# Renal Hemodynamic Effect of Sodium-Glucose Cotransporter 2 Inhibition in Patients With Type 1 Diabetes Mellitus

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***Background***—The primary objective of this mechanistic open-label, stratified clinical trial was to determine the effect of 8 weeks' sodium glucose cotransporter 2 inhibition with empagliflozin 25 mg QD on renal hyperfiltration in subjects with type 1 diabetes mellitus (T1D).

***Methods and Results***—Inulin (glomerular filtration rate; GFR) and paraaminohippurate (effective renal plasma flow) clearances were measured in individuals stratified based on having hyperfiltration (T1D-H, GFR ≥ 135 mL/min/1.73m$^2$, n=27) or normal GFR (T1D-N, GFR 90–134 mL/min/1.73m$^2$, n=13) at baseline. Renal function and circulating levels of renin-angiotensin-aldosterone system mediators and NO were measured under clamped euglycemic (4–6 mmol/L) and hyperglycemic (9–11 mmol/L) conditions at baseline and end of treatment. During clamped euglycemia, hyperfiltration was attenuated by −33 mL/min/1.73m$^2$ with empagliflozin in T1D-H, (GFR 172±23–139±25 mL/min/1.73 m$^2$, $P$<0.01). This effect was accompanied by declines in plasma NO and effective renal plasma flow and an increase in renal vascular resistance (all $P$<0.01). Similar significant effects on GFR and renal function parameters were observed during clamped hyperglycemia. In T1D-N, GFR, other renal function parameters, and plasma NO were not altered by empagliflozin. Empagliflozin reduced hemoglobin A1c significantly in both groups, despite lower insulin doses in each group ($P$≤0.04).

***Conclusions***—In conclusion, short-term treatment with the sodium glucose cotransporter 2 inhibitor empagliflozin attenuated renal hyperfiltration in subjects with T1D, likely by affecting tubular-glomerular feedback mechanisms.

***Clinical Trial Registration***—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01392560.

**(*Circulation*. 2014;129:587-597.)**

**Key Words:** diabetes mellitus ■ diabetic nephropathies ■ hypertension, renal ■ nitric oxide ■ renin-angiotensin system ■ SGLT2 protein

Hyperfiltration is an early renal hemodynamic abnormality in experimental models of diabetes and is thought to reflect increased intraglomerular pressure.[1–3] In humans, the prevalence of renal hyperfiltration in subjects with type 1 diabetes mellitus (T1D) has been reported to be as high as 60%, and this condition is accompanied by a significantly increased risk for development of diabetic nephropathy in many studies.[4–6] The pathogenesis of hyperfiltration, however, is complex and involves changes in both neurohormonal/vascular factors (the vascular hypothesis) as well as tubuloglomerular feedback mechanisms (TGF; the tubular hypothesis).[7] Translational clinical studies aiming to attenuate renal hyperfiltration so far have exclusively focused on the vascular hypothesis through the use of pharmacological interventions that modulate renal arteriolar tone, such as cyclooxygenase-2 inhibitors, renin-angiotensin-aldosterone system (RAAS) blockers, and NO synthase inhibitors such as N$^G$ monomethyl L-arginine (L-NMMA) and investigational protein kinase C inhibitors.[8–11] However, targeting renal arterial tone via blockade of neurohormonal factors has thus far largely neglected the role of TGF (Figure 1) in the pathogenesis of renal hyperfiltration in humans.[8–11]

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The tubular hypothesis is based on an increase in proximal tubular glucose delivery attributable to chronic hyperglycemia in diabetes mellitus. This leads to a maladaptive increase in glucose reabsorption along with sodium via the sodium-glucose cotransporter 2 (SGLT2) in the proximal tubule. As a result, distal sodium chloride delivery to the macular densa is decreased.[12]

Received July 17, 2013; accepted October 17, 2013.

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***Circulation*** **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.113.005081**

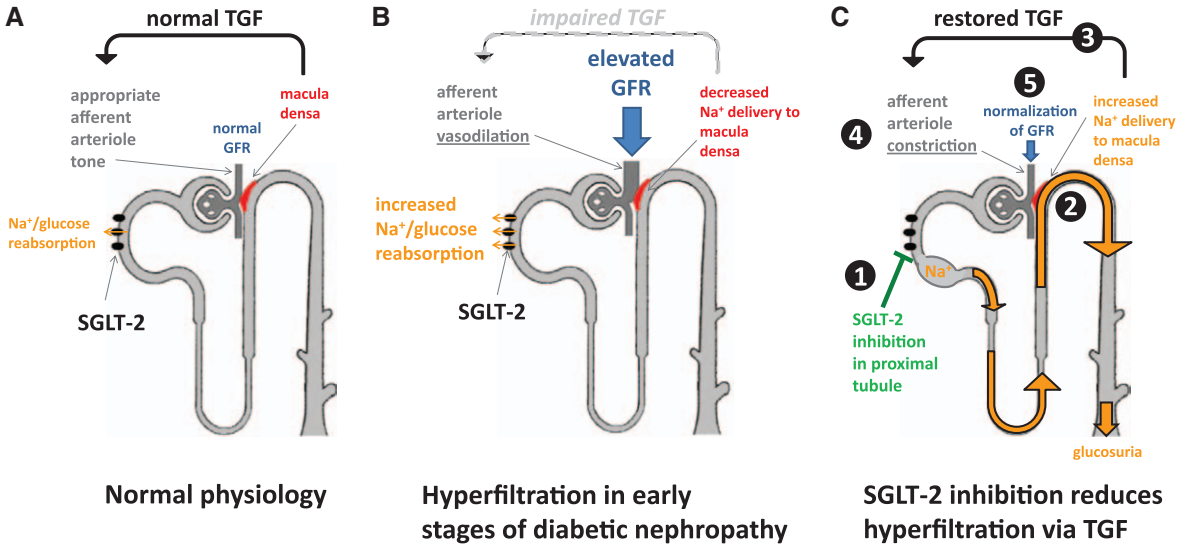


**Figure 1.** Postulated tubuloglomerular feedback (TGF) mechanisms in normal physiology, early stages of diabetic nephropathy, and after sodium-glucose cotransporter (SGLT) 2 inhibition. **A,** Under physiological conditions, TGF signaling maintains stable glomerular filtration rate (GFR) by modulation of preglomerular arteriole tone. In cases of conditional increases in GFR, the macula densa within the juxta-glomerular apparatus senses an increase in distal tubular sodium delivery and adjusts GFR via TGF accordingly. **B,** Under chronic hyperglycemic conditions (diabetes mellitus), increased proximal SGLT2-mediated reabsorption of sodium ($Na^+$) and glucose impairs this feedback mechanism. Thus, despite increased GFR the macula densa is exposed to lowered sodium concentrations. This impairment of TGF signaling likely leads to inadequate arteriole tone and increased renal perfusion. **C,** SGLT2 inhibition with empagliflozin treatment blocks proximal tubule glucose and sodium reabsorption, which leads to increased sodium delivery to the macula densa. This condition restores TGF via appropriate modulation of arteriolar tone (eg, afferent vasoconstriction), which in turn reduces renal plasma flow and hyperfiltration.

