Sodium-Glucose Cotransporter 2 Inhibition and Glycemic Control in Type 1 Diabetes: Results of an 8-Week Open-Label Proof-of-Concept Trial

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OBJECTIVE

Adjunctive-to-insulin therapy with sodium-glucose cotransporter 2 (SGLT2) inhibition may improve glycemic control in type 1 diabetes (T1D).

RESEARCH DESIGN AND METHODS

We evaluated the glycemic efficacy and safety of empagliflozin 25 mg daily in 40 patients treated for 8 weeks in a single-arm open-label proof-of-concept trial (NCT01392560).

RESULTS

Mean A1C decreased from 8.0 ± 0.9% (64 ± 10 mmol/mol) to 7.6 ± 0.9% (60 ± 10 mmol/mol) ($P < 0.0001$), fasting glucose from 9.0 ± 4.3 to 7.0 ± 3.2 mmol/L ($P = 0.008$), symptomatic hypoglycemia (<3.0 mmol/L) from 0.12 to 0.04 events per patient per day ($P = 0.0004$), and daily insulin dose from 54.7 ± 20.4 to 45.8 ± 18.8 units/day ($P < 0.0001$). Mean urinary excretion of glucose increased from 19 ± 19 to 134 ± 61 g/day ($P < 0.0001$). Weight decreased from 72.6 ± 12.7 to 70.0 ± 12.3 kg ($P < 0.0001$), and waist circumference decreased from 82.9 ± 8.7 to 79.1 ± 8.0 cm ($P < 0.0001$).

CONCLUSIONS

This proof-of-concept study strongly supports a randomized clinical trial of adjunctive-to-insulin empagliflozin in patients with T1D.

Results of animal and short-term human studies have suggested that empagliflozin, a highly potent and selective inhibitor of the renal proximal tubular sodium-glucose cotransporter 2 (SGLT2), may be useful as adjunctive-to-insulin therapy in patients with type 1 diabetes (T1D) to improve glycemic control, hypoglycemia risk, and weight (1–4). In a single-arm, open-label study designed with the primary objective of investigating renal hemodynamic effects (5), we sought to determine the feasibility, safety, and efficacy of 8 weeks of treatment with empagliflozin on glycemia in patients with T1D.

RESEARCH DESIGN AND METHODS

In the open-label 8-week Adjunctive-To-Insulin and Renal MechAnistic pilot trial of empagliflozin in T1D (the ATIRMA trial, ClinicalTrials.gov identifier NCT01392560),

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we recruited normotensive, normoalbuminuric adult patients with T1D, free of antihypertensives including renin-angiotensin-aldosterone system antagonists, and A1C 6.5–11.0% (48–97 mmol/mol). Glycemic measures in this trial were exploratory; the primary renal outcomes and detailed design and methods are published elsewhere (5). Forty-two patients underwent baseline assessments and started the study drug. Two patients, described in RESULTS, were withdrawn after diabetic ketoacidosis within 3 days of drug initiation and prior to any follow-up outcome measures.

The clinical trial comprised a 2-week placebo run-in period, 8-week treatment period with open-label empagliflozin 25 mg oral once daily, and 2-week posttreatment follow-up period. Participants documented daily capillary glucose, carbohydrate intake, and insulin doses and used unblinded continuous glucose monitoring (Sof-Sensor electrochemical sensors, Sen-serter insertion device, MiniLink radio frequency transmitter, Guardian REAL-Time Continuous Glucose Monitoring System [Medtronic], and Contour Link Blood Glucose Meter [Bayer]). Given that empagliflozin was predicted to increase daily urinary glucose excretion by 80–90 g, approximately one-third of typical daily

carbohydrate intake, prandial insulin was reduced by 30%, and as an additional safety measure, basal insulin was reduced by 30% (6). Subsequent insulin dose adjustments were performed under investigator guidance based on capillary glucose and not on continuous glucose monitoring data.

Statistical analyses were performed using SAS version 9.2. Sample size calculations were based on the primary end point, defined as the change in glomerular filtration rate (5). Diabetes duration was collected as a categorical variable but is presented here as a continuous variable obtained outside of the clinical trial database. Paired Student t tests were performed to evaluate baseline to end-of-treatment changes. For hypoglycemia events, insulin doses, and carbohydrate intake, baseline and end of treatment corresponded to the mean daily values in the 2-week run-in period and the end of the treatment period.

