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Factors that predict glycaemic response to sodium-glucose linked transporter (SGLT) inhibitors.

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Novelty of data and its impact

- First prospective study to determine the predictors of glycaemic response to SGLT inhibitors
- The demonstration that urine glucose excretion does not improve prediction of glycaemic response recommends against measuring urinary glucose excretion in the clinic
- First prospective study to describe the adverse event profile of SGLT inhibitors in 'real-word' patients, finding higher rates of genitourinary side effects than have been reported in landmark clinical trials

Keywords

Type 2 diabetes; SGLT inhibitor; precision medicine; glycosuria; prospective clinical trial; biomarkers; glucose control.

Author contributions

JW, SF and PC conceived the study and drafted the protocol. PC, SF, JW, AH and AG recruited participants and performed study visits. NB performed statistical analyses. JW drafted the manuscript and all authors edited it.

Abstract

Aim

This study aimed to determine the clinical and biochemical variables associated with change in HbA1c in patients with type 2 diabetes who start sodium-glucose linked transporter (SGLT) inhibitor therapy.

Methods

We performed a prospective cohort study (ACTRN12616000833460) of 48 adults with type 2 diabetes (18 female, 38 male) who attended a tertiary hospital diabetes clinic. Fasting serum and urine samples, collected during clinic visits prior to and at 1, 12 and 24 weeks after commencing SGLT inhibitor treatment, were analysed for HbA1c, electrolytes, urea, creatinine and glucose.

Results

After 12 weeks, SGLT inhibitor therapy was associated with respective median (97% CI) decreases in weight, blood pressure, HbA1c and urine albumin/creatinine ratio of 3.0 (1.7 to 3.4) kg, 8 (2 to 16)/4 (3 to 9) mmHg, 6 (3 to 14) mmol/mol and 0.69 (0.18 to 1.8) mg/mmol. These effects persisted to 24 weeks. Urinary frequency and genitourinary infection were common adverse effects. Baseline HbA1c and eGFR independently predicted ΔHbA1c at 12 weeks whereas only baseline HbA1c independently predicted ΔHbA1c at 24 weeks. Urinary fractional glucose excretion and change in fasting glucose one week after starting SGLT inhibitor did not contribute to prediction of glycaemic response.

Conclusions

SGLT inhibitor therapy in a hospital clinic setting was associated with clinical improvements comparable to those observed in clinical trials but with higher incidence of genitourinary side effects. Baseline HbA1c and eGFR, but not urine fractional glucose excretion, predicted glycaemic response.

Introduction

Sodium-glucose linked transporter (SGLT) inhibitors are being increasingly used as glucose-lowering medications in type 2 diabetes following the publication of landmark trials that demonstrated their ability to promote weight loss, lower blood pressure and improve cardiac and renal outcomes (1-4). 'Real world' registry studies also confirm that SGLT inhibitors promote weight loss, improve HbA1c and are associated with decreased risk of cardiovascular events (5).

Given the importance of glucose control in type 2 diabetes and the increasing number of glucose-lowering medications, there is considerable interest in predicting the glycaemic impact of each drug class. However, despite our expanding knowledge of diabetes pathogenesis and the actions of glucose-lowering medication (6), the glucose-lowering effect of a specific diabetes medication for a specific patient is difficult to predict (7). The glycemic response to SGLT inhibitor therapy correlates with pre-treatment HbA1c and renal function (8, 9), suggesting these measures might be useful predictors of treatment response suitable for routine clinical use. In addition, because the glycosuric response to SGLT inhibition varies substantially between individuals (10), measures of glycosuria might be expected to identify patients most likely to benefit.

To address the relationship between glycosuria and glucose-lowering effects of SGLT inhibitors, we performed a prospective cohort study of patients who were commencing either dapagliflozin or empagliflozin in a tertiary hospital outpatient setting. The study aims were to: i) describe the effects of SGLT inhibition on HbA1c and other clinical outcomes in a 'real-world' type 2 diabetes clinic; and ii) identify clinical variables, including glycosuria, associated with absolute change in HbA1c at 12 and 24 weeks.