This distal tubular condition is sensed as a low effective circulating volume stimulus at the level of the juxtaglomerular apparatus, causing an afferent renal vasodilatory response (Figure 1B). The consequence of this altered TGF results in supranormal glomerular filtration rate (GFR) values into the hyperfiltration range. Targeting TGF in renal hyperfiltration has shown promising results in experimental animal models by using phlorizin, a nonspecific inhibitor of the renal tubular glucose transporters SGLT1 and SGLT2.[13,14] The clinical relevance of these findings, however, could not be conclusively studied in humans, because of the poor tolerability of phlorizin resulting from its low selectivity for SGLT2, SGLT1 inhibition-related gastrointestinal side effects and very limited oral bioavailability.[14] Subsequent studies with selective SGLT2 inhibitors in animals have also shown similar significant effects on renal hyperfiltration.[15]

More recently, several highly selective SGLT2 inhibitors have been developed for use in clinical trials in patients with type 2 diabetes mellitus (T2D).[16,17] These compounds generally do not affect SGLT1 at clinical doses and have pharmacological features that allow once daily oral dosing. In T2D, this class of drugs is well-tolerated and has consistently improved glycemic control, along with weight loss, and antihypertensive effects.[17,18] Available evidence for SGLT2 inhibitors in T1D is however limited, and is mainly derived from experimental animal models. Only 1 clinical pilot study has been conducted, which demonstrated that a single dose of remogliflozin improved postprandial glucose profiles.[19] Based on previous findings with phlorizin and other SGLT2 inhibitors in animals, the concept of altering renal hyperfiltration by blocking renal glucose absorption with SGLT2 inhibitors is intriguing, because reducing this surrogate marker of intraglomerular pressure is renal protective in experimental models of diabetes mellitus.[13,20,21] However, potential renal hemodynamic effects of these drugs in subjects with diabetes mellitus, including effects on renal hyperfiltration, remain unknown.

Accordingly, the primary objective of this 8-week, open-label, stratified clinical trial (NCT01392560) was to determine the impact of treatment with the oral and highly selective SGLT2 inhibitor empagliflozin (Boehringer Ingelheim), 25 mg qd, on renal hyperfiltration in subjects with T1D. Based on previous work in animals, we hypothesized that SGLT2 inhibition with empagliflozin would reduce renal hyperfiltration in patients with uncomplicated T1D under controlled conditions of clamped euglycemia and hyperglycemia. This is the first-in-class study to translate experimental animal findings of renal SGLT2 inhibition into the clinical setting of renal hyperfiltration in patients with T1D.

## Materials and Methods

### Study Participants

The flow chart for participants is shown in Figure 2. Forty participants successfully completed the study and had the primary GFR end point evaluated, including 13 normofiltering subjects (defined by GFR values 90–134 mL/min/1.73m$^2$; T1D-N) and 27 individuals with renal hyperfiltration (defined[9] by GFR ≥135 mL/min/1.73m$^2$; T1D-H; Table 1). In more detail, inclusion criteria at screening were as follows: (1) Male or female subject diagnosed with T1D ≥ 12 months before informed consent; (2) Age ≥ 18 years; (3) Hemoglobin A1c (HbA1c) of 6.5%-11.0%; (4) Body mass index 18.5 to 35.0 kg/m$^2$; (5) Experienced insulin pump users (≥ 3 months of use before the study and willing to use the same insulin pump during the study) or be on multiple daily injections; (6) Ability to follow an established carbohydrate counting method and an insulin titration algorithm based on investigator recommendations; (7) Stable glycemic status (latest HbA1c, measured 2–12 months before screening, within 1.5% of baseline value); and (8) Estimated GFR ≥60 mL/min/1.73 m.$^2$ Exclusion criteria at screening were as follows: (1) Evidence of macroalbuminuria; (2) Leukocyte or nitrite positive urinalysis; (3) Any concomitant medication known to interfere with RAAS

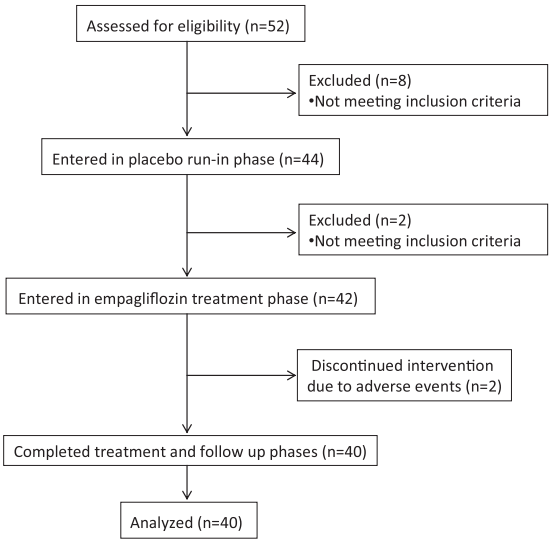


**Figure 2.** Flow diagram for study participants.

activity or renal function based on investigator judgment; (4) Severe hypoglycemia that required emergency hospital treatment within 3 months before screening; (5) History of organ transplantation, cancer, liver disease, macrovascular disease, autonomic neuropathy, proliferative retinopathy, brittle diabetes mellitus, or hypoglycemia unawareness based on investigator judgment; (6) Total daily insulin requirement > 1.5 U/kg; (7) Bariatric surgery or other gastrointestinal surgeries that induce chronic malabsorption within the past 2 years; (8) Treatment with antiobesity drugs, surgery, or aggressive diet regimen leading to unstable body weight 3 months before screening; (9) Treatment with systemic steroids; (10) Blood dyscrasias or any disorders causing hemolysis or unstable red blood cells; (11) Pre-menopausal women who were nursing, pregnant, or of child-bearing potential and not practicing an acceptable method of birth control; (12) Participation in another trial with an investigational drug within 30 days before informed consent; and (13) Alcohol or drug abuse within 3 months before informed consent that would interfere with trial participation or any ongoing clinical condition that would jeopardize subject safety or study compliance based on investigator judgment. The local Research Ethics Board at the University Health Network (Toronto, Canada) approved the protocol and all subjects gave informed consent prior to start of study procedures. The study was conducted according to the International Conference on Harmonization on Good Clinical Practice.

