Dapagliflozin: an effective adjunctive treatment in type 1 diabetes
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Introduction Many people with type 1 diabetes (T1DM) continue to run high HbA1c levels with an associated elevated risk of cardiovascular events and increased mortality. We describe here how adjunctive prescription of an SGLT2 inhibitor has improved the glycaemic control of several people with T1DM, where the new technology has been intensively deployed.

Methods We report outcomes of six adults with T1DM who have been given dapagliflozin in East Cheshire, UK. Initiation was with education/support from the diabetes specialist nurses. All had an HbA1c of 70 mmol/mol (8.6%) or more before this was initiated. All had been monitoring glycaemia with a FreeStyle Libre monitor for at least 6 months prior to this.

Results The age range was 30–68 years. The mean duration of T1DM was 23.3 ± 5.5 years. All were on a basal-bolus regime. Over a 6 month period, HbA1c fell from 78.5 mmol/mol (9.3%) to 55 mmol/mol (7.2%). The greatest reduction in HbA1c was 57 mmol/mol (7.4%). Analysis of the FreeStyle Libre blood glucose records showed that the proportion of blood glucose readings on target (4–10 mmol/L) increased from 33.1 to 65.2% with the addition of dapagliflozin (P = 0.007). The proportion of blood glucose readings above target (>10 mmol/L) decreased from 68.0 to 26.4%, 6 months after initiation of dapagliflozin (P = 0.005). There was no increase in symptomatic hypoglycemia.

Conclusion Dapagliflozin as adjunctive therapy to basal-bolus regime insulin in individuals with T1DM was well tolerated and improved glycemic control with no increase in hypoglycemia. We provide further evidence of the value of this intervention.

Keywords: glycaemic control, HbA1c, SGLT2-inhibitor, type 1 diabetes

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Intensive insulin management is currently the only option for the effective treatment of T1DM. However, even when target HbA1c levels are achieved, there is still evidence for excess mortality in patients with T1DM [8]. Sodium–glucose cotransporter 2 inhibitors (SGLT2-is) block the SGLT2 transporter in the proximal renal tubule resulting in glucosuria and natriuresis and are approved and indicated for T1DM [10]. Owing to their oral route of administration, low risk of hypoglycemia, and proven cardiovascular and renal protection in T1DM, there is increasing interest in using these drugs for the treatment of T1DM, with 2 recent clinical trials demonstrating their efficacy in this regard [11,12].

In the area of Eastern Cheshire, UK, the diabetes specialist nurse (DSN) team has been an early adopter of dapagliflozin in the treatment of T1DM. At the time of writing, this is the only SGLT2-i licensed in the UK for the treatment of T1DM [13].
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Continuous glucose monitoring (CGM) devices which display an estimate of blood glucose levels, along with trends in direction, in real-time and in the eyes of many they are proving to be a step-change in T1DM management and are now widely used in the UK and elsewhere. The use of CGM itself is associated with a reduction in HbA1c [14,15].

The DSN team in Eastern Cheshire, UK, works across a mixed urban and rural catchment area south of the conurbation of Greater Manchester. They provide an outreach service to GP practices across the area, as well as clinics at a central location. There are at least 1000 people known to have T1DM in Eastern Cheshire, of whom the majority are managed in primary care. The specialist service sees people with T1DM in an episodic care model, so once glycemia has been stabilized, the person with diabetes is again looked after in primary care.

Here we describe our experience of the impact of the addition of dapagliflozin on HbA1c and the CGM glycaemic profile over recent months.

Methods

In this real-world study, we report the outcomes of six adults (18 years of age or more) with T1DM who have gone on adjunctive dapagliflozin treatment after continuing to have suboptimal glycaemic control in spite of intensive treatment with a basal-bolus insulin regime. Initiation was with education and support from one of the DSNs. All had an HbA1c of mmol/mol (%) prior to initiation of dapagliflozin. All had been monitoring glycemia with a FreeStyle Libre monitor (Maidenhead, Berkshire, UK) for at least 6 months prior to this.

Dapagliflozin was prescribed at the dose of 5 mg daily. Dose adjustments in insulin were subsequently made, but contact continued at the same frequency as before with the DSN team. None of the participants attended an expert patient program during the follow-up period nor had attended such a program in the previous 12 months.

On average, contact was made every 2 weeks in the first weeks on dapagliflozin, then every 4 weeks. This was usually a telephone review as the LibreView facilitates a remote review of all domains of the FreeStyle Libre glucose record, including day-to-day traces and summary fields.