Methods

The study was approved by the Melbourne Health Human Research Ethics Committee and registered as ACTRN12616000833460. All participants provided written informed consent and the study was sponsored and monitored by Melbourne Health. The protocol is provided in the supplemental material.

Participants were recruited between August 2015 and November 2017. Inclusion criteria were type 2 diabetes, due to commence empagliflozin (10 to 25mg daily) or dapagliflozin (10 mg daily), not anticipated to change lifestyle or prescriptions for lipid- or blood pressure-lowering drugs, and not expected to change other glucose-lowering therapies with the exception of DPP4 inhibitors, which were not subsidised on the Australian Pharmaceutical Benefits Schedule for use in combination with SGLT inhibitors. Exclusion criteria included pregnancy or a desire for pregnancy within the subsequent year and an estimated glomerular filtration rate (eGFR) below 30 ml/min/1.73m^2, in line with the eGFR threshold for entry into the EmpaReg trial of empagliflozin in type 2 diabetes (4).

Study visits were performed prior to commencing SGLT inhibitor and at 1, 12 and 24 weeks afterwards. Participants attended visits between 8 and 11am in the fasting state more than 3 hours after last urinating. At each visit weight and blood pressure were recorded and blood and urine samples were collected.

The primary outcome was HbA1c at week 12. Secondary outcomes included HbA1c at week 24 and, at all time points, blood pressure, weight, body mass index, fasting glucose, lipid profile and urine albumin/creatinine and protein/creatinine ratio.

Missing 24-week data from 3 patients were imputed by carrying forward the 12-week measure. The Friedman test and Chi square test for trend within the Prism v7.0d software package (Graphpad San Diego, CA) were used to compare outcomes relative to baseline. To identify measures associated with glycaemic response at 12 and 24 weeks the *dredge* function within the R software MuMIn library (v1.15.6; www.r-project.org) was used to build linear

models to predict change in HbA1c from baseline to 12 and 24 weeks. Models used one or more of the following inputs: fractional glucose excretion ([serum creatinine]x[urine glucose]x[urine creatinine]$^{-1}$x[serum glucose]$^{-1}$) at week 1, change in fasting glucose from baseline to week 1, and baseline measures of age, diabetes duration, weight, BMI, systolic blood pressure, diastolic blood pressure, HbA1c, total cholesterol, HDL cholesterol, triglycerides, creatinine, eGFR (eGFR>90 was assigned a value of 100ml/min/1.73m^2) and urine albumin/creatinine ratio. Combinations of inputs that resulted in Akaike's information criterion (AIC) scores within 2 units of the lowest value were considered to have equivalent accuracy. For each of the 12- and 24-week time points, the model with the least number of inputs was selected. ANOVA analysis of linear models was then performed to confirm that these simplest models could not be improved by adding other inputs.

Results

Of 78 patients approached to join the study between July 2016 and November 2017, 54 consented to participate and 48 (30 male, 18 female) completed the 12-week assessment. Of these 48 patients, 45 completed the 24-week assessment. At baseline, the median [Q1, Q3] age and diabetes duration were 60 [53, 67] years and 12 [5, 20] years respectively. Nineteen patients (40%) were treated with insulin, 14 (29%) had a history of cardiovascular disease and 4 (8%) were current smokers.

DPP4 inhibitors were ceased in the 11 patients (23%) who were taking these agents prior to starting SGLT inhibitor therapy to comply with Government reimbursement rules. In addition, 5 participants decreased and 2 participants increased doses of other glucose-lowering medication during the study. Polyuria without genitourinary infection prompted two patients to stop empagliflozin after week 12 and another to withhold treatment during weeks 20 to 22. Three patients commenced a new lipid-lowering drug and hydrochlorthiazide was ceased in one. Most patients did not change their usual diet or exercise. However, during the study, 10 participants reported improved diet and 6 reported increased physical activity, compared to 4 and 2 participants, respectively, who reported deterioration in diet and exercise.