RESULTS

The 40 patients had even sex distribution (50% male), were 24.3 ± 5.1 years of age, and had 17.1 ± 7.1 years diabetes duration and BMI 24.5 ± 3.2 kg/m². Twenty-six (65%) were insulin pump users, and the remainder used multiple daily injections (5).

A1C decreased from 8.0 ± 0.9% (64 ± 10 mmol/mol) to 7.6 ± 0.9% (60 ± 10 mmol/mol) at the end of treatment ($P <$ 0.0001) (Fig. 1A). In the 22 patients with baseline levels ≥8% (64 mmol/mol), A1C declined from 8.7 ± 0.6% (72 ± 7 mmol/mol) to 8.3 ± 0.8% (67 ± 9 mmol/mol) (P = 0.001), whereas in the 18 patients with levels <8% (64 mmol/mol), A1C declined from 7.2 ± 0.4% (55 ± 4 mmol/mol) to 6.9 ± 0.5% (52 ± 6 mmol/mol) (P = 0.002). The decrease in A1C was accompanied by a decrease in mean fasting capillary glucose (Fig. 1B). Symptomatic hypoglycemic events with capillary glucose <3.0 mmol/L decreased from 0.12 to 0.04 episodes per patient per day at end of treatment (P = 0.0004) (Fig. 1C). We also observed a decrease in all capillary glucose events <3.9 mmol/L from 0.30 to 0.18 events per patient per day (P = 0.0001). An observed decrease in total daily insulin (Fig. 1D) was primarily due to a reduction in basal insulin (25.7 ± 10.6 to 19.5 ± 7.9 units, $P <$ 0.0001) rather than a reduction in bolus insulin (29.0 ± 15.8 to 27.0 ± 14.2 units, P = 0.19). Despite stable prandial insulin, carbohydrate intake increased from 177 ± 121 to 229 ± 160 g/24 h (P = 0.0007). Urinary glucose excretion increased markedly from 18.9 ± 19.1 to
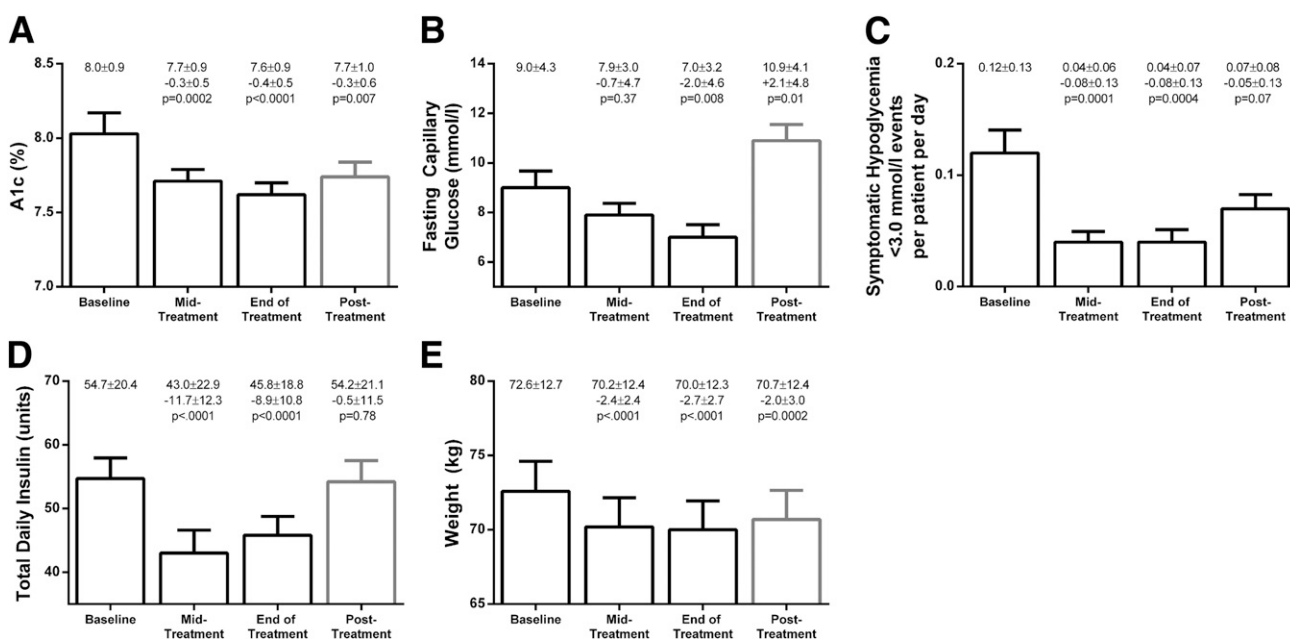

Figure 1—Mean A1C (*A*), fasting capillary glucose (*B*), symptomatic hypoglycemia (*C*), total insulin dose (*D*), and weight (*E*) at each study time point. Bar graphs indicate the mean for each variable, and the error bars indicate the SEM. Mean and SDs, the change in mean from baseline with its SD, and the *P* value for comparison with baseline are shown in each panel for each study time point.