## Experimental Design

This clinical trial comprised 6 sequential phases (Figure 3): (1) a 1-week screening period (Visit 1 to Visit 2); (2) a 2-week placebo run-in period (Visit 2 to Visit 3), (3) 2 back-to-back days of baseline renal assessments conducted under controlled euglycemic (Visit 3) and hyperglycemic (Visit 4) clamp conditions; (4) an 8-week open-label treatment period with empagliflozin 25 mg QD including telephone (Visits 5, 6, 7, 9, and 10) and in-hospital visits (Visit 8 and Visit 11); (5) 2 back-to-back days of renal assessments under controlled euglycemic (Visit 12) and hyperglycemic (Visit 13) clamp conditions; and finally (6) a 2-week post-treatment observation period with 2 in-hospital visits (Visit 14 and Visit 15). At Visit 2, participants were instructed to document their daily glucose levels, insulin, and carbohydrate intake for the remainder of the study using a patient diary. To avoid effective circulating volume contraction and RAAS activation from sodium depletion, or hyperfiltration attributable to high protein intake, participants were instructed to adhere to a high-sodium (>140 mmol/d), moderate protein diet (<1.5 g/kg/d) for 7 days leading up to Visits 3 to 4 and Visits 12 to 13. Treatment compliance was assessed based on tablet count of dispensed and returned medication and was required to be 80% to 120% of the treatment dose.

On the day before the physiology experiments, HbA1c, 24-hour urinary albumin excretion rate, and 24-hour urine sodium, urea and glucose were measured. For baseline and post-treatment physiological experiments (Visit 3 and Visit 12), euglycemic (4–6 mmol/L) conditions were maintained for ≈4 hours preceding and during all investigations.[10] On the following days (Visit 4 and Visit 13), identical experiments were repeated under clamped hyperglycemic conditions (9–11 mmol/L). During the clamp procedures, blood glucose was maintained at a stable level as described previously.[10]

Experiments were performed during clamped euglycemia and hyperglycemia for several reasons. First, the definition of hyperfiltration in our previous work is GFR≥135 mL/min/1.73m$^2$ during clamped euglycemia.[8–11,22,23] This definition based on ambient euglycemia is important because acute induction of modest hyperglycemia can induce a hyperfiltration response, possibly through neurohormonal activation, especially in normofiltering individuals.[10,24] Our second reason for controlling ambient glycemic conditions was to separate the effects of systemic hyperglycemia resulting in glucosuria (ie, essentially uncontrolled diabetes mellitus) from increased glucosuria with simultaneous euglycemia. The latter can be achieved experimentally by combining empagliflozin with a systemic euglycemic clamp. The establishment of a physiological state of euglycemia allowed us to isolate the effects of modulating tubuloglomerular feedback, while at the same time minimizing neurohormonal activation by systemic hyperglycemia. Third, acute, modest hyperglycemia can raise blood pressure and influence circulating neurohormonal mediators in patients with uncomplicated T1D.[24,25] Because the effects of empagliflozin on blood pressure and circulating neurohormones were predefined outcomes of this trial, we performed all studies under clamped euglycemic and hyperglycemic conditions to reduce background variability in these factors. Finally, participants were also studied under clamped hyperglycemic conditions to determine whether the added renal glucose load would result in enhanced TGF and renal hemodynamic effects. The inclusion of the hyperglycemic day was also important to capture renal data during ambient conditions reflective of clinical practice, which frequently includes episodes of hyperglycemia.

During steady state euglycemic or hyperglycemic clamp conditions, blood samples were collected to assess the following parameters: inulin and paraaminohippurate (PAH), plasma renin activity (PRA), angiotensin II, and aldosterone. At corresponding time intervals, urine samples were collected from which urinary NO, prostaglandin E2, D2, F1α, and thromboxane B2 (all corrected for urinary creatinine concentration) were measured. Mean arterial pressure and heart rate were measured by an automated sphygmomanometer over the right brachial artery (DINAMAP sphygmomanometer, Critikon, FL) throughout the study.

For changes in insulin therapy after starting empagliflozin, study subjects were initially instructed to reduce their prandial insulin by 30% at the start of the treatment phase 1 day after V4. As an additional safety measure against nocturnal hypoglycemia, subjects were also required to reduce basal insulin by 30%. All insulin dose adjustments were performed under the investigators' guidance based on home blood glucose measurements.

## Assessment of Renal Hemodynamic Function

After ambient clamp euglycemia or hyperglycemia was stabilized, inulin and PAH were infused via a third intravenous line. The infusion was primed with 25% inulin (60 mg/kg) and 20% PAH (8 mg/kg), which were infused continuously at a rate calculated to maintain plasma concentrations at 20 mg/dL and 1.5 mg/dL, respectively. After a 90-minute equilibration period, blood samples were collected for inulin, PAH, and hematocrit (HCT) with additional blood being drawn 30 minutes later. GFR and effective renal plasma flow (ERPF) were estimated under steady state conditions of infusing inulin and PAH, respectively.[10] Two independent clearance periods were used to calculate mean baseline GFR and ERPF values at baseline and after treatment with empagliflozin. Renal blood flow (RBF) was derived using ERPF/(1−HCT). Renal vascular resistance (RVR) was derived by dividing mean arterial pressure by RBF. All renal hemodynamic measurements were adjusted for body surface area.

**Table 1. Clinical Characteristics and Biochemistry Before and After Empagliflozin in Patients With Type 1 Diabetes Mellitus With Normofiltration or Hyperfiltration (Mean±SD)**

| | Normofiltration Group (n=13) | | Hyperfiltration Group (n=27) | |
|---|---|---|---|---|
| | Baseline | End of Treatment | Baseline | End of Treatment |
| Clinical characteristics | | | | |
| Male, n (%) | 8 (62) | — | 12 (44) | — |
| Age, y | 25.4±6.6 | — | 23.5±4.1 | — |
| Diabetes mellitus duration, y | 18.8±6.2 | — | 16.3±7.4 | — |
| Smoking status - never smoked, % | 92 | — | 85 | — |
| Weight, kg | 75.8±13.1 | 72.8±13.0† | 71.1±12.5 | 68.6±11.9† |
| Body mass index, kg/m$^2$ | 24.8±3.4 | 23.8±3.4 | 24.4±3.2 | 23.5±3.0 |
| HbA1c, % | 7.8±1.0 | 7.3±0.8‖ | 8.2±0.9 | 7.8±1.0‖ |
| Daily insulin dose, units/d | | | | |
| Total | 55.9±23.3 | 48.1±22.0** | 54.1±19.3 | 44.6±17.4** |
| Basal | 26.6±9.2 | 19.2±8.0** | 25.3±11.4 | 19.6±8.0** |
| Bolus | 29.3±19.7 | 29.0±17.8 | 28.8±14.0 | 26.0±12.3 |
| Daily carbohydrate intake (grams/d) | 140.6±40.1 | 184.4±82.5 | 194.3±142.4 | 250.8±184.9*** |
| Biochemistry | | | | |
| Hematocrit, % | 0.381±0.032 | 0.395±0.038‡ | 0.369±0.045 | 0.382±0.038‡ |
| Blood urea, mmol/L | 4.4±1.2 | 5.4±1.2§ | 4.6±1.8 | 5.3±1.6§ |
| Urine albumin/creatinine ratio, mg/mmol | 0.88±0.48 | 1.05±0.42 | 1.31±0.96 | 1.86±2.05 |
| 24-hour urine volume, ml | 1900±848 | 2159±861 | 1463±920 | 2284±1081* |
| 24-hour sodium excretion, mmol/d | 168±112 | 149±76 | 133±71 | 147±70 |
| 24-hour glucose excretion, gram/d | 18.2±19.4 | 106.7±39.5¶ | 19.3±19.3 | 146.5±65.9¶# |
| 24-hour protein intake, gram/kg/d | 0.91±0.18 | 0.95±0.24 | 0.99±0.35 | 1.14±0.48 |

