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A pilot study of the feasibility of empagliflozin in recent-onset type 1 diabetes

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ABSTRACT

Introduction: Sodium-glucose linked transporter (SGLT) inhibitors could improve glycaemia and simplify insulin regimens in recent-onset type 1 diabetes (T1D), provided they were well-tolerated and safe. This study aimed to determine the feasibility and safety of a SGLT inhibitor for the treatment of recent-onset T1D.

Method: An open label, prospective pilot study in adults with recent-onset T1D was performed. Empagliflozin, 25 mg orally daily, was given in combination with insulin and multidisciplinary care during a 24-week treatment phase, followed by wash-out visits at weeks 30 and 36.

Results: Fourteen participants (4 women; median age 26 years) began and 13 completed the study. No treatment-emergent serious adverse events were observed, with fatigue and genital infection the most common side-effects. Four participants stopped mealtime insulin for at least one month when taking empagliflozin. At week 24, median weight, HbA1c and insulin dose decreased by 4.4 kg, 1.5% (17 mmol/mol) and 0.03 units/kg/day, respectively. Meal-stimulated C-peptide was maintained during the treatment phase and then decreased at 36 weeks.

Conclusions: Treatment of adults with empagliflozin within 100 days of T1D diagnosis appeared safe and was associated with improved clinical outcomes. These findings justify a definitive trial to determine if SGLT inhibitors simplify treatment regimens and improve clinical outcomes in recent-onset T1D.

Registration: ACTRN12617000016336.

1. Introduction

In people with long-standing type 1 diabetes (T1D), sodium-glucose cotransporter (SGLT) inhibitors improve glucose control, decrease insulin requirement and promote weight loss [1], but also predispose to genital infection and ketoacidosis [2]. SGLT inhibitors have not been widely used in recent-onset T1D, primarily due to concern about the risk of ketoacidosis [3]. This would be an unreasonable burden for patients to manage while they are adjusting to their diagnosis and learning how to manage their diabetes. However, the presence of residual beta cell function at diagnosis of T1D [4] is likely to decrease the risk of ketosis with SGLT inhibitor treatment [3]. Furthermore, improved postprandial glucose control, observed in people with long-standing T1D who received sotagliflozin [5], may be particularly helpful in recent-onset T1D by decreasing bolus insulin requirements and simplifying insulin regimens. An argument can be made to evaluate SGLT inhibition as a treatment adjunct in recent-onset T1D provided side-effects are tolerable. Therefore, as a prelude to a randomised control trial, we first sought to determine the feasibility and safety of the SGLT2 inhibitor, empagliflozin, in patients with recent-onset T1D.

2. Materials and methods

2.1. Patients and setting

The study was conducted at Royal Melbourne Hospital between January 2017 and May 2019 and registered as ACTRN12617000016336. Inclusion criteria were age 18-40 years,

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T1D diagnosed within 100 days of starting empagliflozin, presence of at least one islet autoantibody and meal-stimulated plasma C-peptide >0.07 nmol/L. Exclusion criteria were a co-morbidity deemed to pose unacceptable risk, pregnancy or planned pregnancy, breast feeding or, if female, refusal to use effective contraception.

2.2. Interventions and data collection

At weeks 0, 12, 24 and 36, participants undertook routine biochemistry, completed a diabetes distress survey [6] and wore a Minimed™ iPro™2 continuous glucose monitor (CGM; Medtronic Minimed™, Northridge, CA) for one week. Mixed meal tolerance tests were performed at the same intervals to determine beta-cell function, calculated by dividing the trapezoidal area under the C-peptide curve by 120 min [7]. Empagliflozin was withheld three days prior to meal tests at weeks 12 and 24 to avoid potential effects on C-peptide release.

At weeks 4, 8, 18 and 30, additional visits were scheduled to review glucose control. Participants accessed dietician and diabetes educator support at all study visits to target fasting and post-prandial glucose to 5 mmol/L and 10 mmol/L respectively. They monitored capillary ketone concentrations weekly using an Optium Neo device (Abbott, Doncaster, Australia).

Adherence with empagliflozin (25 mg daily from weeks 0–24) was assessed by urine dipstick testing for glucose and by counting tablets.

