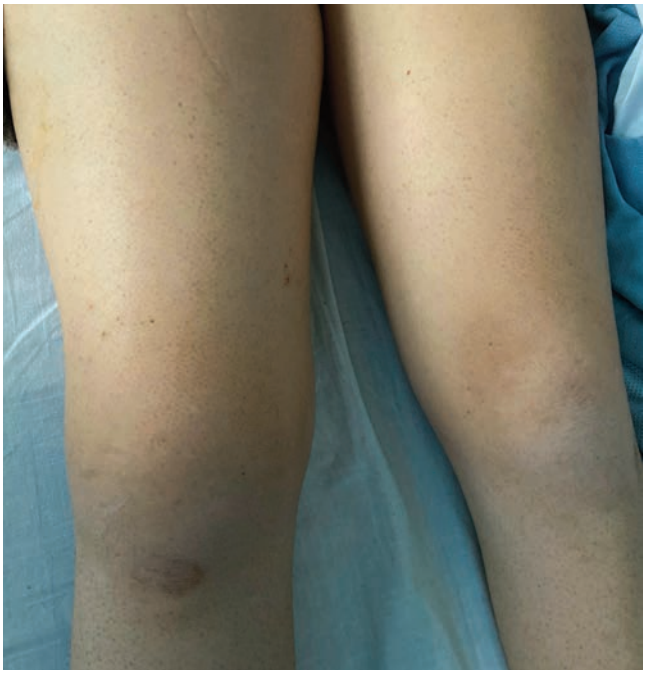
Diabetic myonecrosis (DMN) or diabetic muscle infarction is a rare complication of diabetes mellitus. To date, over half a century since first described in 1965,[1] the pathogenesis and management approach is still incompletely understood. We describe a case of DMN, the multidisciplinary approach adopted and the challenges faced in the management of this patient.

Case presentation

A 29-year-old female presented with acute onset right thigh pain and swelling 24 hours after peritoneal dialysis catheter insertion. She had a background of type 1 diabetes mellitus diagnosed over 20 years prior to presentation. Her glycaemic control had been suboptimal, with multiple episodes of diabetic ketoacidosis and complications including diabetic retinopathy, gastroparesis, autonomic neuropathy and end stage renal disease secondary to diabetic nephropathy, requiring peritoneal dialysis. She was discharged after completing a course of intravenous antibiotics for presumed infection but re-presented one week later to her renal team with worsening right thigh pain and swelling. There was no history of trauma or symptoms to suggest an infective aetiology.

On examination she was in severe pain. She was tachycardic with a pulse rate of 110 bpm, blood pressure was elevated at 158/90 mmHg, she was afebrile and had normal oxygen saturation levels. The peritoneal catheter site appeared clean and her abdomen was soft with no ascites. The right thigh was markedly enlarged, circumference 45 cm compared with 25 cm on the left (Figure 1), very tender and warm to touch and movement limited due to pain. There was no erythema or inguinal lymphadenopathy and peripheral pulses were easily palpable.

Figure 1. Disproportionate swelling of the right thigh



Investigations

Admission blood tests showed a haemoglobin of 106 g/L (normal range (NR) 115–160) and neutrophilia 9.64x10^9/L (NR 2–8) and C-reactive protein (CRP) 133.7 mg/L (NR 0–5). Creatine kinase (CK) was normal at 172 U/L (NR 25–200) and D-dimer was marginally raised at 583 ng/mL (NR 0–500). Peripheral blood cultures and cultures from the peritoneal dialysis catheter were negative. Connective tissue antibody and myositis antibody screens were also negative.

Ultrasound Doppler of the right thigh excluded a focal collection and above-knee deep vein thrombosis (DVT) but did show focal muscle swelling (Figure 2). Magnetic resonance imaging (MRI) of both thighs confirmed unilateral extensive right medial compartment muscle swelling, myositis and ischaemia. This was most severe in portions of the sartorius, adductor longus and vastus intermedius. There was no focal soft tissue or osseous collection, marrow infarct or osteomyelitis (Figures 3 and 4).

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Figure 2. Transverse ultrasound image of the right thigh confirming focal area of muscle and subcutaneous swelling with heterogenous mixed echogenicity (arrow)

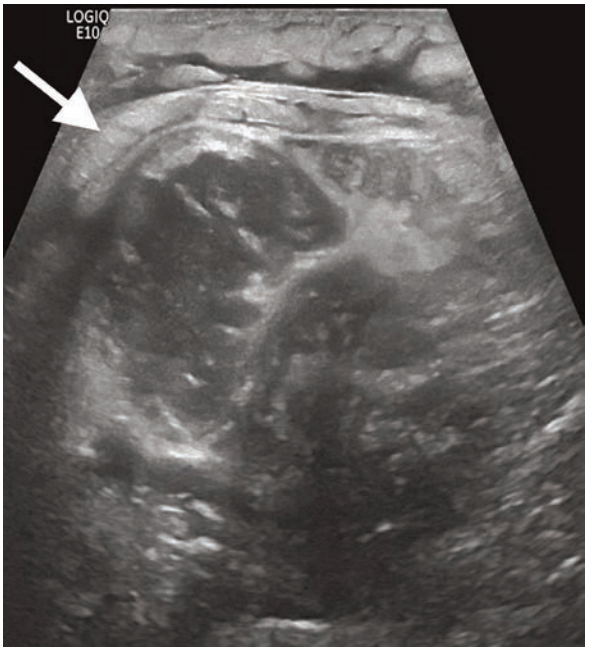


Figure 3. Axial T2-weighted fat-suppressed magnetic resonance image of the thighs, confirmed extensive near unilateral right upper thigh intramuscular swelling and oedema type signal, most severe within the medial compartment (arrow)

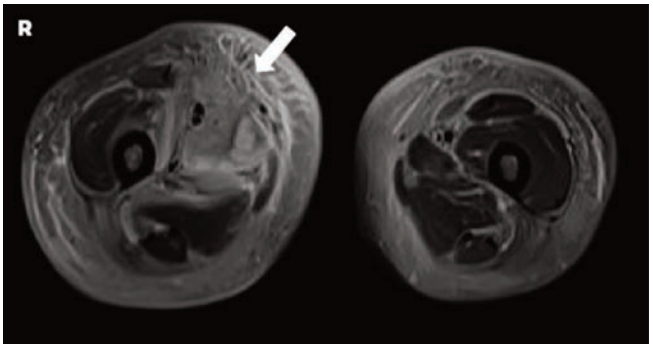
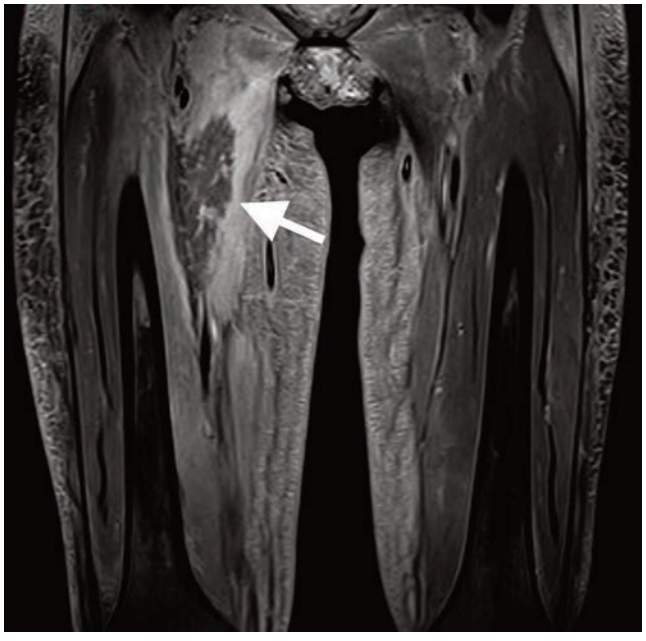


Figure 4. Coronal postcontrast–enhanced T1-weighted fat suppressed image confirming intense muscle, fascial and subcutaneous enhancement within the right upper medial thigh with focal central area of muscular non-enhancement (arrow)



Differential diagnosis and treatment

At presentation the patient was given intravenous antibiotics for potential infective causes such as pyomyositis. Despite a prolonged course of broad-spectrum intravenous antibiotics, there was minimal symptomatic improvement. Microbiological investigations were consistently negative and there were no imaging findings to support an infective cause. The extent of pain prompted reviews from orthopaedic and vascular surgeons to exclude necrotising fasciitis, compartment syndrome and vascular insufficiency. DVT and focal collection were excluded on imaging. A rheumatology opinion was sought, and inflammatory or autoimmune myositis deemed unlikely. The long-standing history of poorly controlled diabetes with microvascular complications together with the clinical presentation and radiological findings pointed towards a diagnosis of DMN. Throughout her admission she had continual input from the diabetic specialist nurse and diabetologist recommending strict glycaemic control, analgesia and bedrest.

Discussion

DMN or diabetic muscle infarction is an uncommonly encountered complication of diabetes mellitus affecting patients with both types 1 and type 2. The mean age of onset ranges between 42 and 45 years and the time from diabetes diagnosis to the onset of DMN ranges from 15 to 20 years.[2–4] DMN largely occurs in patients with poorly controlled diabetes with reported HbA_{1c} at diagnosis over 9% (75 mmol/mol),[4] usually in the presence of other microvascular complications. Diabetic nephropathy is the most common microvascular complication seen in DMN, reported concurrently in 70–80% of cases with a quarter of these dialysis dependent.[2–5]

Local pain and swelling are the usual presenting complaints and the quadriceps is the most commonly affected muscle group. Various pathogenic mechanisms have been postulated including atherosclerosis, diabetic microangiopathy, vasculitis with associated thrombosis, ischaemic-reperfusion injury and hypercoagulability state associated with diabetes mellitus.[4,6] There are no diagnostic laboratory markers for DMN. White cell count, erythrocyte sedimentation rate, CRP and CK are all non-specific markers for DMN.[5]

Key messages

- Early involvement of the diabetes team at the time of admission is crucial in the management of patients with confirmed or suspected diabetic myonecrosis
- When managing patients presenting with suspected diabetic myonecrosis, detailed clinical history, review of diabetes control, physical examination, laboratory investigations and review of radiological images are imperative as the presentation can mimic appearances of necrotising fasciitis, compartment syndrome, vascular insufficiency, deep vein thrombosis, focal collection, inflammatory and autoimmune myositis
- A multidisciplinary approach to the diagnosis and management of diabetic myonecrosis is essential

MRI shows characteristic iso- to hypointensity on T1-weighted and high signal intensity on T2-weighted imaging of the affected muscle area with associated subcutaneous fat oedema.[7,8] Muscle biopsy is not routinely used as a diagnostic tool to support the diagnosis of DMN due to observed increase in time to symptomatic improvement and procedure-associated complications. Histology is usually reserved for cases with atypical clinical presentations.[4]

Non-surgical management shows a statistically significant improvement in the time to recovery compared with surgical intervention such as excision of infarcted muscle (8.1 weeks and 13 weeks, respectively).[9] Treatment with antiplatelet therapy or steroids has not been shown to be beneficial.[9] To date there is no evidence from randomised controlled trials to support the optimal management for DMN.

A multidisciplinary approach to the management of DMN is indispensable. As described in our case, input from medical, surgical and radiological specialties was necessary to establish the diagnosis. Patient education and support is vital to improve understanding of the condition and to optimise glycaemic control as relapse of DMN is reported in up to 45% of cases. The mean mortality rate associated with DMN is 10% within 2 years of diagnosis with macrovascular events such as myocardial infarction, stroke or gangrene the predominant causes of death.[3]

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Anticoagulation in hyperosmolar hyperglycaemic state: a case report and review of the literature

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Key words: type 2 diabetes, hyperosmolar hyperglycaemic state, case report, anticoagulation, venous thromboembolism, low molecular weight heparin

Introduction

Hyperosmolar hyperglycaemic state (HHS) is one of two serious metabolic derangements that occur in people with diabetes mellitus. The first cases of HHS were described by von Frerichs and Dreschfeld in the 1880s with an 'unusual diabetic coma'. It is a serious, life-threatening, but fortunately rare emergency that, although less common than its counterpart, diabetic ketoacidosis (DKA), has around a 10 times higher mortality rate, up to 15–20%.[1] HHS accounts for around 1% of hospital admissions in people with diabetes, typically in the elderly. Increasing prevalence of obesity has additionally increased the incidence of HHS in the paediatric population. Prognosis is worse when associated with increasing comorbidities, age and significant electrolyte abnormalities.[2] It is well known that diabetes can affect the clotting pathway, resulting in endothelial dysfunction, eventually enhancing the activation of procoagulant factors, predisposing towards thrombosis. This process is further amplified in both hyperosmolarity and DKA.[3]

Several case reports highlight the significant mortality and morbidity that can be associated with venous thromboembolism (VTE) and its complications in people with hyperosmolarity including fatality from massive pulmonary embolism.[1] Patients having major orthopaedic surgery tend to receive extended VTE prophylaxis and demonstrate significant reduction in VTE with this therapy. Given the paucity of evidence for prophylactic versus therapeutic anticoagulation in HHS, we looked at the evidence surrounding orthopaedic surgery where there has been considerable research. Direct oral anticoagulants are now being used for VTE prophylaxis in orthopaedic patients and may have a role in acutely unwell medical patients with a low risk of bleeding.[4]

The evidence regarding the potential benefit of prolonged anticoagulation in HHS remains unclear.[5] We performed a literature review to look at the evidence.

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Case report

Patient information

A 63-year-old man with diet-controlled type 2 diabetes mellitus for 2 years, with body mass index 28.3 kg/m^2, was admitted with a two-week history of lethargy and a one-month history of severe osmotic symptoms (polyuria and polydipsia). He had recently been treated for a urinary tract infection. He reported weight loss of 3 kg in the week preceding admission. Three weeks prior to presentation he had returned from the USA on a long-haul flight. He had a 24-hour history of confusion, with no associated chest pain, shortness of breath or palpitations. There was no history of alcohol consumption or smoking. There was a family history of type 2 diabetes mellitus.

Clinical findings

On admission he had a Glasgow Coma Scale of 14/15. He was tachycardic with pulse rate 100 bpm, but was otherwise haemodynamically stable although clinically dehydrated. A venous blood gas highlighted metabolic acidosis (pH 7.2), blood ketones were 3.3 mmol/L and additional laboratory investigations indicated acute renal impairment with hypernatraemia (Na^+ 155 mmol/L, K^+ 4.9 mmol/L, urea 39.8 mmol/L, creatinine 460 µmol/L, estimated glomerular filtration rate (eGFR) 12 mL/min and glucose 70 mmol/L, normal full blood count). His HbA_{1c} was 6.8% (51 mmol/mol) 6 months previously. Calculated serum osmolality was 429.6 mOsm/kg (normal range 278–305).

Diagnostic assessment

The working diagnosis on admission was a combination of HHS/DKA with infection (likely urinary tract infection) as a precipitant, acute kidney injury stage 3 and delirium presumed secondary to these conditions.

Therapeutic intervention

He was started on the trust's HHS treatment protocol which is similar to the JBDS guidance. He was also commenced on

Table 1 Timeline: serum sodium, platelets, haemoglobin, white cell count and creatinine results over course of admission

Date	Na+ (mmol/L)	Platelets ($x10^9$/L)	Haemoglobin (g/L)	WCC ($x10^9$/L)	Creatinine (µmol/L)
25/03/16	155,170	123,107	166,155	7.8, 8.6	460,345
26/03/16	168,161,164	58,45,38	142,128,127	10.1, 8.5, 8.9	272,269,245
27/03/16	164,158	28,28	121,115	7.1, 6.9	173,159
28/03/16	161,154	30,55	115,121	5.8, 5.6	134,120
29/03/16	149	35	128	4.5	98
30/03/16	150,146	61,84	115,114	4.7, 4.7	105,91
31/03/16	146	84	119	5	90
02/04/16	144	165	104	4.9	96

WCC, white cell count.

prophylactic low molecular weight heparin (LMWH; dalteparin) which was accurately dosed according to weight and eGFR and stopped after 3 days as his platelet count dropped (see Table 1) after discussion with the haematology team. Although he had recently returned from a long-haul flight, the admitting team did not feel VTE was likely as he did not have clinical features suggestive of thromboembolism and had not had surgery in the previous 4 weeks. The focus was on the treatment of sepsis and HHS/DKA. He was treated with intravenous antibiotics in a dose appropriate for his renal function. His biochemical parameters, notably renal function, improved with fluid resuscitation (Table 1).

On day 2 of admission he was noted to have dynamic ECG changes with raised troponin-I (2,673 ng/L peaking at 3,820 ng/L [normal <40 ng/L]). He was initially treated for a non-ST elevation myocardial infarction. On advice of the cardiologist and the haematologist, he was started on aspirin without clopidogrel and continued on 5,000 units of dalteparin instead of enoxaparin. On day 5 of admission he became acutely hypoxic with shortness of breath whilst walking to the toilet and a CT pulmonary angiogram (CTPA) was performed which showed extensive pulmonary embolism (saddle embolus with extension into the segmental pulmonary arteries bilaterally) without right ventricular strain. The CTPA also revealed bilateral basal pneumonia. His capillary blood glucose was 15 mmol/L and his serum sodium was 149 mmol/L on the day of his CTPA. Anticoagulation treatment was challenging in view of his thrombocytopenia. He was not thrombolysed. On the advice of the haematology team he was given a platelet transfusion, aiming for a platelet count of >$50x10^9$/L. He was then commenced on a treatment dose of dalteparin (15,000 units) and later switched to warfarin under the guidance of the haematology team. The drop in platelet count was felt to be due to consumption coagulopathy. The plan was to give warfarin for 6 months and to be reviewed by the haematology team.

He had a coronary angiogram as an inpatient which showed unobstructed coronaries. An echocardiogram showed mild to moderate concentric left ventricular hypertrophy, no significant left ventricular outflow tract obstruction, normal systolic function and no significant valvular abnormalities. The raised troponin-I was attributed to subendocardial ischaemia in the right ventricle which is seen in acute pulmonary embolism.

Follow-up and outcome

He was discharged home taking Humulin I insulin twice a day. When reviewed in the outpatient clinic two months later, his insulin was stopped and treatment switched to metformin alone.

Discussion

HHS is associated with a hypercoagulable state. The onset of HHS is usually over days with significant metabolic derangements, dehydration and hyperglycaemia. This occurs due to increased levels of counter-regulatory hormones such as glucagon, catecholamines, cortisol and growth hormone from a relatively insulin-deficient state. Hyperglycaemia develops due to increased glycogenolysis, reduction in glucose utilisation and gluconeogenesis. In contrast to DKA, in HHS the insulin level is adequate to prevent lipolysis and ketogenesis, but not to stimulate glucose utilisation.[6] This leads to an osmotic diuresis, resulting in intracellular dehydration and a hyperosmolar state. In HHS it can lead to significant intravascular dehydration (6–13 L in a person weighing 60 kg).[1,7] There is also an increase in pro-inflammatory cytokines creating a pro-thrombotic environment.[7] This can lead to thromboembolic events, cerebrovascular accident, disseminated intravascular coagulopathy, myocardial infarction and peripheral or central vascular occlusion. Chaudhuri and Umpierrez noted normalisation of circulating pro-inflammatory cytokines upon reduction of blood glucose concentration.[8] The large increase in reactive oxygen species leads to damage of lipids and proteins at the cellular level.

Common precipitants include sepsis (up to 60%), poor medication adherence (21%), undiagnosed diabetes (11%) and medical illness such as stroke or myocardial infarction that causes release of counter-regulatory hormones.[7,9]

Methodology and review

We carried out a literature search using our own Clinical Information Search System (CISS) through Medline, Embase, Pubmed, Uptodate and BMJ best practice using the terms "Hyperosmolar or HHS" in association with "DVT or PE". We found 19 papers in total. After excluding six paediatric papers, one paper focusing on DKA and another seven papers based on their title and content, we were left with five papers describing some form of association between HHS, thromboembolism and clinical approach (Table 2 and Figure 1).

HHS and VTE management

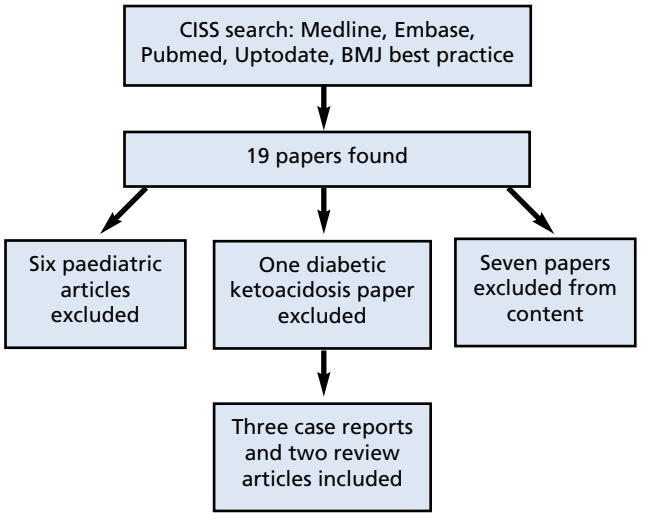
Diabetes alone is a risk factor for VTE in comparison with the non-diabetic population. A retrospective study of 302 adult patients (56 patients with diabetes and 246 without) identified an annual VTE incidence rate among people with diabetes of 432 per 100,000 compared with 78 per 100,000 in those without diabetes.[10] Patients with diabetes have a 1.7-fold increased risk of VTE compared with those without diabetes. After adjusting for age, there remains a two-fold risk increase in patients with diabetes.

Table 2 Summary of articles reviewed

Author	Type of article	Cohort/subject	Learning points	Limitations
Park *et al,* 2006[11]	Case report	HHS patient complicated by extensive upper extremity venous thrombosis	Current experiences support the safety and efficacy of catheter-directed thrombolysis. There is inadequate clinical evidence for full anticoagulation.	Case report on one patient
Hamblin *et al,* 1989[12]	Journal article	Hyperglycaemic complications of diabetes in people with diabetic ketoacidosis and HHS	The mortality rate was 14.6% (12 deaths) for 82 episodes of HHS. Six cases of mesenteric and iliac thromboses, eight cases of myocardial infarction and two cases of cerebral haemorrhage were identified	Therapeutic anticoagulation not given to patients prior to diagnosis of VTE
Keenan *et al,* 2007[13]	Journal article	Risk of VTE in patients hospitalised for HHS	32 (1.2%) of 2,859 people with HHS developed VTE in hospital. HHS (HR=3.0) compared to DKA (HR=1.2)	Recommended extended duration of VTE prophylaxis in HHS patients, but duration unclear
Sinson *et al,* 2016[14]	Case report	Renal vein thrombosis developed in an HHS patient	Poorly controlled type 2 diabetes is associated with high levels of plasminogen activator inhibitor-1 resulting in reduced fibrinolysis	Case report of one patient and no recommendations given for duration of VTE prophylaxis
Wordsworth *et al,* 2014[19]	Case report	Massive pulmonary embolism associated with HHS		Case report of one patient, prophylaxis anticoagulation given

DKA, diabetic ketoacidosis; HHS, hyperosmolar hyperglycaemic state; HR, hazard ratio; VTE, venous thromboembolism.

Figure 1. Methodology and review



Park *et al*[11] reported a case of extensive venous thrombosis of the upper extremity 30 hours after placement of a subclavian venous catheter in a patient with HHS. The patient was treated with early catheter-directed thrombolysis followed by anticoagulation. Full anticoagulation was not recommended due to bleeding risk.

Hamblin *et al*[12] reported a mortality rate of 14.6% in 82 patients diagnosed with HHS. They identified six cases of mesenteric and iliac thromboses, eight cases of myocardial infarction and two cases of cerebral haemorrhage in these patients.

Keenan *et al*[13] identified an incidence of VTE in patients with HHS of 1.7%; 71% were diagnosed during hospital stay and a further 29% were diagnosed within 3 months following hospital discharge. In comparison, patients undergoing total hip replacement had a VTE incidence of around 2.8%, suggesting that patients with HHS are at very high risk of VTE. Furthermore, the incidence of VTE in those with HHS – even after adjusting for age, ethnicity, gender and recent hospitalisation – was found to be higher than that of people with uncomplicated diabetes and DKA. This work suggests that the increased thrombotic risk in patients with HHS can be attributed to the more profound hyperosmolarity and hyperglycaemia. Keenan et al have suggested extended duration of VTE prophylaxis, especially in very high-risk groups. The VTE risk is comparable to patients with sepsis and acute connective tissue disease.[13]

Sinson *et al*[14] reported a case of acute pyelonephritis with renal vein and inferior vena cava thrombosis. This patient was initially managed according to the HHS protocol and given prophylactic anticoagulation. Subsequently, the patient developed renal vein thrombosis and pulmonary embolism. There is an associated increase in plasminogen activator inhibitor-1 inhibiting fibrinolysis and increasing the thrombosis risk in patients with poorly controlled type 2 diabetes. Once again there were no clear recommendations for anticoagulation.

Heparin and bleeding prediction scores

It is still debatable whether all patients with HHS should be given treatment dose anticoagulation. HHS tends to occur in the older population. The risk of VTE increases significantly with age, particularly in those aged ≥75 years, with an odds ratio of 1.5 for every 10 years of increase in age. Campbell *et al*[15] found that ageing is associated with increased heparin levels after standard heparin doses and therefore lower heparin dose requirements. A decline in renal function, especially in patients with creatinine clearance <30 mL/min, genetic polymorphisms and drug inter-

Key messages

- HHS is a hypercoagulable state associated with signifi-cant risk of venous thromboembolism and high mortality
- Clinicians need to assess each patient's risks independently. High risk patients with low bleeding risk should be considered for therapeutic anticoagulation throughout their hospital stay
- Careful monitoring of the clinical status and discussion involving the haematology team if needed will help decide the optimal anticoagulation therapy

action particularly affecting cytochrome P450 activity, can all have an impact on thrombotic versus bleeding risk. Elderly patients on vitamin K antagonists (warfarin) for metallic heart valve or previous thromboembolic events can have significant variability in their INR level due to poor dietary vitamin K intake and poor absorption from altered intestinal flora.[15]

The use of bleeding prediction scores can help guide management in patients with thromboembolic events. Klok *et al*[16] reviewed the performance of the VTE-BLEED score (consisting of six objective clinical variables) and found the VTE-BLEED score to be superior to other bleeding scores in predicting bleeding risk. It is mainly used as a tool in patients with a previous diagnosis of VTE, on anticoagulation to predict bleeding risk. It also helps to guide clinicians in decision making regarding extension of anticoagulation, depending on a patient's risk of long-term VTE recurrence. They found therapeutic anticoagulation to be safe in low-risk people, but in high-risk people more studies are required. This tool is awaiting further prospective validation before being incorporated into clinical practice.[16] It is unclear whether patients with HHS were included in this study.

With the COVID-19 pandemic there have been numerous studies looking at therapeutic anticoagulation. The ATTAC/ACTIV-4a and REMAP-CAP multiplatform randomised controlled trial suggested giving a therapeutic dose of thromboprophylaxis to hospitalised non-intensive care patients with COVID-19. The dose is weight-based unless the creatinine clearance is <30 mL/min, for which heparin assay needs to be checked on day 3. However, the evidence surrounding therapeutic anticoagulation in HHS remains limited.[17]

A study in Canada evaluated the efficacy of extending VTE prophylaxis in acutely unwell medical patients. Using extended duration of enoxaparin reduced VTE by 1.5% but increased major bleeding events by 0.5%. This was only beneficial in the cohort of people who were aged >75 years and female.[18] There is a need for a clearer evidence-based risk stratification tool to guide clinicians about duration and dosing of VTE prophylaxis.

Conclusion

This case highlights the increased and potentially fatal thrombosis risk associated with hyperosmolarity and HHS, highlighting the difficulties in the production of guidelines for prophylactic versus treatment dose anticoagulation in the absence of a strong evidence base.

The current JBDS guidelines recommend prophylactic LMWH for the full duration of hospital stay in people with HHS. However, there remains limited evidence on using treatment anticoagulation in people with HHS who are at high risk of thromboembolism. Most guidelines available are based on case reports and observational studies alone. Currently, an extended course of LMWH is only recommended for people at high risk. A therapeutic dose of LMWH is not currently recommended due to associated bleeding risks, unless there is evidence of acute coronary syndrome or thrombosis.

Clinicians should assess each patient's risks independently. If a person is deemed to be at high risk of thrombosis, full dose anticoagulation should be given. We have been agonising about the clinical management decision regarding anticoagulation in HHS for far too long and there is an urgent need for a randomised controlled trial.

Conflict of interest All authors have none to declare.
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Severe insulin resistance in long-term acute leukaemia survivors: lesson learned from a clinical case and review of the literature

BILAL BASHIR, MOULINATH BANERJEE

Key words: insulin resistance, metabolic syndrome, leukaemia, chemotherapy, radiotherapy, thiazolidinediones, metformin

Abstract

With the improvement of haematopoietic stem cell transplantation (HSCT) and radiotherapy, the population of cancer survivors is increasing and therefore increasing the number of patients living with late metabolic complications. We describe a case of a childhood acute lymphoblastic leukaemia survivor who developed insulin resistance 10 years after HSCT and total body radiation requiring a high dose of insulin (>1,500 IU). Using insulin-sensitising agents metformin and thiazolidinediones improved the control and reduced the insulin requirement – eventually stopping insulin. We describe for the first time the phenomenon of reverse diurnal variation in insulin sensitivity based on the clinical picture alone, which has not previously been described in the literature. We have reviewed the plausible mechanisms of developing insulin resistance, reverse diurnal variation and the role of thiazolidinediones in reducing lipotoxicity and adipocyte differentiation resulting in improved insulin sensitivity in such cases.

Introduction

The prevalence of developing type 2 diabetes and metabolic syndrome is 3% with autologous stem cell transplantation and 8–41% in allogeneic stem cell transplantation.[1] Recognition of late development of metabolic syndrome is important with an increasing number of childhood cancer survivors.