Table 1 summarises clinical variables at baseline, 1, 12 and 24 weeks. Within a week of starting SGLT inhibitor, there was a significant median decrease in body weight (-0.7kg), fasting glucose (-0.8mmol/l) and eGFR (-5ml/min/1.73m^2). At weeks 12 and 24, SGLT inhibitor therapy was associated with median weight loss of 2.2 and 1.5kg respectively and corresponding median decreases in systolic/diastolic blood pressure of 13/5 and 10/6mmHg, in HbA1c of 8 and 10mmol/mol and in urinary albumin/creatinine ratio of 1.2 and 0.8mg/mmol. Serum creatinine and lipid profile did not change significantly during the study.

Adverse events (AEs) during the study are summarised in the Supplemental File. Eighteen episodes of polyuria or nocturia affected 18 participants (38%), prompting 2 to stop SGLT inhibitor therapy. There were 10 episodes of mild to moderate genital infection affecting 8

participants (17%) and one episode of urinary tract infection. There were 10 serious AEs affecting 10 patients. Seven events were deemed by investigators to be unlikely or definitely not related to SGLT inhibitor treatment whereas 3 events (retinal vein occlusion, ulnar fracture following a fall and foot sepsis leading to toe amputation) were considered possibly related to SGLT inhibitor treatment. There were no cases of ketoacidosis. Analysis of morning blood ketone concentrations collected from all participants for 2-5 days after each study visit (N=832 measurements) identified only 6 measurements greater than 0.7mmol/l, all of which were recorded after the start of SGLT inhibitor therapy. Three of these measurements were obtained on consecutive days by a participant who was following a low-carbohydrate diet and the other 3 were observed on one occasion in each of 3 participants. None of the patients with high ketone readings were symptomatic.

To identify clinical and biochemical measures that could predict the glycemic effect of SGLT inhibitor therapy, Akaike Information Criterion (AIC) analysis was performed to identify the most accurate of all possible linear models based on one or more (up to a maximum of 15) of the following inputs: age, sex, diabetes duration, baseline clinical measures presented in Table 1, fractional glucose excretion (FGE) at week 1 and the change in fasting glucose from baseline to week 1. AIC analysis identified 8 models based on 2 to 4 inputs to predict ΔHbA1c at 12 weeks and 21 models based on 1 to 4 inputs to predict ΔHbA1c at 24 weeks. Components of these models are presented in the Supplemental File. The simplest model to predict ΔHbA1c at 12 weeks used HbA1c and eGFR, measures that were also inputs for the other 7 models to calculate ΔHbA1c at 12 weeks. The simplest model to predict ΔHbA1c at 24 weeks used only HbA1c, which was also an input for each of the other 20 models to calculate ΔHbA1c at 24 weeks. These findings indicate that, in our population, baseline HbA1c was a universal predictor of ΔHbA1c 12 and 24 weeks after starting SGLT inhibitor therapy and that baseline eGFR was also an independent predictor of ΔHbA1c at 12 weeks. No other early clinical indicator, including FGE or change in fasting glucose after 1 week of treatment, improved prediction of glycaemic outcome.

Discussion

There are few detailed reports of 'real world' outcomes of SGLT inhibitor therapy in the outpatient setting and none that have combined blood and urine biochemistry to determine the ability of urinary glucose excretion to predict glucose-lowering efficacy. Despite the high complexity of our patient group, addition of SGLT inhibitor therapy delivered meaningful improvements in glucose, weight and blood pressure that were similar in magnitude to those observed in clinical trial (11) and registry (5, 12) populations.