2.3. Outcomes

The primary outcome of feasibility was assessed as adherence with the study protocol and safety. Secondary outcomes were numbers and severity of adverse events, body weight, stimulated C-peptide, HbA1c, insulin dose, CGM measures and diabetes distress score [6].

2.4. Statistical analyses

Data were complete with the exception of CGM results at week 12 for one participant, which were imputed by averaging the measures at 0 and 24 weeks. Statistical analyses were performed with Prism software (V8, GraphPad, San Diego, CA). The Friedman test was used to assess differences across time, with correction for multiple comparisons by the two-stage linear step-up procedure of Benjamini, Krieger and Yekutieli [8].

3. Results

3.1. Participant recruitment and baseline characteristics

Sixty-one individuals were referred to the study. Fifteen did not meet eligibility and 32 declined to participate due to perceived treatment risks and the study demands. All 14 participants who enrolled were on multiple daily insulin injections. Their baseline characteristics are presented in Table 1. Median [Q1, Q3] age was 26 [22, 32] years, body mass index 24 [23, 26] kg/m^2, disease duration 72 [54, 92] days and HbA1c 7.1 [6.1, 8.5] percentage units (54 [42, 69] mmol/mol).

3.2. Medication adherence and safety

The median rate of empagliflozin adherence was 0.89 [0.74, 1.0]. Four serious adverse events (SAEs) affecting four participants were observed. One (alcohol intoxication without ketosis) occurred during week 24 and the other three (concussion, finger dislocation and supraventricular tachycardia) occurred during weeks 24–36, after empagliflozin was ceased.

3.3. Other adverse events

During weeks 0–24, 14 episodes of generalised fatigue affected 9 participants. These episodes were associated with capillary blood glucose readings in the lower range (between 3.5 and 6 mmol/l) and resolved after 1-5 days in 7 of the affected participants. However, fatigue was sufficiently severe to prompt 2 participants to stop taking empagliflozin: one noted fatigue in week 1 and withdrew from the trial; the other took the tablet intermittently over the first 10 weeks due to fatigue before stopping it. On re-exposure during week 16, fatigue recurred and no further doses were taken. In addition, 5 episodes of mild to moderate genital infection affected four participants, all of whom received topical or oral anti-fungal treatment for up to a week and continued taking empagliflozin.

3.4. Capillary ketone measures

During the 24-week empagliflozin treatment phase, the 13 participants who completed the study performed a median [Q1, Q3] of 35 [20, 66] home capillary ketone measurements, only one of which exceeded 1 mmol/l. This occurred in week 15 associated with headache, that resolved after 4 h, when ketones were 0.6 mmol/l.

3.5. Diabetes outcomes

After 24 weeks, median body weight decreased by 4.4 kg and median HbA1c by 1.5% units (17 mmol/mol; Fig. 1a and b). Insulin doses decreased to week 24 and then increased (Fig. 1c), with 4 participants stopping bolus insulin for at least a month. Meal-stimulated C-peptide did not change significantly during the first 24 weeks and then decreased (Fig. 1d and e). CGM mean glucose decreased initially and then increased between weeks 12 and 36 (Fig. 1f), while glucose time within and below range, and %CV did not change significantly (Fig. 1g, h, i). Diabetes distress did not change significantly (Fig. 1j).

4. Discussion

We demonstrate a high level of treatment adherence and no concerning ketosis or other adverse events when empagliflozin 25 mg daily was combined with basal/bolus insulin therapy within 100 days of T1D diagnosis. Empagliflozin treatment was associated with decreased body weight and improved glucose control despite decreased frequency and doses of insulin injections. Together, these findings demonstrate the feasibility of this approach to T1D therapy, and suggest it may deliver clinical benefit.

Strengths of this study include the prospective collection of measures of capillary ketones, CGM data and beta-cell function (meal-stimulated C-peptide). Ketoacidosis is reported to occur at a rate of 5 events per 100 patient years in established T1D [3]. Our sample size was too small to determine the risk of ketoacidosis but the finding of only one home ketone measurement over 1 mmol/l suggests it was not increased by treatment with empagliflozin. Glucose time in the 3.9–10 mmol/l range did not improve during empagliflozin treatment, in contrast to prior studies of SGLT inhibitors in long-standing T1D [5,9,10]. However, at baseline, the percentage of time in range was much lower in these studies (40-52% compared to 83% in this study), so any change with SGLT inhibitor treatment would have been smaller in magnitude and therefore more difficult to detect. Meal-stimulated C-peptide did not change significantly during the 24-week treatment phase, indicating no substantial effect of empagliflozin on beta-cell

Table 1
Baseline characteristics.