Case report

A 26-year-old Caucasian female presented 18 months after receiving a diagnosis of type 2 diabetes mellitus. She had been diagnosed with acute lymphoblastic leukaemia (ALL) at the age of 10 years in 1986. She was treated with UKALL-10 (schedule D including 18 Gy cranial irradiation) followed by total body irradiation (TBI) and bone marrow allograft after pre-conditioning in 1990 leading to long-term remission. This was followed by growth hormone deficiency, premature ovarian failure which was treated with hormone replacement therapy, bilateral ovarian masses requiring salpingo-oophorectomy at 16 years, bilateral cataracts at 19 years and breast cancer at 41 years resulting in left mastectomy and adjuvant chemotherapy. She did not have a family history of diabetes in her first-degree relatives. She developed diabetes in 2000 at the age of 24 years, and had her first consultation with our team in 2002 when she was being treated with pre-mixed twice daily insulin with a total daily dose of 32 units. Her self-monitored blood glucose readings averaged 16–20 mmol/L and her HbA_{1c} was 12% (IFCC 108 mmol/mol). Her insulin dose and regimen were altered over the next few years and she was transitioned from pre-mixed twice daily insulin to a multiple daily injection basal-bolus regime with the dose gradually escalated up to 1,500 units/day over the next 10 years, yet glycaemic control remained suboptimal with HbA_{1c} at 12 years from the diagnosis (2012) 10.4% (90 mmol/mol). She was commenced on metformin, pioglitazone and rosiglitazone during this period on more than one occasion; however, compliance with oral hypoglycaemic agents remained suboptimal due to patient-reported gastrointestinal side effects.

She developed severe acanthosis nigricans in 2005 at the neck and in the axilla and, at that point, marked diurnal variation in insulin sensitivity was observed. Diurnal variation in insulin sensitivity became more apparent while she was on continuous subcutaneous insulin infusion during 2007–2018, when she was advised to suspend the insulin infusion overnight, yet maintaining capillary blood glucose 4–8 mmol/L. However, her capillary blood glucose rose to 16–20 mmol/L during the day time even during carbohydrate-free days. She was not on any prescribed or over-the-counter drugs to account for this remarkable variation in glycaemia/insulin resistance.

Eighteen years from diagnosis she was tried again on slow-release metformin and pioglitazone (15 mg once daily). She was compliant with these drugs and did not report any significant side effects. With the introduction of these agents we observed a significant improvement in her glycaemic control and a marked reduction in her insulin requirement. She was gradually weaned off insulin therapy and stopped later in the year 2018.

Her current therapeutic regimen includes pioglitazone 30 mg once daily and metformin SR 1000 mg twice daily with HbA_{1c} of

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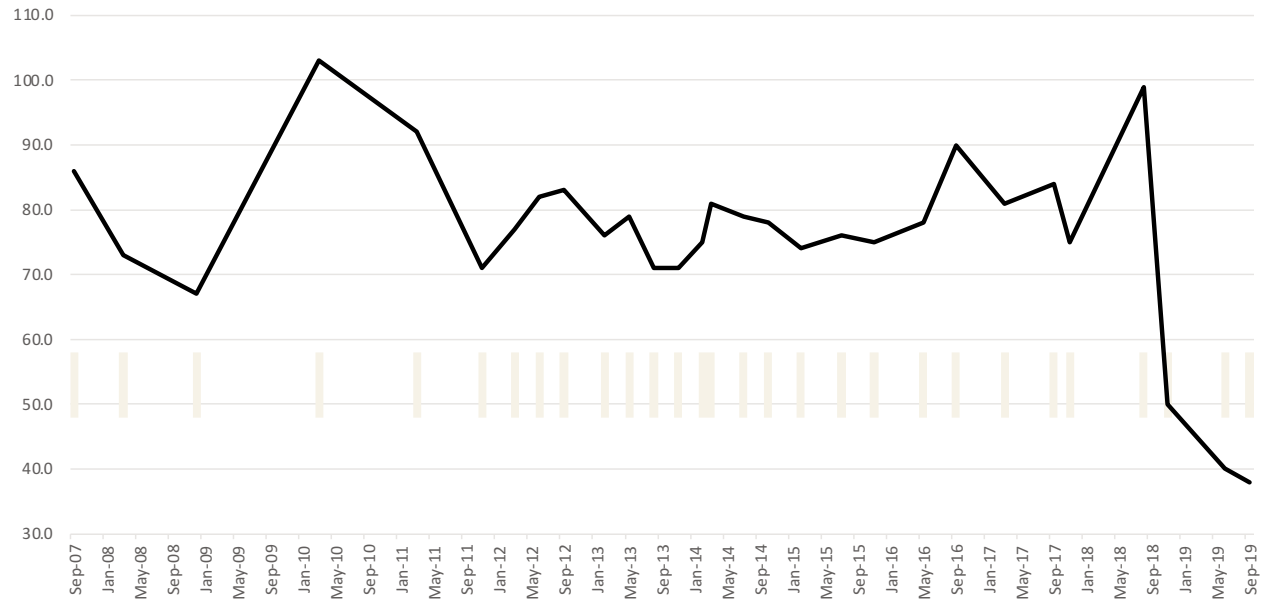
Figure 1. Serial HbA_{1c} over time



6% (IFCC 39 mmol/mol), average self-monitored blood glucose 4–10 mmol/L, a steady body mass index of 24.3 kg/m^2 (28.1 kg/m^2 in 2000) and a normal renal and lipid profile. Despite improvement in her glycaemic profile, we did not observe a significant improvement in acanthosis nigricans. Her serial HbA_{1c} is shown in Figure 1 and the journey of escalation and de-escalation of treatment is shown in Table 1.

Discussion

Our unique case depicts severe insulin resistance manifested by severe acanthosis nigricans and suboptimal glycaemic control despite being on extremely high doses of insulin with a significant response to insulin-sensitising agents. She also demonstrated a reversal of diurnal insulin resistance that has not been reported before.

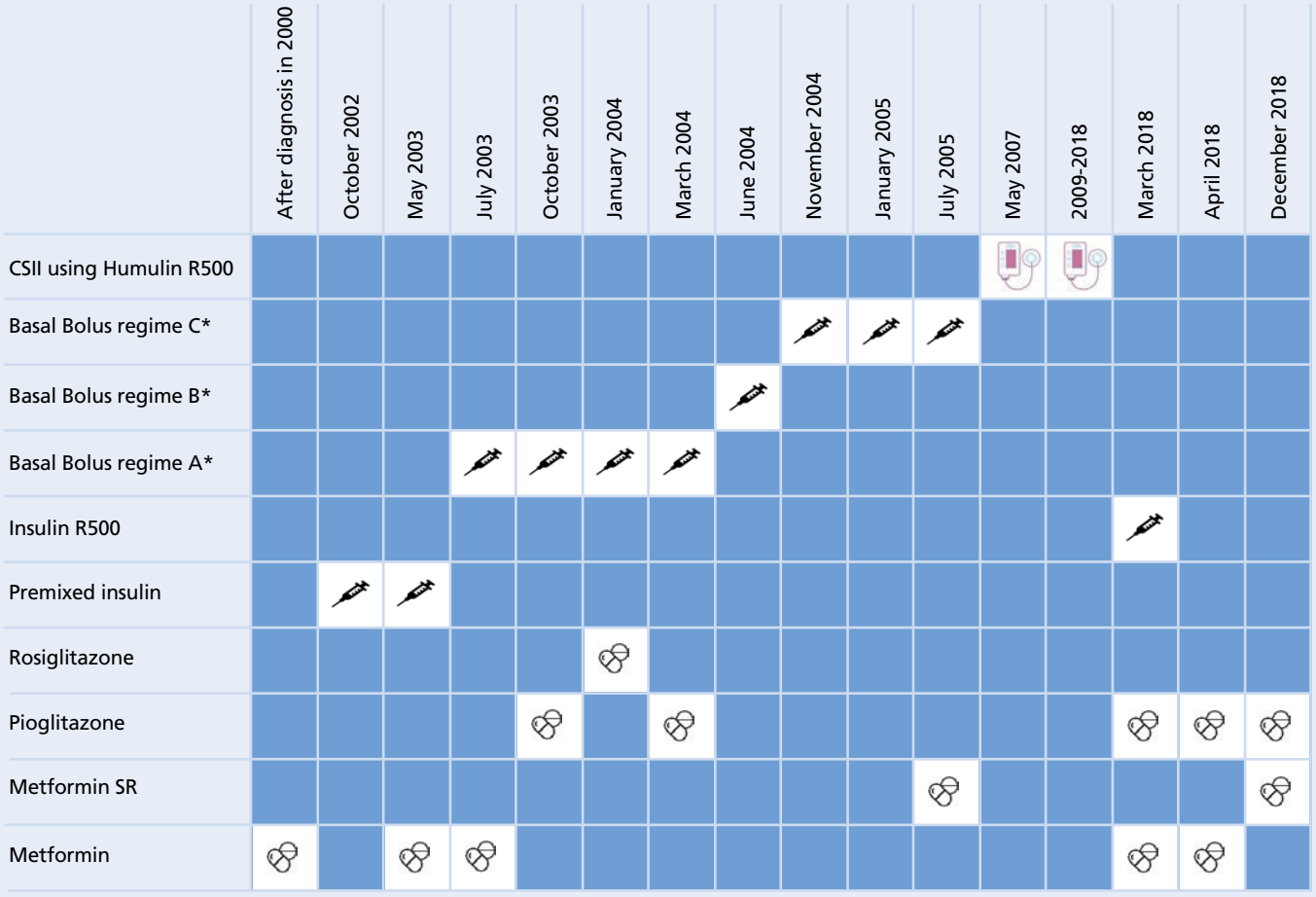
The genesis of insulin resistance and diabetes after HSCT/TBI is poorly understood. Proposed mechanisms involve increased fat mass, reduced lean body mass, anthropometric changes from abnormal fat distribution leading to a phenotypic picture of sarcopenic obesity and lipodystrophy, altered dynamics of adipokines secondary to abnormal fat distribution, chronic inflammatory milieu and accelerated cellular aging process.[2]

The exact mechanism of abnormal fat dynamics in these individuals is not known. Cranial irradiation leads to hypothalamic-pituitary dysfunction and leptin resistance which reduces lean body mass and increases fat mass and insulin resistance.[3,4] After irradiation, depletion of the adipocyte pool, changes in its morphology and the inability of adipose tissue to store lipids upon reaching its maximal capacity lead to ectopic fat deposition in the muscles, liver and pancreas.[5] This hypothesis is supported by Lei *et al* who found a lower body mass index and higher intramuscular to total fat ratio in HSCT+TBI recipients compared with those receiving chemotherapy alone or an obese otherwise healthy adult group (Figure 2).[6]

Severe insulin resistance and its metabolic consequences are reversed to some extent by thiazolidinediones via their action on adipocytes, as observed in our case and seen in patients with lipodystrophies.[7] Thiazolidinediones induce differentiation of preadipocytes leading to the production of smaller more insulin-sensitive adipocytes and apoptosis of larger insulin-resistant visceral adipocytes, reduce circulating triglycerides, decrease the expression of resistin, interleukin 6 and tumour necrosis factor α and promote adiponectin. This change in the metabolomic and proteomic profile is associated with an improvement in insulin sensitivity. Thiazolidinediones also enhance the expression of GLUT1 and GLUT4 in skeletal muscles and adipocytes increasing their glucose uptake, which contributes to a reduction in the glucose load and thereby improves insulin sensitivity.[8]

Another striking feature observed in our case was severe acanthosis nigricans, which has been considered as a surrogate marker for laboratory measurement of insulin resistance. Neck acanthosis nigricans has been described as having a sensitivity of 96% for insulin resistance.[9] This is in contrast to localised acanthosis nigricans, which can develop in response to cutaneous injection of insulin and is reversible upon cessation of insulin or changing the site of injection.[10] Neck and axilla acanthosis nigricans in our patient indeed suggest extreme insulin resistance rather than high-dose insulin as a cause of acanthosis nigricans. Phiske *et al* postulated increased adiposity and an imbalance in adipokine secretion (decreased serum adiponectin, increased serum resistin and decreased adiponectin gene expression) as a possible mechanism for the development of insulin resistance in these patients and hence acanthosis nigricans.[9] Our case demonstrated improved insulin sensitivity in response to thiazolidinedione which is in keeping with the probable mechanism proposed by Kodawaki *et al* where thiazolidinedione is believed to increase the circulating levels of adiponectin by altering the mor-

Table 1 Summary of escalation and de-escalation of treatment over time



*Regime A: Insulin NPH BD and Insulin aspart TDS, Regime B: Glargine BD and Humulin R U500 TDS, Regime C: Levemir BD and Humulin R U500 TDS.

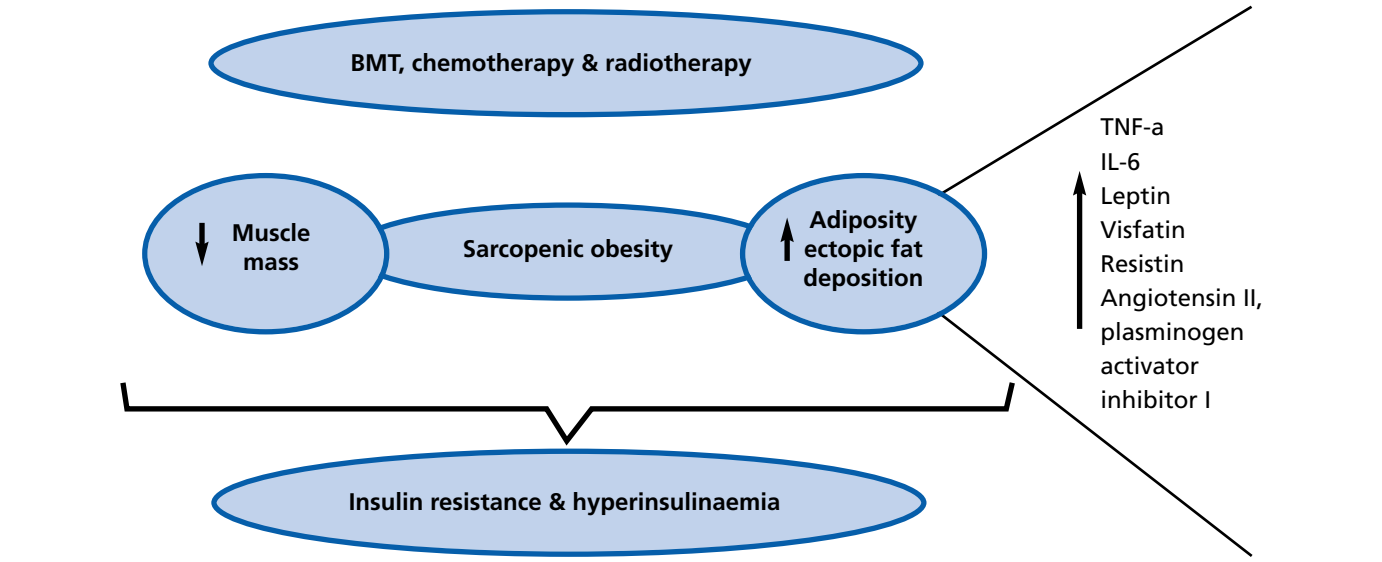
phology and differentiation of adipocytes and upregulating the adiponectin receptors AdipoR1 and AdipoR2.[11] Although acanthosis nigricans is a sensitive surrogate marker for insulin resistance, improvement in acanthosis nigricans was not observed in our case, consistent with reported literature.

The literature on the insulin-sensitising effect of metformin in lipodystrophy phenotypes is limited and confined to HIV-associated lipodystrophies. A meta-analysis of six trials has demonstrated significant improvement in insulin sensitivity in this cohort of patients.[12] There is a paucity of data on the effect of metformin on lipodystrophy phenotype secondary to HSCT/TBI; however, the beneficial effect of the insulin-sensitising action of metformin in this scenario cannot be overlooked, as demonstrated in our patient where we used a combination of metformin and thiazolidinedione and a case reported by Wedrychowicz *et al* where the introduction of only metformin halved the insulin requirement in a patient with diabetes post-HSCT/TBI.[13]

The diurnal variation in insulin sensitivity, which has been described in the literature, shows increased insulin resistance during the dark phase (ie, night-time during sleep). The proposed mechanisms to explain this phenomenon include alteration in free fatty acid availability, clock genes influencing insulin sensitivity at different times of day, diurnal rhythm in sympathetic activity and expression of intrinsic circadian rhythm in adipose tissue.[14,15] Reverse diurnal variation has been described in animal models after reversing the light-dark cycle and has been attributed to diurnal variation in growth hormone and nocturnal surges of growth hormone,[16] but not in humans. Ding *et al* have demonstrated differential expression of nuclear receptors in the suprachiasmatic nucleus which controls the diurnal rhythm of insulin sensitivity.[17] Similarly, the diurnal variation in free fatty acid availability governed by previous meals and diurnal expression of the PDK4 gene responsible for the availability of free fatty acids govern insulin sensitivity.[18] It is not known if cytotoxic chemotherapy and radiotherapy, which work by inducing DNA, can disrupt the intrinsic circadian rhythm leading to insulin resistance. However, altered expression of these clock genes has been shown to induce changes in the glycometabolic profile.[17,19] We believe that growth hormone deficiency and the lack of nocturnal growth hormone surges alone are insufficient to explain insulin sensitivity in our case.

An increasing number of cases of childhood leukaemia are surviving with improvement in oncological management. They pose a

Figure 2. Figure 2 Pathophysiology of insulin resistance after bone marrow transplantation (BMT), chemotherapy and radiotherapy



Key messages

- Development of metabolic syndrome is a known late complication of haematopoietic stem cell transplantation/ total body irradiation in long-term cancer survivors
- Extreme insulin resistance is conferred due to re-distribution of fat mass and reduction in lean body mass
- Literature on the role of pharmacological agents in reversing extreme insulin resistance in these cases is limited to case reports
- Reversal of extreme insulin resistance is possible with thiazolidinediones and metformin
- We have demonstrated and reviewed the potential mechanisms of extreme diurnal variation in insulin resistance that have not previously been reported
- Clinicians are encountering an increasing number of childhood cancer survivors with metabolic syndrome and diabetes. The standard escalation regimen to achieve adequate glycaemic control in these cases might not work
- Early initiation of insulin sensitisers rather than insulin secretagogues or insulin itself is important in such cases. The role of newer antidiabetic regimens (ie, sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 agonists) has not been studied in this subgroup and provides a potential avenue for further research

significant therapeutic challenge. In these patients, sensitivity would need to be preserved with insulin sensitisers rather than insulin secretagogues or insulin itself. The role of glycosuric agents (sodium-glucose cotransporter-2 inhibitors) in this group of patients is not yet known. Further studies are required to address late metabolic complications and optimum pharmacological management in this subset of patients.

Study limitations

This study has the following limitations: (1) acute lymphoblastic leukaemia treatment, induction, maintenance chemotherapy and radiotherapy were carried out at a different centre and we were unable to retrieve the complete details from that centre; (2) we did not measure C-peptide and hence baseline insulin reserve at presentation; and (3) we have not quantified the insulin resistance by formal testing; however, the development of severe acanthosis nigricans suggests marked insulin resistance.

Conflict of interest None.
Funding None.
Ethical approval Written informed consent was obtained from the patient.
Author contributions BB: literature review and writing the original draft. MB: conception of the idea, management of the case, reviewing and editing the draft, supervision.

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Bilateral extensive leg pyomyositis presenting with diabetic ketoacidosis

JIL SHAH, KHYATISHA SEEJORE, MICHAEL W MANSFIELD

Key words: pyomyositis, diabetic ketoacidosis, surgical drainage, intramuscular abscesses

Abstract

Pyomyositis is a rare and serious acute purulent bacterial infection of the skeletal muscle. Diabetes is the most important predisposing factor and, if left untreated, the infection has significant complications. We report the case of an adult male who presented acutely with a history of abdominal pain, nausea and vomiting and bilateral thigh pain. His abdominal examination was unremarkable, but a fluctuant swelling was identified in both thighs. Biochemical investigations revealed raised inflammatory markers and diagnostic chemistry of diabetic ketoacidosis. Pyomyositis was treated with intravenous antibiotics and surgical abscess drainage. MRI is the definitive investigation of choice to diagnose pyomyositis. Differential diagnoses include cellulitis, septic arthritis and deep vein thrombosis.

Introduction

Pyomyositis is a rare and serious acute purulent bacterial infection of the skeletal muscle.[1,2] Early diagnosis and surgical drainage with appropriate antibiotics is required to prevent complications.[2,3] MRI is the definitive investigation of choice to diagnose pyomyositis. We report a case of pyomyositis which was treated with intravenous antibiotics and surgical abscess drainage.

Case presentation

A 38-year-old man with a known background of chronic pancreatitis (alcohol-related), depression and chronic hepatitis B infection presented to the emergency department after 3–4 days of abdominal pain, nausea and vomiting. He also reported bilateral thigh pain causing inability to weight-bear for 10 days prior. There was no history of trauma or fever and the patient also denied intravenous drug use. There was no prior diagnosis of diabetes. Pre-admission blood testing in primary care had shown elevated circulating D-dimer levels (1139 ng/mL: NR <230 ng/mL) and the referring clinician had requested exclusion of deep vein thrombosis.

On presentation he was tachycardic (heart rate 126 bpm) and was noted to have bilateral fluctuant thigh swelling, redness, warmth and tenderness just above the knees. Blood chemistry showed diabetic ketoacidosis (serum glucose 27.0 mmol/L (NR: 3.5–6.0), serum bicarbonate 10.9 mmol/L, blood pH 7.16 and blood ketones (hydroxybutyrate) 7 mmol/L). He was treated in line with current UK JBDS guidelines for diabetic ketoacidosis.[4]

Important and relevant acute investigations were as follows: Hb 142 g/L (NR: 135–180), white blood cells 24.24 (NR: 4.00–11.00), neutrophils 22.1 (NR: 2.0–7.5), C-reactive protein 512 mg/L (NR: <5), estimated glomerular filtration rate >90, serum amylase <20 IU/L. Blood cultures showed no growth. Echocardiogram was normal. Leg ultrasound imaging showed collections in the right biceps femoris muscle (10×7×2 cm), left sartorius muscle (6×4×2 cm) and the left external oblique muscle of the left flank (6×2×2 cm).

Magnetic resonance imaging (MRI) confirmed multiple large multiloculated intramuscular abscesses with surrounding subcutaneous tissue oedema. The collection involving the right biceps femoris (19.5×6.6×4.1 cm) was associated with marked oedema along the right sciatic nerve. Another infected collection was noted in the left vastus intermedius (12×3.8×3.3 cm) and a smaller 2.4 cm abscess was identified in the left biceps femoris. These are shown in Figures 1, 2 and 3. There was also mild bone marrow oedema at the posterolateral femoral condyle on the left with mild cortical irregularities and left-sided knee joint effusion and synovitis, concerning for early osteoarthritis.

Aspirate from the right thigh abscess grew methicillin-sensitive Staphylococcus aureus (MSSA) sensitive to flucloxacillin. Knee joint aspirate did not show any pus and culture was negative.

The patient had multiple bilateral large intramuscular abscesses along with concern about risk of femoral bone and knee joint involvement, coinciding with a new diagnosis of diabetes which presented as diabetic ketoacidosis. He was initially treated with intravenous flucloxacillin for 3 weeks and eventually underwent subsequent surgical drainage bilaterally. He underwent intensive physiotherapy and was discharged one week later.

Discussion

Pyomyositis is a rare bacterial infection occurring in the skeletal muscles of the body without any obvious source of infection. In the majority of cases, pyomyositis affects the lower extremities and is usually unifocal.[5] Pyomyositis was first reported in the tropical regions of the world, occurring in active and healthy individuals. In temperate climates it is found in patients who are

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Figure 1. STIR (Short Tau Inversion Recovery sequence) axial image of the right thigh. This shows a large collection (arrows) involving the short head of the right biceps femoris and related to the adductor magnus with marked oedema along the right sciatic nerve (arrowhead).

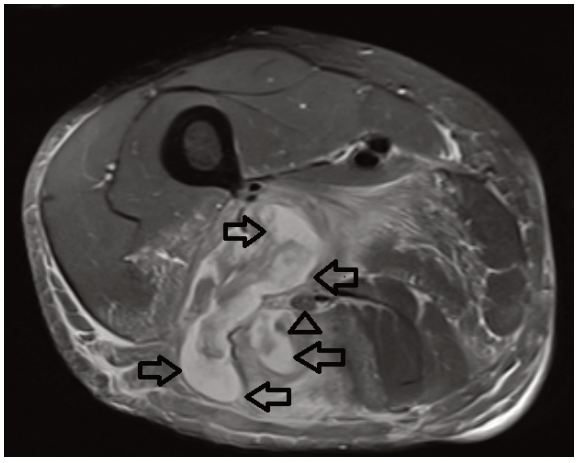


Figure 2. STIR (Short Tau Inversion Recovery sequence) large field of view coronal image of the pelvis and thighs showing multiple infected intramuscular collections with surrounding muscle, intermuscular fascial plane and subcutaneous tissue oedema. The collections are identified by arrows. The right proximal femur lesion is long standing and benign.

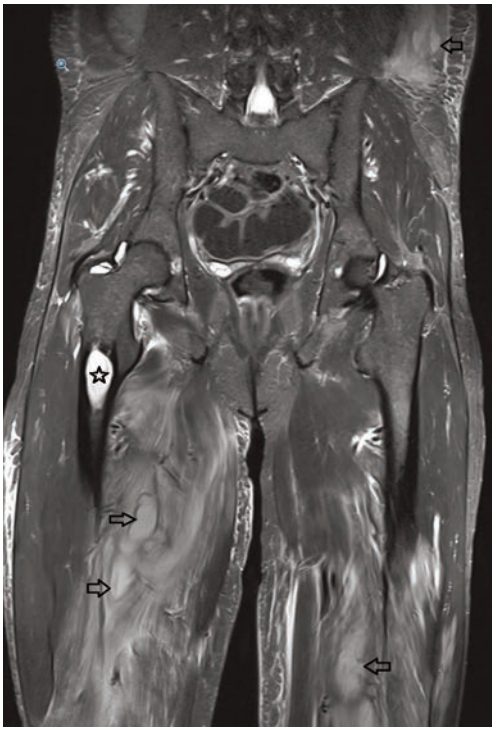
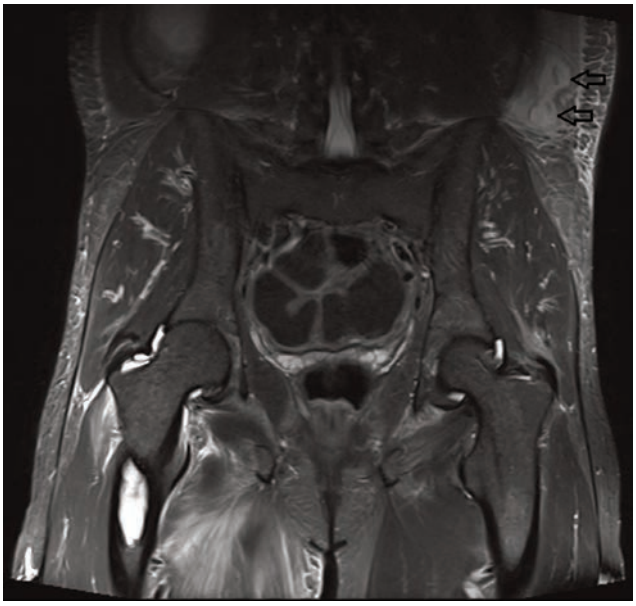


Figure 3. STIR (Short Tau Inversion Recovery sequence) coronal image of the pelvis showing the left external oblique collection. The collections are marked by arrows.



immunocompromised secondary to human immunodeficiency virus (HIV), hepatitis C or B infection, but the main risk factors typically include diabetes and trauma.[6] The most common causative organisms are *Staphylococcus aureus*, Group B *Streptococcus*, *Pneumococcus*, *Neisseria* and *Pseudomonas*.[2,5]

Pyomyositis progression is divided into three stages. Stage 1 (invasive stage) is considered to be mild, comprising fever and muscle pain. At this early stage it is very difficult to identify anything significant on examination but, in a few cases, a woody texture of the affected group of muscles may be noticeable on palpation. Blood tests may reveal leucocytosis at this stage. Stage 2 (suppurative stage) usually starts 2–3 weeks after stage 1 and is characterised by fever, severe cramp-like muscle pain and localised tenderness. At this stage a fluctuant swelling may be palpable, and aspiration of the affected muscle typically shows pus. Blood tests may reveal raised inflammatory markers such as C-reactive protein, white cell count and procalcitonin. About 90% of patients seek medical attention at this stage. Stage 3 (late stage) consists of complications of pyomyositis which include systemic sepsis, disseminated infection, acute kidney injury and death if left untreated.[2,7]

MRI is the gold standard diagnostic investigation. MRI helps in recognising the pathological cause, the extent of involvement of the internal structures and also helps in localising the fluid collection. If MRI is not accessible, a CT scan with or without contrast can also aid in diagnosis. Ultrasound is preferred if both CT and MRI are not available.[5,8]

Once diagnosis is confirmed, surgical debridement and drainage together with a course of intravenous antibiotics are the recommended treatment options. For treating methicillin-sensitive

Key messages

- Pyomyositis is a rare and serious acute purulent bacterial infection of the skeletal muscles
- It was first reported in the tropical regions of the world
- It is found more commonly in immunocompromised patients with conditions such as HIV, Hepatitis B or C
- Major risk factors include trauma and diabetes
- MRI is the gold standard diagnostic investigation of choice for pyomyositis
- Surgical debridement and drainage alongwith intravenous antibiotics are the recommended treatment options
- It is important to remember that pyomyositis is a rare infectious disease, but physicians should be aware of its possibility in patients with poorly controlled diabetes

Staphylococcus aureus (MSSA) infection, flucloxacillin is the drug of choice. If pus collection identifies methicillin-resistant *Staphylococcus aureus* infection, vancomycin is recommended.[9] It is always recommended to discuss the antibiotic of choice with the microbiology team before initiating any form of antimicrobial treatment.[7, 10]

Pyomyositis is a rare and serious infectious disease, and physicians should be aware of its possibility in patients with poorly controlled diabetes.

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Clinical practice guidelines for management of hyperglycaemia in adults with diabetic kidney disease

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Abstract

A significant percentage of people with diabetes develop chronic kidney disease and diabetes is also a leading cause of end-stage kidney disease (ESKD). The term diabetic kidney disease (DKD) includes both diabetic nephropathy (DN) and diabetes mellitus and chronic kidney disease (DM CKD). DKD is associated with high morbidity and mortality, which are predominantly related to cardiovascular disease.

Hyperglycaemia is a modifiable risk factor for cardiovascular complications and progression of DKD. Recent clinical trials of people with DKD have demonstrated improvement in clinical outcomes with sodium glucose co-transporter-2 (SGLT-2) inhibitors. SGLT-2 inhibitors have significantly reduced progression of DKD and onset of ESKD, and these reno-protective effects are independent of glucose lowering. At the time of this update, canagliflozin and dapagliflozin have been approved for delaying the progression of DKD.