24-h protein intake estimated according to the formula [(24-h urine urea × 0.18) +14] / body weight.[27] Hematocrit and blood urea values are for V3 vs V12; Urine albumin/creatinine ratio is the average of values taken on V3/V4 compared to V12/V13. The calculation for mean diabetes duration was performed outside the clinical trials database, which only included categorical data as presented in the results section. HbA1c indicates hemoglobin A1c.

*$P$<0.01 for change in urine volume in the T1D-H group.

†$P$<0.01 for the within group changes in weight and body mass index.

‡$P$<0.02 for within group changes in hematocrit.

§$P$<0.04 for within group changes in blood urea concentration.

‖ $P$<0.01 for T1D-H and $P$=0.0003 for T1D-N for within group changes in HbA1c.

¶$P$<0.01 for within group increase in urine glucose excretion.

#$P$<0.05 for the change in urine glucose excretion in T1D-H vs T1D-N.

**$P$<0.05 for within group decreases in insulin doses.

***$P$<0.01 for within group change in carbohydrate intake in T1D-H.

## Sample Collection and Analytical Methods

### *Inulin and PAH*

Blood samples were immediately centrifuged at 3000 rpm for 10 minutes at 4°C. Plasma was separated, placed on ice, and stored at −70° C before assay. Inulin and PAH were measured in serum by colorimetric assays using anthrone and N-(1-naphthy) ethylenediamine, respectively.

### *Angiotensin II*

Blood samples were collected into prechilled tubes containing EDTA and angiotensinase inhibitor (0.1 mL Bestatin Solution, Buhlmann Laboratories, Switzerland). After centrifugation, plasma was stored at −70°C until analysis. On the day of analysis, plasma samples were extracted on phenylsilysilica columns followed by a competitive angiotensin II radioimmunoassay kit supplied by Buhlmann Laboratories AG (Switzerland). Aldosterone was measured by

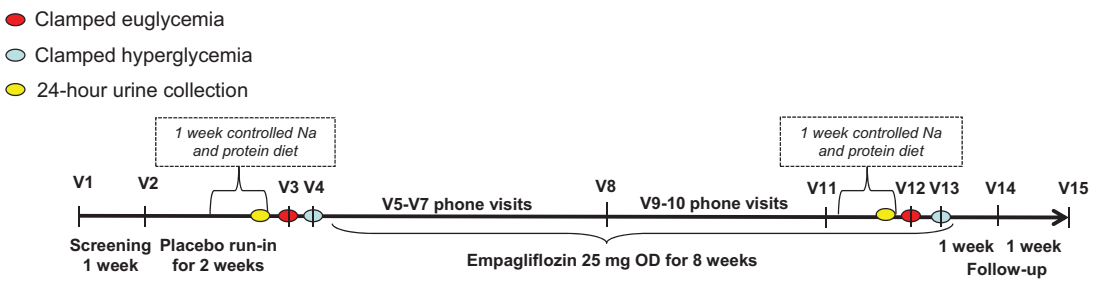


**Figure 3.** Study outline for renal hemodynamic function tests.

radioimmunoassay (Coat-A-Count system, Siemens). Renin Activity: PRA was measured with a radioimmunoassay kit (GammaCoat Plasma Renin Activity $^{125}$I RIA Kit, CA-1533, Diasorin, Stillwater, MN). PRA determination involves an initial incubation of plasma to generate angiotensin I, followed by quantitation of angiotensin I by radioimmunoassay. In the GammaCoat PRA $^{125}$I RIA Kit, the antibody is immobilized onto the lower inner wall of the GammaCoat tube. After incubation of standards, unknown samples and $^{125}$I angiotensin I in the GammaCoat tube, the reaction mixture is removed by aspiration and the bound tracer counted in a gamma counter. A standard curve is constructed and the concentration of angiotensin I of the unknown sample obtained by interpolation.

### *Nitric Oxide*

To assess NO formation,[26] plasma and urine NO levels were measured at baseline and after 8 weeks of empagliflozin during clamped euglycemia and hyperglycemia. For NO levels (NO, R&D Systems, Minneapolis, MN; total NO/Nitrite/Nitrate assay kit, Cat No.KGE001) the assay determines NO concentration based on the enzymatic conversion of nitrate to nitrite by nitrate reductase. The reaction is followed by colorimetric detection of nitrite as an azo dye product of the Griess Reaction. The Griess Reaction is based on the 2-step diazotation reaction in which acidified nitrite produces a nitrosating agent which reacts with sulfanilic acid to produce the diazonium ion. This ion is then coupled to N-(1-naphthyl)ethylenediamine to form the chromophoric azo-derivative, which absorbs light at 540 to 570 nm. Urine NO concentrations were also measured accordingly and were corrected for urinary creatinine concentrations. To assess possible influences of renal prostanoids on hemodynamic function, urinary prostaglandin E2, D2, F1$\alpha$, and thromboxane B2 levels (corrected for urinary creatinine) were measured as described previously.[8]

Urinary albumin excretion rate was determined by immunoturbidimetry, and 24-hour urine sodium, urea, and glucose were assessed by standard laboratory methods. HbA1c was measured by high-performance liquid chromatography. Other end points related to glucose-lowering effects of empagliflozin in patients with T1D will be presented elsewhere.