The study's prospective design enabled accurate capture of SGLT inhibitor AEs in our patient population. One in five of our patients developed a genitourinary infection within 6 months of starting SGLT inhibitor therapy, a rate that is more than 3-fold higher than rates reported in prospective randomised trials (4, 13). Similarly, polyuria affected 38% of patients and led two to stop SGLT inhibitor treatment. Polyuria has been reported to affect between 1 and 5% of clinical trial participants who received a SGLT inhibitor (1, 4, 13), suggesting our clinic population may be more susceptible to this side effect.

Ketoacidosis is emerging as a significant serious side effect of SGLT inhibitor therapy (14, 15). Home ketone monitoring has the potential to identify ketosis early and is recommended for all patients who use SGLT inhibitors. Our finding that 3-monthly ketone monitoring did not identify any serious ketonaemic events implies routine home ketone monitoring may not be a helpful prevention measure in asymptomatic patients. Rather, our findings suggest home ketone monitoring for type 2 diabetes patients might be best reserved for periods of intercurrent illness or the emergence of ketoacidosis symptoms such as general fatigue, nausea or vomiting.

There is great interest in developing tests to predict the glycaemic impact of glucose-lowering medication in an individual patient as a basis for precision diabetes care (16). Unbiased AIC analysis of the trial data identified baseline HbA1c and eGFR as key determinants of the glucose-lowering effects of SGLT inhibitors in our patient population. This finding is consistent with the mechanism of action of this drug class, which best facilitates glucose loss

in the urine when the circulating glucose concentration is high and there is good renal function. It also accords with prior analyses of clinical trial datasets that have shown a relationship between baseline HbA1c (17) and eGFR (9) with ΔHbA1c as well as with a metanalysis of data from 4 tofagliflozin clinical trials that identified HbA1c and eGFR among several other inputs as predictors of glycaemic response (8). We also demonstrate that whilst urinary glucose excretion is a direct measure of SGLT inhibitor action, FGE did not improve prediction of ΔHbA1c in this study. This finding accords with that of a retrospective Korean study that found no association between urine glucose/creatinine ratio and ΔHbA1c 12 weeks after starting either dapagliflozin or ipragliflozin (18). It is possible that changes in medication, diet and exercise during the study hampered our ability to identify a relationship between glycosuria and ΔHbA1c. However, because such changes are an expected part of routine care, they do not limit our conclusion that FGE is not a useful test to predict the glycaemic impact of SGLT inhibitors in the clinic.

Limitations of this study include the relatively small sample size and relatively brief trial duration of 24 weeks. Longer studies are required to determine the durability of SGLT inhibitor treatment effects and the risks of side-effects in the longer term in 'real world' patients. Furthermore, whilst HbA1c is an important treatment outcome, the recently reported CREDENCE trial showed that SGLT inhibition in people with type 2 diabetes and renal impairment decreased incident renal and cardiovascular events despite relatively modest reduction in HbA1c (2). ΔHbA1c is therefore not the only important treatment outcome to consider when prescribing SGLT inhibitors.

In summary, SGLT inhibitor therapy in a 'real world' tertiary hospital diabetes clinic was associated with significant decreases in body weight, blood pressure and HbA1c. Baseline HbA1c and eGFR, but not FGE, predicted glycaemic response in this patient population.

Conflict of interest statement

None of the authors has a relevant conflict of interest to declare

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Table 1. Clinical and biochemical values of the 48 participants at each study visit