The Association of British Clinical Diabetologists (ABCD) and UK Kidney Association (UKKA) Diabetic Kidney Disease Clinical Speciality Group have undertaken a systematic review and critical appraisal of the available evidence to inform clinical practice guidelines for management of hyperglycaemia in adults with DKD. This 2021 guidance is for the variety of clinicians who treat people with DKD, including GPs and specialists in diabetes, cardiology and nephrology. The full guidelines are endorsed by Diabetes UK and the Royal College of Physicians of London and are available online at https://abcd.care/position-papers.

This article is an abridged version of the updated clinical guideline and summarises the key recommendations for practice. For definitions of the evidence grades, see appendix A online www.bjd-abcd.com.

These recommendations are based on a review of the Cochrane Library, PubMed/MEDLINE, Google Scholar and Embase carried out initially between October 2013 and December 2016 and further review carried out in June 2020 for the current update, using the following keywords: type 1 diabetes, insulin, chronic kidney disease, nephropathy, hyperglycaemia, hypoglycaemia, insulin, sulfonylureas, metformin, SGLT-2 inhibitors, pioglitazone, DPP-4 inhibitors, GLP-1 analogues and meglitinides.

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Key words: diabetic kidney disease, management of hyperglycaemia, clinical guideline

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Glycaemic targets for the prevention and management of diabetic kidney disease

The management of diabetes is predicated on the basis of reducing hyperglycaemia to improve osmotic symptoms, with supportive evidence that this will prevent the onset, and slow down progression, of renal and vascular complications over time.

The precise level of glycaemic control that delivers optimal benefit remains contentious because, inevitably, the individualised approach to care and the evidence base from different cohorts do not allow clear extrapolation. People with DKD require multifaceted and comprehensive care, and other aspects such as blood

Table 1 Proposed glycaemic targets in people with diabetic kidney disease (DKD)

Condition	Glycaemic target range	CKD stage and albuminuria	Age
Type 1 diabetes	48–58 mmol/mol (6.5–7.5%)*	CKD stage 2 with variable microalbuminuria	Younger adults (>18) within 10 years' duration of diabetes
	58–62 mmol/mol (7.5–7.8%)	CKD stages 3–4 and/or albuminuria	The majority of people
	58–68 mmol/mol (7.5–8.5%)	CKD stage 5 – dialysis	Any age
Type 2 diabetes	48–58 mmol/mol (6.5–7.5%)* Aim for <52 mmol/mol (6.9%)	CKD stages 1–2	People who are aged <40 Diet controlled at any age‡
	52–58 mmol/mol (6.9–7.5%)	CKD stages 3–4 May be appropriate with a GLP-1 and/or SGLT-2 inhibitor-based treatment regime without insulin	Any age
	58–68 mmol/mol (7.5–8.5%)	CKD stages 3–4 and those with CKD stage 5 who are on dialysis. Especially in people with albuminuria who are on an insulin-based regime†	Any age

*Confirmatory blood glucose or flash glucose monitoring if concern of hypoglycaemia and/or anaemia.
†Recognition of cardio-renal benefits with SGLT-2 inhibitors (and potentially GLP-1 analogue therapy) independent of glycaemic effect.
‡Over 20% of people with DKD (especially older people aged >75) solely dietary controlled can have HbA_{1c} 42–48 mmol/mol (6–6.5%) without hypoglycaemia.
These recommendations are based on the opinion of the Writing Group as there is limited high-grade evidence in DKD.
CKD, chronic kidney disease; GLP-1, glucagon-like peptide 1; SGLT-2, sodium glucose co-transporter-2.

pressure and lipid management are reviewed separately (see https://abcd.care/position-papers).

The glycaemic management of type 1 diabetes and type 2 diabetes and the respective renal benefits require separate consideration, which in part reflects the different evidence base and lifetime risks of complications, with the greater risk for hypoglycaemia that arises when several concurrent therapies are used alongside insulin as renal function deteriorates. In addition, the risk–benefit equation of tighter glycaemic control for renal and vascular complications alters as DKD progresses.

Individualised HbA_{1c} targets should be applied in the management of people with DKD, using the levels suggested in Table 1.

There has been an important shift in emphasis in recent guidance from the American Diabetes Association, the European Association for the Study of Diabetes and the European Society for Cardiology. There is now specific emphasis on selection of SGLT-2 inhibitors or glucagon-like peptide-1 (GLP-1) receptor agonists where, in addition to glucose lowering, these therapies should be considered in people with DKD where there is an evidence base for cardio-renal protection.[1,2]

HbA_{1c} targets for people who have type 2 diabetes and DKD

Individualised HbA_{1c} targets should be applied in the management of people with DKD, using the levels suggested in Table 1. These target ranges are based on the opinion of the Writing Committee as there is limited high-grade evidence in people with DKD.

At present, it would be prudent to consider a HbA_{1c} target of 58 mmol/mol (7.5%) for most people with DKD if their glucose-lowering therapies include insulin and a target of up to 68 mmol/mol (8.4%) in older people with more advanced CKD (stage 4 and above). The risks of hypoglycaemia are greater in people with diabetes and CKD, especially if people are on insulin treatment or sulfonylurea or glinides. Individualised pragmatic glycaemic goals that balance the benefits and risks of intensive glucose lowering in people with type 2 diabetes and DKD and patient education on hypoglycaemia avoidance and self-management are needed.

It remains to be seen whether it is appropriate and safe to have a lower glycaemic HbA_{1c} target of 52 mmol/mol (6.9%) as more GLP-1 and SGLT-2 inhibitor-focused treatments are being used when the estimated glomerular filtration rate (eGFR) is >30 mL/min/1.73 m^2, both for people with and without cardiovascular disease.

From the current evidence, there is no basis to seek HbA_{1c} values of lower than 52 mmol/mol (6.9%) in older people with type 2 diabetes and DKD through medication.

Renal function measurements in determining medication dosages in diabetes

We recommend that eGFR is used, preferably using the more accurate Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation when determining whether certain therapies can be used or to adjust medication dosages in diabetes.[3] It is important to recognise that eGFR equations have several limitations.[4] There is also an ongoing important discussion on the continued use of ethnicity in eGFR equations and its potential impact on prescribing practice and clinical care.[5]

Glucose-lowering therapies for people who have type 2 diabetes and DKD

The selection of individual classes of drug, tailored to the additional comorbidities that are frequently seen alongside DKD, will also influence therapy selection (Table 2). In addition, certain combinations of different classes of drugs would need judicious consideration. Although these guidelines focus on individual classes of glucose-lowering drug, combinations of different classes will frequently be prescribed to people with DKD. There is a relative dearth of studies that specifically evaluate different drug combinations in people with DKD, and this is clearly an area for both further research and clinical audit.

Table 2 Contraindications to the selection of blood glucose-lowering therapies in people with diabetic kidney disease (DKD) with diabetes mellitus complications

Condition	Drug	Note
Retinopathy	Pioglitazone	Absolute contraindication in diabetic maculopathy
	Semaglutide	Relative contraindication in people with marked hyperglycaemia (HbA_{1c} >91 mmol/mol (10.5%)) who have diabetic retinopathy requiring active ophthalmology follow-up: caution is advised
Bone health	Pioglitazone	Absolute contraindication in people who have had previous osteoporotic fractures; or relative contraindication in those with post-menopausal osteoporosis with neuropathy
	SGLT-2 inhibitors	Relative contraindication in people with established osteoporotic fractures
Foot health	SGLT-2 inhibitors	Absolute contraindication if a person has active diabetic foot disease with vascular complications or sepsis
Cardiac failure	Pioglitazone	Absolute contraindication in people with established treated heart failure and where at-risk people have a raised serum brain natriuretic peptide (BNP)
	Saxagliptin	Absolute contraindication in people with treated established heart failure
Pancreatic health	GLP-1 analogues	Absolute contraindication of GLP-1 analogues where an individual has previously documented pancreatitis; relative contraindication in people who are at risk of pancreatitis with raised triglycerides, those on steroid therapy, those using other drugs that are associated with pancreatitis or those with documented alcoholism
Bladder health	SGLT-2 inhibitors	Relative contraindication of all medications in this class in people who have documented neuropathic bladder and recurrent urinary infections
	Pioglitazone	Bladder cancer – no current absolute contraindication to continuation of pioglitazone and SGLT-2 inhibitors; relative contraindication/caution to initiation of pioglitazone and SGLT-2 inhibitors in those with bladder cancer or without investigation of unexplained haematuria
Biliary tract health	GLP-1 analogues	Relative contraindication if a person has active gall bladder disease

GLP-1, glucagon-like peptide 1; SGLT-2, sodium glucose co-transporter-2.

Recommendations

1. *Individualised HbA_{1c} targets should be applied in the management of people with DKD, using the levels suggested in Table 1 (Grade 1B).*
2 *Additional comorbidities that are frequently seen alongside DKD and risk of hypoglycaemia should also influence therapy selection and HbA_{1c} targets. In people who progress to advanced stages of DKD (eGFR <45 mL/min/1.73 m^2) or those with fast progression of DKD, more frequent monitoring of HbA_{1c} and renal function may be required (Tables 1 and 2) (Grade 1B).*
3 *Certain combinations of different classes of drugs need judicious consideration, but appropriate combinations of different classes will frequently be needed to manage DKD (Grade 2D).*

Insulin therapy in people with DKD

Recommendations

1. *There is no firm evidence that insulin therapy reduces the risk of progressive renal disease. Therefore, the aim of insulin therapy should be to improve glycaemic control and improve quality of life, with a low risk of hypoglycaemia (Grade 1C).*
2 *Insulin requirements are likely to rise in the early stages of DKD due to increased insulin resistance (Grade 1C).*
3 *As GFR declines, insulin requirements are likely to diminish through reduced renal insulin clearance. Insulin doses should be reduced as GFR falls, especially in chronic kidney disease (CKD) stage 3b and below. In people with CKD stage 3b and below who are on insulin, and whose HbA_{1c} is 58 mmol/mol (7.5%) or below, reduction of insulin dose should be considered (Grade 1C).*
4 *People with DKD who are treated with insulin should undertake regular glucose monitoring (Grade 1C).*
5 *In people who are less able to comply with the requirements of a basal bolus regime, once-daily regimes with longer-acting insulins should be considered (Grade 1D).*
6 *If people experience hypoglycaemia on neutral protamine Hagedorn (NPH) insulin or premixed insulins, conversion to analogue insulins may be of benefit (Grade 1C).*

Sulfonylureas

There is very little comparative randomised controlled trial evidence of the use of sulfonylureas (SUs) in DKD. People with type 2 diabetes and DKD who are on SU treatment are at increased risk of hypoglycaemia. We therefore advise regular capillary blood glucose (CBG) monitoring for people with DKD on SU treatment. All SUs should be avoided where possible in advanced renal impairment. Please see the full guidance document for detailed information on the use of SUs in DKD (https://abcd.care/position-papers).

Metformin

Metformin has been used as a first-line oral drug for people with type 2 diabetes for over 60 years. The dose of metformin should be decreased if eGFR is <45 mL/min/1.73 m^2 and omitted if eGFR is <30 mL/min/1.73 m^2. Treatment should be interrupted in people at risk of tissue hypoxia or sudden deterioration in renal function (eg, dehydration, severe infection, shock, sepsis, acute heart failure, respiratory failure or hepatic impairment) or those who have recently had a myocardial infarction.[6]

For most people, the benefits of metformin greatly outweigh the very small lactic acidosis risk: a 30–40% reduction in cardiovascular and diabetes events versus a risk of lactic acidosis of a maximum 5–10 episodes per 100,000 patient-years. Even if the presence of impaired renal function increases this risk by 10- or even 100-fold, the benefits continue to outweigh the risks. In recognising that there may be subgroups of people who are at higher risk of lactic acidosis (not just due to impaired renal function), however, the practical advice for clinicians and people contained in Table 3 is relevant and in general supports the ongoing use of metformin for people with stable CKD stage 3.

Recommendations

1. *Metformin can be used down to an eGFR of 30 mL/min/1.73 m^2. The dosage should be reduced when the eGFR falls below 45 mL/min/1.73 m^2 (Grade 1B).*
2 *Metformin should be withheld during periods of acute illness, particularly when a person has acute kidney injury (AKI). Everyone who is treated with metformin should be given sick day guidance, which should be reiterated at every medication review (Grade 1B).*
3 *Metformin should be withheld prior to and shortly after any procedure that requires the use of radiographic contrast media (Grade 1B).*

Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) bind selectively to DPP-4 and prevent the rapid hydrolysis of glucagon-like peptide 1 (GLP-1). They have a modest glucose-lowering effect compared with other oral hypoglycaemic agents. DPP-4 inhibitors are known to have a very low risk of hypoglycaemia and are generally associated with a favourable safety and tolerability profile in people with type 2 diabetes and mild-to-severe renal impairment.[7]

Recommendations

1. *People with DKD of all stages are suitable for treatment with DPP-4 inhibitors (Grade 1B).*
2. *We recommend that doses of DPP-4 inhibitors are appropriately reduced in accordance with the degree of renal impairment (including maintenance haemodialysis) except linagliptin (Grade 1B).*
3. *People with DKD can be safely prescribed DPP-4 inhibitors without the risk of hypoglycaemia or weight gain at all stages of renal disease (Grade 1B).*
4. *There are no current data to suggest that DPP-4 inhibitors (except saxagliptin) are associated with an excess risk of hospitalisation for heart failure (Grade 1A).*

Pioglitazone

Pioglitazone is one of the few oral glucose-lowering drugs that is licensed for use in people with eGFR <30 mL/min/1.73 m^2. Pioglitazone should be avoided if there is evidence of heart failure or macular oedema. People should be carefully and regularly monitored for fluid retention. Please see the full guidance for detailed information on the use of pioglitazone in DKD (https://abcd.care/position-papers).

Sodium glucose co-transporter-2 (SGLT-2) inhibitors

Systematic reviews and meta-analyses suggest a clear beneficial class effect of SGLT-2 inhibitors on the risk of cardiovascular disease (CVD) and hospitalisation for heart failure.[8,9] These benefits are consistently observed in people with DKD even at early stages of disease. In view of the high risk of CVD in DKD, multifactorial interventions that can reduce the burden of CVD are needed and the SGLT-2 inhibitor class offers unique advantages in the context of CVD and renal protection. Recent meta-analyses have demonstrated the beneficial effects of SGLT-2 inhibitors on CVD and renal endpoints (such as dialysis, transplantation and death due to kidney disease) and these effects are seen irrespective of baseline albuminuria, eGFR, HbA_{1c} and are independent of blood glucose-lowering effect or use of renin angiotensin system (RAS) blockade.[8–10]

Two recent outcome trials have been published where renal outcomes were assessed as the primary endpoint in DKD.

Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) was the first study of an SGLT-2 inhibitor to have renal outcomes in its primary composite endpoint.[11] People with type 2 diabetes and albuminuric CKD were randomised to receive canagliflozin 100 mg once daily or placebo. All participants had an eGFR of ranging from 30 to <90 mL/min/1.73 m^2, albuminuria (urine albumin:creatinine ratio (ACR) >33.9–565 mg/mmol (>300 to 5,000 mg/g)) and received RAS blockade. Sixty per cent of recruits had an eGFR of 30–60 mL/min/1.73 m^2. The primary endpoint was a composite of ESKD (dialysis, transplantation or sustained eGFR of <15 mL/min/1.73 m^2), a doubling of the serum creatinine or death from renal or cardiovascular causes.

The trial was halted early after a planned interim analysis, at which point 4,401 people had been randomised with median follow-up of 2.6 years. The relative risk of the primary endpoint was significantly lower in the canagliflozin group with event rates of 43.2 versus 61.2 per 1,000 patient-years (HR 0.70; 95% CI 0.59 to 0.82; p=0.00001). The relative risk of the renal-specific composite of ESKD, doubling of the creatinine level or death from renal causes was lower by 34% (HR 0.66; 95% CI 0.53 to 0.81; p<0.001) and ESKD was lower by 32% (HR 0.68; 95% CI 0.54 to 0.86; p=0.002). Participants in the canagliflozin group also had a significantly lower risk of cardiovascular death, myocardial infarction or stroke (HR 0.80; 95% CI 0.67 to 0.95; p=0.01) and hospitalisation for heart failure (HR 0.61; 95% CI 0.47 to 0.80; p<0.001).[11] Of note, in this high-risk population there were no significant increases in rates of lower limb amputation or fracture.

The Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial assessed the effect of dapagliflozin on renal and cardiovascular events in people with CKD (both with and without diabetes).[12] In this study 4,094 participants with an eGFR of 25–75 mL/min/1.73 m^2 and urine ACR 22.6–565 mg/mmol (200–5,000 mg/g) were randomised to receive dapagliflozin 10 mg once daily or placebo. Participants were on a stable dose of RAS blockade, although those who were unable to take these medications could be included. The mean baseline eGFR was 41.1 mL/min/1.73 m^2 and the median

Table 3 Action to be taken for selected medications when treating people with diabetic kidney disease (DKD)

eGFR level	Action to be taken
Metformin	
For all	• Practitioners have to weigh up the glycaemic and cardiovascular benefits against the rare risk of associated lactic acidosis.
>60 mL/min/1.73 m^2	• No renal contraindication to metformin. • Some of these people are at increased risk due to other risk factors (see advice for increased vigilance groups in the bottom row of this table).
45–60 mL/min/1.73 m^2	• Continue use in people who were established on metformin, but review the dose in light of glucose control needs. • For new individuals who have no major active co-morbidities, metformin commencement can be considered if age-related life expectancy is normal and vascular/diabetes risks are present. • Increase monitoring of renal function (to every 3–6 months).
30–45 mL/min/1.73 m^2	• Continue or commence with caution and explain the risks and benefits to the person. • Use lowest dose that achieves glycaemic control (suggest a 50% dose up to 1,000 mg/day). • Closely monitor renal function (every 3 months).
<30 mL/min/1.73 m^2	• At this level of renal function we cannot give firm recommendations about the ongoing use of metformin. • Some specialists may choose to use metformin in selected people where they see that the benefits outweigh the risks. • Pharmacokinetic work would suggest that, if metformin is used, a dose of 500–1,000 mg/day would result in 95% of people having peak metformin concentrations of <5 mg/L.
Dialysis	• No current role
AKI (or at risk of AKI)	Review and consider (temporarily) stopping* metformin in those who: • have acute changes in renal function (a fall in eGFR of >10 mL/min/1.73 m^2 over a period of days or weeks) • are at risk of AKI such as: o acute volume depletion and dehydration (eg, gastrointestinal upset, stomas, change in diuretic dose) o during operative procedures with a high risk of hypotension or volume depletion o in the presence of hypotension or shock (eg, severe infection) o intravascular administration of iodinated contrast drugs (stop metformin on the day of and 2 days after X-ray related intravenous contrast use) o co-administration with nephrotoxic drugs (eg, non-steroidal anti-inflammatory drugs) o those with acute illness who are also on drugs that are known precipitants of AKI in association with any angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) (such as non-steroidal anti-inflammatory drugs), especially combined with diuretics • those with previous episodes of AKI. *Duration of stopping metformin should be based on the likely period of risk. In general, it should be resumed at a low dose after discharge.
Recovery from AKI	• Once urine flow has returned to normal and GFR is >30 mL/min/1.73 m^2, resume metformin at a low dose (eg, 500–1,000 mg/day). • Monitor glucose control in outpatients and primary care before considering the further need for increasing doses.
Increased vigilance	Increased vigilance is needed for the following groups of people who are likely to be at a higher risk of lactic acidosis even with normal renal function: • those with decompensated cardiac or respiratory failure • those with acute conditions that may cause tissue hypoxia (eg, recent myocardial infarction or shock) • those with hepatic insufficiency, acute alcohol intoxication or alcoholism.
GLP-1 receptor agonists: exenatide (Byetta™ and Bydureon™), liraglutide, lixisenatide, dulaglutide, semaglutide	
For all	• Older people: no dose adjustment is required based on age. Therapeutic experience in people ≥75 years of age is limited • Paediatric population: the safety and efficacy in children aged up to 18 years have not yet been established. No data are available. • Should not be used in people with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. • No experience in those with congestive heart failure NYHA class IV and therefore not recommended in these people. • If pancreatitis is suspected, drug should be discontinued; if confirmed, then should not be restarted. Caution should be exercised in people with a history of pancreatitis.
>60 mL/min/1.73 m^2	• No renal contraindication to initiation or continuation.
45–60 mL/min/1.73 m^2	• No renal contraindication to initiation or continuation.
30–45 mL/min/1.73 m^2	• Byetta™ and lixisenatide to be used 'with caution' in people with creatinine clearance 30–50 mL/min, Bydureon™ should be stopped. Liraglutide, dulaglutide and semaglutide have no renal contraindication to initiation or continuation at standard doses.
<30 mL/min/1.73 m^2	• Liraglutide, dulaglutide and semaglutide have no renal contraindication to initiation or continuation at standard doses.
Dialysis	• No current role
AKI (or at risk of AKI)	Review and consider (temporarily) stopping* in people who: • have acute changes in renal function (a fall in eGFR of >10 mL/min/1.73 m^2 over a period of days or weeks) • are at risk of AKI such as: ◦ acute volume depletion and dehydration (eg, gastrointestinal upset, stomas, change in diuretic dose) ◦ operative procedures with a high risk of hypotension or volume depletion ◦ in the presence of hypotension or shock (eg, severe infection) • have had previous episodes of AKI. *Duration of stopping GLP-1 receptor agonist should be based on the likely period of risk.

AKI, acute kidney injury; DPP-4i, dipeptidyl peptidase-4 inhibitors; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide 1; SGLT-2i, sodium glucose co-transporter-2 inhibitor.

Table 3 Action to be taken for selected medications when treating people with diabetic kidney disease (DKD) *(continued)*

eGFR level	Action to be taken
DPP-4 inhibitors: vildagliptin, saxagliptin, sitagliptin, linagliptin, alogliptin	
For all	• Older people (≥65 years): in general, no dose adjustment is recommended based on age. • Paediatric population: the safety and efficacy of DPP-4 inhibitors in children aged 0 to <18 years have not yet been established. No data are available. • No dose adjustments are needed for mild to moderate hepatic impairment. Caution needs to be exercised with alogliptin use in those with severe hepatic impairment. Vildagliptin should not be used in hepatic impairment. Alogliptin and saxagliptin are not recommended in severe hepatic impairment. Only linagliptin is licensed for use in severe hepatic impairment. • Acute pancreatitis: DPP-4 inhibitors are associated with risk of developing acute pancreatitis. Caution should be exercised in those with a history of pancreatitis. • Heart failure: DPP-4 inhibitors do not increase risk of major CV events or risk of hospitalisation for heart failure except saxagliptin, which is contraindicated in heart failure.
>60 mL/min/1.73 m^2	• No renal contraindication to initiation or continuation.
45–60 mL/min/ 1.73 m^2	• eGFR <50 mL/min/1.73 m^2, reduce dose of sitagliptin to 50 mg daily, vildagliptin to 50 mg once daily, alogliptin to 12.5 mg daily and saxagliptin to 2.5 mg daily. No dose reduction needed for linagliptin.
30–45 mL/min/ 1.73 m^2	• Reduce dose of sitagliptin to 50 mg daily, vildagliptin to 50 mg once daily, alogliptin to 12.5 mg daily and saxagliptin to 2.5 mg daily. No dose reduction needed for linagliptin. Vildagliptin has limited data and should be used with caution.
<30 mL/min/1.73 m^2	• Reduce dose of sitagliptin to 25 mg daily, alogliptin to 6.25 mg daily and saxagliptin to 2.5 mg daily. No dose reduction needed for linagliptin. Vildagliptin has limited data and should be used with caution.
Dialysis	• Reduce dose of sitagliptin to 25 mg daily, and alogliptin to 6.25 mg daily. No dose reduction needed for linagliptin. Saxagliptin is not recommended. Vildagliptin has limited data and should be used with caution.
SGLT-2 inhibitors: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	
For all	• Older people (≥65 years): in general, no dose adjustment is recommended based on age. • Paediatric population: the safety and efficacy of dapagliflozin in children aged up to 18 years have not yet been established. No data are available. • Active foot disease (either ulceration with sepsis or ischaemia) avoid initiation and withdraw if this occurs. • Diabetic ketoacidosis (DKA): permanently discontinue if people develop DKA on treatment.
>60 mL/min/1.73 m^2	• No renal contraindication to initiation or continuation.
45–60 mL/min/ 1.73 m^2	• Canagliflozin 100 mg daily may be commenced for glucose lowering and reno-protection. • Dapagliflozin 10 mg daily may be commenced/continued for heart failure and reno-protection. • Empagliflozin may be commenced/continued for heart failure • For other drugs, current licence recommends against initiation (but see recommendations). Continuation of medication should be at the lower dose for canagliflozin and empagliflozin.
30–45 mL/min/ 1.73 m^2	• Canagliflozin 100 mg daily may be commenced for reno-protection. • Dapagliflozin 10 mg daily may be commenced/continued for reno-protection and heart failure. • Empagliflozin may be commenced/continued for heart failure. • For glucose lowering, current licence recommends against initiation or continuation.
15–30 mL/min/ 1.73 m^2	• Canagliflozin 100 mg daily may be continued for reno-protection until dialysis or renal transplantation. • Empagliflozin may be commenced/continued for heart failure • Dapagliflozin 10mg daily may be commenced/continued for reno-protection until dialysis or renal transplantation. • Dapagliflozin 10 mg daily may be commenced/continued for heart failure.
Dialysis	• No current role
AKI (or at risk of AKI)	• Review and consider (temporarily) stopping* in people who: • have acute major changes in renal function (a fall in eGFR of >10 mL/min/1.73 m2 over a period of days or weeks)* • are at risk of AKI such as: ◦ acute volume depletion and dehydration (eg, gastrointestinal upset, stomas, change in diuretic dose) ◦ operative procedures with a high risk of hypotension or volume depletion ◦ in the presence of hypotension or shock (eg severe infection) • have had previous episodes of AKI. *Duration of stopping SGLT-2 inhibitor should be based on the likely period of risk.

AKI, acute kidney injury; DPP-4i, dipeptidyl peptidase-4 inhibitors; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide 1; SGLT-2i, sodium glucose co-transporter-2 inhibitor.

urine ACR was 107.2 mg/mmol (949 mg/g). The primary outcome was a composite of sustained decline in eGFR of at least 50%, ESKD or death from renal or cardiovascular causes. The trial was stopped early because of efficacy. Over a median of 2.4 years, the primary outcome event occurred in 197 of 2,152 participants (9.2%) in the dapagliflozin group and 312 of 2,152 participants (14.5%) in the placebo group (HR 0.61; 95% CI 0.51 to 0.72; p<0.001) and the number needed to treat to prevent one primary outcome event was 19 (95% CI 15 to 27). The hazard ratio for the renal composite of a sustained decline in eGFR of at least 50%, ESKD or death from renal causes was 0.56 (95% CI 0.45 to 0.68; p<0.001). All-cause mortality was 101 subjects in dapagliflozin participants (4.7%) versus 146 subjects (6.8%) in the placebo group (HR 0.69; 95% CI 0.53 to 0.88; p=0.004). The effects were similar in people with type 2 diabetes to those without.[12]

Practical aspects of using SGLT-2 inhibitors

The observed renal and cardiovascular benefits of SGLT-2 inhibitors are independent of the HbA_{1c} lowering effects of these agents in people with type 2 diabetes and eGFR >45 mL/min/1.73 m^2. In people with diabetes and eGFR <45 mL/min/1.73 m^2, treatment with SGLT-2 inhibitors does not lower HbA_{1c} significantly. An SGLT-2 inhibitor can be initiated or continued for cardiorenal protection; however, if further glucose lowering is required, adding another class of medications to optimise diabetes control is recommended.

If dapagliflozin or canagliflozin is started for DKD, the medication can be continued until ESKD.

Regardless of urine ACR, we also recommend the initiation of dapagliflozin as licensed for people with diabetes, heart failure and CKD where eGFR is >30 mL/min/1.73 m^2. It is likely that all SGLT-2 inhibitors will be effective in these individuals but licence updates are awaited (see Tables 3 and 4 for more detailed information on the use of SGLT-2 inhibitors).

DKA secondary to SGLT-2 inhibitors is rare in type 2 diabetes with a reported incidence between 1 in 1,000 to 1 in 10,000 people. In the DAPA-CKD trial, no increased risk of DKA was observed with dapagliflozin. However, in the CREDENCE trial, rates of DKA were higher in the canagliflozin group than in the placebo group (2.2 vs 0.2 per 1,000 patient-years).[10] SGLT-2 inhibitor-induced DKA can present with normoglycaemia or moderately raised glucose levels. It is important for clinicians to be aware of this so that diagnosis is not missed.

Recommendations

1. *We recommend the consideration of SGLT-2 inhibitors in all individuals with type 2 diabetes and DKD with an eGFR ≥30 mL/min/1.73 m^2, irrespective of glycaemic control, recognising that this is currently off-licence practice for some drugs in the SGLT-2 inhibitor class. For those with established albuminuria, canagliflozin 100 mg once daily is licensed for renoprotection in DKD and dapagliflozin 10 mg can be initiated down to an eGFR of 15 mL/min irrespective of the level of albuminuria (Grade 1A).*
2. *Where individuals are already receiving treatment with insulin or sulfonylureas, a reduction in dose of these drugs should be considered, so as to reduce the risk of hypoglycaemia (Grade 1A).*
3. *The initiation of SGLT-2 inhibitors in people who have active foot disease (ulceration, infection, sepsis and ischaemia) should be avoided and these agents should be withdrawn in people who develop active infected and/or vascular foot complications while on treatment. SGLT-2 inhibitors should only be reinstated after foot problems have fully resolved and following discussion with the multidisciplinary foot team (expert opinion, no high grade evidence).*
4. *SGLT-2 inhibitors should be withdrawn in all people who develop DKA. However, if a definitive cause for DKA is identified (eg, low calorie diet, postoperative catabolic state), reinstatement of SGLT-2 inhibitors may be considered depending on careful assessment of the individualised risks and benefits by a diabetes specialist (expert opinion, no high grade evidence).*
5. *We do not recommend routine assessment of renal function (creatinine and/or eGFR) within 6–8 weeks of SGLT-2 initiation since there is likely to be a transient and physiological deterioration and this is not a reason to withdraw the drug (expert opinion, no high grade evidence).*
6. *We recommend that sick day guidance applies, during which SGLT-2 inhibitors should be temporarily withheld (expert opinion, no high grade evidence).*

Glucagon-like peptide-1 receptor agonists

In 2021, six licensed GLP-1 receptor agonist (GLP1-RA) injectables are available for use in Europe and two involve differing delivery mechanisms for the same molecule (exenatide).