## Statistical Analyses

The primary end point of this study was change from baseline in GFR after treatment with empagliflozin 25 mg QD for 8 weeks under stable euglycemic and hyperglycemic clamp conditions. The primary hypothesis of interest and related primary analysis was to evaluate change in GFR within T1D subjects with hyperfiltration. The selected sample size was chosen to evaluate both within-group and between-group differences in GFR, where the 2 groups were T1D subjects with (T1D-H) and without (T1D-N) renal hyperfiltration. Within the T1D-H group: Assuming a standard deviation of 5 mL/min/1.73 m$^2$, a paired *t* test, with a 2-sided significance level of 0.05 and a sample size of 4 subjects, would provide 80% power to detect a mean difference in GFR of 11 mL/min/1.73m$^2$ from baseline to 8 weeks. Between groups: Assuming a standard deviation of 5 mL/min/1.73 m$^2$, a 2-group *t* test, with a 2-sided significance level of 0.05 and a sample size of 12 subjects per group, would provide 80% power to detect a mean difference in GFR of 6 mL/min/1.73 m$^2$ from baseline to 8 weeks. To have an adequate sample size for both within-group and between-group comparisons, we therefore planned to include 12 participants per group. The effect sizes and standard deviations were estimated based on previous experiments.[10,11] Paired *t* tests were performed to evaluate within-group differences in GFR after treatment with empagliflozin. Comparisons between the groups were performed using an analysis of variance (ANOVA). Similar statistical analyses were performed on other renal hemodynamic parameters and on blood and urinary biochemical parameters.

# Results

## Baseline Clinical and Anthropometric Characteristics

The study population comprised 27 patients in the T1D-H group (GFR 172±23 mL/min/1.73 m$^2$) and 13 patients in the T1D-N group (GFR 117±11 mL/min/1.73 m$^2$). Overall, clinical and anthropometric baseline characteristics and daily insulin doses were similar between the groups, whereas carbohydrate intake tended to be higher in T1D-H (Table 1).[27] In T1D-N, all patients had a diabetes mellitus duration of >5 years except for 1 individual. Similarly, in T1D-H, all patients had a diabetes mellitus duration of >5 years except for 3 individuals. Mean diabetes mellitus duration values for each group are reported in Table 1. HbA1c levels were similar in the 2 groups at baseline (Table 1). Body weight was comparable between the groups (Table 1). Mean systolic and diastolic blood pressure values were similar and within the normotensive range in each group (Table 2).

## Effect of Empagliflozin on Renal Function and Blood Pressure

### *Euglycemic Clamp Conditions*

After 8 weeks of treatment, empagliflozin significantly lowered GFR by 33 mL/min/1.73 m$^2$ in T1D-H under euglycemic conditions (baseline: 172±23, 8 weeks: 139±25 mL/min/1.73 m$^2$; $P$<0.01; Figure 4A). This GFR effect in T1D-H was accompanied by significant declines in ERPF and RBF, a significant rise in RVR ($P$<0.01 for all), and a significant decline in systolic blood pressure ($P$<0.05; Table 2). In contrast, treatment with empagliflozin did not significantly alter GFR or other renal parameters in T1D-N under euglycemic conditions (baseline: 117±11, 8 weeks: 126±15, $P$=0.15, Figure 4A). Consistent with these findings, the between-group differences in change from baseline for GFR, ERPF, RBF, and RVR for T1D subjects with and without hyperfiltration during euglycemia were significant ($P$<0.01).

### *Hyperglycemic Clamp Conditions*

The significant effect of empagliflozin on GFR in subjects with T1D and hyperfiltration was confirmed under hyperglycemic clamp conditions. GFR dropped significantly by 44 mL/min/1.73 m$^2$ (baseline: 186±33; 8 weeks: 142±29 mL/min/1.73 m$^2$; $P$<0.01; Figure 4B). This was again accompanied by significant changes in ERPF, RBF, and RVR ($P$<0.01 for all) but not by significant changes in blood pressure (Table 3). Consistent with euglycemic conditions, empagliflozin had no effect on renal parameters in T1D-N in the hyperglycemic setting (GFR baseline: 136±27, 8 weeks: 134±18, $P$=0.76, Figure 4B). Finally, the between-group differences in change from baseline for GFR, ERPF, RBF, and RVR for T1D subjects with and without hyperfiltration were also significant during clamped hyperglycemia ($P$<0.01).

## Effect of Empagliflozin on RAAS Mediators, NO, and Urinary Prostanoids

During baseline clamped euglycemia, circulating levels of angiotensin II, aldosterone, PRA, and NO were similar between the groups (Table 2). After treatment with empagliflozin, angiotensin II and aldosterone levels increased significantly in the T1D-H group, whereas only aldosterone levels rose significantly in T1D-N. In addition, empagliflozin significantly lowered plasma NO in T1D-H, but not in T1D-N (Table 2). Changes in circulating RAAS mediators and NO after empagliflozin under euglycemia were similar to those observed during clamped hyperglycemia (Table 3).

**Table 2. Hemodynamic Responses to Empagliflozin During Clamped Euglycemia in Patients With Type 1 Diabetes Mellitus With Normofiltration or Hyperfiltration (Mean±SD)**

| | Normofiltration Group | | | Hyperfiltration Group | | |
|---|---|---|---|---|---|---|
| | Baseline | EMPA | *P* Value | Baseline | EMPA | *P* Value |
| Renal hemodynamic function | | | | | | |
| Effective renal plasma flow | 642±90 | 637±88 | 0.89 | 1042±287 | 724±148 | <0.01 |
| Filtration fraction | 0.185±0.026 | 0.200±0.025 | 0.19 | 0.176±0.047 | 0.197±0.042 | 0.02 |
| Renal blood flow | 1030±160 | 1042±138 | 0.82 | 1641±458 | 1156±219 | <0.01 |
| Renal vascular resistance | 0.081±0.013 | 0.077±0.011 | 0.35 | 0.052±0.016 | 0.071±0.014 | <0.01 |
| Blood pressure | | | | | | |
| Heart rate, bpm | 71±11 | 69±14 | 0.50 | 76±14 | 73±14 | 0.27 |
| Systolic blood pressure, mm Hg | 111±7 | 109±9 | 0.21 | 111±10 | 108±9 | <0.05 |
| Diastolic blood pressure, mm Hg | 63±9 | 64±10 | 0.83 | 64±9 | 63±7 | 0.43 |
| Plasma biochemistry | | | | | | |
| Plasma angiotensin II, pmol/L | 3.1±3.9 | 10.4±20.2 | 0.14 | 3.6±3.9 | 6.4±6.8 | 0.04 |
| Plasma aldosterone, pmol/L | 49±31 | 81±41 | <0.01 | 43±26 | 66±44 | 0.02 |
| Plasma renin activity, ng/mL/hr | 0.539±0.528 | 0.502±0.432 | 0.81 | 0.570±0.417 | 0.883±1.07 | 0.16 |
| Plasma nitric oxide, μmol/L | 46±21 | 44±24 | 0.76 | 48±21 | 29±23 | <0.01 |
| Urine biochemistry | | | | | | |
| Prostaglandin D2, pmol/mg creatinine | 0.487±0.349 | 0.463±0.241 | 0.81 | 0.342±0.301 | 0.422±0.371 | 0.23 |
| Prostaglandin E2, pmol/mg creatinine | 0.087±0.041 | 0.086±0.071 | 0.97 | 0.119±0.083 | 0.103±0.062 | 0.26 |
| Prostaglandin F1α, pmol/mg creatinine | 0.185±0.070 | 0.204±0.060 | 0.43 | 0.196±0.059 | 0.241±0.145 | 0.08 |
| Thromboxane B2, pmol/mg creatinine | 0.188±0.094 | 0.160±0.035 | 0.27 | 0.216±0.156 | 0.212±0.110 | 0.89 |
| Urine nitric oxide, μmol/mmol creatinine | 132±96 | 123±96 | 0.80 | 153±148 | 126±91 | 0.25 |