133.5 ± 61.1 g/24 h ($P < 0.0001$). Weight decreased from 72.6 ± 12.7 to 70.0 ± 12.3 kg ($P < 0.0001$) (Fig. 1*E*) and waist circumference from 82.9 ± 8.7 to 79.1 ± 8.0 cm ($P < 0.0001$).

Overall adverse events have been detailed previously (5). Two patients (5%) reported hypoglycemia requiring assistance from a family member, one in placebo run-in and one during treatment. Two patients withdrawn after early occurrence of diabetic ketoacidosis had severe gastroenteritis and insulin pump failure. In these cases, according to investigator judgment in response to capillary glucose readings, total insulin doses were reduced by 70 and 50% of pretreatment levels shortly after initiating empagliflozin. One patient presented with nausea and vomiting, plasma glucose 17.0 mmol/L, and pH 7.01, and the second presented with nausea, plasma glucose 11.8 mmol/L, and pH 7.26. Both patients fully recovered.

CONCLUSIONS

Empagliflozin treatment for 8 weeks improved glycemic control and reduced hypoglycemic events, insulin doses, and weight in patients with T1D. These results complement the observation of improved renal hemodynamic profiles and blood pressure described in a recent publication (5) and are consistent with the salutary effects of SGLT2 inhibitors added to insulin in patients with type 2 diabetes (7–10).

Knowledge of efficacy of SGLT2 inhibition in humans with T1D prior to this work was restricted to a single-dose study of remogliflozin (2). Remogliflozin compared with placebo was associated with substantial improvements in the glucose profile over 10 h (2). The current study extends this work by way of an observation of improved fasting blood glucose and A1C durable to 8 weeks.

Although we cannot confirm through this single-arm study that SGLT2 inhibition as adjunctive-to-insulin therapy poses a low risk of hypoglycemia, we speculate that it may be advantageous because of the insulin-independent mechanism of action, the partial inhibition of glucose reabsorption by SGLT2 inhibitors (11), the diminished effect of SGLT2 owing to a physiological decline in glomerular filtration rate during sympathetic nervous system activation

associated with hypoglycemia (12), and the putative compensatory increase in hepatic gluconeogenesis (13). Finally, SGLT2 inhibition in insulin-treated patients with type 2 diabetes does not substantially increase the risk of hypoglycemia (8,9). We recognize that a smaller and individualized reduction in insulin doses at initiation of study drug may have provided greater glycemic efficacy in the current study. The development of clinical protocols to determine the magnitude of individualized basal and prandial insulin dose adjustment at the initiation of SGLT2 inhibition requires further study.

A further advantage identified in this study is the effect of empagliflozin on weight and waist circumference. Through reducing unphysiological overinsulination and through the caloric loss induced by enhanced urinary glucose excretion, SGLT2 inhibition may provide an additional strategy to lifestyle interventions for maintenance of healthy weight in patients with T1D. Future work should assess whether increased urinary glucose excretion can stimulate a compensatory increase in food intake.

Although the presentation of two cases of diabetic ketoacidosis did not imply a causal relationship with empagliflozin in that the episodes occurred in the presence of clear clinical precipitants (gastroenteritis and insulin pump failure) in combination with exaggerated insulin dose reductions, we considered the possibility that empagliflozin may have modified the clinical presentation. Specifically, both patients presented with plasma glucose concentrations that could be interpreted as lower than typically associated with diabetic ketoacidosis. Although speculative, increased urinary glucose disposal induced by SGLT2 inhibition may be akin to the disposal observed in fasting, prolonged activity or pregnancy in which lower plasma glucose concentrations have been observed (14,15). The risk of ketosis should be carefully evaluated in future trials.

Although limited by the single-arm design, the improvement in glycemic control, reduced hypoglycemic events, insulin doses, and weight strongly supports the design of a longer-term randomized and placebo-controlled clinical trial of adjunctive-to-insulin SGLT2 inhibition in patients with T1D.

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