Systematic reviews and meta-analyses suggest a clear beneficial class effect of GLP-1 receptor agonists on the risk of CVD.[8,13] CVOTs have demonstrated CVD benefits with liraglutide, injectable semaglutide and dulaglutide. There are currently no primary renal endpoint studies with this class of agent published. However, the impact of GLP-1RAs on renal safety and renal outcomes has been assessed in several studies as secondary or exploratory outcomes.

There have been isolated case reports of AKI and interstitial nephritis resulting from exenatide and liraglutide use, and these are referred to in their summary of product characteristics.[14] Acute hypovolaemia from severe gastrointestinal side effects was considered to be a more likely cause of AKI than a direct nephrotoxic effect of these drugs. In practice, it would be reasonable to apply caution for people who have DKD and acute illness via the temporary cessation of GLP-1RA therapy through general sick day guidance.

The current data on potential reno-protection are based on secondary or exploratory CVOTs. However, a placebo-controlled trial of semaglutide with primary renal endpoints is currently ongoing and expected to report in 2024.

Recommendations

1. *To date, there has been no reported reduction in hard clinical endpoints, such as a doubling of serum creatinine or the need for continuous renal replacement therapy with GLP-1 RA. There is evidence that treatment with some GLP-1RAs reduce the progression of renal disease in people with type 2 diabetes, but this mainly relates to the new onset of persistent macroalbuminuria (Grade 2B).*
2. *Hence, the main aim of GLP-1 RA therapy in people with DKD should be the improvement of glycaemic control with a low risk of both hypoglycaemia and weight gain (Grade 1A).*
3. *There is evidence of protection from cardiovascular disease with some GLP 1RAs in people who have type 2 diabetes and a high risk of cardiovascular disease (Grade 1A).*
4. *In one sub-group analysis, this protection was more pronounced in people with stage 3 CKD; GLP 1RAs are therefore preferred over alternative glucose-lowering therapies (eg, sulfonylureas and insulins) in this scenario (Grade 2B).*
5. *People with DKD who are treated with GLP-1RAs need to only perform regular self-monitoring of blood glucose when they are also being treated with drugs that can cause hypoglycaemia (sulfonylureas and insulins) (Grade 1A).*
6. *There is no role for the combination of GLP-1 analogues and DPP-4 inhibitors (Grade 1C).*

Table 4 Glucose-lowering therapies: current licensing based on estimated glomerular filtration rate (eGFR) and cardio-renal protection

		Renal impairment – CKD stage and eGFR (mL/min/1.73 m²)					
Drug	**Class of drug**	**1 eGFR ≥90**	**2 eGFR 60–89**	**3a eGFR 45–59**	**3b eGFR 30–44**	**4 eGFR 15–29**	**5 eGFR <15**
Metformin	Biguanide				Reduce dose to 500 mg twice daily	eGFR may underestimate in obesity, potential role for 500 mg	
Gliclazide	Sulfonylurea	Monitor CBG	Monitor CBG	Monitor CBG	Dose reduction advised. Monitor CBG	Off licence – high risk of hypoglycaemia; monitor CBG	
Repaglinide	Meglitinide	Monitor CBG	Monitor CBG	Monitor CBG	Monitor CBG	Dose reduction advised Monitor CBG	Dose reduction advised Monitor CBG
Sitagliptin	DPP-4i			<50 mL/min reduce dose to 50 mg	Reduce dose to 50 mg	Reduce dose to 25 mg	Reduce dose to 25 mg
Saxagliptin	DPP-4i			<50 mL/min reduce dose to 2.5 mg	Reduce dose to 2.5 mg	Reduce dose to 25 mg	
Linagliptin	DPP-4i						
Pioglitazone*	Thiazolinedione						
Lixisenatide	GLP-1 agonist			Caution if CrCl <50 mL/min			
Exenatide	GLP-1 agonist			Caution if CrCl <50 mL/min			
Exenatide MR	GLP-1 agonist			**Stop** if CrCl <50 mL/min			
Liraglutide	GLP-1 agonist						
Dulaglutide	GLP-1 agonist						
Semaglutide (oral/injectable)	GLP-1 agonist						
Dapagliflozin†‡	SGLT-2i			May initiate at 10 mg and /or continue for reno-protection and treatment of heart failure	May initiate at 10 mg and /or continue for reno-protection and treatment of heart failure	May initiate at 10 mg and/or continue for reno-protection and treatment of heart failure Limited experience for treatment of heart failure and reno-protection.	Can be continued at 10 mg until renal replacement therapy
Canagliflozin§	SGLT-2i			May initiate at 100 mg and/or continue for reno-protection	May initiate at 100 mg and/or continue for reno-protection	Continue at 100 mg for reno-protection until renal replacement therapy	
Empagliflozin	SGLT-2i			May initiate at 10 mg for treatment of heart failure	May initiate at 10 mg for treatment of heart failure	May initiate at 10 mg for treatment of heart failure Limited experience for treatment of heart failure	
Ertugliflozin	SGLT-2i			Do not initiate			
Insulin					Dose reduction may be needed	Dose reduction should be needed	Dose reduction should be needed

Note that Sick day guidance applies to metformin, all SGLT-2 inhibitors and GLP-1 agonists.
*Monitor for fluid retention, contraindicated in heart failure, macular oedema.
†Dapagliflozin can be initiated and continued for treatment of heart failure without reference to renal function,
‡Dapagliflozin can be initiated for reno-protection down to an eGFR of 15 mL/min/1.73 m² and be continued thereafter until the onset of dialysis or transplantation.
§Canagliflozin can be initiated for reno-protection down to an eGFR of 30 mL/min/1.73 m² and be continued thereafter until the onset of dialysis or transplantation.

CBG, capillary blood glucose; CKD, chronic kidney disease; CrCl, creatinine clearance as an estimate of glomerular filtration rate, usually calculated using Cockcroft–Gault equation; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1, glucagon-like peptide 1; SGLT-2i, sodium glucose co-transporter-2 inhibitor.

Key messages

- People with diabetic kidney disease (DKD) have an increased risk of CVD morbidity and mortality
- Individualised HbA_{1c} targets should be applied in the management of people with DKD
- SGLT-2 inhibitors significantly reduce progression of DKD and prevent ESKD in people with T2DM
- We recommend the consideration of SGLT-2 inhibitors in all individuals with type 2 diabetes and DKD with an eGFR ≥30 mL/min/1.73 m^2

Conclusion

People with DKD have an increased risk of morbidity and mortality. Hyperglycaemia is a modifiable risk factor for cardiovascular complications and progression of DKD. Individualised HbA_{1c} targets should be applied in the management of people with DKD, using the levels suggested in this guidance. Delaying ESKD and reducing CVD risk are essential to improve outcomes in this high-risk population. There is now conclusive evidence and consensus that SGLT-2 inhibitors significantly reduce progression of DKD and onset of ESKD in people with type 2 diabetes and albuminuria. The results of ongoing studies will determine the renal benefits of this class in people with DKD and normoalbuminuria and in people with type 1 diabetes.

Conflict of interest SB has received honoraria, teaching and research sponsorship/grants from Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, Roche and Sanofi Aventis. He has also received funding for the development of educational programmes from: Elsevier, OmniaMed and Medscape. He is a partner in Glycosmedia, which carries sponsorship declared on its website. DB was previously funded for research by the British Heart Foundation (BHF). He is funded by ESR AstraZeneca for clinical trials. He has received speaker fees from Vifor Pharma and AstraZeneca. TC has no conflicts of interest. DP has received honoraria for advisory work and/or lecture fees from AstraZeneca, Boehinger Ingelheim Eli Lilly, MSD and Napp Pharmaceuticals, Novo Nordisk and Sanofi. ID has previously received research grants from Medtronic and Daiichi Sankyo. He has been a member of advisory committees and received educational grants from AstraZeneca, Amgen, Sanofi, MSD, Pfizer, GSK, Mitsubishi Pharma, Otsuka, Vifor Pharmaceuticals, Fresenius and Roche. PD has received honoraria for educational meetings from AstraZeneca, Janssen, Boehringer Ingelheim, Novo, Sanofi, Novartis, Abbott, MSD, Takeda, Roche, Lilly, Ascensia, BD, Internis, GSK, Menarini, Bayer and Besins. PM has received honoraria from Pfizer, AstraZeneca, Novartis, Bristol Myers Squibb, Napp, Vifor and Pharmacosmos and research support from Boehringer Ingelheim outside this work. DF has received honoraria for delivering educational meetings and/or attending advisory boards from AstraZeneca, Sanofi, Vifor Pharmaceuticals and Baxter. He provides consultancy for adjudication of endpoint in RCTs to ACI. AF has received research grants, and he prepares educational materials and attends drug advisory boards for Boehringer Ingelheim/Lilly Alliance, AstraZeneca, Novo Nordisk, Merck and Johnson & Johnson. AP has received honoraria for attending and delivering non-promotional educational meetings and advisory boards from Lilly, NovoNordisk and Boehringer Ingelheim. PW has received honoraria for delivering educational meetings and/or attending advisory boards for AstraZeneca, Eli Lilly, Novo Nordisk, Sanofi, MSD, Janssen and Vifor Pharmaceuticals. JK has received honoraria for delivering educational meetings and/or attending advisory boards Boehringer Ingelheim, AstraZeneca, Sanofi, Janssen, Novo Nordisk and research grants from AstraZeneca, Sanofi. RMM has no conflicts of interest to declare. AS has received honoraria for delivering educational meetings and/or attending advisory boards for Boehringer Ingelheim/Lilly Alliance, Napp Pharmaceuticals, Novo Nordisk, Astellas, Sandoz and Atara Biotherapeutics. He currently has grant funding from Chiesi UK.

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Appendix 1. Evidence grades for the recommendations

The following evidence grading has been used to determine the strength of the recommendations:

1A Strong recommendation: high-quality evidence
1B Strong recommendation: moderate-quality evidence
1C Strong recommendation: low-quality evidence
1D Strong recommendation: very low-quality evidence
2A Weak recommendation: high-quality evidence
2B Weak recommendation: moderate-quality evidence
2C Weak recommendation: low-quality evidence
2D Weak recommendation: very low-quality evidence

Integrated diabetes care: The Association of British Clinical Diabetologists (ABCD) national survey report

DINESH NAGI, SUSANNAH ROWLES, ANDREW MACKLIN, UMESH DASHORA, HEATHER OLIVER, DIPESH PATEL, ON BEHALF OF THE ABCD

Executive Summary

A national survey on integrated diabetes services was carried out by the Association of British Clinical Diabetologists (ABCD) during the COVID-19 pandemic and has provided some very useful insights into the current state of integration to deliver a joined-up diabetes service in the UK.

This survey was carried out during the second half of 2020 and explored three main areas: (1) current state of clinical integration between primary and secondary (specialist) diabetes services; (2) the state of IT integration among the diabetes IT systems and hospital-based electronic patient records (EPR) and between hospital and primary care; (3) to ascertain the membership of their views on a 'one-stop service' for collecting annual review data for diabetes and the potential barriers to achieve this. The results presented are a summary of the survey, while the full unedited survey report, especially on the qualitative aspects, is available to ABCD members.

The survey was mailed to 518 individuals, of which 431 (83.2%) were consultants and 53 (10.2%) were specialist registrars. Of the 83 replies received, 98% were from consultants and the responses represented a total of 73 hospital diabetes services.

The findings of this survey revealed that full integration of clinical services among primary care and specialist diabetes teams is uncommon, although there are good examples of clinical integration in different formats. In a number of areas, primary care and specialist diabetes services continue to work in silos despite a universal recognition that integrated services are desirable and are likely to improve quality of care. Clinical leadership, resources and buy-in from those who commission services were deemed important factors to help improve the development of integrated care systems.

In hospitals with dedicated diabetes IT systems the information flow from these diabetes systems to the EPR was not universal, raising concerns that vital information about an individual's diabetes may not be available to other hospital clinical specialities at the time of delivery of care, posing a significant clinical risk. IT integration among primary and specialist diabetes teams in England was only available in certain areas and was mostly based around the use of SystmOne.

The survey also identified a diversity of opinions regarding the current arrangements of the Quality Outcome Framework (QOF), where GPs are incentivised to collect data for annual review of routine diabetes care. Many were of the opinion that annual review processes should be performed by clinical teams who are tasked to deliver diabetes care to the individual, while others felt that the status quo should continue with primary care GPs being responsible. A one-stop service for eye screening for diabetes and other annual measurements nearer to people's homes was identified as an improvement, but several logistic barriers were identified.

We recognise the limitations of any survey which expresses opinions of participants. However, we believe the present survey represents a significant proportion of diabetes units in the UK and provides insights into the current state of integrated services in diabetes. There are significant learnings for diabetes communities, and the information can be used to improve and galvanise delivery of integrated diabetes care in the UK.

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Key words: diabetes, integrated services, survey, annual review process, primary care, specialist diabetes services

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Introduction

Context of COVID

The Association of British Clinical Diabetologists (ABCD) has been active in producing several guidelines and reports during the COVID-19 pandemic. These reports were mostly designed to provide guidance for specialist diabetes teams to enable the delivery of diabetes care at the peak of the viral pandemic, where the emphasis was to support acute services for people admitted to hospital,[1,2] to support people with diabetes at high risk of poor outcomes[3] and to alter systems to focus care on those deemed at high risk.

One positive result of the pandemic was that it has afforded clinicians in the UK and worldwide the opportunity to innovate to help support patients in new ways. It is clear to healthcare professionals and the wider NHS that provision of clinical services will never be the same again, and opens the possibility of shaping a 'new normal' for clinical service provision. ABCD has also published its own guidelines on individual risk stratification and recovery of diabetes services.[2]

With the delivery of a widespread vaccination programme and proposed 'roadmap out of lockdown', ABCD was keen to produce a 'real-time' piece of work to help promote positive evolution of diabetes services post COVID, to ensure the learning and innovation during the pandemic becomes embedded and is not lost.[4,5] ABCD would regard a return to 'business as usual' arrangements to deliver diabetes services as a wasted opportunity for long-term change to reconfigure services.

This survey was conceived, designed and piloted by the ABCD Executive team and then sent to the organisation's membership. The membership comprises four nations (England, Scotland, Northern Ireland and Wales) and represents a diversity of practice including small district hospital teams, community services and larger academic institutions.

The aim was to benchmark diabetes services as they are now, drawing on the expertise and experience of those who have shaped them to date, and asking them what a better future would look like and how it could be achieved.

The survey had three sections focusing on evidence-based key elements of successful delivery of diabetes services:

(1) integration of clinical services among specialist and primary care teams (Section A)
(2) the current state of IT support available to the specialist diabetes teams to support clinical integration (Section B)
(3) how the current provision of an annual review process for the collection of vital data may be improved (Section C)

Definition of integration

The concept of an 'integrated diabetes service' is not new and means different things to different healthcare professionals, managers and health policy makers. Integrated diabetes care involves both integration of a healthcare system and coordination of services around a patient. "An approach that seeks to improve the quality of care for individual patients, service users and carers by ensuring that services are well co-ordinated around their needs".[6-8] In essence, diabetes integration is the whole health community joining in partnership to 'own' healthcare delivery and outcomes of patients with diabetes in each locality.[8,9]

However, for the context of this survey, we defined integrated diabetes care as "clinical care in a given health economy where the delivery of diabetes care is seamless among specialist and primary care and is well supported with IT systems, where planning, delivery and learning from these services is joined up with sharing of information, and where services are efficient and provide value for money". Delivering integrated care is challenging for numerous reasons, including the complexity of diabetes care and organisations working in silos focusing on their own priorities which are not necessarily aligned with each other.[10,11] Moreover, measuring the success of an integrated care system is extremely challenging; however, several key indicators to measure the success of clinical integration have been proposed.[11]

The aims of this survey were to gather information and intelligence at a national level for each of the above three elements and to produce a summary to inform future recommendations and catalyse discussions around the topic. A definition and explanation of integrated care was provided to help complete the survey questions related to this (Section A).

Survey methods

The first draft of the survey questions was written by one of the authors (DN) with contributions and further refinements by the ABCD executive team, and was shared with Diabetes UK and NHS England before it was disseminated via email to diabetologists who are members of ABCD. Due to the nature of this survey, we had invited open comments from participants to gather as much qualitative information as possible which is included in this report. The responses to the survey were handled by the ABCD secretariat and preliminary data analyses were produced.

Results

The survey was sent to 518 individuals comprising 431 (83.2%) consultant grade, 53 (10.2%) specialist registrars, 30 others and two retired healthcare professionals, one paediatric diabetologist and one dietician. Of the 83 replies received, 98% were from consultants. Although the original survey response was 17%, we believe that it represents 73 hospital-based diabetes services. The number of those who responded by region is shown in Table 1.

Quantitative results

The results are given as absolute numbers and percentages which are rounded up to the nearest number. Where there was more than one potential answer, percentages exceed 100% (see survey results Sections A, B and C).

Table 1 Responder number by region

Region	Number
East Midlands	2
East of England	5
Greater London	14
North East	1
North West	7
South Central	5
South East	7
South West	11
West Midlands	4
Yorkshire & Humber	6
Northern Ireland	1
Scotland	4
Wales	5

Survey results

Section A: Integrated Care (Figure 1a–c)

Do you think that your secondary care-based service is integrated with primary care?	
Yes	47 (57%)
No	34 (41%)
Don't know	2 (2%)
What is the nature of this clinical integration?	
Fully integrated service	20 (25%)
Partial integrated service	40 (50 %)
Little clinical integration	21 (25%)
Do you think that the wider diabetes services (primary and secondary care) work in a joined-up way?	
Yes	37 (45%)
No	36 (44%)
Don't know	9 (1%)
Do you have a regular review and evidence (including collection of evidence)?	
Yes	36 (44%)
No	45 (56%)
Of those who responded Yes to the above question, we asked if this has made a difference	
Yes	27 (79%)
Don't know	7 (21%)
Are you planning to have a clinically integrated service with primary care within the next 12 months?	
Yes	22 (28%)
No	29 (36%)
Already in place	29 (36%)
Has the COVID-19 pandemic (only those who responded Yes)	
Speeded up planning	4 (18%)
Slowed down planning	16 (72%)
Made no difference to planning	2 (10%)

Section B: Diabetes IT (Information Technology) Systems (Figure 2a–d)

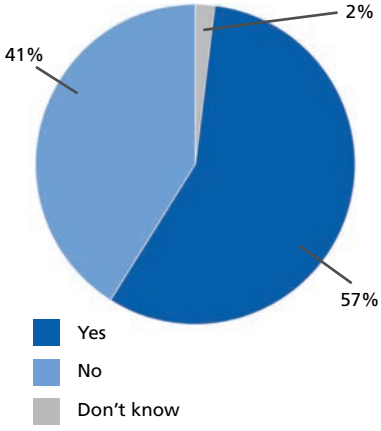
Do you have an EPR (electronic patient record) in your hospital?	
Yes	59 (72%)
No	23 (28%)
Do you have a dedicated diabetes IT system within your Trust?	
Yes	39 (46%)
No	43 (54%)
Was it commercially purchased or was it built in-house?	
Commercially purchased	28 (72%)
Built in-house	11 (28%)
Who can access this system?	
All clinical users (read only)	1 (3%)
All clinical users (read/write)	11 (28%)
Those who have been authorised to log in	20 (51%)
Only members of the diabetes MDT	7 (18%)
How does your diabetes IT system interact with EPR?	
Both systems work as standalone systems	25 (68%)
Diabetes system data visible from the EPR	4 (11%)
Diabetes data accessible from the EPR as a read-only view which is not displayed by default	5 (14%)
Bidirectional connected to share information with the EPR	3 (7%)
Do you have full, partial or no IT integration of diabetes IT systems with primary care IT systems?	
Read only	11 (29%)
Read/write	11 (29%)
One directional or bidirectional	6 (16%)
Is messaging and tasking supported?	5 (13%)
Does the community access apply to all community settings or only selected ones?	5 (13%)
In your view, how important is IT integration with primary care to help deliver seamless care?	
Crucial	29 (74%)
Important	10 (26%)
Does your locality have plans for IT integration with primary care in the near future (ie, <12 months)?	
Yes	23 (29%)
No	37 (47%)
Don't know	18 (24%)
If yes – has this been prompted by the COVID-19 pandemic?	
Yes	1 (4%)
No	21 (82%)
Don't know	1 (4%)
What are the main barriers to having an integrated IT system across specialist and primary care? (Figure 3)	
Lack of prioritisation by senior decision makers	49 (39%)
Funding issues	35 (28%)
Lack of suitable systems (ie, have tried and failed)	18 (15%)
Other	20 (16%)

Section C: Annual Diabetes Reviews

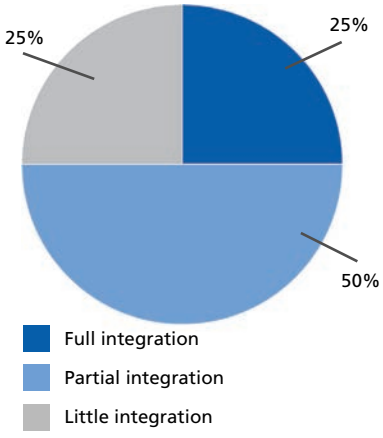
The existing arrangements are adequate and should continue without any change	
Yes	17 (21%)
No	60 (73%)
Don't know	5 (6%)
When looking at the process of annual review, what are the potential alternatives?	
Annual reviews should be performed by the clinical teams primarily responsible for regular follow-up for diabetes. For example, people with type 1 or type 2 diabetes under hospital follow-up should have their annual review with the hospital team	27 (34%)
Primary care should be responsible for review of all patients	21 (26%)
Annual review arrangements should change and should take place as a 'one-stop shop'	32 (40%)
Looking at the logistics of a 'one-stop shop' to collect annual review data, which would be your preferred option?	
At the time of retinal screening but delivered by a dedicated and trained team	45 (60%)
At a different time from the retinal screening but in the community setting	30 (40%)
If a 'one-stop shop' service could be delivered in the community set-up (nearer to home), where could these be located?	
GP surgeries	39 (34%)
Pharmacies	15 (13%)
Opticians	9 (8%)
Supermarkets (eg, ASDA)	5 (4%)
Any of the above	38 (33%)
Other location (please specify)	8 (7%)
Do your patients have direct access to any of their healthcare information (or healthcare records)?	
Yes	33 (41%)
No	37 (46%)
Don't know	10 (13%)

Figure 1. Results of the integrated diabetes services

a. Do you think that your secondary care based service is integrated with primary care?



b. What is the nature of this clinical integration?



c. Do you think that the wider diabetes services (primary and secondary care) work in a joined-up way?

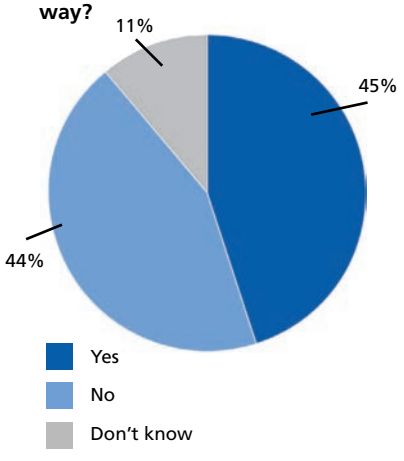
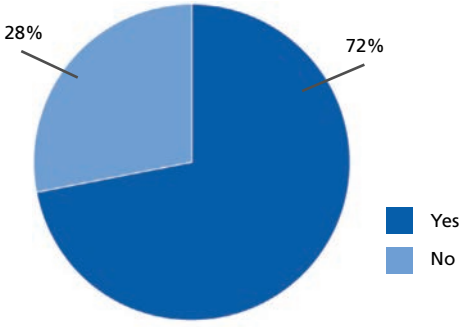
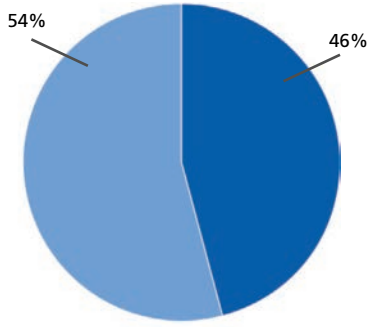


Figure 2. Results of the IT integration within and outside the organisation

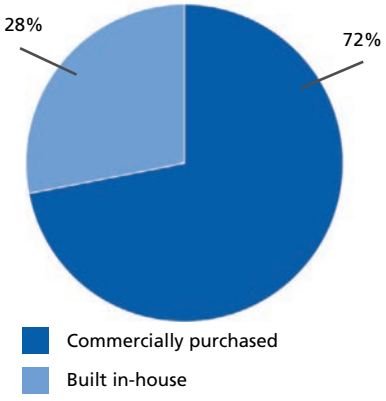
a. Diabetes IT (Information Technology) Systems: Do you have an EPR (Electronic Patient Record) in your hospital?



b. Do you have dedicated Diabetes IT system in your trust



c. Was it commercially purchased or was it build "in house"?



d. Does your locality have plans for IT integration with primary care in the near future? i.e. <12 months?

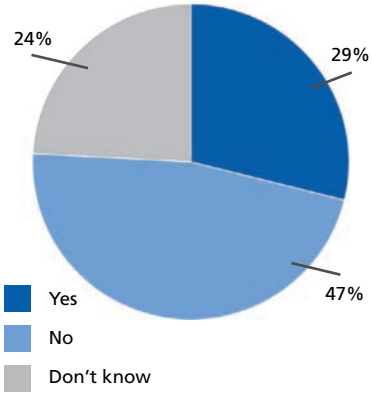
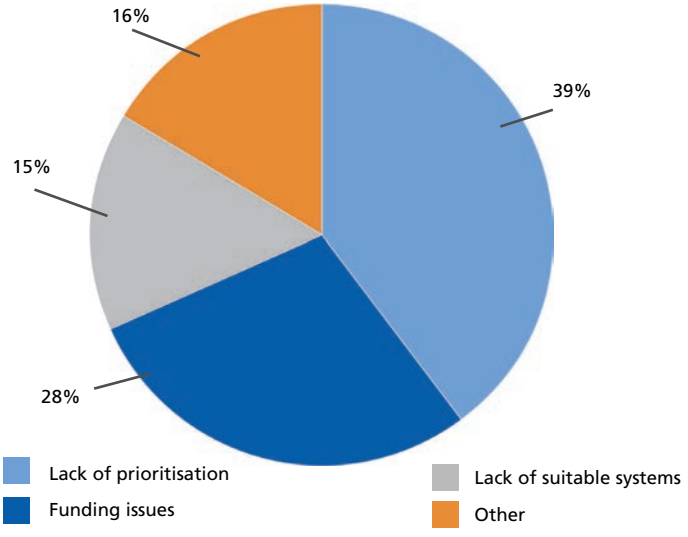


Figure 3. What are the main barriers to having an integrated IT system across specialist and primary care?



Box 1 Levels of integration seen in the survey

Different levels of integration among specialist and primary care services exist within the UK

1. Intermediate Diabetes Services Model

- There are examples of community diabetes teams (as intermediate services) which provide a link between primary care and specialist diabetes services.
- Intermediate services are predominantly made up of community-based Diabetes Specialist Nurses (DSNs), but some services include community-based diabetologists.
- In some services consultants are integrated with community diabetes teams but the diabetes nurse teams are not.
- Where intermediate services are run by DSNs, support is provided from the specialist teams based in hospital, with extremely close liaison between the workforce to some services where DSN working was almost in total isolation.
- In some services DSNs were based with the specialist teams but were responsible for supporting primary care for less complex cases including insulin start and injectable therapies.

2. Primary care support by hospital-based specialist services

- Diabetes services are planned together with clear commissioning of the level of services provided by the specialist teams (ie, Super Six Model, Derby Model, Wakefield integrated Services), where specialist diabetes teams (consultants and DSNs) provide regular joint sessions in primary care including virtual reviews.
- Primary and specialist care hold regular MDT discussions of complex cases including telephone or e-consultation.
- Specialist and primary care teams meet regularly outside the clinical context to learn together and ensure regular clinical updates regarding new therapies.

3. Integration in Scotland

- Clinical data are shared between primary and secondary teams. There is good dialogue between primary and secondary care clinicians for some patients, but much better dialogue and alignment of practice would be better. Also, centralised complication screening for all patients is our desire but needs funding at the Health Board level since primary and secondary care presently all do their own screening (or not, since COVID). Scotland has a very different model of care from England, hence many more patients are seen in secondary care clinics.

Qualitative results

The survey generated significant information on the views, ideas and experiences of diabetes specialists, which are summarised below.

Integrated care: 69 separate comments and 30 separate comments about the planning for integration between primary and specialist diabetes services, which are summarised in Box 1.

General comments: (37 comments). Participants were invited to give their general comments which were deemed to be important to them in relation to the survey. We were encouraged by the comments that "The survey has worked well" and provide a summary of these comments in Boxes 1 and 2.

Annual review process and potential barriers to one-stop service: (29 separate comments). These are summarised in Box 3.

The survey comments provided a useful insight into the various levels of integration among primary and specialist diabetes services. A thematic summary of these comments is provided in Boxes 1–3.

Box 2 General comments about integrated diabetes services

1. Integration (General comments)

- A shared vision and the key focus on the importance of the management of a high-risk population to prevent avoidable harm.
- Poor leadership of the diabetes service has unfortunately led to an inability to move forward.
- Fully integrated services would be useful from a patient perspective. It is essential to evaluate the barriers preventing this.
- Integration is definitely the direction of travel. It is often difficult to work across boundaries but diabetes clinicians should take the lead in this alongside 'GP champions'.
- Specialist and primary care working in silos is simply not possible in current times and such working would be of extremely poor quality and costly with associated poor outcomes for people with diabetes.
- Their providers are not willing to let any integration of such systems happen likely due to commercial pressures.
- A national approach to this issue is needed to standardise the IT system

2. IT Integration (General Comments)

- Let's embed a dedicated IT specialist within each diabetes team to start.
- Don't wait for IT to find a solution to better integration. The way forward is to move away from the old model of hospital-based diabetes care and work more closely with primary care in the community.
- Data sharing across primary and secondary care is needed. There are still some barriers in both primary and secondary care.
- Integrated IT support does take central place in establishing an integrated service. Independent trusts and GP services are using a variety of IT support services which do not talk to each other.
- We therefore need IT systems that link primary and secondary care.
- The Scottish Diabetes Group could give an overview of how this functions throughout the country.