Effective renal plasma flow in ml/min/1.73 $m^2$; renal blood flow in ml/min/1.73 $m^2$; renal vascular resistance in mm Hg/L/min. EMPA indicates empagliflozin.

Empagliflozin did not influence urinary NO or prostanoid excretion, aside from a modest but significant rise in prostaglandin F1α in the T1D-H group, which was only observed during clamped hyperglycemia (Table 3).

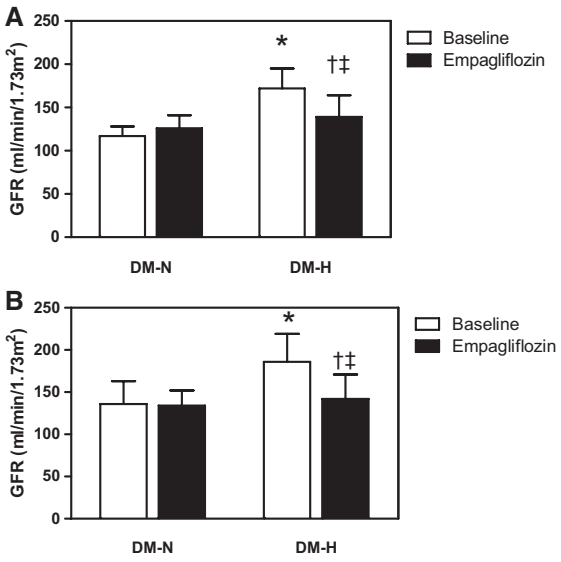


**Figure 4.** Glomerular filtration rate (GFR) responses to empagliflozin during clamped euglycemia (**A**) and hyperglycemia (**B**; mean±SD). **P*<0.01 for baseline GFR in type 1 diabetes mellitus subjects without (T1D-N) vs with (T1D-H) renal hyperfiltration. †*P*<0.01 for the within-group change in GFR in T1D-H. ‡*P*<0.01 for the between-group effect of empagliflozin on change in GFR.

## Effects of Empagliflozin on Glucose Control, Body Weight, and Laboratory Parameters

Significant declines in HbA1c in conjunction with significant decreases in total daily insulin doses were observed within each group at end of treatment compared with baseline, and these changes were similar in the 2 groups (Table 1). Carbohydrate intake increased in both groups by similar amounts, and based on the larger sample size in T1D-H, within-group changes reached significance in this group. Despite increased carbohydrate intake, body weight and body mass index decreased to a similar extent in both groups (Table 1); 24-hour urinary glucose excretion increased significantly in both groups after empagliflozin treatment (within-group changes, *P*<0.01) with greater changes in glucose excretion in T1D-H versus T1D-N (Table 1), and 24-hour urine volume did not increase significantly versus baseline in T1D-N (+13.6%; *P*=0.23). However, there was a significant 56% rise in T1D-H (*P*<0.01); 24-hour urinary sodium excretion rates were not significantly altered by empagliflozin in either group. Urinary albumin to creatinine ratio was within the normal range at baseline and did not change at week 8 (Table 1).

After treatment with empagliflozin, there were no clinically relevant changes in the biochemical and hematologic parameters assessed, including serum sodium, potassium, calcium, magnesium, chloride, phosphate, bicarbonate, blood count, erythropoietin, liver enzymes, lactate dehydrogenase, creatine kinase, lipase, lipid profiles, and uric acid. When subjects from both groups were pooled there were, however, small but significant increases in hematocrit (0.373±0.041–0.386±0.038; *P*<0.01)

**Table 3. Hemodynamic Responses to Empagliflozin During Clamped Hyperglycemia in Type 1 Diabetes Mellitus Patients With Normofiltration or Hyperfiltration (Mean±SD)**

| | Normofiltration Group | | | Hyperfiltration Group | | |
|---|---|---|---|---|---|---|
| | Baseline | EMPA | *P* Value | Baseline | EMPA | *P* Value |
| Renal hemodynamic function | | | | | | |
| Effective renal plasma flow | 706±157 | 688±101 | 0.74 | 1051±251 | 748±144 | <0.01 |
| Filtration fraction | 0.195±0.024 | 0.196±0.019 | 0.95 | 0.185±0.046 | 0.192±0.032 | 0.40 |
| Renal blood flow | 1117±240 | 1140±154 | 0.79 | 1633±430 | 1193±227 | <0.01 |
| Renal vascular resistance | 0.078±0.015 | 0.073±0.012 | 0.37 | 0.054±0.015 | 0.072±0.015 | <0.01 |
| Blood pressure | | | | | | |
| Heart rate, bpm | 68±10 | 63±11 | 0.06 | 74±11 | 75±12 | 0.79 |
| Systolic blood pressure, mm Hg | 115±8 | 113±8 | 0.41 | 111±10 | 110±10 | 0.47 |
| Diastolic blood pressure, mm Hg | 65±9 | 63±9 | 0.54 | 66±8 | 64±6 | 0.34 |
| Plasma biochemistry | | | | | | |
| Plasma angiotensin II, pmol/L | 2.6±2.4 | 4.2±4.0 | 0.17 | 2.3±2.5 | 3.6±3.0 | 0.03 |
| Plasma aldosterone, pmol/L | 27±4 | 47±32 | 0.04 | 29±8 | 50±43 | 0.03 |
| Plasma renin activity, ng/mL/hr | 0.317±0.281 | 0.368±0.389 | 0.36 | 0.328±0.273 | 0.356±0.241 | 0.61 |
| Plasma nitric oxide, μmol/L | 40±23 | 42±20 | 0.73 | 46±20 | 28±23 | <0.01 |
| Urine biochemistry | | | | | | |
| Prostaglandin D2, pmol/mg creatinine | 0.610±0.356 | 0.633±0.295 | 0.85 | 0.509±0.344 | 0.631±0.404 | 0.15 |
| Prostaglandin E2, pmol/mg creatinine | 0.096±0.092 | 0.084±0.070 | 0.69 | 0.090±0.054 | 0.099±0.060 | 0.52 |
| Prostaglandin F1α, pmol/mg creatinine | 0.225±0.099 | 0.265±0.100 | 0.20 | 0.223±0.095 | 0.298±0.162 | 0.03 |
| Thromboxane B2, pmol/mg creatinine | 0.175±0.056 | 0.191±0.061 | 0.18 | 0.206±0.075 | 0.207±0.066 | 0.98 |
| Urine nitric oxide, μmol/mmol creatinine | 98±58 | 112±58 | 0.43 | 138±108 | 162±124 | 0.37 |