HbA1c was measured using the Menarini autoanalyzer (Menarini Diagnostics UK, Wokingham, Berkshire). HbA1c was recorded at baseline, 3 months after the start of monitoring in all users and after 6 months in the majority of users. BMI was recorded at the time of initiation of monitoring. Subsequent monitoring of BMI was not possible because of the changes in patient contact with general practice and specialist services in the UK as a consequence of the limitations related to COVID-19.

Each of the patients were asked to check for urine ketones. We ensured that they had a supply of urine ketone test strips. Also, they were asked about whether they had any history of genital yeast infections or of urinary tract infections.

This was a quality improvement project. Ethics approval was not obtained for this study, as the treatment was being given as part of standard care according to National Institute for Health and Clinical Excellence (NICE) guidance (NICE 2016) [13]. All individual patient data were anonymized prior to statistical analysis.

This follow-up study ran between 1 August 2019 and 30 July 2020.

Statistical analysis

Comparison of HbA1c pre- and postdapagliflozin was made by paired t test. Outcomes were reported as mean with 95% confidence interval (CI) and their range using STATA 14 (StataCorp. 2015. Stata Statistical Software: Release 14, College Station, Texas, USA: StataCorp LP).

Results

Baseline characteristics and are given in Table 1. The duration of T1DM was 9.3–37.4 years with a mean duration of 23.3 years. Baseline HbA1c varied from 70 to 104 mmol/mol.

The mean age of the individuals was 43.8 years, with an age range 30–68 years.

All six people were on a basal-bolus regime prior to going on dapagliflozin. One of the individuals was on insulin Glargine, and five were on insulin Degludec. In relation to short-acting analog, four were on Novorapid, one on Apidra and one on Fiasp.

The mean preintervention HbA1c was 78.5 mmol/mol (9.3%) (95% CI, 64.4–92.6 mmol/mol; 9.0–10.6%). At 3 months after the intervention, mean HbA1c fell significantly to 59.0 mmol/mol (7.5%) (95% CI, 48.2–69.8 mmol/mol; 6.6–8.5%), a reduction of 19.5 mmol/mol (1.8%).

| Table 1 Baseline characteristics and HbA1c pre- and postdapagliflozin |
|---------------------------------------------------------------|
| (n = 6)                                                       |
| Age (years) (range)                                          | 43.8 (30.1–68.1) |
| BMI (kg/m²) (range)                                          | 31.0 (18.7–42.3) |
| Duration of T1DM (years) (range)                             | 23.3 (7.2–43.0)  |
| Baseline HbA1c (mmol/mol) (range)                            | 78.5 (66–104)    |
| 6 months postdapagliflozin HbA1c (mmol/mol) (range)          | 55.0 (45.0–65.0) |

Data are presented as mean (range). T1DM, type 1 diabetes.
At 6 months, mean HbA1c had fallen further by 23.5 mmol/mol (2.1%) compared with baseline ($P = 0.005$) to 55.0 mmol/mol (7.2%) (95% CI, 47.6–62.4; 6.5–7.9%) (Fig. 1).

Analysis of the FreeStyle Libre blood glucose records showed that the proportion of blood glucose readings on target (4–10 mmol/L) increased from 33.1 to 65.2% with the addition of dapagliflozin ($P = 0.007$). The proportion of blood glucose readings above target (>10 mmol/L) decreased from 68.0 to 26.4% 6 months after initiation of dapagliflozin ($P = 0.005$). The proportion of blood glucose readings below target (<4 mmol/L) increased slightly from 1.5 to 5.6% 6 months after initiation of dapagliflozin ($P = 0.04$).

There was no increase in the incidence of symptomatic hypoglycemia with the addition of dapagliflozin (average 3.4 predapagliflozin symptomatic episodes over 6 months vs. 3.1 symptomatic episodes in the 6 months postdapagliflozin). None of the users discontinued dapagliflozin over the 6-month follow-up period.

**Representative FreeStyle Libre traces**

We have shown a representative trace pre- and postdapagliflozin in Fig. 2a, b for patient 3. In this trace, we see that the mean blood glucose through the day decreased with dapagliflozin, with the range of blood glucose readings becoming much more closely distributed around the mean through the 24 h period. Predapagliflozin addition, the majority of blood glucose readings through the 14 day period were >10 mmol/L. Six months postdapagliflozin, only a small proportion of blood glucose readings were above 10 mmol/L. There was a similar improvement in glycaemic profile for all patients.