Discussion

Opportunities to reshape clinical services are not common events and usually arise out of the necessity to do things differently, with the aim to improve quality and efficiency of care. While quality improvement initiatives are mostly driven by scientific, societal, economic and technological developments, opportunities sometimes arise at times during adversity, such as the COVID-19 pandemic.

To the best of our knowledge, this is the first survey of its kind in the UK, giving us a unique snapshot of the current state of integration of clinical services for diabetes. The survey represents a sizeable response from the specialist community and we feel that, in general, the data are representative of the UK. We acknowledge that there are several examples of attempts at collaborative working in various areas,[13–18] although the general uptake in the UK has been relatively slow. This survey provides some insights into the current state and the barriers to such developments.

Opinion of respondents on the degree of clinical service integration in their area

The main results show that more than 50% of respondents reported a lack of integration within primary care. While 46% reported some form of integration of services, only 20% of those

Box 3 Annual review process and barriers

1. Logistics

- GPs should be responsible for providing annual complication screening, whether at their surgery, at retinal screening or another clinical setting, to ensure maximum inclusion.
- However, annual review should be done by whoever is seeing the patient at the time and the data should then be accessible for all electronically.
- If secondary care were to take on the annual review for patients under their care, this would not be met.
- Patients love one-stop shops; if you are serious about reaching those who are of working age or are hard to engage with, you have to make the most of one contact as that is the only opportunity you might get in a year.
- The logistics of a one-stop shop may be a bit too much for patients, with concerns that if they miss the one stop they will miss all screening.
- If retinal screening is done more than every 12 months, there should be a one-stop shop without the need for retinal screening.
- The one-stop shop should include all key care processes alongside a pharmacist to aid compliance/concordance of medication (polypharmacy) plus a dietetic review.

2. Barriers and concerns

These fall into GP factors, IT issues and service user factors:

- Clinical continuity. We need to look at how this links in with the rest of diabetes care. So, having someone do an annual review should, ideally, fit in with the team making ongoing adjustments. This may create silos and stop things happening.
- Local logistics: GP surgeries perceive a risk of reduced income and GPs wanting to retain control of the annual review process.
- GPs and PNs may resist this element of care being removed from their workstreams. Separating the care processes from those with primary responsibility for care of the individual could lead to a breakdown in the pathway.
- Coordination and dismantling of current set-up; getting all stakeholders on board; administration/management support.
- Lack of IT system integration and infrastructure.
- Setting up IT systems: up-skilling staff to undertake these reviews.

3. Other issues and suggestions

- A one-stop service could be considered a backward step in an era where we should be supporting improved patient engagement through care and support planning.
- Perhaps a 'two-stop shop' should be considered – that is, leaving retinal screening alone but using the Diabetes Eye Screening Programme (DESP) registers to schedule separate urine/blood/foot screens on a different date.
- Post COVID, perhaps we should actually be looking to develop community screening services where all biomedical parameters can be collected/assessed close to home in an accessible location. "My Diabetes My Way" to allow time to digest the information and inform the formal consultation which should happen 2–3 weeks afterwards.

reported full integration which included most elements of the components outlined earlier.

The survey reported that 72% of respondents thought the pandemic had slowed down planning for integration and only 18% thought it had speeded things up. We are unclear of the reasons behind this and can only surmise that overriding priorities during COVID at the front line may have impeded these developments.

Specialist colleagues in diabetes almost universally acknowledge that clinical integration and joined-up working would improve clinical care and is considered optimal for the development of efficient services for people with diabetes in a given locality. However, many expressed dissatisfaction with the lack of wider system support such as lack of clinical leadership, lack of priority by senior management and inadequate funding.

While ABCD would like a deeper understanding of the reasons behind the abovementioned views, we believe that the key missing elements in each locality to improve services and deliver integrated diabetes care may be important.

The findings of this survey indicate that, whilst some CCGs/STPs have taken responsibility to coordinate diabetes services for a locality, this appears to be an exception rather than a universal phenomenon. There remains a feeling among clinicians that commissioners of diabetes services could contribute much more to support the development of integrated clinical services. Examples of good clinical practice delivering integrated care have been previously published.[13–19]

However, the survey data also showed that there are several examples of high levels of integration in some units where local clinical leaders have driven the integration, realising the importance of this to the delivery of high quality and efficient services. The results of this survey show that a very high proportion of specialists are cognisant of the importance of integration but feel constrained in their ability to catalyse successful change. Several barriers were identified which are outlined in the data provided.

This is potentially the first national survey of diabetes integration and there may be a case to repeat this in the future, with more clear benchmarking of the key areas to observe how integration evolves in the future and how it influences outcomes and components of diabetes care such as skill development in primary care. We have previously shown that joined-up working and supporting primary care can lead to upskilling of practices and clinical staff in the provision of levels of care.[19]

Our interpretation is that, while there has been progress since the report on integrated care by the Societies in 2013, a high proportion of primary and specialist diabetes services still continue to work in their silos with little evidence of integrated and joined-up working.

Opinion of respondents on integration of information technology (IT) systems

The second part of our survey focused on the level of IT integration among hospital systems and also between primary and specialist diabetes teams. The importance of integrated IT systems is recognised as it may allow seamless sharing of clinical information across systems and facilitate improved timely communication between caregivers. Importantly, it has the potential to increase the individual's involvement in their own healthcare. Such systems may avoid duplication and hence expenditure.

While 72% reported that their hospital had an EPR, a specialist diabetes database was only present in 46%. However, there was evidence of integration among hospital-based IT systems. IT integration between specialist and primary care systems was only reported in a minority of services (29% 'read & write' facility, 29%

'read only' facility). A substantial proportion reported lack of IT integration among GP/hospital/podiatrists/retinal screening services and reported no shared electronic data between various service providers. IT solutions need to be found to help share data across clinical service units in a consistent manner to improve the present situation observed in this survey.

While nearly half of the specialist teams who replied reported the use of an IT system to deliver specialist diabetes services, low levels of interaction between diabetes systems and the hospital EPR suggest that vital clinical information pertaining to diabetes is not widely visible to other clinicians, posing a substantial clinical risk.

Although ABCD accepts that IT integration is vital to achieve clinical integration as it helps facilitate sharing of clinical information, in isolation it is not enough to achieve the necessary changes. IT systems should be viewed as a vital enabler. Integration is more than the development, acquisition and installation of robust IT systems (in itself a challenge); it requires a joined-up approach with various stakeholders, including those who can enable these changes. This has been highlighted in a recently published government White Paper. The recent formation of primary care networks may facilitate leadership required from primary care. Indeed, the diabetes primary care community has recently launched a document highlighting a renewed vision of joined-up care for people with diabetes.[20]

We observed that, in localities where IT integration has happened, it was based around the use of SystmOne which allows sharing of clinical data. This allows a number of functions which have become so useful in the delivery of diabetes care including rapid communication, instant clinical messaging across teams and e-consultation between primary and specialist teams.

Perhaps the UK diabetes community should help endorse a finite number of excellent IT platforms whereby individual choice can be based on local needs and interconnectivity with existing systems. This may help reduce inertia precluding commitment to IT systems.

Opinion of respondents on annual diabetes clinical reviews

The final part of our survey focused on the annual review process for diabetes, a process that has been shown to improve outcomes and which has been key to the collection of vital datasets which form a key area for the care planning process. During the COVID-19 pandemic there have been huge challenges to the collection of routine data due to the need for shielding of those at highest risk. We were not surprised that up to 60% of colleagues felt that the arrangements of the annual review process were unsatisfactory and that changes should be made to ensure the process was more efficient, better coordinated and provisions made for feedback to the patients.

Whilst many colleagues were in support of a one-stop service for the annual review process at the retinal screening, it was acknowledged that this raised logistical challenges and also barriers with regard to workforce and flows of finance. The current lack of joined-up IT also proves to be a hurdle.

There was some support for the view that annual reviews should be organised by teams who are primarily responsible for delivery of diabetes clinical care. In other words, patients who attend specialist diabetes teams routinely should receive annual review processes from these teams. However, significant numbers reported that current systems for annual review as part of the QOF set-up should continue.[20]

To deliver a one-stop service, the type of location was not deemed important as long as it was near to a patient's home and accessible with some flexibility. Coordination and sharing of the data collected during annual review was deemed to be important. Therefore, the location of one-stop services could be determined by service users and community healthcare teams.

Integrating care has meant that more people are seeing the benefits of joined-up care between GPs, care at home and in care homes, community health services, acute trusts and mental health services. For staff, it has enabled people to work outside individual organisational silos, deliver more user-centred and personalised approaches to care, and identify and help tackle barriers preventing optimal care for people with diabetes. It enables greater ambition on tackling health inequalities and the wider determinants of health.

The results of this survey point out clearly that we are some way off the universal existence of an acceptable standard of integrated diabetes services in the UK. Solutions need to be developed and put in place to address this urgently; fortunately, none of the barriers are insurmountable.

ABCD believes that the experience of the pandemic has made the case for integrated care even more strongly and believes the insights from this survey should serve as a stimulus for wider discussions among stakeholders. The results of this survey should form the basis for making firm recommendations to commissioners for improving the state of clinical and IT integration in the UK, similar to that in Scotland.

We believe urgent prioritisation and resources are needed from NHS England to develop truly integrated diabetes services. We hope the planned legislation based on the government White Paper will facilitate delivery of this and call upon our membership to help drive this process.

Government plans for integrated services have been outlined recently in a White Paper for integrated services, highlighting the two principal forms of integration which will need to be underpinned by the legislation:[21]

(a) Integration within the NHS to remove some of the cumbersome and unnecessary boundaries which inhibit collaboration and to make working together a high-level organising principle.
(b) Greater collaboration between the NHS and local government, as well as wider delivery partners, to deliver improved outcomes to health and wellbeing for local people.

In theory, this should enable different parts of the health and care system to work together effectively in a way that will improve outcomes and address inequalities. Clearly, the details of this crucial legislation have the mechanism to facilitate true integration.

The NHS has experienced several cycles of high-level organisational changes and some of these have led to greater bureaucracy and added barriers to joined-up and collaborative working, which

remains the essence of integrated care. Keeping this in mind, the White Paper plans to give additional power to the Secretary of State for Health and Social Care to intervene in how NHS England operates.

The White Paper proposes substantial legislative changes which aim to:

- Make permanent the innovations that COVID-19 has accelerated and encourage the system to improvise new and better ways of working.
- Integrate healthcare in England by enshrining integrated care systems in law.
- Reduce bureaucracy and create flexibility.
- Improve NHS England accountability and enhance public confidence.

We welcome the recent signals from government with regard to their determination to ensure that public health, social care and healthcare work more closely together in the future than ever before. We recommend simplicity, clarity and commitment for legislative changes to help delivery of these objectives to be achieved – namely, to deliver true integrated care. We hope the planned legislation based on the government White Paper will ultimately facilitate delivery of this promise and we call upon our membership to step into the driving seat.

Recommendations

Based on the results of this important survey, ABCD recommends that, in addition to the enablers for integrated care outlined, clinical services in a given locality should aspire to at minimum:

1. A joined-up approach to planning and delivery of diabetes services among commissioners, specialist diabetes teams and primary care.
2. The aim should be to improve quality of diabetes services to a higher level and to improve clinical outcome of individuals with diabetes.
3. A designated lead who will be responsible for overseeing that integrated services are developed and allowed to expand in a given locality (ie, there is governance and accountability for this).
4. Each diabetes specialist team should be supported by a dedicated IT system/s and diabetes database in their units.
5. Specialist diabetes IT systems must interact and be integrated with local EPR and primary care systems, allowing easy sharing of data for ease of delivery of clinical care.
6. There should be a high-level NHS mandate for the above recommendation during future re-organisation of chronic disease management in the UK, as suggested in the recent White Paper.

Limitations of the survey

1. No service user involvement during survey design. Hopefully, discussion fuelled by this paper will allow a more structured dialogue with service users in future surveys. Any future recommendations for redesign of services must involve patients and careers.
2. The survey did not ask if the IT system allowed direct patient access to their data (in either 'read-only' or 'read and write' format) or issues related to data protection.

Key messages

- This survey shows, that the level of integration among primary and specialist diabetes teams is far from ideal and leaves much room for improvement
- Many Primary and Specialist Diabetes services continue to work in their own silos and in isolation, which is not delivering good quality diabetes care our service users deserve
- Many Specialist diabetes services do not have a dedicated diabetes specific IT system, which is essential to the delivery of diabetes care in this era
- Hospital based EPR (Electronic Patient Records) systems and the diabetes system do not communicate with each other, therefore limiting the flow of clinical information from one to the other system, creating a degree of clinical risk
- The findings of this survey, should provide a vital platform for discussions among wider diabetes teams and commissioners as to how integrated care can be developed in local health economies.

3. The survey was limited to the ABCD membership, which may skew the responses.
4. The information provided is based on the view of individual clinicians rather than data collected using a more structured and robust method, and is open to over- or under-reporting of the true picture.
5. The overall survey response was low, which may limit the conclusions of the survey.
6. There were some leading questions which might have biased the reply from the respondent.
7. As the participation was voluntary, we cannot exclude a self-selection bias.
8. Under-representation of some areas (eg, East Midlands, North East, Northern Ireland).

Strengths of the survey

1. The survey questions were designed after significant discussion within the executive committee, a group of experienced diabetologists. We asked contemporary and targeted questions; answers to these are likely to help future diabetes care.
2. This is the first comprehensive attempt to acquire a view from all diabetes hospital services in the country. A representation of 73 different diabetes units with different levels of integration provides a picture which is likely to be reliable.
3. The qualitative aspect of this survey enriches the practical value and applicability of the survey.
4. Those constructing future surveys in this area can learn from omissions and the limitations and strengths of the present survey.

5. The survey was collected during the pandemic and revealed serious gaps in our existing services, especially integration with primary care and IT solutions. The survey captured the current and new beliefs informed by the challenges of diabetes care during the pandemic.
6. The survey represents views of specialists across four nations, which will allow us to learn from the strengths/weaknesses of these services.

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C-peptide is not a simple laboratory test

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We welcome correspondence and research letters to the journal.

Research letters should be no more than 800 words with a maximum of 10 references, one table and/or one figure. These will usually be short reports of interim work or final reports of research that do not warrant a full research paper publication.

Letters to the editor relating to any articles published in the Journal. Letters should ideally be submitted within two months following publication of the article on which the authors wish to comment, and should be no more than 600 words with up to five references

Key words: C-peptide, diabetes, therapeutic

The polypeptide molecule known as C-peptide produced by beta cells and a precursor of insulin[1,2] is not a simple laboratory test to reclassify diabetes, as described in the article by Morrison *et al*.[3] Significant clinical studies are being carried out which show that it is an active metabolite that fulfills functions with biological potential for the treatment of complications associated with diabetes, avoiding endothelial dysfunction, increasing vasodilation at the expense of nitric oxide, with a substantial decrease in the production of inflammatory chemokines and reduction in proteinuria at the renal level, as well as other in vitro evidence.[4]

C-peptide should be taken into account not only as a laboratory test but also as a future therapeutic option for patients with or without microvascular or macrovascular complications. This study paves the way for a more rigorous and methodological quality follow-up investigation.[5] This case report outlines both a diagnostic and a therapeutic option at the same time.

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Dear Dr Villarreal,

We agree that C-peptide may have some biological activity of its own. The case report mentions C-peptide being used to aid diagnosis of type of diabetes and not as a treatment.

Dr Marie-France Kong
on behalf of the authors

The argument against everyone with hyperosmolar hyperglycaemic syndrome being given prophylactic treatment dose anticoagulation

KETAN DHATARIYA,[1,2] PHILIP WESTON[3]

In this edition of the journal, Sim *et al* have written a case report of a 63-year-old man with type 2 diabetes admitted with hyperosmolar hyperglycaemic syndrome (HHS) who developed extensive venous thromboembolic disease (VTE). The authors carried out a literature review and suggest that "If a person is deemed to be at high risk of thrombosis, full dose anticoagulation should be given". This suggestion is correct and we would discourage the use of full dose anticoagulation as the standard of care for everyone presenting with HHS. This subject has been debated in these pages before.[1]

Recent data have confirmed that people with diabetes are at increased risk of developing VTE.[2] It has also been recognised that, in HHS, arterial and venous thromboembolic disease is more common than in those with diabetes,[3,4] but also more common than in those who present with diabetic ketoacidosis (DKA).[3,5,6] It may well be due to the hypernatraemia or raised vasopressin concentrations, which are recognised as thrombogenic.[7] Hyperglycaemia per se is also associated with a pro-inflammatory effect on the endothelium, which improves with insulin therapy.[8] However, these data are not consistent, with some authors suggesting that the risk of VTE in those with diabetes and hyperosmolarity is similar – or only marginally above – those with other conditions such as sepsis, acute renal failure or acute connective tissue disease.[9,10]

The original HHS guideline from the Joint British Diabetes Societies for Inpatient Care (JBDS) said the following:

> *"All patients should receive prophylactic low molecular weight heparin for the full duration of admission unless contraindicated … Full anticoagulation should only be considered in patients with suspected thrombosis or acute coronary syndrome".*[11]

Of course, one may argue that the case described was at high risk, having been on a flight from the USA a short time before presentation and significant myocardial injury the day after presenting in HHS. Furthermore, the case presented was not of HHS but of a mixed picture – the mild acidosis (pH 7.2, ketones 3.3 mmol/L) suggesting a mixed picture of HHS and DKA – a situation associated with higher 30-day mortality than HHS or DKA alone.[12]

These and other data highlighted by Sim *et al* show that there is not currently enough evidence to recommend treatment dose prophylaxis in everyone presenting with HHS. The small number of case reports and case series are heterogeneous in nature and the individuals described had a variety of medical and surgical conditions that meant that anticoagulation was not indicated or appropriate. We maintain the view as laid down in the JBDS HHS guidelines that an individual risk assessment for VTE should be performed for all patients presenting with HHS. We cannot support therapeutic dose anticoagulation in all patients presenting with HHS based on the available limited clinical trial data.

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COVID-19 (Coronavirus) Information for Healthcare Professionals

The coronavirus outbreak is a rapidly developing situation. Please visit the NHS website for the most up-to-date information for people in the UK.

There is rapidly evolving data concerning COVID-19 and we will try and keep our members appraised of the lasted evidence based, specialist society supported, information. One of the most useful things that we can do is to ensure that patients are very well educated as to "sick day rules", and which medications to "pause" at times of inter-current illness (which is covered in out SGLT2 document).

Visit https://abcd.care/coronavirus for links to the detail below and more

The National Diabetes Inpatient COVID Response Team

- View letter from The National Diabetes Inpatient COVID Response Team highlighting the need to maintain patient safety whilst accelerating patient flow through the system including preventing avoidable admissions and readmissions.
- Maintaining acute diabetes services in response to COVID-19
- peciality template for acute diabetes services
- SBar for COVID-19 and Diabetes
- COncise adVice on Inpatient Diabetes (COVID:Diabetes) - Front Door Guidance (*Version 3.1, Updated November 2020)*
- COncise adVice on Inpatient Diabetes - Guidelines for managing DKA using subcutaneous insulin
- COncise adVice on Inpatient Diabetes - Guidance for managing inpatient hyperglycaemia
- COncise adVice on Inpatient Diabetes - Dexamethasone therapy in covid-19 patients: implications and guidance for the management of blood glucose in people with and without diabetes. *(Updated November 2020)*
- COncise adVice on Inpatient Diabetes - Safe and supported discharge to reduce readmissions and improve patient flow
- COncise adVice on Inpatient Diabetes - Hyperglycaemia/diabetes Guidance For People With COVID-19 Infections Managed In A Virtual Ward
- COncise adVice on Inpatient Diabetes - Post COVID-19 diebetes discharge pathway - risk stratification and follow up guidance for people being discharged from secondary care after COVID-19 infection

The benefits of flash glucose monitoring in the UK

MASA JOSIPOVIC,[1] MARK EVANS[2]

A century after the life-transforming discovery and purification of insulin, many people living with type 1 diabetes (T1D) are not reaching glycaemic goals.[1,2] Therapeutic approaches to help people with T1D achieve glucose targets and (equally importantly) reduce the burden of living with diabetes include structured education, new insulins and technology for delivering insulin, measuring glucose, decision support and closed loop technology to automate insulin delivery. The Freestyle Libre was first launched in Europe in 2014 with uptake in UK use having increased since it was made available on NHS prescription in 2017. There have been changes from the original device with the introduction of an algorithm to improve accuracy and the launch of the second generation Libre2 device allowing the optional use of alarms. Current UK T1D penetrance is around 50% in England (with a marked increase since April 2019 facilitated by NHS England as part of the NHS Long Term Plan), with higher rates in Scotland, Wales and Northern Ireland. A recent Health Technology Wales guidance has recommended broader use for all people with insulin-treated diabetes, not just T1D.[3]

Worldwide use is also increasing markedly. This global growth in the use of the Libre has occurred despite the lack of a supporting body of evidence from randomised controlled trials (RCTs) showing lowering of HbA_{1c}, the traditional outcome metric for diabetes trials.[4] For readers' interest, an RCT (FLASH-UK) has been examining this in the UK, with participants with T1D randomised to Libre2 versus control finger prick testing.[5] At the time of writing, FLASH-UK had just completed follow-up and the results are eagerly anticipated. Despite the current absence of RCT data, there are, however, many real-world observations showing improved clinical outcomes with the Libre.[6] In the UK, data show reductions in HbA_{1c} and a striking reduction in severe hypoglycaemia and diabetic ketoacidosis with use of the Libre in Scotland.[7] The Association of British Clinical Diabetologists (ABCD) has been running nationwide audits of medications introduced into real-world use in the UK since 2004. An ABCD audit of Libre outcomes has been running since 2017, reporting reduced HbA_{1c}, improved hypoglycaemia awareness and reductions in hospital attendances for dysglycaemia.[8]

This edition of the journal contains an examination of data from the ABCD Libre audit, asking whether prior structured education affects the outcomes with flash glucose monitoring. In particular, clinical outcomes were compared between those who had undergone Dose Adjustment for Normal Eating (DAFNE) structured education, other structured education or neither. Structured education to support self-management of T1D includes a variety of programmes across the UK and elsewhere with variable approaches/quality assurance, evidence and governance/structure.[9] DAFNE is currently delivered in 99 centres and based on principles of therapeutic education with a written curriculum, multidisciplinary team working with defined accreditation, quality assurance and RCT and real-world evidence for efficacy.[10,11] This includes (but is not limited to) equipping participants with the ability to appraise and utilise glucose information judiciously.

A priori, it would have been possible to hypothesise that those undergoing structured education/DAFNE might be better placed to interpret and benefit from more comprehensive glucose data provided by the Libre. An alternative hypothesis would be that those who had undergone structured education had already part-benefited from the ability to interpret glucose information and would have less incremental gain from the Libre. Of note, there is a large repository of free online training (including the Diabetes Technology Network-UK resources cited in the paper) targeted specifically at how to use and interpret Libre data which would have been available to all regardless of previous structured education and, indeed, many services would have encouraged or even mandated evidence that people had undergone this more targeted training.

The study included 14,880 patients, stratified into three groups based on prior structured education status: 4,215 DAFNE graduates, 3,964 other structured education graduates and 6,701 patients who had not received structured education. The main outcomes were the impact of previous education on glycaemic control assessed by HbA_{1c} levels, and hypoglycaemia awareness measured by the standardised GOLD score. At follow-up, all three groups showed improvements from Libre initiation, with reduced HbA_{1c} (by 8.10 mmol/mol, 6.61 mmol/mol and 6.22 mmol/mol, respectively) and GOLD score (by 0.33, 0.30 and 0.34, respectively). There was no statistical difference between groups in terms of the magnitude of these changes ($p=0.83$ for HbA_{1c}, $p=0.42$ for GOLD). Interestingly, on linear regression modelling, the authors show that a higher baseline

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HbA_{1c}, frequency of flash monitoring and other structured education (but not DAFNE) were predictors of HbA_{1c} reduction.

What does this mean for clinicians? Firstly, the authors and indeed all who have contributed to the ongoing ABCD audit are to be congratulated. This is an impressive repository of data. As with any real-world data, there are advantages and drawbacks compared with RCT data. Perhaps unsurprisingly, there were significant and clinically meaningful differences between groups. Those who had undergone DAFNE training were older with a longer duration of diabetes and insulin pump use. Readers should be cautious in assigning too much weight to group comparisons.

Taken together, we suggest that there are two key 'take-home' messages from this paper. First, it does not show that flash glucose monitoring means that structured education is now a vestigial offering. DAFNE in particular continues to empower people with T1D to self-manage their diabetes and, based on the supporting evidence, was the only structured education programme specifically cited in NICE NG17 T1D guidelines.[12] Second, although of critical importance, access to structured education should not be regarded as an impediment to receiving and benefiting from blood glucose monitoring technology. All groups benefited from FLASH with reductions in HbA_{1c} and improvements in hypoglycaemia awareness scores. Not all are able to access and/or willing to commit time to undergoing structured education despite changes to make programmes like DAFNE more accessible including remote access. This paper clearly shows that this group still benefit from access to the Libre. We suggest that structured education and technology are complementary tools in the growing clinical armamentarium to support people living with T1D. The case for widespread use of flash glucose monitoring for all with insulin-treated diabetes across the whole of the UK continues to grow!

Conflict of interest MLE is a member of the national DAFNE executive and a trialist in the FLASH-UK study. He has received honoraria for advisory boards and speakers' fees from Abbott Diabetes Care (manufacturer of Freestyle Libre). MJ reports no conflicts of interest.

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ABCD debate at the annual ABCD virtual meeting 18 December 2020

DINESH NAGI,[1] UMESH DASHORA[2]

Motion: This house believes that cardiologists should initiate SGLT-2 inhibitors in patients admitted under cardiology care

Speakers ***For the motion:*** Dr Stephen Wheatcroft, Consultant Cardiologist and Professor of Cardiometabolic Medicine, University of Leeds, West Yorkshire

Against the motion: Professor John Wilding. Department of Cardiovascular and Metabolic Medicine, Institute of Life Course and Medical Sciences, Clinical Sciences Centre, Aintree University Hospital, Liverpool

Introduction

ABCD debates have been a regular feature of the ABCD annual meetings and delegate feedback have previously shown the debate to be a very popular part of the programme. It has always fulfilled the aims and objectives to provide high quality CME to delegates through a light-hearted debate on a suitable topic which is an important component of day-to-day clinical practice.

Format

The format is generally to allow both speakers to present their argument (both for and against) based on evidence, current guidance and pragmatism, to make their case for the audience. The debate generally starts with an introduction from the Chairperson to describe the aims and objectives of the debate and outline the process, which starts with delegates voting for and against the motion, at the outset. This is followed by presentation from an expert, speaking for the motion. Apart from fact checking about the presentation, questions are not allowed at this stage. This is then followed by the speaker against the motion. Audience participation is encouraged during the Q&A session including any astute observations or comments from the floor. Both speakers are then given time to summarise their evidence and recommendation to the participants, followed by another vote to see if the motion is carried or defeated.

Context of the current debate

There has been a plethora of recent trials looking at the cardiovascular outcome trial data for the class of drugs known as sodium-glucose co-transporter 2 (SGLT2) inhibitors.[1–8] Although these started as drugs to manage hyperglycaemia in type 2 diabetes, they have shown improvements in cardiovascular and renal outcomes. Dapagliflozin, one of the SGLT2 inhibitors, is now licensed for heart failure and renal failure with or without diabetes.[9] Given that one of the major aims of treatment of type 2 diabetes is cardiovascular protection, this class of drugs has become a very potent tool in the management of type 2 diabetes. The recent evidence of their benefit in reducing mortality in patients with heart failure means that cardiologists are able to prescribe these drugs. These drugs are associated with a small but serious risk of diabetic ketoacidosis (DKA).[10] The Association of British Clinical Diabetologists (ABCD) has made considerable efforts to ensure these drugs are used by non-diabetologists safely and effectively.[11,12]

Table 1 Salient and evidenced-based reminders about the relationship of diabetes with cardiovascular disease (Professor S Wheatfield)

1	Type 2 diabetes in essence is a cardiovascular disease. Cardiovascular events are a leading cause of mortality in people with diabetes
2	Type 2 diabetes is associated with poorer outcome after an acute myocardial infarction than in people without diabetes and this has not significantly improved over recent years
3	Diabetes is associated with poor outcomes after admission to hospital with acute heart failure
4	People with type 2 diabetes are most likely to see a cardiologist. • The EuroAspire study showed that 27.2% of subjects with coronary artery disease had diabetes • 34% of people admitted to hospital with heart failure in England and Wales had type 2 diabetes
5	We therefore need new therapies and tools to change this particular narrative

Table 2 Benefits of SGLT2 inhibitors in people with type 2 diabetes (summarised by both speakers)

1	This novel class of drugs works on the kidneys and has multiple mechanisms of action, with consequent metabolic and haemodynamic effects on the heart, kidneys, adipose tissue and liver
2	Multiple trials have shown that SGLT2 inhibitors reduce major adverse cardiovascular events and heart failure in people with type 2 diabetes with established cardiovascular disease
3	Reduction in heart failure hospitalisation is also seen in people with diabetes and risk factors for cardiovascular disease and in people with heart failure whether or not they have diabetes
4	The reduction in risk of cardiovascular disease is comparable to early landmark trials with simvastatin (4S Study) and ramipril (HOPE trial)
5	The risk of serious side effects with these agents has been low in published trials
6	The incidence of diabetic ketoacidosis and hypotension is low and it may therefore be safe to start these drugs in the acute setting in those patients who are haemodynamically stable, but there are currently few data to support this

Table 3 How can we maximise the benefit of SGLT2 inhibitors in patients with type 2 diabetes?