Effective renal plasma flow in ml/min/1.73 $m^2$; renal blood flow in ml/min/1.73 $m^2$; renal vascular resistance in mm Hg/L/min. EMPA indicates empagliflozin.

and blood urea (4.6±1.6–5.4±1.5 mmol/L; $P<0.01$). These findings were also evident within each of the groups (Table 1).

### Adverse Events

Few adverse events related to renal function were reported. Pollakuria was reported by 33 (78.6%) patients, thirst by 31 (73.8%) patients, and 1 patient (2.4%) reported each of nocturia, dysuria, and increase in urine output. No cases of acute renal failure or tubular necrosis occurred. Two cases of diabetic ketoacidosis leading to discontinuation occurred during the study: one in the context of insulin pump failure and the other in the setting of acute gastroenteritis. These patients were withdrawn within the first 3 days of drug exposure and were not included in the analysis of the remaining 40 subjects. The overall incidence of reported adverse effects for the 42 patients who took study drug is reported in Table 4.

## Discussion

Animal studies have demonstrated that acute and chronic SGLT2 blockade significantly reduced hyperfiltration, confirming the crucial contribution of TGF in early renal hemodynamic abnormalities related to diabetes mellitus.[13,15,20] This experimental evidence was so far only explored in 1 human study performed almost 8 decades ago. In this landmark study, Shannon et al[28] demonstrated that phlorizin, a nonselective inhibitor of SGLT1 and SGLT2, acutely reduced GFR in 5 healthy humans. Unfortunately, because of poor tolerability of phlorizin, the role of TGF in humans subsequently remained unstudied for the last 75 years as a result of a lack of appropriate physiological probes to modulate TGF. The recent development of selective oral SGLT2 inhibitors for the treatment of diabetes mellitus has led to the opportunity to study the tubular component of diabetes-related renal hyperfiltration, providing a unique approach to connect novel pharmaceutical interventions with the work by Shannon et al.[28]

Our first major novel observation was that among T1D subjects with renal hyperfiltration, treatment with empagliflozin for 8 weeks led to a significant reduction in hyperfiltration during clamped euglycemic and hyperglycemic conditions. This, to our knowledge, is the first study to demonstrate that pharmacological inhibition of SGLT2 attenuates hyperfiltration in patients with diabetes mellitus. Corrections of elevated GFR in T1D-H during clamped euglycemia resulted in a mean end-of-study GFR value that was close to the threshold for normal. Attenuation of hyperfiltration by SGLT2 inhibition in our study was likely mediated via effects on ERPF, RBF, and RVR. This particular pattern of renal hemodynamic function change is compatible with preglomerular vasoconstriction. In contrast, renal hemodynamic parameters remained unchanged in T1D subjects with normal renal function, suggesting that TGF does not contribute significantly to the regulation of renal function in these individuals. Because changes in weight, glycemic control, metabolic parameters, and dietary factors after treatment with empagliflozin were similar between the T1D-H and T1D-N groups, our results support the concept that baseline differences in renal hemodynamic function were mainly attributable to increased proximal tubular sodium-glucose cotransport and that SGLT2 inhibition resulted in an

**Table 4. Adverse Events in 42 Participants With T1D Who Took Empagliflozin**

| Condition | Number (%) |
|---|---|
| Infections | |
| Nasopharyngitis | 11 (26) |
| Genitourinary tract infection | 6 (14) |
| Gastroenteritis (viral) | 1 (2) |
| Influenza | 4 (10) |
| Gastroenteritis | 2 (5) |
| Vaginal infection | 2 (5) |
| Ear infection | 1 (2) |
| Eye infection | 1 (2) |
| Lung infection | 1 (2) |
| Tooth infection | 1 (2) |
| Metabolism and nutrition | |
| Hypoglycemia – all episodes | 40 (95) |
| Hypoglycemia – severe requiring assistance | 1 (2) |
| Decreased appetite | 2 (5) |
| Diabetic ketoacidosis | 2 (5) |
| Increased appetite | 1 (2) |
| Psychiatric | |
| Anxiety | 2 (5) |
| Insomnia | 2 (5) |
| Stress | 1 (2) |
| Nervous system disorders | |
| Headache | 13 (31) |
| Dizziness | 10 (24) |
| Tinnitus | 6 (14) |
| Vertigo | 1 (2) |
| Respiratory conditions | |
| Nasal sinus congestion or | 2 (5) |
| Sinus congestion | 1 (2) |
| Throat irritation | 1 (2) |
| Gastrointestinal disorders | |
| Dry mouth | 7 (17) |
| Nausea | 7 (17) |
| Vomiting | 6 (14) |
| Abdominal pain | 5 (12) |
| Abdominal discomfort | 1 (2) |
| Abdominal distension | 1 (2) |
| Abdominal pain upper | 1 (2) |
| Hemorrhoids | 1 (2) |
| Mallory-Weiss tear | 1 (2) |
| Skin and musculoskeletal disorders | |
| Pruritus | 1 (2) |
| Skin irritation | 1 (2) |
| Back pain | 4 (10) |
| Myalgia | 1 (2) |
| Reproductive and breast disorders | |
| Dysmenorrhea | 1 (2) |
| Menstrual disorder | 1 (2) |
| Menstruation delayed | 1 (2) |
| Menstruation irregular | 1 (2) |
| Polymenorrhea | 1 (2) |
| Vaginal hemorrhage | 1 (2) |
| Vulvovaginal dryness | 1 (2) |
| General disorders | |
| Thirst | 33 (74) |
| Fatigue | 2 (5) |
| Pyrexia | 2 (5) |
| Chest discomfort | 1 (2) |
| Influenza-like illness | 1 (2) |
| Pollakiuria | 33 (79) |
| Nocturia | 1 (2) |
| Urine output increased | 1 (2) |
| Dysuria | 1 (2) |

enhanced physiological effect in T1D subjects with hyperfiltration. The pronounced impact of empagliflozin on urine volume and urinary glucose excretion parameters in T1D-H further suggest that greater renal hemodynamic responses in this group were related to increased sodium chloride delivery to the distal tubule, which occurs as a result of decreased NaCl reabsorption along with glucose in the proximal tubule. It is also noteworthy that the magnitude of GFR reduction (−33 mL/min/1.73 $m^2$) during clamped euglycemia in this group is similar to changes in hyperfiltration associated with ACE inhibition in young patients with uncomplicated T1D, highlighting that the effect size of this drug class on a surrogate marker of intraglomerular pressure in humans is in the same range expected with pharmacological RAAS blockade.[11]