**Patient narrative (patient 4)**

‘I was diagnosed with type 1 diabetes at the age of 30 and 18 years on I felt no further forward with my control. It seemed that the harder I tried, the worse my control was, and at times, it just felt that insulin didn’t work, as in general, my blood sugar was always high.

When my specialist nurse L… told me about dapagliflozin I was skeptical to say the least! I just didn’t like the description of how it worked and the possible side effects. However, after some thinking, I decided to try the tablets.

Almost instantly, things changed! It felt like suddenly insulin started to work properly, and I started to get straight lines within target on my chart; I had never had this before, in fact, I have had some days of 100% in target. It’s the type of control that I just didn’t think was possible for me.

It has now been approximately 6 months since I started taking dapagliflozin, and I have had no noticeable side effects.

Of course, nothing with diabetics is perfect, and I still have the occasional bad day, but now I can tell why and fix things quickly.
In my experience, dapagliflozin has been a total game changer!'

Discussion
We have here provided persuasive evidence for the addition of dapagliflozin in people with T1DM whose blood glucose levels are above target. The mean reduction in HbA1c was 23.5 mmol/mol (2.1%) in the individuals that we studied at 6 months postinitiation of dapagliflozin. Thus addition of an SGLT-2-i has the potential to help people to manage their T1DM more effectively. This has major implications in terms of potentially reduced complication rate and reduced mortality in the future [6–9].

The benefits of using SGLT2 inhibitors in the treatment of T1DM should be balanced against the increased risk of diabetic ketoacidosis (DKA). The incidence of definite DKA events in DEPICT-2 was higher compared with DEPICT-1 (dapagliflozin 5 mg vs. dapagliflozin 10 mg vs. placebo) [12]. None of our patients suffered an episode of DKA on dapagliflozin, and the incidence of hypoglycemia was similar at 83% experiencing one or more episodes of symptomatic hypoglycemia compared with 82% in DEPICT-2 [12].

The patient narrative gives a moving account of the way that this treatment changed the life of one person, ‘It felt like suddenly insulin started to work properly, and I started to get straight lines within target on my chart; I had never had this before; in fact, I have had some days of 100% in target. It’s the type of control that I just didn’t think was possible for me’. This describes the way that one person experienced a change in their life with T1DM as a result of the addition of dapagliflozin.

None of the users in this study attended a structured expert patient program during the 6-month follow-up or in the previous 12 months. Therefore, the changes in glycemia are likely to be a result of the addition of dapagliflozin—as far as it is possible to say in a real-world case series, as reported here. For most participants, the follow-up period included some of the time when the UK was in ‘lockdown 1’. This, if anything, might result in people being more sedentary and having a higher calorie intake, emphasizing the benefits of dapagliflozin here.

The increase in absolute risk of DKA, even in closely supervised patients participating in clinical trials, raises a serious concern that DKA will be even more common if SGLT-2-is are used in routine clinical practice. A number of study participants [16,17] have presented with euglycemic DKA (near-normal or only mildly elevated blood glucose levels), which delayed recognition, diagnosis and treatment. Under experimental conditions, the rate of ketogenesis is not accelerated after interrupting insulin delivery [18]. The increased risk of DKA appears to be attributable to the failure of patients on SGLT inhibitors to promptly recognize early metabolic decompensation, which occurs at substantially lower than usual glucose levels.

It would be prudent to limit adjunctive use of SGLT-2s in T1DM to diabetes specialists cognisant of the potential risks associated with such therapy with appropriately selected people offered the option of adjunctive dapagliflozin [19].

Strengths/limitations
The strength of our study is that it demonstrates in a real-world community diabetes setting the benefit of adding in dapagliflozin where appropriate on T1DM. The most significant limitation is the fact that this is a case series with relatively low numbers. Also, we have not included details of change in BMI and blood pressure which will be covered elsewhere.

Nevertheless, the results and patient narrative bear out the value of adjunctive dapagliflozin treatment in relation to improving blood glucose levels in people with T1DM.

Conclusion
We have shown that the addition of dapagliflozin is an effective intervention to improve glycaemic control in people with historically not well-controlled T1DM.
If sustained, the improvements seen here in glycaemic control with dapagliflozin should associate with reduced diabetes-related complications over the life course of T1DM treatment.

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Any requests for data extracts will be considered by Dr. Adrian Heald as the corresponding author.

Conflicts of interest
There are no conflicts of interest.

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