1	The hospital setting provides a window of opportunity to start this class of drugs under specialist care
2	The attitudes of UK cardiologists to prescribing these drugs is changing, with more of them aware of the benefits of SGLT2 inhibitors and therefore willing to start these drugs on cardiology wards
3	Cardiologists need to become more aware of the recent published evidence about the benefit of SGLT2 inhibitors in people with and without diabetes
4	Cardiologists should be informed and educated about the safe and appropriate use of this class of drugs
5	The American College of Cardiology in their recent guidance has suggested that these agents should be considered for use in: • Patients with type 2 diabetes and ASCVD • At the time of diagnosis of ASCVD in a patient with type 2 diabetes on a drug regimen that does not currently include a GLP1-RA or SGLT2 inhibitor with proven cardiovascular benefit • At the time of diagnosis of type 2 diabetes in patients with clinical ASCVD • At hospital discharge after admission for an ASCVD- or diabetes-related clinical event

ASCVD, atherosclerotic cardiovascular disease; GLP1-RA, glucagon-like peptide-1 receptor agonist.

That context provided the organisers of the ABCD meeting with an excellent opportunity to set up this debate.

Speaking for the motion

Introducing and speaking for the motion, Professor Wheatcroft, who is an academic and interventional cardiologist at one of the biggest centres in the UK in Leeds, made his case by reminding us of the relationship between type 2 diabetes and cardiovascular disease and by reviewing the benefits of SGLT2 inhibitors (Tables 1 and 2). His reasons that cardiologists should prescribe these drugs in those patients admitted under cardiology are summarised in the Table 3. He reminded the delegates that cardiologists were best placed to prescribe this class of medication, and an inpatient cardiology setting was a perfect opportunity to address this. He asserted that, despite SLGT2 inhibitors being considered primarily as 'diabetes drugs', cardiologists had shown an ample interest and have learnt how to use them in patients with acute coronary syndrome and cardiac failure in cardiology wards. He was concerned that, if the initiation of SGLT2 inhibitors was left to GPs, it will increase primary care workload and, in a large proportion of patients, there will be an unnecessary delay in starting and a reduction in the clinical effectiveness which is seen within the first 6 months of starting this class of drugs. He shared the results of a recent national audit providing evidence to support his argument. Indeed, he was very optimistic that diabetologists and cardiologists could work together to ensure that these drugs are used wisely and in a timely manner for suitable patients.

He summarised his presentation with conclusions that cardiologists now have the right tools to improve outcomes with cardiovascular disease and type 2 diabetes and they are ideally placed for opportunistic initiation of these agents in the highest risk patients. He urged delegates to use guidance developed in collaboration with diabetes colleagues. He stressed that cardiologists, diabetologists, pharmacists and primary care need to work in collaboration for the benefit of patients with type 2 diabetes.

He acknowledged that education and training of patients was an important and significant concern but felt that the cardiology units had the set-up to achieve that, especially when it came to follow-up, particularly during cardiac rehabilitation which has become an established clinical practice in cardiology. In general, he made his point persuasively based on the available evidence and his own clinical practice of having joint clinics involving Cardiology and Diabetes services in Leeds. He acknowledged that this is not yet common practice elsewhere in the UK.

Speaking against the motion

Professor Wilding started his presentation by reviewing the data on the SGLT2 class of drugs in some detail before getting to the crux of the debate. His assertion was that, although he did not disagree with the previous speaker in terms of evidence and benefits of the SGLT2 inhibitors, none of the participants included in any of the trials were inpatients with acute coronary syndrome or heart failure. Evidence in this acute setting was therefore woefully lacking (Table 4). He was of the view that current ongoing trials on the safety of prescribing SGLT2 inhibitors in acute cardiac conditions such as after myocardial infarction or during hospitalisation for heart failure may provide the answer to this question (Table 5). He felt that during management of patients with acute coronary syndrome or cardiac failure, a high proportion of patients can be haemodynamically unstable and may have impaired cardiorenal function. In addition, several of their medications may change with either modification of previous medication or addition of several new drugs. Therefore, adding another agent which can potentially cause diuresis, hypotension and increase the risk of DKA will not be an evidence-based practice and in theory could cause more harm than good. Such a practice could potentially jeopardise the potential benefits from the increased uptake of these medications in the outpatient setting. He stressed that we should await further evidence before making hasty conclusions and changing our clinical practice – a view completely opposite to the speaker for the motion who suggested that we should not waste time and wait for the outcome of trials outlined in Table 5.

The debate

The Q&A session was lively and several clinical issues were raised by audience participation in relation to the use of these agents.

After the Q&A session, both speakers

Table 4 Some limitations of the published trials on SGLT2 inhibitors

1	Published trials to date did not include people with recent myocardial infarction or re-vascularisation
2	These trials also did not include people with acute/unstable heart failure
3	The risk of starting SGLT2 inhibitors in hospitalised patients is unclear and may be greater than seen in published trials
4	The current evidence only supports initiation of these drugs in stable patients in the outpatient setting

Table 5 Ongoing trials related to SGLT2 inhibitors which may have an impact on prescribing in future

1	EMPACT- MI
2	EMPULSE
3	DAPA-MI: Dapagliflozin effects on CV events in patients with acute heart attack
4	DICTATE-AHF: Efficacy and safety of Dapagliflozin in Acute Heart Failure
5	Ertugliflozin in Acute Heart Failure
6	EMPAG-HF: Effect of Empagliflozin on diuresis and renal function in patients with acute decompensated heart failure

Table 6 Vote count before and after the live debate

	Yes (for the motion)	No (against the motion)	Abstain
Before	51%	35%	14%
After	35%	65%	5%

Based on the above vote, the motion was therefore not supported. However, the Chairman acknowledged that this very lively and important debate provided an excellent CME for the delegates, and he closed the session expressing his sincere thanks to both the eminent speakers.

were graceful in acknowledging several excellent and practical issues raised both for and against the use of this class of drug in the acute setting of cardiology wards. The voting at the outset and after the debate is shown in Table 6. The counting of votes showed that several delegates had changed their minds and were now against the motion and therefore the motion was not carried.

The Chairperson remarked that he felt there was no winner or loser in this debate and that both speakers had increased our awareness and raised several issues which will impact on the safe prescribing of these drugs in the future. They both agreed that the advent of these drugs gives us an excellent opportunity to lower the burden of cardiovascular disease in type 2 diabetes in the community and that this was an excellent opportunity for diabetes, cardiology and colleagues in primary care to work together so that no one misses out on the huge benefits shown in several landmark clinical trials.

Acknowledgements

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Overview of the 81st Scientific Sessions of the American Diabetes Association

Dr Caroline Day logs in to the meeting whisked from Washington DC to the worldwide web 25th-29nd June, 2021

Introduction

As COVID-19 continued to hold the world to ransom, the American Diabetes Association (ADA) again transitioned the annual scientific sessions from the real world to the virtual world. Despite the assumed eco-friendliness and 'stay-at-home' convenience of this year's meeting, participant numbers were again lower (~11,500) than when the last physical meeting was held (>15,000) – perhaps the diabetes world prefers active transfer of information.

The final programme for the 2021 Scientific Sessions has a useful 'Day-at-a-glance schedule' with the detailed timetable to permit presentation/poster selection commencing on page 27. The complete 220-page document can be downloaded from https://res.cloudinary.com/freemanoeptest/image/upload/v1624327340/OEPro%20-%202021%20Events/ada2021/2021_Final_Program_tisytf.pdf and the Scientific Sessions Abstracts (including later breakers) are published online as a supplement to the journal *Diabetes* (Volume 70, Suppl 1; https://diabetes.diabetesjournals.org/content/scientific-sessions-abstracts).

The 2021 Scientific Sessions abstracts, posters and webcasts can be accessed at https://professional.diabetes.org/content-page/previous-scientific-sessions-abstracts-posters-and-webcasts and the ADA 2021 highlights (www.adahighlights.com) offer free daily highlights plus conference summaries, expert overviews and commentaries plus interviews with key speakers and the ADA leadership as well as poster podcasts and downloadable slides.

Highlights

As always, the named lectures are worth perusing (Table 1). Unsurprisingly, COVID featured strongly at this meeting, with several presentations drawing attention to the interplay between the virus and diabetes and strategies to reduce risk and optimise positive outcomes in those infected (symposia: 25 June, 8am and 2pm; 27 June, 2.15pm and 4.30pm; 28 June, 4.30pm; plus 103 COVID-related abstracts).

The DARE-19 study reported on 27 June (2pm) and included a live question-answer session. In this international study in patients with cardiometabolic risk hospitalised due to COVID-19, patients were assigned to dapagliflozin 10 mg (n=625) or placebo (n=625). Although dapagliflozin appeared to improve outcomes (eg, recovery 87.5% vs 85.1%; death 6.6% vs 8.6%; serious adverse events 10.6% vs 13.3% in dapagliflozin-treated versus placebo, respectively), it did not result in a statistically significant reduction in organ dysfunction or death, or enhanced clinical recovery.[1]

The GRADE study, a pragmatic unmasked clinical trial to compare glucose-lowering efficacy and patient-centred outcomes of drugs (glimepiride, sitagliptin, liraglutide, insulin glargine) used as add-on to metformin therapy in over 5,000 people with type 2 diabetes commenced in May 2013 and completed in April 2021.[2] This trial (symposium 28 June, 4.30pm) showed that, over an average of 5 years, liraglutide and glargine were most effective at maintaining HbA_{1c} <7% whilst sitagliptin was the least effective; however, unlike glimepiride, liraglutide and sitagliptin

Table 1 Awards 2021

National Scientific & Health Care Achievement Awards and Lectures	Recipient
Banting Medal for Scientific Achievement Award Lecture: *In the beginning was the gut – and then something happened – a story about the incretins.* (Sunday, 27 June, 10.15am)	Jens J Holst, Denmark
Kelly West Award for Outstanding Achievement in Epidemiology Lecture: *Risk factors and type 2 diabetes.* (Sunday, 27 June, 2.15pm)	Nicholas J Wareham, UK
Outstanding Scientific Achievement Award Lecture: *Unique cardiometabolic mechanisms and consequences of youth-onset type 1 and type 2 diabetes.* (Monday, 28 June, 10.10am)	Kristen J Nadeau, USA
Outstanding Educator in Diabetes Award Lecture: *It Takes a Brain, a Heart, Courage, ... Support.* (Saturday, 26 June, 10.15am)	Denise Charron-Prochownik, USA
Outstanding Achievement in Clinical Diabetes Research Award	Hans-Henrik Parving, Denmark
Outstanding Physician-Clinician in Diabetes Award	Silvio E Inzucchi, USA
Albert Renold Award	Bruce M. Spiegelman, USA
Harold Rifkin Award for Distinguished International Service in the Cause of Diabetes	Juleen R Zierath, Sweden/ Denmark
Professional Interest Group Award Lectures	
Edwin Bierman Award (Complications) Lecture: *Posttranslational control of HMG CoA reductase – The molecular target of cholesterol-lowering statins.* (Saturday, 26 June,1.45pm)	Russell A DeBose-Boyd, USA
Norbert Freinkel Award (Pregnancy) Lecture: *Therapeutic advances in pregnancy for women with pre-existing diabetes – How far have we come?* (Saturday, 26 June, 4pm)	Denise Feig, Canada
Roger Pecorara Award (Foot care) Lecture: *Causation research on diabetic foot complications – What I learned from Roger Pecoraro?* (Monday, 28 June, 2.15pm)	Edward J Boyko, USA
Richard R Rubin Award (Behavioural Medicine and Psychology) Lecture: *Diabetes prevention and treatment in the American southwest* (Saturday, 26 June, 1.45pm)	David G Marrero, USA

were associated with weight loss. Preliminary results suggest that liraglutide also offered relative benefit of a reduction in the composite outcome of heart attack, stroke and other heart and vascular complications.

The results of the first phase 3 clinical trials with novel dual glucose-dependent insulinotropic peptide/glucagon-like peptide-1 receptor agonist (GIP/GLP-1ra) tirzepatide – SURPASS 1, 2, 3 and 5 – were released in a symposium (29 June, 8am) which included a 30-minute live video question and answer session.[3,4] Tirzepatide treatment was compared with placebo in SURPASS 1 (see 100-OR and 81-LB), with semaglutide in SURPASS 2 (Abs 84-LB) and insulins degludec and glargine in SURPASS 3 (Abs 78-LB) and 5 (Abs 80-LB), respectively. In summary, once-weekly injection with tirzepatide (5 mg, 10 mg or 15 mg) dose dependently decreased HbA_{1c} (1.87–2.07%; 20–23 mmol/mol), with >90% of patients achieving an HbA_{1c} <7%. Treatment also reduced body weight (~7–9.5 kg) from baseline.

AMPLITUDE-O, a multinational study in more than 4,000 people with type 2 diabetes and cardiovascular and/or kidney disease, reported at a dedicated symposium (28 June, 2.15pm). Treatment for a median of 1.81 years with once-weekly injections of the GLP-1ra efpeglenatide (4 mg or 6 mg) with/without a sodium glucose co-transporter 2 (SGLT2) inhibitor reduced the risk of heart attack, stroke or cardiovascular death by 27% and risk of kidney disease progression by 32% compared with placebo. Similar effects were observed in the presence and absence of a SGLT2 inhibitor and there were no serious side effects.[5] The efficacy and safety of efpeglenatide were assessed in AMPLITUDE-M (102-OR).

Sotagliflozin is a dual SGLT1/2 inhibitor. The initial results of the multinational phase 3 trials SCORED (a study in which type 2 diabetes patients with chronic kidney disease (± albuminuria) were treated with sotagliflozin for a median of 16 months) and SOLOIST (a study in which type 2 diabetes patients recently hospitalised for worsening heart failure were assigned to sotagliflozin for a median of 9 months) showed that sotagliflozin treatment significantly reduced the composite risk of deaths from cardiovascular causes, hospitalisation for heart failure and urgent visits for heart failure.[6,7] Originally reported in November 2020, the main results were shared for the first time with the diabetes community. A paired analysis of these studies indicated that sotagliflozin provides benefits across the range of albuminuria and decreases the risk of a heart attack by 32% and a stroke by 34% and, when initiated in patients hospitalised with acute heart failure, sotagliflozin reduced the risk of death from cardiovascular causes and hospitalisation or urgent visits for heart failure by 33%. The growing body of data indicates that type 2 diabetes patients with kidney disease or heart failure should be assessed for initiation of this class of glucose-lowering agent.

It is thought that the development of both efpeglenatide and sotagliflozin has been stalled due to the impact of COVID-19 and lack of financial investment.

Trial acronyms

AMPLITUDE-O	Effect of efpeglenatide on cardiovascular outcomes
DARE-19	DApagliflozin in REspiratory failure in patients with COVID-19
GRADE	Glycemia Reduction Approaches in Diabetes: a comparative Effectiveness study
SCORED	Effect of sotagliflozin on cardiovascular and renal events in patients with type 2 diabetes and moderate renal impairment who are at cardiovascular risk
SOLOIST	Effect of sotagliflozin on cardiovascular events in patients with type 2 diabetes post worsening heart failure (SOLOIST-WHF)
SURPASS	A study of tirzepatide (LY3298176)

1: in participants with type 2 diabetes not controlled with diet and exercise alone
2: versus semaglutide once weekly as add-on therapy to metformin in participants with type 2 diabetes
3: versus insulin degludec in participants with type 2 diabetes
5: versus placebo in participants with type 2 diabetes inadequately controlled on insulin glargine with or without metformin

Diary date

ADA 2022 is currently scheduled to take place at the Ernest N Morial Convention Center on the banks of the Mississippi (and next to a shopping mall) in New Orleans on 3–7 June (submit your abstract by 10 January). After nearly 3 years apart with altered waistlines and hairstyles, will we readily recognise each other – even unmasked? Hopefully it won't be necessary to again transition to a virtual meeting.

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Impressions from EASD 2021

Dr Caroline Day reports on the European Association for the Study of Diabetes 57th Annual Meeting, aka Virtual EASD 2021

Introduction

The 57th Annual EASD meeting was due to be held in Stockholm but, courtesy of COVID-19, it was again hosted exclusively in cyberspace. Nevertheless, every cloud has a silver lining: no promotional banners, signage and exhibition stands to be constructed, demolished and consigned to landfill; delegates and conference professionals are spared the rigours of international travel and carbon footprint concerns, whilst the reduced costs (time, energy, money) of conference attendance facilitates diversity and inclusivity, ideally improving intellectual intercourse.[1] This year virtual attendance (n=14,373) was similar to actual attendance in 2019 (n=14,562). Participants were from 136 countries, with large contingencies from beyond Europe – eg, Mexico (n=490), USA (n=430), Egypt (n=368), Columbia (n=333) – and UK attendance ranked third (n=657) behind Germany (n=1,081) and Brazil (n=770).

Abstracts and access

Accessing an online flipbook from the Virtual Meeting or downloading a 306-page pdf of the final programme via your My-EASD. account or https://upload.easd.org/download/EASD2021/Flipbook/mobile/index.html allows easy navigation of the event – the programme at a glance starts on page 20, symposia are listed from page 213 and industry sessions commence on page 228. The meeting day is highly civilised, commencing at 10am and ending with a daily 'wrap up' session, the latest of which commenced at 5.30pm. The abstracts (n=702) are published in *Diabetologia* and can be accessed online (downloadable pdf).[2] At the meeting Abstracts 1–260 were presented in 47 oral sessions (OP) and, in lieu of posters, Abstracts 261–702 were presented during six (A–F) short oral discussion events (SO). Abstracts and webcasts can be viewed free of charge on the EASD virtual meeting site.[3]

Highlights

As usual it was worth dropping in on the prize lectures (Table 1). Trials which had devoted sessions at EASD are listed in Table 2. The EASD e-learning sessions proved popular with >260,000 on-demand views during the meeting. Naturally, COVID-19 was an area of interest at this meeting, warranting two dedicated sessions (Wednesday, 4.30pm and Friday, 10am) as well as several individual presentations (eg, Abstracts 30, 307–309, 343, 578, 690–695.

Table 1 Award lectures at EASD 2021

Prize	Lecturer	Title (day and time of presentation)
53rd Claude Bernard Lecture	Juleen R Zierath Sweden/Denmark	Sending the right signals – how exercise keeps the rhythm in metabolism Tuesday, 10.30am
36th Camillo Golgi Lecture	Hiddo J L Heerspink Netherlands	Personalising the treatment for patients with type 2 diabetes: the mean is meaningless Tuesday, 3pm
15th Albert Renold Lecture	Pedro L Herrera Switzerland	Metabolic and functional specialisation of the pancreatic beta cell Tuesday, 3pm
7th EASD-Novo Nordisk Foundation Diabetes Prize for Excellence	John A Todd UK	From HLA-DQ position 57 and back again Wednesday, 3.15pm
56th Minkowski Lecture	Amelie Bonnefond France	Hunt for variants and pretty little things in the genetics of diabetes Thursday, 3.15pm

The centenary of the discovery of insulin by the Toronto team was celebrated at this year's meeting (Wednesday, 4.30pm) and a special issue of Diabetologia was available to download.[4] There were EASD e-learning Insulin@100 sessions (Wednesday, 10am and 3.15pm; Thursday, 11.45am and 3.15pm; Friday, 12.30pm) as well as a session to launch the 2021 ADA-EASD consensus report on the management of type 1 diabetes.[5]

There was a lot of interest in incretin-based therapies, with two dedicated sessions at 10am and one at 4.15pm on Thursday 30th, plus an Insulin@100 session (11.45am) and dedicated oral presentation sessions (eg, OP 04 Abstracts 19–24; OP 30 Abstracts 175–180; OP 32 Abstracts 187–192) and short discussion events (eg, SO 28 Abstracts 452–459 (GLP-1 RA and weight loss); SO 30 Abstracts 470–476 (dual agonists); and SO 31 Abstracts 477–486 (focusing on semaglutide), plus presentations in non-incretin-related sections (eg, Abstracts 426, 446–449, 427, 460, 467, 500).

The sodium glucose co-transporter-2 inhibitors (SGLT2i) dapagliflozin and empagliflozin had sessions providing updates from the DAPA-CKD and EMPEROR Preserved studies (Thursday, 3.15pm and 4.15pm, respectively) and there was a session considering use of this drug class in patients at cardiorenal risk (Tuesday 26, 5.40pm). There were also SGLT2i dedicated oral presentation sessions (eg, OP 9 Abstracts 49–54; OP 34 Abstracts 199–204) and short discussion events (eg, SO 26 Abstracts 437–443; SO 32 Abstracts 487–493) plus presentations in non-SGLT2i sections (eg, Abstracts 444, 445, 496, 497).

In DAPA-CKD, in addition to chronic kidney disease (CKD), 11% (n=468) of subjects had heart failure (HF) at baseline. Treatment with dapagliflozin improved all outcomes regardless of HF status, and improvements were greater in patients with HF. Similarly, in patients with and without peripheral artery disease (PAD) and in patients with and without atrial fibrillation (AF), dapagliflozin treatment improved outcomes and the dapagliflozin-associated risk reductions were greater in patients with PAD or AF.[6] Dapagliflozin slowed the long-term eGFR decline in patients with CKD ± type 2 diabetes, with benefits being greater in patients with type 2 diabetes, higher HbA_{1c} and higher urinary albumin: creatinine ratio.[7] Albuminuria was reduced in patients taking dapagliflozin, with a larger relative reduction being observed in patients with type 2 diabetes.[8] A combined analysis of data from DAPA-HF and DAPA-CKD (both trials included patients with and without type 2 diabetes at baseline: 55% and 33%, respectively) showed that use of dapagliflozin

Table 2 Trials with devoted sessions

Trial	Presenters
DAPA-CKD A study to evaluate the effect of DAPAgliflozin on renal outcomes and cardiovascular mortality in patients with Chronic Kidney Disease	S E Inzucchi, D C Wheeler, J J McMurray
EMPEROR-Preserved EMPagliflozin outcomE tRial in patients with chrOnic heart failuRe with Preserved ejection fraction	J Butler, S D Anker, G Filipatos, M Packer, A Norhammar
GRADE Glycaemia Reduction Approaches in Diabetes: a comparative Effectiveness study	D M Nathan, J B Buse, M A Tiktin, N Younes, D R Matthews
HARPdoc RCT Hypoglycaemia Awareness Restoration Programme Randomised Controlled Trial	H Rogers, N De Zoysa, S A Amiel, R A Aljan
TriMASTER A 3-way cross-over trial of precision medicine strategy of 2nd/3rd line therapy in type 2 diabetes	A T Hattersley, E R Pearson, C Angwin, B Shields, C Kirstorp

reduced new-onset diabetes by 33%.

Data from a pooled analysis of the EMPEROR Preserved study and EMPEROR Reduced study (trials in patients with heart failure with preserved and reduced ejection fraction (HFpEF and HFrEF), respectively, with and without type 2 diabetes) showed that the effects of empagliflozin to reduce HF outcomes in both studies were highly concordant. A ≥30% reduction in hospitalisations for HF (ejection fractions <25%–<65%) was observed, but ejection fraction influenced the effect of empagliflozin on major renal outcomes – decreasing the risk in patients with HFrEF.

The TriMASTER trial is a three-way crossover study in which patients were randomised to an oral agent (canagliflozin, pioglitazone, sitagliptin) as add-on to metformin, with the add-on agent being switched every 16 weeks without a washout period. Overall, HbA_{1c} lowering was similar with all treatments. In patients with BMI <30 kg/m^2, sitagliptin was more effective at improving HbA_{1c} than pioglitazone, but the opposite was observed in patients with BMI >30 kg/m^2. Sitagliptin reduced HbA_{1c} more effectively in patients with eGFR 60–90, whereas canaglifolozin was the more effective agent in patients with eGFR >90. Patient add-on drug preferences were canagliflozin 39%, sitagliptin 35% and pioglitazone 26%. When these responses were checked at an individual level, it became evident that the preferred drug was the agent which resulted in fewest side effects and provided the greatest improvement in HbA_{1c}.

The session on INNODIA (Thursday, 4.15pm) is not available as an EASD webcast. INNODIA (www.innodia.eu) is a consortium which collects blood samples from people throughout Europe with newly diagnosed type 1 diabetes and their first-degree relatives to facilitate research to predict risk of diabetes development and mechanisms to reduce risk and cure diabetes. INNODIA's current intervention studies are called VER-A-T1D, MELD-ATG, CFZ533 and IMPACT.

The GRADE study (Friday, 1.45pm) discussed the results of the trial to date, which appeared to be as elucidated at the 2021 American Diabetes Association annual meeting. The webcast commentary provides an excellent synopsis. The HARPdoc RCT (Friday, 1.45pm) compared two educational approaches to obviate problematic hypoglycaemia in adults with type 1 diabetes for ≥4 years: HARPdoc and blood glucose awareness training (BGAT). At 12 and 24 months the incidence of severe hypoglycaemia was the same on each programme, but the HARPdoc programme was more effective than the BGAT programme at reducing diabetes distress, anxiety and depression. Webcasts of the session on finerenone (Friday, 11.15am) are not available, but use of selective non-steroidal mineralocorticoid receptor antagonist has improved cardiorenal outcomes in patients with type 2 diabetes and CKD with elevated albuminuria. Compared with placebo, finerenone treatment improved cardiovascular outcomes – notably hospitalisation for HF – in type 2 diabetes patients with CKD stages 2–4 and moderate albuminuria, or CKD stage 1 or 2 with elevated albuminuria.[9]

The future

The 58th EASD is scheduled to be held in Sweden on 19–23 September 2022. Hopefully, next year we will be able to choose between virtual or actual attendance

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ABCD Abstracts

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Abstract ID: 338

The impact of empagliflozin dose on HbA1c and weight outcomes at 6 and 12 months: updated analysis from the ABCD empagliflozin audit programme

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Introduction: Previously, phase IIb trials demonstrated dose-dependent reductions in HbA1c. Changes in weight were significant across all doses assessed but not dose-dependent. The aim of this analysis is to establish how exposure to the 25 mg empagliflozin dose impacts HbA1c and weight outcomes.
Methods: Datasets were extracted from the ABCD audit if they included a minimum of baseline and relevant follow-up data and stratified by exposure to high-dose empagliflozin: Group 1 (10 mg throughout); Group 2 (25 mg from commencement); Group 3 (increased from 10 mg to 25 mg at 6 months). Changes were assessed using paired t-tests (within groups) and ANOVA with Bonferroni corrections (between groups) in Stata 16 SE.
Results: 9,371 datasets were included (Group 1, n=5,765; Group 2, n=1,887; Group 3, n=1,719) with mean±SD baseline age 60.3±10.3 years, HbA1c 75.7±16.8 mmol/mol and weight 96.9±22.1 kg. 61.5% were male. Median diabetes duration was 8.3 years (IQR 4.5–12.6), which was broadly similar across all groups. At 6 months and 12 months, HbA1c decreased by –11.1 mmol/mol (p<0.001, 95% CI –10.8 to –11.5) and –11.4 mmol/mol (p<0.001, 95% CI –11.1 to –11.8), respectively and weight by –3.6 kg (p<0.001, 95% CI –3.4 to –3.7) and –3.8 kg (p<0.001, 95% CI –3.6 to –3.9), respectively. No significant difference was found between groups at 6 months for weight or HbA1c change. At 12 months, groups 2 and 3 had greater HbA1c reductions compared with group 1 (p=0.01 and p<0.001, respectively) but no difference between each other (p=0.51). At 12 months there was no significant difference in weight changes between group 1 and groups 2 or 3; group 3 lost more weight (–4.4 kg, 95% CI –4.1 to –4.7) than group 2 (–3.4 kg, 95% CI –3.1 to –3.7) (p=0.02).
Conclusions: HbA1c reductions appear to be greatest among those taking higher doses of empagliflozin by 12 months. Weight reductions were greater in group 3 than in those who were started immediately on high dose (group 2). Reasons for this are unclear and further work should explore how high-dose empagliflozin impacts other important parameters.

Abstract ID: 394

Glycaemic outcomes associated with do-it-yourself artificial pancreas systems (DIYAPS): initial insights from the Association of British Clinical Diabetologists' (ABCD) DIYAPS audit programme

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Introduction: Use of DIYAPS is increasing internationally with several thousand users worldwide. Given their unapproved and unlicensed status, objective glycaemic and safety data are needed. The ABCD DIYAPS audit programme launched in 2020 with the aim of providing clinically validated data. We report preliminary findings.
Methods: Clinicians were asked to enter user data as captured in routine clinical encounters into a bespoke online audit tool for this data analysis. Changes from baseline for HbA1c and weight were assessed using paired t-tests. Where baseline data were not available due to the retrospective nature of the audit (eg, time in range), we have reported outcomes at follow-up only. Analyses were conducted in Stata 16 SE, expressed in mean ±SD unless stated otherwise.
Results: One hundred and five users were included, 83.8% white British or Irish, 66.4% female, median duration of diabetes 26 years (IQR 17–33.3), mean±SD baseline HbA1c 55.9±10.3 mmol/mol, weight 82.2±24.3 kg and BMI 28.6±9.5 kg/m2. Over a median follow-up of 0.7 years (IQR 0.4–1.8) HbA1c reduced by –7.7 mmol/mol (95% CI 5.4 to 10.0, p<0.001) and weight increased by 1.2 kg (95% CI 0.2 to 2.2, p=0.02). At follow-up, mean time in range (TIR, glucose 3.9–10 mmol/L) was 74.2±19.6% with a mean time below range (TBR, glucose <3.9 mmol/L) of 3.1±2.3%. 69.4% achieved the recommended TIR >70% and 77.6% achieved TBR <5%. Three episodes of severe hypoglycaemia were reported, two of which required admission. There was one admission for hyperglycaemia. No other admissions or paramedic callouts were recorded. Four user-reported adverse events were noted including insulin over-delivery due to interference from another application (n=1), excessive weight gain (n=1) and hypoglycaemia due to exercise (n=2).
Conclusion: Our initial analysis suggests that DIYAPS use is associated with improvements in HbA1c at follow-up, with achievement of TIR similar to commercial closed loop systems. Most users achieved the recommended % TIR and TBR target ranges. Current safety outcomes are reassuring but continued surveillance for potential adverse outcomes is required, with ongoing healthcare professional understanding and oversight.

Abstract ID: 370

Screening for gestational diabetes:comparing NICE criteria versus RCOG criteria recommended during the COVID pandemic – the role of HbA1c in GDM screening

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Aims: To examine the disparity in identification of gestational diabetes (GDM) using the RCOG criteria (HbA1c ≥39 mmol/mol or FBG ≥5.6 mmol/L) during the COVID-19 pandemic from the conventional NICE guidelines.
Methods: Of 40,740 deliveries at our University Hospital from year 2009 (pre-COVID pandemic) in women without pre-existing diabetes, 8,542 were deemed 'high-risk' based on NICE risk stratifica-

tion and had an oral gluose tolerance test (OGTT) for GDM screening. Locally, HbA1c is routinely undertaken along with an OGTT. Data were analysed retrospectively to explore variation in GDM diagnosis using the two criteria.