	Baseline	Week 1	Week 12	Week 24	P-value (BL v W1)	P-value (BL v W12)	P-value (BL v W24)
Weight (kg)	91.6 [78.5, 118.3]	90.9 [77.7, 116.9]	89.4 [76, 117.6]	90.1 [75, 115.7]	0.0032	<0.0001	<0.0001
BMI (kg/m^2)	33.1 [29.7, 38.9]	33 [29.1, 38.6]	32.3 [28.5, 38.6]	32.7 [28.7, 38]	0.0806	<0.0001	<0.0001
Systolic BP (mmHg)	148 [139, 159]	142 [130, 155]	135 [124, 158]	138 [125, 144]	0.2071	0.007	<0.0001
Diastolic BP (mmHg)	88 [78, 99]	87 [76, 95]	83 [75, 92]	82 [74, 90]	0.8051	0.1896	0.0041
Fasting glucose (mmol/l)	9.3 [7.8, 12.2]	8.5 [6.8, 10.3]	7.5 [6.3, 8.7]	8.2 [6.2, 9.9]	0.0133	<0.0001	0.0010
HbA1c (mmol/mol)	68 [57, 83]	np	60 [49, 69]	58 [50, 72]	.	<0.0001	0.0037
HbA1c (%)	8.4 [7.4, 9.7]	np	7.6 [6.6, 8.5]	7.5 [6.7, 8.7]	.	<0.0001	0.0026
eGFR (ml/min/1.73m^2)†	88 [70, 100]	83 [63, 100]	86 [67, 100]	88 [69, 100]	0.0216	0.5763	0.4995
eGFR>90ml/min/1.73m^2 (N, %)	21 (44)	19 (40)	20 (42)	19 (40)	0.4097	0.6729	0.9153
90≥eGFR>60ml/min/1.73m^2 (N, %)	20 (42)	18 (38)	19 (40)	22 (48)			
60≥eGFR>30ml/min/1.73m^2 (N, %)	7 (15)	11 (23)	9 (19)	6 (13)			
Total cholesterol (mmol/l)	4.2 [3.5, 5.3]	np	4.2 [3.6, 5.3]	4.2 [3.3, 4.9]	.	0.7713	0.1655
Triglycerides (mmol/l)	1.9 [1.2, 2.8]	np	1.7 [1.3, 2.6]	1.7 [1.1, 2.9]	.	>0.9999	0.4041
HDL cholesterol (mmol/l)	1.1 [0.9, 1.2]	np	1.1 [0.9, 1.3]	1.1 [0.9, 1.3]	.	>0.9999	0.8284
Urine albumin/creatinine ratio (mg/mmol)	3.2 [1.1, 9.4]	2.7 [1.1, 8.2]	2.0 [1.0, 4.8]	2.4 [1.1, 7.8]	0.1733	0.0002	0.0047
Normoalbuminuria (N, %)	22 (46)	25 (52)	33 (69)	26 (54)	0.3033	0.0469	0.2407
Microalbuminuria (N, %)	18 (38)	19 (40)	10 (21)	18 (38)			

Macroalbuminuira (N, %)	8 (16)	4 (8)	5 (10)	4 (8)			
Urine protein/creatinine ratio (mg/mmol)	15.6 [11.8, 25.5]	16.1 [11.9, 26.9]	15.2 [10.9, 27.9]	18.1 [9.6, 27.5]	>0.9999	0.4642	0.3415

Continuous data are median [Q1, Q3]. Statistical correction for multiple comparisons has been performed within but not between different measures.
BL: baseline; W: week; np: not performed; eGFR: estimated glomerular filtration based on CKD-EPI equation
† eGFR calculated using CKD-EPI formula where values >90ml/min were ascribed a value of 100

Table 2. Coefficients for the most accurate and simplest models to predict ΔHbA1c at 12 and 24 weeks. Shown are estimates of β, standard errors (se) and β/se

Variables	ΔHbA1c 12 weeks	ΔHbA1c 24 weeks
Baseline HbA1c (mmol/mol): β	-0.449	-0.402
se(β)	0.0820	0.117
β / se(β)	-5.48	-3.44
eGFR (ml/min): β	-0.233	-
se(β)	0.0806	-
β / se(β)	-2.89	-
Intercept: β	41.5	20.4
se(β)	8.14	8.43

The most accurate models were determined by AIC analysis, as described in *Methods*. A full list of these models is provided in Supplemental Material. The model with the least number of inputs was considered the simplest model to predict ΔHbA1c.