ID	Sex	Age (years)	Diabetes duration[a] (days)	Weight (kg)	BMI (kg/m^2)	DKA at diagnosis	Polyuria/polydipsia at diagnosis	Antibody specificity	HLA-DR genotype	HbA1c (%)	HbA1c (mmol/mol)	Insulin dose (U/kg/day)	Stimulated C-peptide (nmol/l)
1	M	31	58	95.3	26.4	Yes	Yes	GAD, ZnT8	4/X	8.3	67	0.24	0.524
2	F	18	92	84.1	33.7	No	No	GAD, ZnT8	4/X	6.0	42	0.27	1.169
3	M	22	92	63.7	21.5	Yes	Yes	GAD	3/3	6.0	42	0.36	0.489
4	F	34	94	77.7	25.1	Yes	Yes	GAD	NP	6.5	47	0.12	0.640
5	M	22	72	81.2	25.9	No	Yes	GAD, IA2	4/X	5.9	41	0.15	0.920
6	M	27	80	84.0	24.0	No	Yes	GAD, IA2	4/4	8.1	65	0.18	0.399
7	M	18	96	82.9	26.2	No	Yes	GAD, IA2, ZnT8	3/3	5.9	41	0.44	0.493
8	M	22	55	82.9	24.2	No	Yes	GAD, IA2, ZnT8	3/4	7.6	60	0.11	1.042
9	M	27	72	80.0	25.0	No	Yes	GAD	3/4	6.5	48	0.40	1.084
10	F	37	28	64.5	22.5	No	Yes	ZnT8	4/X	10.4	90	0.22	0.392
11	M	31	72	76.1	24.0	No	Yes	GAD, IA2, ZnT8	3/4	6.5	48	0.12	0.435
12	M	22	68	65.8	22.8	No	Yes	GAD	3/X	9.5	80	1.52	0.283
13	F	25	50	56.3	19.7	No	Yes	GAD, ZnT8	3/3	8.9	74	0.52	0.865
14	M	36	28	71.8	23.3	No	Yes	GAD, ZnT8	4/X	7.9	63	0.35	0.552

NP: not performed.
[a] at time of taking first dose of empagliflozin.