Results: Using NICE criteria and RCOG criteria, 11.3% and 15.3% respectively of 'high-risk' women were diagnosed with GDM. HbA1c ≥39 mmol/mol was observed in 13.5%. When RCOG criteria were used, the diagnosis would have been missed in 43.5% of GDM diagnosed with an OGTT (4.9% of the 'high-risk' cohort; $\chi 2=1423$, $p<0.001$). 8.9% with a normal OGTT would have been diagnosed with GDM with the RCOG criteria. The proportion of Asians was higher in the cohort with HbA1c ≥39 mmol/mol compared with those diagnosed with OGTT alone (26% vs 18%, $p<0.001$). HbA1c ≥39 mmol/mol was associated with significantly higher fetal macrosomia (birthweight ≥4500 g) compared with GDM diagnosed with OGTT (3.5% vs 0.9%; $\chi 2=47.7$, $p<0.001$), although the women with GDM received intensive antenatal management.

Conclusions: The RCOG and NICE criteria, when used in isolation for GDM screening, identify different populations with a risk of missing a GDM diagnosis in a proportion of women when RCOG criteria are solely applied. HbA1c could have a supplementary role when used in addition to OGTT in 'high-risk' women to identify and to potentially reduce maternal-fetal complications through intensive antenatal management.

Abstract ID: 347

Outcomes in patients with lipodystrophy receiving treatment with metreleptin via the National Severe Insulin Resistance Service at Addenbrookes Hospital, Cambridge

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Introduction: Lipodystrophy is a rare condition characterised by complete or partial loss of subcutaneous adipose tissue. It is associated with severe insulin resistance, diabetes, hypertriglyceridaemia, pancreatitis and non-alcoholic fatty liver disease. The mainstay of treatment is a low-fat, energy-restricted diet.[1] Deficiency of the appetite-regulating hormone leptin causes difficulty in adherence to dietary restrictions. Metreleptin replacement therapy has been available for several years to lipodystrophy patients attending the National Severe Insulin Resistance (NSIR) Service via a compassionate use programme. NICE have recently approved NHS funding.[2] We describe outcomes in 25 lipodystrophy patients treated with metreleptin in addition to diet and standard medical therapies.

Patients: 25 patients (21 female, median age 31 years (range 1–54)) were followed up for a median of 8.3 years (range 2.5–9.3). Seven patients have congenital generalised lipodystrophy, 3 acquired generalised lipodystrophy, 14 familial partial lipodystrophy (12 LMNA and 2 PPARG mutation) and 1 acquired partial lipodystrophy.

Results: Median baseline HbA1c was 71.5 mmol/mol (IQR 50.2–83.8) and fasting triglycerides were 3.4 mmol/L (1.4–4.4) compared with HbA1c 64.0 mmol/mol (44.0–69.0) and fasting triglycerides 3.1 mmol/L (1.7–6.1) at the most recent visit. Most patients reported a significant reduction in hyperphagia. Three patients have died, one had a liver transplant and one a renal transplant.

Conclusion: Patients with lipodystrophy and leptin deficiency attending the NSIR service, treated with metreleptin, reported a reduction in hyperphagia. There was also an improvement in metabolic status. Morbidity and mortality rates in this patient group remain high. The availability of NHS funding will enable earlier access to metreleptin therapy which may improve outcomes.

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Abstract ID: 389

Mental health case-management significantly reduces hospital admissions and bed days in adults with type 1 diabetes mellitus

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Background: Mental health problems are associated with recurrent hyperglycaemia and diabetic ketoacidosis in type 1 diabetes mellitus (T1DM).[1–3] A recent systematic review showed limited evidence for the use of mental health interventions to reduce acute diabetes presentations, with no studies in the T1DM population.[4]

Aims: To describe the effect of a case-management mental health approach to reduce readmissions, hospital bed days and HbA1c for T1DM patients.

Methods: T1DM patients readmitted to three acute hospitals in East London for diabetes-related issues with one previous hospital presentation in the prior year were offered a pilot intervention with case-management by a consultant psychiatrist specialised in diabetes. Case-management includes: (a) treatment of underlying mental health problems and (b) a psychotherapeutic approach to understand the causes of admissions and, where necessary, increase self-management of diabetes. Outcome measures were hospital attendance rates, hospital bed days and glycaemic control (HbA1c).
Patients: 20 patients (15 females, median age 27 years (IQR 22–38)) agreed to mental health intervention. All participants had ≥1 mental health diagnosis. The mean duration of diabetes was 10.7 years and the mean treatment length was 15±6 months.

Outcomes: Hospital attendance rates: In two years prior to intervention, the mean number of hospital admissions was 9.5±8.4 episodes. Following intervention this significantly reduced to 3.9±5.3 episodes ($p<0.05$). Approximately 75% of attendances were diabetes-related with considerable overlap with non-diabetes attendances. Hospital bed days: There was a significant reduction following intervention. The pre-treatment median bed days was 0.69 days/month (IQR 0.30–0.96) and post-treatment was 0.17 days/month (IQR 0.00–0.98) ($p=0.029$). An estimated 125 bed days were saved over 12 months and the total cost saved from this was £159,875. HbA1c levels: The mean pre- and post-treatment HbA1c was 102±24 and 94±19 mmol/mol ($p=0.250$).

Conclusions: Specialist mental health case-management can significantly reduce all hospital attendances, hospital bed days and recurrent admissions in T1DM population.

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Abstract ID: 364

Cortisol measurement post steroids (dexamethasone) treatment for COVID-19

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Introduction: The RECOVERY trial 2 reported patients with COVID-19 receiving/requiring invasive mechanical ventilation or oxygen in whom the use of dexamethasone (6 mg for 10 days) resulted in lower 28-day mortality. Adrenal insufficiency from hypothalamic-pituitary-adrenal axis suppression is a serious, potentially life-threatening side effect of glucocorticoid treatment.
Objective: To investigate the effect of COVID-dexamethasone protocols on adrenal function.
Methods: Data were collected from patients admitted with a diagnosis of COVID-19 treated with dexamethasone/hydrocortisone between November 2020 and March 2021. Adrenal function was assessed using 09:00am cortisol, at least 48 hours off steroids. Cortisol levels >300 nmol/L excluded adrenal insufficiency. Patients with levels of 100–300 nmol/L underwent further assessment and those with levels <100 nmol/L were started on hydrocortisone replacement.
Results: 79 patients were alive at initial data collection. 51/79 had 7–10 days of 6 mg dexamethasone whilst 28/79 had an additional ARDS regimen of dexamethasone. Eight of the group died, and data are available for 60 patients. 18/60 had suboptimal cortisol <300 nmol/L and 5/60 had cortisol <100 nmol/L (4 of these having had ARDS regimen of prolonged dexamethasone). 10 patients recovered their axis prior to confirmatory testing within 1–4 weeks. Confirmatory testing was undertaken SST on 6/18 patients; 5 had satisfactory results and 1 has been unable to attend yet.
Conclusions: These data demonstrate a minimal risk of adrenal insufficiency after treating with RECOVERY doses of dexamethasone 6 mg. Almost 50% of patients on ARDS regimen had early evidence of adrenal insufficiency; the rate of recovery is unclear because of deaths in this cohort. Steroid cover may be needed for invasive procures such as tracheostomy in this group. These data also suggest that COVID-19 itself does not cause adrenal insufficiency, which is reassuring.

Abstract ID: 356

The absence of diabetic autoantibodies when routinely tested in adult-onset type 1 diabetes is associated with a high prevalence of treatment change and successful insulin cessation

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Background and aims: Recent ADA/EASD guidelines recommend islet-autoantibody (AA) testing in all adults with suspected type 1 diabetes (T1D). We aimed to assess the impact of routine AA testing in adults with newly diagnosed T1D.
Methods: We assessed the clinical, biomarker and genetic characteristics associated with positive and negative AA status (GAD, IA-2 and ZNT8) in 713 adults with recently diagnosed T1D (clinical diagnosis T1D and insulin from diagnosis and duration <12 months) in the prospective StartRight study. We then evaluated changes in treatment and glycaemic control over 2 years after informing participants and their clinicians of AA results.
Results: 25.0% (178/713) of participants were AA negative. This group had genetic and C-peptide characteristics suggestive of a high prevalence of type 2 diabetes (T2D): mean T1D genetic risk score (T1DGRS), AA negative vs positive, 0.244 vs 0.267 ($p<0.001$) (T2D mean 0.231), C-peptide (median duration 4 months) 998 vs 555 pmol/L, rate of decline in C-peptide (urine C-peptide creatinine ratio measured annually) 0.19 nmol/mmol/year vs 0.35 ($p=0.001$), (T2D 0.22 nmol/mmol/year). After a median follow-up of 22 months, 21.1% (31/147) of AA negative participants had stopped insulin with maintained glycaemic control (recruitment HbA1c 67.7 mmol/mol, final HbA1c 60.7 mmol/mol) and 15.6% (23/147) added oral agents to continued insulin. Treatment change was rare in AA positive participants and none stopped insulin.
Conclusions: In adult onset clinically diagnosed T1D, negative islet AAs should raise a high suspicion of underlying T2D and is associated with successful insulin cessation. These findings support recent recommendations for routine islet AA assessment in adult-onset T1D.

Abstract ID: 323

The rare occurence of type B insulin resistance syndrome (TBRIS) in a T1DM patient: could an insulin pump be the solution?

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Introduction: Type B insulin resistance syndrome (TBRIS) is a rare phenomenon of abnormal glucose homeostasis. This condition can manifest with severe hypoglycaemia to extreme insulin-resistant hyperglycaemia and is caused by the presence of insulin receptor autoantibodies.
Case report: A 27-year-old female diagnosed with type 1 diabetes mellitus (T1DM) at 12 years of age presented with an episode of diabetic ketoacidosis. Her glutamic acid decarboxylase antibody was found to be positive and she was commenced on an insulin basal bolus regime. Her initial diabetes control for the first 5 years as reflected by her HbA1c was suboptimal. Five years after her initial diagnosis she presented with multiple episodes of hypoglycaemia despite reductions in her insulin doses. A battery of tests which included a short Synacthen test and coeliac screen was found to be normal. Her insulin levels, on the other hand, were found to be elevated at 34500 pmol/L and she had positive insulin antibodies. She was commenced on an insulin pump due to severe recurrent hypoglycaemic episodes. Whilst being on the pump, her insulin levels reduced and her hypoglycaemic episodes resolved. She was thereafter taken off the pump but her hypoglycaemic episodes recurred and her insulin levels rose to >500 pmol/L. She was recommenced on the insulin pump and her hypoglycaemic episodes resolved, her insulin levels normalised and eventually her insulin antibodies became undetectable.
Conclusion: This case highlights the rare occurrence of TBRIS in a

T1DM patient and the unusual phenomenon of insulin antibody clearance and normalisation of blood glucose with the use of an insulin pump.

Abstract ID: 316

Replacing all but essential face-to-face visits with virtual support for gestational diabetes care during the COVID pandemic maintains outcomes

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Background: Gestational diabetes mellitus (GDM) is associated with increased perinatal complications. Our service historically saw patients with GDM monthly. Self-monitoring blood glucose (SMBG) levels were reviewed weekly via email.
During COVID lockdown (23 March 2020–14 September 2020) we limited face-to-face contact and started using an App-based communication platform (GDm-HealthTM). Patients recorded SMBG on the App. Face-to-face contact was reduced to monthly scans or if insulin start was needed. Otherwise, contact was made via the app or telephone. We wanted to establish whether reduced face-to-face contact had impacted glucose control or postnatal outcomes.
Methods: A retrospective analysis was performed comparing fasting glucose data and postnatal outcomes for women with the App (1 June 2020–31 December 2020) and standard care (1 June 2019–31 December 2019).
Results: There were 62 women in the before App group (BA) and 61 in the with App group (WA). There was no significant difference in baseline characteristics. Results are shown as mean (SD). Treatment at 36 weeks gestation: diet only BA 22 vs WA 26 (p=0.40); metformin only BA 16 vs WA 22 (p=0.28); insulin (+metformin) 24 vs 13 (p=0.06). Fasting glucose at 36 weeks: BA 5.0 (1.1) vs WA 4.7 (0.3) mmol/L (p=0.12). Birth weight: BA 3.4 (0.6) vs WA 3.3 (0.5) kg (p=0.43) and Z score 0.3 (1.1) vs 0.4 (0.9) (p=0.77). Mode of delivery: vaginal BA 27 vs WA 14; instrumental BA 5 vs WA 7; caesarean section BA 30 vs WA 27 (p=0.78). Gestation at birth: BA 40 vs WA 38 weeks (p=0.16).
Conclusion: App-based communication is effective with outcomes matching standard face-to-face GDM care.

Abstract ID: 353

Managing hyperglycaemia and reducing glycaemic variability in critically ill COVID-19 patients

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Background: There are limited data on interventions to improve glycaemic control in critically ill COVID-19 patients, who often have high intravenous insulin requirements and challenging hyperglycaemia.
Aims: To evaluate if a safe reduction in carbohydrate content received from enteral feeding improved time in range (TIR) in critically ill patients with COVID-19.
Methods: We studied 21 critically ill patients (14 male, median age 57 years) with blood glucose levels >10 mmol/L despite high intravenous insulin requirements of >5 units/hour for >24 hours. All patients were on continuous enteral feeding and on >6 mg/day dexamethasone. Our intervention was a 30% reduction in the amount of carbohydrate delivered hourly via individualised enteral feed rate adjustments while still keeping within the recommended 20–30 kcal/kg ideal body weight/day. TIR was defined as the percentage of time blood glucose values were 6–10 mmol/L. TIR, time above range, mean blood glucose levels (using hourly venous blood glucose readings) and intravenous insulin requirements were evaluated 48 hours before and after the intervention.
Results: TIR more than doubled post intervention from median (interquartile range) 20.0% (7.64–40.4%) to 47.1% (24.3–56.3%), p=0.001. Significant reductions in time above range, mean blood glucose levels and intravenous insulin requirements (median (interquartile range) 8.96 (6.97–10.4) units/hour to 5.22 (4.25–7.59) units/hour) were also observed (p<0.05 for all).
Conclusions: In a cohort of critically ill COVID-19 patients, a safe reduction in the carbohydrate content from enteral feeding reduced glycaemic variability, more than doubling TIR, with concomitant reductions in intravenous insulin requirements.

Abstract ID: 380

Empagliflozin reduced the total burden of events leading to or prolonging hospitalisation in EMPA-REG OUTCOME

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Background: In EMPA-REG OUTCOME, empagliflozin (EMPA) reduced the risk of all-cause mortality (ACM) and total (first plus recurrent) events leading to all-cause hospitalisation in patients with type 2 diabetes (T2D) and established atherosclerotic cardiovascular disease (ASCVD). We assessed the effect of EMPA on the total burden of events leading to or prolonging all-cause hospitalisation (ACPH) as well as the composite of ACPH and ACM.
Methods: Patients were randomised to EMPA 10 mg, 25 mg or placebo. Post hoc, we assessed the effect of pooled EMPA versus placebo on total events of ACPH, as reported by investigators, and an ACPH/ACM composite, using a negative binomial model.
Results: Among 7,020 patients there were 5,256 ACPH events (5,031 leading to and 225 prolonging hospitalisation) and 5,617 ACPH/ACM events. EMPA reduced the risk of total events of ACPH by 22% versus placebo (rate ratio 0.78 (95% CI 0.70 to 0.87)) and ACPH/ACM by 24% versus placebo (0.76 (95% CI 0.69 to 0.85)). The number of ACPH/ACM events prevented with EMPA versus placebo was 67.7 per 1000 patient years; the number needed to treat (NNT) over the three years of the trial to prevent one event was 4.9 (95% CI 3.5 to 8.4).
Conclusions: EMPA showed a sizeable reduction in the total burden of mortality and events leading to or prolonging hospitalisation in patients with T2D and ASCVD, with a clinically relevant number of events prevented and a low NNT.

Book review

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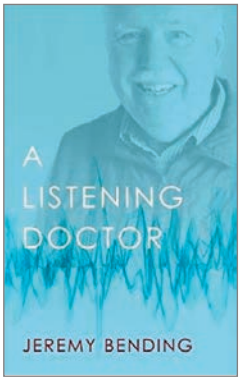

Title: A Listening Doctor

Author: Jeremy Bending

Publisher: Quartet Books Limited, 2018

ISBN: 978-0-70437-453-9

The author Jeremy Bending was a consultant in diabetes and endocrinology in Eastbourne for 27 years where he founded and championed the award winning Diabetes Centre. Over a total of 226 pages divided into 35 short chapters, he offers an almost chronological journey through a medical career from undergraduate to retired consultant physician – including a brush with surgery (Chapter 4). He was the only student in his year to be awarded an honours viva in surgery, but he wanted to be a physician and turned down an invitation to apply to be house surgeon to the eminent Professor Harold Ellis (a role expecting you to be on-call one in one – ie: living in, working full time without a break for the 6-month duration of the post; such were the halcyon days of training in the 1970s).

Listening is the recurring theme of each chapter, supported by anecdotes which give a range of insights into the work of a physician, the life of a physician and the interplay of the two – an especially useful feature of the book for a wannabe medic (somewhat different to the modern media portrayal) – a text recommended for the Careers library. Educationalists and students of any discipline would be well advised to read Chapters 2–5.

Medicine provided the author with an opportunity for travel: from his student elective in Ghana (Chapter 11) to working in the outports of Newfoundland and locum consultant physician posts in this remote land which shone another light on medicine. Standing in for a diabetes and endocrinology consultant led to the author returning to the UK to train to be a specialist. The ups and downs of specialist training and the rigours of research are recounted with humour and candour – there is much to be learnt from this listening doctor who was involved in the development of insulin pump treatment when it was a pioneering technology. Chapter 18 is pertinent to this COVID-centric era when face-to-face consultations are being avoided – "Listening isn't everything".

In the late 1980s consultant posts were few and far between – for each UK vacancy there were about 29 senior registrar applicants. However, the consultant role elucidated by the author was a far cry from that of Sir Lancelot Spratt of Doctor in the House fame (a surgeon who bellows at his entourage to 'listen' and treatment is always 'cut it out' – see clips of 1954 film on YouTube). No leisurely lunches and afternoons on the golf course for consultant diabetologists. Jeremy describes being on the acute general medicine on-call rota for more than 25 years (once a week for 24 hours and one weekend every month, no compensatory time off, and rolling directly into the morning's work).

This book offers a journey through the changing face of diabetes care. Jeremy was the first diabetes consultant to be appointed at Eastbourne. At the time type 2 diabetes was perceived as a 'mild' disease (the Diabetes Control and Complications Study and United Kingdom Prospective Diabetes Study were works in progress). The number of people with type 2 diabetes was burgeoning and Eastbourne was an early adopter of innovative practice from group training sessions for patients, joint clinics with other specialists (Chapter 25 is based on an article in this journal in 2007 p.202), formation of multidisciplinary care teams to the setting up of a Diabetes Centre and maintaining the service (regardless of management interference).[1]

The writing style is very comfortable, generating a sense that Jeremy is in the room talking to you, recounting incidents from his working and personal life (particularly poignant is the birth and death of baby Oliver – Chapter 19). His observations on care delivery – as a patient lamenting the demise of the British nurse (re-modelled by the Project 2000 initiative) to the machinations of hospital management impacting the well-being of professionals and patients – will resonate with many readers.

The erudite relating of patient stories makes this a book that will help patients to better understand their diabetes (and their health professionals) and serve as a useful text for students and practitioners who work with people – listen and you will learn. An excellent read.

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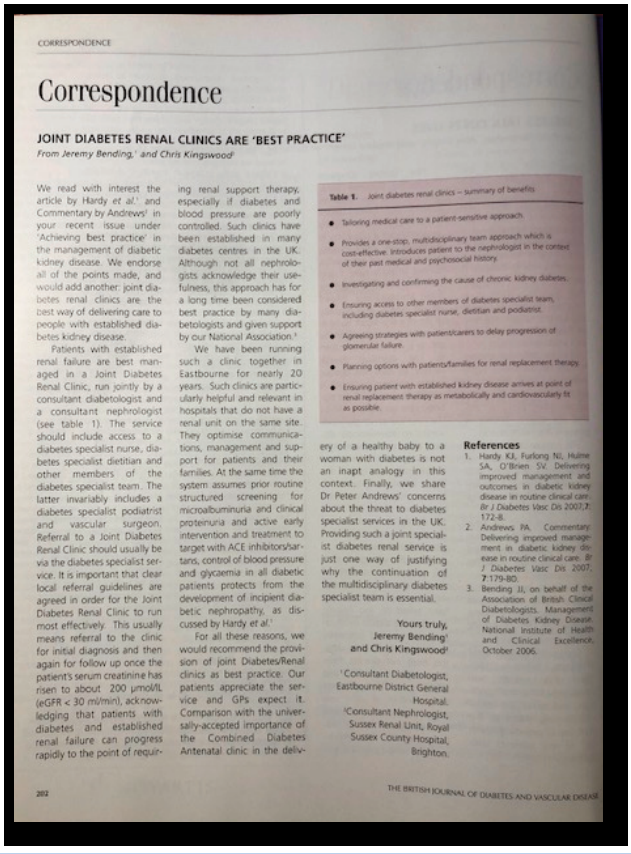

CORRESPONDENCE

Correspondence

JOINT DIABETES RENAL CLINICS ARE 'BEST PRACTICE'

From Jeremy Bending,[1] and Chris Kingswood[2]

We read with interest the article by Hardy *et al.*[1] and Commentary by Andrews[2] in your recent issue under 'Achieving best practice' in the management of diabetic kidney disease. We endorse all of the points made, and would add another: joint diabetes renal clinics are the best way of delivering care to people with established diabetes kidney disease.

Patients with established renal failure are best managed in a Joint Diabetes Renal Clinic, run jointly by a consultant diabetologist and a consultant nephrologist (see table 1). The service should include access to a diabetes specialist nurse, diabetes specialist dietitian and other members of the diabetes specialist team. The latter invariably includes a diabetes specialist podiatrist and vascular surgeon. Referral to a Joint Diabetes Renal Clinic should usually be via the diabetes specialist service. It is important that clear local referral guidelines are agreed in order for the Joint Diabetes Renal Clinic to run most effectively. This usually means referral to the clinic for initial diagnosis and then again for follow up once the patient's serum creatinine has risen to about 200 µmol/L (eGFR < 30 ml/min), acknowledging that patients with diabetes and established renal failure can progress rapidly to the point of requiring renal support therapy, especially if diabetes and blood pressure are poorly controlled. Such clinics have been established in many diabetes centres in the UK. Although not all nephrologists acknowledge their usefulness, this approach has for a long time been considered best practice by many diabetologists and given support by our National Association.[3]

We have been running such a clinic together in Eastbourne for nearly 20 years. Such clinics are particularly helpful and relevant in hospitals that do not have a renal unit on the same site. They optimise communications, management and support for patients and their families. At the same time the system assumes prior routine structured screening for microalbuminuria and clinical proteinuria and active early intervention and treatment to target with ACE inhibitors/sartans, control of blood pressure and glycaemia in all diabetic patients protects from the development of incipient diabetic nephropathy, as discussed by Hardy *et al.*[1]

For all these reasons, we would recommend the provision of joint Diabetes/Renal clinics as best practice. Our patients appreciate the service and GPs expect it. Comparison with the universally-accepted importance of the Combined Diabetes Antenatal clinic in the delivery of a healthy baby to a woman with diabetes is not an inapt analogy in this context. Finally, we share Dr Peter Andrews' concerns about the threat to diabetes specialist services in the UK. Providing such a joint specialist diabetes renal service is just one way of justifying why the continuation of the multidisciplinary diabetes specialist team is essential.

Yours truly,
Jeremy Bending[1]
and Chris Kingswood[2]

[1]Consultant Diabetologist, Eastbourne District General Hospital, [2]Consultant Nephrologist, Sussex Renal Unit, Royal Sussex County Hospital, Brighton.

Table 1. Joint diabetes renal clinics – summary of benefits

- Tailoring medical care to a patient-sensitive approach
- Provides a one-stop, multidisciplinary team approach which is cost-effective. Introduces patient to the nephrologist in the context of their past medical and psychosocial history
- Investigating and confirming the cause of chronic kidney diabetes.
- Ensuring access to other members of diabetes specialist team, including diabetes specialist nurse, dietitian and podiatrist
- Agreeing strategies with patient/carers to delay progression of glomerular failure
- Planning options with patients/families for renal replacement therapy
- Ensuring patient with established kidney disease arrives at point of renal replacement therapy as metabolically and cardiovascularly fit as possible.

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THE BRITISH JOURNAL OF DIABETES AND VASCULAR DISEASE

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NEWS

Br J Diabetes 2021;**21**:298-306

From the desk of the Chairman, Dipesh Patel

2021 continues to be dominated by the COVID-19 pandemic. As I write this report during half term and the late changing of seasonal colours, we are continuing to see high rates of new infections daily. Thankfully, numbers of patients in hospital are not rising significantly so far, but the effect of the winter months is uncertain. Reassuringly, double vaccination rates in the UK and in our patients is high, and the booster jab programme appears to be going well.

The COncise adVice on Inpatient Diabetes (COVID) resources led by Gerry Rayman continues to provide much good support (https://abcd.care/coronavirus). Existing resources have been updated and new resources such as the post COVID-19 diabetes discharge pathway, risk stratification and follow-up guidance for people being discharged from secondary care have been added. I sincerely hope we do not need much of this in the coming months.

ABCD continues to run our educational programme of monthly webinars featuring a wide range of topics. Members can catch up with our webinars on demand at their leisure via our website at https://abcd.care/abcd-webinars-series and we have aimed to partner with organisations such as YDEF, GIRFT, PCDS and JBDS so that current and future webinars will have wide interest.

This year's DTN meeting and ABCD Annual Conference proved to be outstanding successes, and we have been delighted with the feedback even though the events had to take place virtually. Over 334 delegates registered for our DTN meeting with 283 attending live and 213 delegates registered for the ABCD conference with 188 attending live. Our thanks go out to all the speakers and faculty for their support in ensuring such high-quality relevant sessions in our flagship events.

During the year we have also run a number of regional meetings and resumed our Consultant Development Programme, which was the first face-to-face meeting for ABCD since the pandemic. We have face-to-face sessions planned at the Diabetes Professional Conference (DPC) in November in London and hope this provides a safe environment for many of us to meet once again. You can also catch the ongoing sessions and workshops with our EXTOD programme (Exercise and Nutrition in Type I Diabetes) https://abcd.care/extod-2021/programme. Fortunately, many events have an 'on-demand' facility for more convenient viewing. Our educational programme concludes this year on 2 December with our Southeast regional meeting (https://abcd.care/events/abcd-regional-meeting-south-east).

I am delighted to report that our membership is growing by almost 20% in a year, with more SpRs joining the association, so our future remains bright and thriving. Reassuringly, we have a strong voice and presence with policy makers and stakeholders in the diabetes community. We continue to work with and provide specialist input to other diabetes organisations and the NHS including the RCP, NICE, NHSE, JBDS and many more. Our participation with these organisations helps us ensure that the voice of the specialist diabetologist is featured and carefully considered in new guidance and reports.

One such recent collaboration with the UK Kidney Association (previously known as Renal Association) has resulted in joint management guidelines on monitoring and treatment approaches designed to improve safety and assist in more effective treatment of individuals who have advanced chronic kidney disease requiring dialysis alongside their diabetes. This had led to a number of publications and key updates in 2021 which I would recommend reading. These can be found at https://abcd.care/position-papers.

This year we have further invested in our flagship journal *British Journal of Diabetes* (BJD) and huge amounts of work are going on behind the scenes to prepare the journal for PubMed submission early in 2022. As part of these preparations, we have updated the BJD website where you can already view our articles ahead of print (https://bjd-abcd.com/index.php/bjd/issue/view/5). Please do submit your work to the BJD as it has a wide specialist readership. Submission is easy via our portal and we are happy to support those who are new to submitting their work (https://bjd-abcd.com/index.php/bjd/submit-a-manuscript).

This year, in partnership with the Diabetes Care Trust, we have also undertaken a major piece of work to formalise our process for ABCD research grant submissions in line with Association of Medical Research Charity (AMRC) guidelines, and we have already reviewed the first round of grant applications and need to publicise this to everyone who is looking for early research funding. This work is designed to promote and support early clinical researchers in diabetes and is being led by Dr Parth Narendran. Our thanks to him and the entire academic subgroup for their dedication and commitment to this important workstream.

The ABCD Diabetes Technology Network (DTN) continues to grow and thrive. The amazing collection of resources via the ABCD DTN web pages include educational resources from a virtual showroom demonstrating devices and their use, expert views on devices, educational resources for patients, a virtual academy and a series of videos on virtual consulting. This year we have also undertaken a series of webinars on closed loop systems which have been very successful and are available for on-demand viewing. I am delighted ABCD have been asked to audit the forthcoming NHSE closed loop pilot initiative. Thanks go to Professor Pratik Choudhary and his colleagues for their vision and enthusiasm in this important and evolving area.

Make sure you also save the date of 11 January 2022 for our once-in-a-generation meeting to commemorate the centenary of the first administration of insulin into a human. ABCD has ambitious plans for this free special event to be hosted at the Royal College of Physicians in London to commemorate the occasion. Many thanks to Dr Bob Ryder for leading to curate this quite amazing programme.

Our nationwide audit programme continues to go from strength to strength led by Dr Bob Ryder. This year we have published three new publications from the real-world audit of the FreeStyle Libre system (FSL) in people with type 1 diabetes who use FSL. Find out more at https://abcd.care/announcement/three-new-publications-abcd-nationwide-freestyle-libre-audit-published-during-september. The worldwide audit of testosterone

deficiency in men with type 2 diabetes has recently been launched so please submit your own data for this global audit, http://www.diabetologists-abcd.org.uk/n3/previous_ABCD_audits.htm. We have an active ABCD COVID-19 national audit group who are analysing and maximising the learning from the pandemic, now with international collaborators. I am sure this work will lead to more exciting outputs with global relevance.

We hope you continue to enjoy our fortnightly newsletters which help keep you abreast of new developments, news, events and other diabetes-related information. If you have news to share with the membership, please feel free to drop us a line at info@abcd.care.