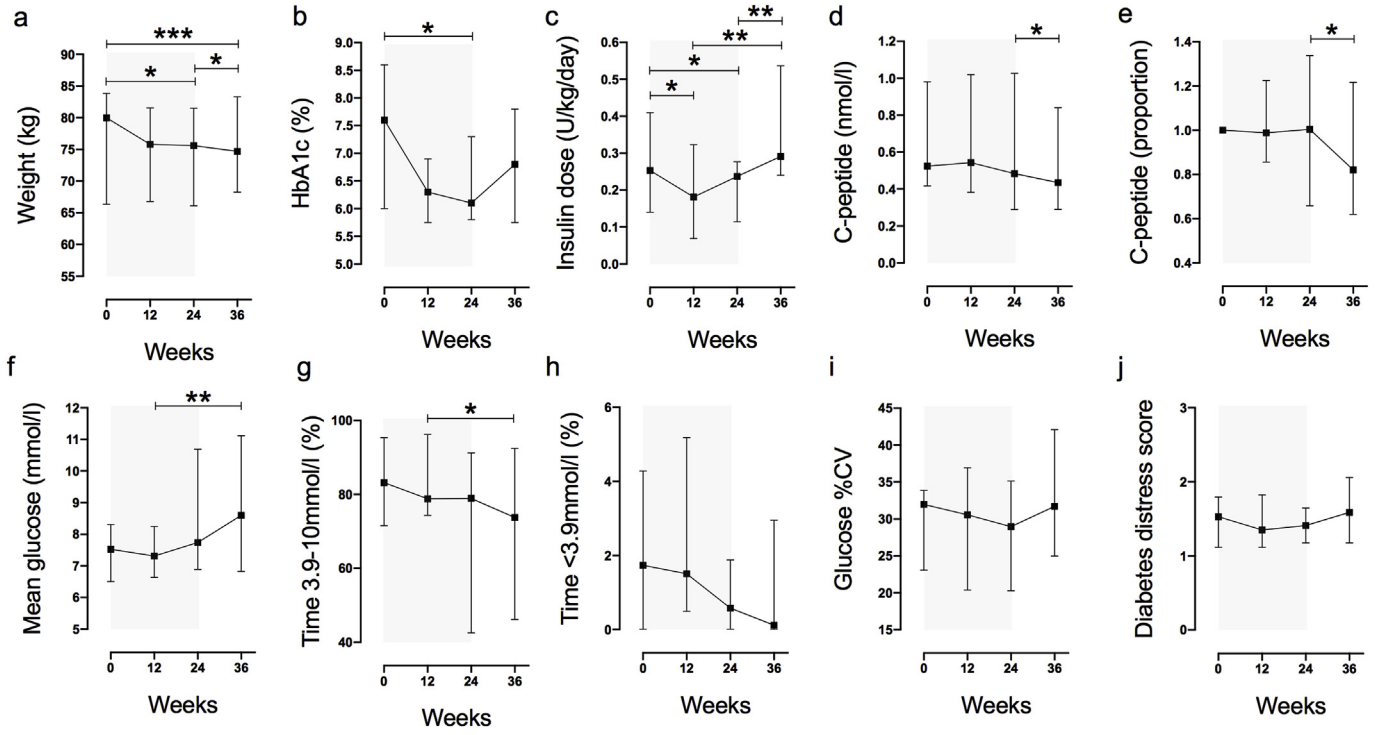

Fig. 1. ***Clinical outcomes for the 13 participants who completed the study***. Weight (a), HbA1c (b), insulin dose (c), meal-stimulated C-peptide (d, e), CGM measures of mean daily glucose (f), time between 3.9 and 10 mmol/L (g), time <3.9 mmol/L (h) and glucose variability %CV (i), and diabetes distress score (j) are shown as median with interquartile range. The grey shaded area corresponds to the empagliflozin treatment phase from weeks 0–24. *, ** and *** depict $p < 0.05$, <0.01 and < 0.001 respectively.

function. The significant decrease in C-peptide between weeks 24 and 36 during the washout phase does however raise the possibility that empagliflozin might preserve beta-cell function in recent-onset T1D. Because the visit schedule of this study mirrored that used by trials of disease-modifying therapy in T1D (e.g. Ref. [11]), our outcome data should aid the design of a placebo-controlled trial involving a similar population to determine the effects of SGLT inhibition on beta-cell function.

This study identified two common adverse events that may limit tolerability of SGLT inhibitors in recent-onset T1D. Genital infection was not unexpected [9,10,12] and was mild to moderate in severity. However, the observation of generalised fatigue affecting 9 participants and causing 2 to stop empagliflozin treatment early was unexpected. Its association with low-normal capillary glucose measures suggests this side-effect might be alleviated by gradual dose escalation of empagliflozin.

5. Conclusion

Our findings provide support for a definitive trial to determine

the effects of SGLT inhibitors on clinical outcomes and on beta-cell function, either alone or in combination with newer non-insulin therapies [11,13].

Declaration of competing interestCOI

None of the authors reports a conflict of interest.

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Research involving human participants and/or animals and informed consent

The study was approved by the Melbourne Health Human Research Ethics Committee and all participants provided written informed consent.

Contributor statements

JMW, PGC and LCH devised the study and drafted the protocol. JMW, PGC and SF oversaw participant recruitment and care. JMW collated and analyzed the data, and drafted the manuscript, which all authors edited.

Data availability

Data for this trial are available from Dr Wentworth upon request.

CRediT authorship contribution statement

John M. Wentworth: Conceptualization, Funding acquisition, Project administration, Formal analysis, Writing - review & editing. **Spiros Fourlanos:** Writing - review & editing. **Peter G. Colman:** Conceptualization, Writing - review & editing. **Leonard C. Harrison:** Conceptualization, Funding acquisition, Writing - review & editing.

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