I would like to take this opportunity to thank and acknowledge the hard work of Dr Susannah Rowles, Honorary General Secretary, and Dr Andrew Macklin, Honorary Treasurer who have both completed their terms of office this year. I would like to warmly welcome in Vijay Jayagopal as our newly elected treasurer, whose appointment was recently ratified at our AGM. The role of treasurer is hugely important and mainly goes unseen by the membership, but nevertheless involves a huge dedication and commitment. We will share news of the new incoming general secretary with you very soon.

As chair of the ABCD committee, I would also like to remind everyone and wish to thank all our corporate sponsors of both ABCD and DTN, without whom few of the programmes and supporting activities would be possible. Our sponsors are AstraZeneca, Besins Healthcare (UK) Ltd, Lilly, Novo Nordisk, Abbott Laboratories Ltd, Roche Diabetes Care, Insulet International Ltd, Medtronic Ltd, Medtrum Ltd, ViCentra, Advanced Therapeutics (UK) Ltd, Air Liquide Healthcare Ltd, CamDiab and Dexcom.

Finally, I wish you all a happy, healthy Diwali, Hanukah, Christmas and New Year and hope that you are all able to spend quality time away from work with friends and loved ones. In the meantime, between fireworks and mince pies, do make sure you register for our 100 Years of Insulin centenary meeting (11 and 12 January 2022 at the RCP, London) as numbers are limited. Do join us for a special dinner event on the 11th, which promises to be a fantastic commemoration of this centenary. You can register now at https://abcd.care/events/abcd-meeting-commemorate-centenary-first-administration-insulin-human

Dipesh Patel, ABCD Chair

From the desk of the News Editor, Umesh Dashora

JBDS News (Ketan Dhatariya)

- The medical variable rate insulin infusion (VRII) guideline is being updated, as is the enteral feeding guideline. Questionnaires will be going out on how teams are using them at the moment, so watch out for them in the next few weeks. The updated versions of the hyperosmolar hyperglycaemic state (HHS) guideline will be ready in a few weeks, as will the peripartum guidelines, so look out for them.
- We have also revised the update of the self-management guideline after some input from the CQC.
- We are also developing a new guideline on the use of devices in hospital.
- Due to changes in working circumstances, some of the JBDS steering group have stepped down and vacancies will be advertised in the very near future, so look out for these.
- You can follow JBDS on Twitter @JBDSIP or on Facebook (www.facebook.com/JBDSIP/).

Results of Rowan Hillson Inpatient Safety Award 2022

This JBDS-IP award for 2021 is postponed due to the second wave of COVID-19. The project is led by Umesh Dashora and Erwin Castro.

In view of the second wave and on the suggestion of Dr Rowan Hillson, the subject of the award will be modified to include the fantastic innovations that people have made during this pandemic. The title for the 2022 award will be 'The Rowan Hillson Inpatient Safety Award – The best interventions: Redesigning, rebuilding and maintaining safe inpatient diabetes care during COVID'. Entries are welcome from September, with the last date in February 2022. Please prepare for a submission in September from your team.

https://abcd.care/announcement/rowan-hillson-inpatient-safety-award-2021-relaunched

Guidance for the use of SGLT-2 inhibitors in general practice

Dr U Dashora and co-authors from the CaReMe group have produced guidance for GPs on how to use SGLT-2 inhibitors safely.

Dashora U, *et al*. Manage diabetes and comorbidities with a joined-up strategy. Guidelines in Practice

https://www.guidelinesinpractice.co.uk/diabetes/manage-diabetes-and-comorbidities-with-a-joined-up-strategy/456004.article

Dr Bob Ryder gets a lifetime achievement award (Dipesh Patel)

ABCD would like to congratulate Dr Bob Ryder on his recent Lifetime Achievement Award. Dr Ryder received this award during the 7th International Diabetes and Endocrine Conference for services to MRCP and UK Audits via ABCD. I am sure you will join me to wish him many congratulations on this achievement!

From the desk of Rebecca Reeve (Sanofi)

UK NHS drops from 1st to 4th in global rankings

A study from the Commonwealth Fund has ranked health systems in 11 comparator countries against access, care process, equity, efficiency and healthcare outcomes. In terms of overall ranking, the UK health system has moved down from 1st to 4th out of 11 comparator countries. Norway now takes the highest overall rank, despite Norway (10.5%) and the UK (10.2%) having spent similar amounts on healthcare as a percentage of GDP in 2019. The UK ranked 9th out of 11 comparator countries in terms of health outcomes, despite coming 4th for access to care, efficiency and equity. Asthma was one of the diseases used to measure performance with regard to avoidable hospital admissions and population health outcomes.

https://www.commonwealthfund.org/publications/fund-reports/2021/aug/mirror-mirror-2021-reflecting-poorly#rank

NHSE waiting lists could rise to 14 million by next autumn

Institute for Fiscal Studies (IFS) research warns that up to 14 million people could be on NHS England (NHSE) waiting lists by next autumn. The IFS projection comes as NHSE consultant-led referral to treatment figures show how, between March 2020 and March 2021, 7.4 million fewer people joined the waiting list. A record number are currently waiting for surgery with over 385,000 patients waiting over a year, compared with 1,600 before the pandemic. The British Heart Foundation similarly warns that the number of people awaiting heart surgery in England could rise by over 40%, estimating it may take 5 years to overcome the backlog in cardiac care.

Could NHS waiting lists really reach 13 million? Institute for Fiscal Studies (IFS) https://ifs.org.uk/publications/15557

Amanda Pritchard announced as NHSE Chief Executive

The current NHS England (NHSE) Chief Operations Officer, Amanda Pritchard, has been announced as NHS Chief Executive with effect from 1 August. Prichard was previously the Chief Operating Officer of NHS England, and Chief Executive and Chief Operating Officer of NHS Improvement for two years, from July 2019 to July 2021. Before working for NHSE, Pritchard was Chief Executive of Guys and St Thomas' NHS Foundation Trust for two and a half years.

https://www.england.nhs.uk/2021/07/amanda-pritchard-appointed-nhs-chief-executive/

Third of middle-aged people have ≥3 chronic diseases

A UCL study has found that more than one in three UK adults aged 46–48 years have at least two chronic health conditions including poor mental health and diabetes. 34% of this cohort (N=7,951) had multiple chronic health problems, with 21% having recurrent back issues and 19% with mental health problems. 16% reported high blood pressure, 12% asthma or bronchitis, 8% arthritis and 5% diabetes.

https://bmcpublichealth.biomedcentral.com/articles/10.1186/s12889-021-11291-w

Shortage of blood collection tubes

GPs have been told to stop routine blood tests until 17th September and hospitals must cut the number of tests by 25% in response to a shortage of blood collection tubes. Shortages are said to be due to 'UK border challenges' as well as a surge in demand, in part due to COVID testing. Many patient charities have expressed concerns that this would delay the diagnoses for many patients due to cancelled appointments. :

https://www.thetimes.co.uk/article/lack-of-collection-tubes-forces-gps-to-stop-blood-tests-for-three-weeks-hlg5c86c5

Interesting recent research

(Umesh Dashora)

A rapid-fire collection (extract) of interesting recent developments in diabetes

Authors, Journal	Type of study	Main results
Reid *et al*, *Diabetologia*	Retrospective cohort study	**Continuous subcutaneous insulin infusion reduces the incidence of retinopathy compared with multiple daily injection therapy** CSII was associated with reduced risk of retinopathy progression over 2.3 years compared with those continuing MDI, with greatest benefit for those with the highest baseline HbA1c. The reduction was not related to improvement in HbA1c Reid LJ, Gibb FW, Colhoun H, et al. Continuous subcutaneous insulin infusion therapy is associated with reduced retinopathy progression compared with multiple daily injections of insulin. Diabetologia 2021;64:1725–36. https://doi.org/10.1007/s00125-021-05456-w
Sasaki *et al*, *Diabetologia*	Analysis of pancreatic samples	**Reduced beta cell number rather than size is the major contributor to type 2 diabetes** The reduction in beta cell mass in people with type 2 diabetes is more due to reduction in the number of beta cells (37%) than to diminished cell size (10%), is associated with the diagnosis of diabetes and is inversely correlated to HbA1c. Sasaki H, Saisho Y, Inaishi J, et al. Reduced beta cell number rather than size is a major contributor to beta cell loss in type 2 diabetes. Diabetologia 2021;64:1816–21. https://doi.org/10.1007/s00125-021-05467-7
Saeedi *et al*, *Diabetes Res Clin Pract*	Systematic review	**Increasing prevalence of gestational diabetes when implementing IADPSG criteria** There was a 75% increase in the prevalence of GDM in this systematic review of 31 cohort and cross-sectional studies over 8 years including nearly 137, 000 women when new IADPSG criteria were used. Saeedi M, Cao Y, Fadl H, Gustafson H, Simmons D. Increasing prevalence of gestational diabetes mellitus when implementing the IADPSG criteria: a systematic review and meta-analysis. Diabetes Res Clin Pract 2021;172:108642. https://doi.org/10.1016/j.diabres.2020.108642
Corona *et al*, *Rev Endocr Metab Disord*	Systematic review and meta-analysis	**Diabetes is the most important factor in COVID-related mortality** Diabetes was the strongest predictor of mortality with COVID-19 after adjustment for confounders in this review whicht included nearly 3,700 articles, 87 studies, 35,000 patients and 6,000 deaths. Chronic obstructive pulmonary disease and malignancies were the next important predictors for mortality. Mortality was higher in the USA (25%) and Europe (20%) than in Asia (13%). Dyspnoea, fatigue/myalgia along with the respiratory rate were the best clinical predictors of mortality. Reduced lymphocyte count, reduced platelet count and increased D-dimer levels were all associated with increased mortality. Corona G, Pizzocaro A, Vena W, et al. Diabetes is most important cause for mortality in COVID-19 hospitalized patients: Systematic review and meta-analysis. Rev Endocr Metab Disord 2021;22:275–96. https://doi.org/10.1007/s11154-021-09630-8
Due *et al*, *Diabetologia*	Population-based cohort study	**Maternal diabetes increased the risk of high refractive error in offspring** After adjusting for multiple potential confounders, diabetes of any type before or during pregnancy was associated with 39% increase in the risk of high refractive error (HR 1.39, hypermetropia 1.37, myopia 1.34%, astigmatism 1.58%) in the offspring at 25 years of age. The risk was higher in mothers with diabetic complications. Du J, Li J, Liu X, et al. Association of maternal diabetes during pregnancy with high refractive error in offspring: a nationwide population-based cohort study. Diabetologia 2021;64:2466–77. https://doi.org/10.1007/s00125-021-05526-z

Authors, Journal	Type of study	Main results
Salem *et al*, *Diabetes Care*	Functional MRI study	**Weight regain after very low calorie diet (VLCD) compared with enduring weight loss after Roux-en-Y gastric bypass surgery (RYGB) may be due to divergent brain activation patterns to food cues** VLCD resulted in increased brain reward centre food cue responsiveness, higher neuronal activation of cognitive centres in response to food cues associated with increased cognitive restraint over eating and less engaged homeostatic appetitive system in hypothalamus compared to RYGB. This may explain why there is more weight gain relapse after VLCD compared with sustained weight loss after RYGB. Salem V, Demetriou L, Behary P, et al. Weight loss by low-calorie diet versus gastric bypass surgery in people with diabetes results in divergent brain activation patterns: a functional MRI study. Diabetes Care 2021;44:1842–51. https://doi.org/10.2337/dc20-2641
Øyen *et al*, *Diabetes Care*	Cohort study	**Intake of lean fish but not fatty fish or long chain n-3 PUFA supplements can reduce the risk of medication treated type 2 diabetes in women after 90 days of delivery who are overweight or obese in pregnancy** 1.1% of women developed diabetes and the risk was lower with lean fish intake only in women with BMI ≥25 kg/m2. There was no association with the intake of total fish, fatty fish, LCn-3 PUFA supplements and type 2 diabetes. Øyen J, Brantsæter AL, Nøstbakken OJ, et al. Intakes of fish and long-chain n-3 polyunsaturated fatty acid supplements during pregnancy and subsequent risk of type 2 diabetes in a large prospective cohort study of Norwegian women. Diabetes Care 2021 Aug 18;dc210447. https://doi.org/10.2337/dc21-0447
Fonseka *et al*, *Clin Diabetes*	Review	**Combination injectable therapy with basal insulin and GLP-1 agonist for people with type 2 diabetes who have high HbA1c and/or long duration (>8 years) of diabetes** About 15% people have high HbA1c >9%. With long duration, beta cell function declines considerably and a combination therapy may be more appropriate in this group of people. Fonseca VA, Sood M, Galindo RJ. Rationale for the use of combination injectable therapy in patients with type 2 diabetes who have high A1c (≥9%) and/or long duration (>8 years): Executive summary. Clin Diabetes 2021;39(2):141–5. https://doi.org/10.2337/cd20-0121
Do *et al*, *Diabetes Care*	Prospective observational cohort study	**Prophylactic aspirin for all pregnant women with diabetes did not change the incidence of pre-eclampsia vs risk-based aspirin strategy** In the all-women group vs selected women group, the incidence of pre-eclampsia was similar (12% vs 11%). Fewer women had type 2 diabetes and BMI was lower in all-cohort. Prevalence of preterm delivery, preterm pre-eclampsia, large for gestational age and small for gestational age was similar for both groups. Do NC, Vestgaard M, Ásbjörnsdóttir B, et al. Unchanged prevalence of preeclampsia after implementation of prophylactic aspirin for all pregnant women with preexisting diabetes: a prospective cohort study. Diabetes Care 2021 Aug 13:dc21-1182 https://doi.org/10.2337/dc21-1182
Lee *et al*, *Diabetes Care*	RCT	**Fast-acting insulin aspart vs insulin aspart (IAsp) using a second generation hybrid closed-loop system in adults with type 1 diabetes** Faster aspart achieved greater Time in Range (TIR) compared with IAsp (82.3% vs 79.6%). Four-hour postprandial glucose TIR was higher using faster aspart compared with IAsp for all meals combined. Lee MH, Paldus B, Vogrin S, et al. Fast-acting insulin aspart versus insulin aspart using a second-generation hybrid closed-loop system in adults with type 1 diabetes: a randomized, open-label, crossover trial. Diabetes Care 2021 Aug 6:dc210814. https://doi.org/10.2337/dc21-0814
Ryg *et al*, *Diabetes Care*	Randomised controlled study	**Patient-initiated visits had better outcome than the scheduled visits** In this study of 357 people with type 1 diabetes comparing the two approaches after 24 months, the intervention group of patient-initiated visits experienced more benefits from consultations compared with standard care ($p<0.05$) with fewer unnecessary visits ($p<0.05$). There was no significant change in HbA1c, LDL, blood pressure and complication status. The mean number of outpatient visits over 24 months was lower in the intervention group compared with the control group (4.4 vs 6.3, $p<0.001$), but the number of telephone contacts was higher (3.1 vs 2.5, $p<0.001$). Ryg ND, Gram J, Haghighi M, Juhl CB. Effects of patient-initiated visits on patient satisfaction and clinical outcomes in a type 1 diabetes outpatient clinic: a 2-year randomized controlled study. Diabetes Care 2021 Jul 22:dc203083. https://doi.org/10.2337/dc20-3083
Rosenstock *et al*, *Diabetes Care*	RCT	**IGlarLixi (SoliMix) achieved lower HbA1c with less weight gain and lower incidence of hypoglycaemia compared to BIasp30 in people not achieving good control with basal insulin only** HbA1c reduction was greater (1.3 vs 1.1 meeting non-inferiority and reaching superiority, $p<0.001$), body weight change was lower (–1.9 kg) and percentage of participants achieving HbA1c <7 % without weight gain and hypoglycaemia were all in favour of IGlarLixi. Rosenstock J, Emral R, Sauque-Reyna L, et al. Advancing therapy in suboptimally controlled basal insulin-treated type 2 diabetes: clinical outcomes with iGlarLixi versus premix BIAsp 30 in the SoliMix randomized controlled trial. Diabetes Care 2021 Jun 28:dc210393. https://doi.org/10.2337/dc21-0393

Authors, Journal	Type of study	Main results
Garcia-Tirado *et al*, *Diabetes Care*	RCT (crossover)	**Advanced closed-loop control system is better to control postprandial glucose than hybrid closed-loop following an unannounced meal** TIR and time in tight range were significantly higher using RocketAP than using USS-Virginia in the 6 h period following an unannounced meal (83% vs 53%, p=0.004 and 49% vs 27%, p=0.002, respectively), primarily driven by reduced time-above-range (17% vs 47%) with no increase in time-below-range. RocketAP also improved control following the announced meal overall and overnight and delivered less insulin overall. Garcia-Tirado J, Diaz JL, Esquivel-Zuniga R, et al. Advanced closed-loop control system improves postprandial glycemic control compared with a hybrid closed-loop system following unannounced meal. Diabetes Care 2021 Aug 15:dc210932. https://doi.org/10.2337/dc21-0932
Cohen *et al*, *Diabetes Care*	Post hoc analysis of RCT	**Renoprotective effect of the combination of empagliflozin and liraglutide combination is less than the effect of metabolic surgery** Both the interventions were effective in reducing urine ACR but RYGB was significantly superior (mean difference 14.99). The % of patients achieving remission of albuminuria/DKD was 59.3% in the combination therapy vs 81.8% in the RYGB group. RYGB was also superior for HbA1c reduction (mean difference 0.49) and LDL cholesterol but not systolic blood pressure. Cohen RV, Petry TB, Miras AD, et al. Renoprotective effects of the combination of empagliflozin and liraglutide compared with roux-en-y gastric bypass in early-stage diabetic kidney disease: a post hoc analysis of the Microvascular Outcomes after Metabolic Surgery (MOMS) randomized controlled clinical trial. Diabetes Care 2021 Aug 6:dc211192. https://doi.org/10.2337/dc21-1192
Todd *et al*, *Diabetes Care*	Evaluation of whole-exome sequence data of youth with diagnosis of type 2 diabetes	**2.8% of youth diagnosed with type 2 diabetes were found to have MODY** Out of 3,333 participants, 2.3% carries a likely pathogenic or pathogenic variant of one of the MODY genes (HNF4A, GCK, HNF1A, PDX1, INS and CEL). MODY youth had a younger age at diagnosis, lower fasting C-peptide levels, lower incidence of hypertension and higher HDL cholesterol. Todd JN, Kleinberger JW, Zhang H, et al. Monogenic diabetes in youth with presumed type 2 diabetes: results from the Progress in Diabetes Genetics in Youth (ProDiGY) Collaboration. Diabetes Care 2021 Aug 6:dc210491. https://doi.org/10.2337/dc21-0491
Voss *et al*, *Diabetes Care*	Analysis of data from studies	**Time to peak glucose and C-peptide during OGTT may predict the development of type 1 diabetes in antibody positive relatives** Higher 5-year diabetes progression risk was seen in those with time to peak glucose >30 min and time to peak C-peptide >60 min. The association was greater with time to peak C-peptide vs peak C-peptide level. Voss MG, Cuthbertson DD, Cleves MM, et al. Time to peak glucose and peak c-peptide during the progression to type 1 diabetes in the Diabetes Prevention Trial and TrialNet cohorts. Diabetes Care 2021;44:2329–36. https://doi.org/10.2337/dc21-0226
Hansen *et al*, *Diabet Med*	Review	**Semaglutide in real world** HbA1c reduced by 12.8 mmol/mol in GLP1 agonist naïve and 6.4 in GLP-1 experienced people with type 2 diabetes in real world data from a clinic. Body weight reduced by 5 kg and 3.2 kg in the respective populations. 75% received 1 mg QW semaglutide. Hansen KB, Svendstrup M, Lund A, Knop FK, Vilsbøll T, Vestergaard H. Once weekly subcutaneous semaglutide treatment for persons with type 2 diabetes: real world data from a diabetes out patient clinic. Diabet Med 2021;38(10):e14655. https://doi.org/10.1111/dme.14655
Smith *et al*, *Diabet Med*	Systemic review/ meta-analysis	**Insulin dose for meals containing protein and fat** In this review of 18 studies, additional insulin was given in 13 studies. Five studies gave an additional 30–43% on the insulin-to-carbohydrate ratio (ICR) for 32–50 g of fat and 31–51% ICR for 7–35 g of fat and 12–27 g of protein added to control meals. Overall, there was glycaemic benefit of an additional 24–75% ICR for fat and fat and protein meals. There was some supportive evidence for insulin delivery in a combination bolus with a minimum upfront dose of 60% ICR, 15 min before the meal. Smith TA, Marlow AA, King BR, Smart CE. Insulin strategies for dietary fat and protein in type 1 diabetes: a systematic review. Diabet Med 2021;38(11):e14641. https://doi.org/10.1111/dme.14641
Foo *et al*, *Diabetes, Obes Metab*	Database study	**The impact of obesity on COVID-19 prevalence and mortality globally** Higher obesity prevalence was associated with increased COVID-19 mortality and prevalence rate. For every 1% increase in obesity prevalence, the mortality rate increased by 8.3% and the case rate was higher by 6.6%. Higher median population age, greater female ratio, higher human development index, lower population density and lower hospital bed availability were all significantly associated with higher COVID-19 mortality rate. Stricter government actions, higher HDI and lower mean annual temperature were significantly associated with higher COVID-19 case rate. Foo O, Hiu S, Teare D, Syed AA, Razvi S. A global country level analysis of the relationship between obesity and COVID-19 cases and mortality. Diabetes Obes Metab 2021 Aug 16:10.1111/dom.14523. https://doi.org/10.1111/dom.14523

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1. Carlson, A.L. et al. 97-P- Safety and glycaemic outcomes of the MiniMed™ AHCL System in subjects with T1D. 80th ADA International Conference, June 2020, Chicago
2. Collyns .O. et al. 199-OR- Improved glycaemic Outcomes with MiniMed™ AHCL Delivery. 80th ADA International Conference, June 2020
3. Bergenstal, R. M. et al.Safety of a Hybrid Closed-Loop Insulin Delivery System in Patients With Type 1 Diabetes Jama. 2016; 316 (13): 1407 – 1408
4. Data on file. Medtronic pivotal trial (age 14-75) Ahe 14-75 2020; 16 US sites

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Further, Together

Authors, Journal	Type of study	Main results
Thiele *et al*, *Diabetes, Obes Metab*	Randomised study	**Empagliflozin improves haematological variables** In this study, haematocrit and haemoglobin increased after 3 months of treatment. After 3 months, red blood cell count and transferrin concentration increased. There was a trend towards increased erythropoietin levels while ferritin, total iron and transferrin saturation levels decreased after 3 months. Increase in urine glucose excretion was significantly correlated with the induction of erythropoietin. The mechanism may be reduced tubular glucose re-sorption resulting in diminished cellular stress leading to higher renal erythropoietin secretion. Thiele K, Rau M, Hartmann NU, et al. Effects of empagliflozin on erythropoiesis in patients with type 2 diabetes – data from a randomized, placebo controlled study. Diabetes Obes Metab 2021 Aug 11. https://doi.org/10.1111/dom.14517
Eldor *et al*, *Diabetes, Obes Metab*	Safety and efficacy study	**Oral insulin (ORMD-0801)** In this 28-day safety and efficacy study on 188 people with type 2 diabetes, mean night-time CGM increase was lower in the insulin group compared to placebo (1.7 vs 13.7 mg/dL). Glycaemic control variables (24-hour, fasting and day time CGM glucose) also displayed smaller increases with insulin compared with placebo. Change from baseline HbA1c was –0.01% in the insulin arm vs +0.20% in the placebo group (p=0.0149). There was no increase in hypoglycaemia or safety events. Eldor R, Neutel J, Homer K, Kidron M. Efficacy and safety of 28 day treatment with oral insulin (ORMD 0801) in patients with type 2 diabetes mellitus: a randomized placebo controlled trial. Diabetes Obes Metab 2021;23(11):2529–38. https://doi.org/10.1111/dom.14499
Pratley *et al*, *Diabetes, Obes Metab*	Bucher indirect comparison	**Semaglutide 1.0 mg vs dulaglutide 3.0 and 4.5 mg** Semaglutide 1.0 mg significantly reduced HbA1c versus dulaglutide 3.0 mg with an estimated treatment difference of 0.24% points and comparable reduction of HbA1c versus dulaglutide 4.5 mg. Semaglutide 1.0 mg significantly reduced body weight versus dulaglutide 3.0 and 4.5 mg with an ETD of –2.65 kg and –1.95 kg, respectively. Pratley RE, Catarig AM, Lingvay I, et al. An indirect treatment comparison of the efficacy of semaglutide 1.0 mg versus dulaglutide 3.0 mg and 4.5 mg. Diabetes Obes Metab 2021;23(11):2513–20.https://doi.org/10.1111/dom.14497

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UPDATE
www.abcd.care/dtn

It has been a busy few months for the DTN.

Hybrid closed loop pilot project

NHS England announced a project to provide hybrid closed loop therapy to up to 1,000 people with type 1 diabetes through 25 adult and seven paediatric sites as part of a pilot. The ABCD and DTN were closely involved in developing online data collection tools through the ABCD audit system. DTN also hosted a series of webinars led by Dr Sufyan Hussein from GSTT and Geraldine Gallen from KCH to support teams on how to choose the best systems and how to on-board patients to this treatment. The DTN also hosts a weekly catch-up call with all the pilot centres and NHS England, which has been invaluable in ironing out some of the logistical and implementation details that are inevitable with a project like this.

Academy

It has been great to see an ongoing high uptake to the Academy education programme. After a slight dip in August, we have seen a lot of activity on this platform through September. It is great to see all the work we put into this platform being used by clinicians and been heart-warming to receive the messages of support showing how useful this has been for teams across the country. We are working to make this a desirable addition for all trainees in Diabetes & Endocrinology and we should be sharing the data on uptake in different departments with the team at NHS England. It was great for Academy to be nominated as a finalist for the annual QIC awards.

Expert opinions on devices

In this virtual world, supporting people with diabetes on the choice of device has become even more difficult. They are not able to have a look at devices and handle them before choosing. To try and help teams support patients through this, we filmed a series of videos on expert opinions on devices with two experienced educators. Sara Hartnell from Cambridge and Geraldine Gallen from King's provide their opinions on the pros and cons of all the different devices available currently.

Annual DTN day

We ran our annual conference, twinned with the ABCD Conference, on Wednesday 13th October. We were hoping so much that we would be able to hold this meeting face-to-face but, sadly, the COVID-19 situation meant that we had to run it virtually again this year. The silver lining to running the meeting virtually was that we actually had a lot more attendance than we would have had face-to-face. We had over 350 people registered for the meeting and attendance levels were over 250 for most of the day. We had a fantastic programme with a number of great presentations covering closed loops, connected pens, the latest glucose monitoring data in Scotland and finishing up with valuable talks on type 1 diabetes and eating disorders, as well as how to manage hypoglycaemia that is resistant to treatment with technology. A focused meeting report will follow in the next issue.

Dr Pratik Choudhary
Contact: pratik.choudhary@kcl.ac.uk

YDEF NEWS

EDUCATION • ADVOCACY • SUPPORT

YDEF continues to develop from the recent pandemic period in strong form, under the leadership of Giulia Argentesi. The committee held their first face-face meeting following the recent restrictions with exciting future plans ahead. New committee members have been interviewed (watch this space) and new positions created on the committee to better represent trainees including our first less than full time training rep, an international medical graduate representative and a deputy chair and a future IMT representative. This will allow YDEF to fully embrace the changes ahead for trainees and NHS in general.

We were delighted to lead a heavily oversubscribed diabetes technology course working directly with ABCD DTN – a unique residential course that allows people to wear diabetes devices to experience what the patients we care for live with on a daily basis. As ever, the feedback from the course was fantastic and we are truly grateful to the speakers who attended and gave their insights. Noting the very high demand for the course, we are signposting the other great diabetes technology courses available and look to run an additional course this year to meet demand.

We have launched our first ever Marjorie Award looking to recognise junior doctors and medical students who have worked to reduce healthcare inequalities in relation to diabetes diagnosis, monitoring and treatment. Marjorie was a dog who was the first animal to ever be injected with insulin, a drug that has transformed and saved so many lives since its discovery 100 years ago. To mark the occasion of the first injection of insulin into a human on 11th January 1922, the Association of British Clinical Diabetologists (ABCD) are hosting a two-day event (11th and 12th January 2022) at the Royal College of Physicians, London, including a celebratory dinner on 11th January. In honour of the 100-year anniversary of insulin and Marjorie the dog, the YDEF Team has launched the Marjorie Prize, with five awardees fully funded to attend this event, awarded to those working to reduce diabetes-related healthcare inequalities.

We hope this year to run our YDEF day in-person, this year asynchronous with the Diabetes UK Professional Conference as a one-off. Watch this space for more information.

Virtual opportunities remain available. ABCD and Lilly have kindly supported the Diabetes Masterclass series which has been incredible with fantastic attendance. The Obesity course held its first of three webinars in the last few weeks and was very well received and over-subscribed.

On behalf of the rest of the committee I would like to thank our outgoing chair Najaf Haider for all his efforts, guidance and leadership during what has been a very turbulent year for YDEF and the NHS as a whole. We look forward to delivering an exciting range of education and advocacy programmes in the face of new challenges, new curriculums and new national guidelines. We are particularly excited to be continually strengthening our relationship with partner organisations such as ABCD and the Society for Endocrinology, amongst others.

Dr Tim Robbins
on behalf of YDEF Committee
University Hospitals Coventry &
Warwickshire NHS Trust, UK
Contact: timothy.robbins@nhs.net

YDEF is dedicated to all diabetes and endocrine trainees and is open for new members to register on our website. Take advantage of our regular newsletters and up-to-date advertising of a wide variety of courses and meetings to complement your training. As always, we are continuously looking to develop and propagate our specialty so do not hesitate to contact us if you have any suggestions or questions!

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1 Feig DS, *et al.* Lancet 2017;390(10110):2347-59. *For a list of compatible devices, visit www.dexcom.com/compatibility. †A non-Dexcom system was used for this study. ‡Internet connectivity required for data sharing. Following requires the use of the Follow App. Followers should always confirm readings on the Dexcom G6 App or Receiver before making treatment decisions. Dexcom, Dexcom Follow, Dexcom Clarity and Dexcom G6 are registered trademarks of Dexcom, Inc. in the U.S., and may be registered in other countries. © 2020 Dexcom Inc. All rights reserved. Dexcom, International, Ltd. and its affiliated European entities. 1 Tanfield, Suite 6, Level 1 Tanfield, Edinburgh EH3 5DA. LBL018757 Rev001.