The neurohormonal factors that may have contributed to preglomerular vasoconstriction after empagliflozin merit some additional consideration. Animal work has suggested that NO is an important mediator of TGF. NO is released during activation of TGF, thereby blunting the vasoconstrictor response, resulting in decreased TGF sensitivity.[29,30] The interaction between angiotensin II and NO also modulates TGF, because intrarenal RAAS activation exaggerates TGF-mediated vasoconstriction through inhibition of neuronal NO synthase.[31] In addition to interactions with the intrarenal RAAS, NO blunts the effect of another major vasoconstrictor involved in TGF, adenosine.[32] Under conditions of chronic hyperglycemia and DM, the role of NO in TGF physiology may be of particular importance because blockade of NO augments renal vasoconstriction in DM animals versus controls.[33] Despite what has been shown in experimental models of diabetes mellitus, preglomerular vasodilators (urine NO and prostanoids) did not decline significantly after SGLT2 inhibition, suggesting that TGF-mediated renal hemodynamic changes were independent of these neurohormonal mediators.[8,10] Nevertheless, our results do not rule out paracrine changes in NO bioactivity after SGLT2 inhibition. Furthermore, because we have previously shown that NO synthase inhibition alone can partially

reduce hyperfiltration in humans with T1D, future studies should combine NO synthase inhibitors with SGLT2 inhibition to determine whether a further correction of hyperfiltration can be achieved[8]

Consistent with previous clinical trials in patients with T2D, SGLT2 inhibition in our study was associated with a modest but significant blood pressure lowering effect.[17] Interestingly this was accompanied by a significant increase in circulating RAAS mediators, predominantly in T1D subjects with renal hyperfiltration. Our results are consistent with studies involving patients with T2D that demonstrated that SGLT2 inhibition significantly lowered systolic and diastolic blood pressure partly by inducing effective circulating volume contraction via a mild diuretic effect.[17,34–36] This is further reflected by mild but significant increases in hematocrit and plasma urea within the normal range.[18] Our study is the first to demonstrate that similar to familial renal glucosuria, pharmacological SGLT2 inhibition-induced effective circulating volume contraction is accompanied by an increase in circulating RAAS mediators.[37] This observation has important clinical implications. First, activation of the RAAS serves as further evidence for an effective circulating volume contraction after SGLT2 inhibition. Second, a rise in circulating RAAS mediators may be of particular importance in patients concomitantly treated with RAAS inhibitors. It is well known that the use of RAAS blockers in combination with other agents that induce diuresis leads to additive antihypertensive and antiproteinuric effects.[38,39] Importantly, RAAS blockade with SGLT2 inhibition in animals has recently been shown to lead to additive renoprotective effects compared to either drug alone.[21] Hence, it is tempting to speculate that combined use of SGLT2 and RAAS inhibitors may lead to similar synergistic effects through combined blockade of neurohormonal and tubular factors in humans. Future studies should examine whether a combined strategy of dual RAAS and SGLT2 inhibition has the potential to exert long-term renal and systemic vascular protection, in part through normalizing hyperfiltration.

Treatment with the SGLT2 inhibitor empagliflozin was associated with a significant change in body weight in subjects with T1D. This is an important consideration for the overall blood pressure effects of empagliflozin, because even small changes in weight are known to be associated with significant antihypertensive effects.[40] Thus, our results suggest that several mechanisms may underlie the antihypertensive effects of SGLT2 inhibitors in humans. These may not be limited to but certainly include (1) improved glycemic control, (2) an effective circulating volume contraction, and (3) weight loss.[24] Although we cannot determine which of these factors is dominant for lowering systemic blood pressure, it is fair to conclude that these effects outweigh the increase in circulating RAAS mediators and decline in plasma NO, because both of these effects would be expected to increase systemic vascular tone and blood pressure. The glucose-lowering effect of empagliflozin is interesting from the perspectives of blood pressure lowering and renal protection, particularly because the drug was generally well tolerated aside from the development of diabetic ketoacidosis in the context of obvious clinical precipitants in 2 participants. The risk of ketosis should therefore be carefully evaluated in future trials.

Although the effect of SGLT2 inhibition on long-term renal protection is not yet known, it is important to consider the clinical context in which this class of agents could optimally be used to prevent the development of diabetic nephropathy for future clinical trials. Assuming that renal protective effects of SGLT2 inhibitors are mainly mediated through reduced intraglomerular pressure akin to the effect of RAAS inhibitors, then these agents should be effective in patients with sufficient renal function that permits glucosuric and hence TGF effects, including patients with moderate and even severe renal function impairment. This is supported by data demonstrating that canagliflozin reduces estimated GFR and proteinuria within 3 weeks in patients with T2D and estimated GFR values between 30 to 50 mL/min/1.73 $m^2$.[41] Similar subacute changes in GFR occur with empagliflozin in patients with stages 3 and 4 chronic kidney disease, and are maintained at 52 weeks.[42,43] Perhaps most importantly, the decline in GFR was fully reversible after a 3-week wash-out period.[42,43] Together, these observations strongly suggest that renal hemodynamic functional effects of SGLT2 inhibition are attributable to a reduction in intraglomerular pressure, similar to what would be expected with traditional renal protective therapies such as RAAS inhibition, or intensified glycemic control.[44] However, in contrast with RAAS inhibitors, which do not improve renal outcomes in normoalbuminuric patients with T1D and normal renal function,[45] our results suggest that SGLT2 inhibition reduces hyperfiltration,[4] which has been implicated in the initiation and progression of diabetic nephropathy, and also improve glycemic control. Therefore, in addition to examining the effect of these agents in patients with established renal disease, future studies should consider SGLT2 inhibition as a primary prevention strategy in T1D. This is of particular importance in light of the glucose-lowering and antihypertensive effects achieved with SGLT2 inhibition, which we have now shown for the first time in patients with uncomplicated T1D, and which may independently augment renal hemodynamic protective effects.

The present set of experiments demonstrates that modulation of TGF exerts greater renal hemodynamic effects in patients with renal hyperfiltration compared with those with normofiltration. However, the initiating factor leading to hyperfiltration in those with the condition compared with those with normal GFR values remains unknown. Although speculative, several possibilities exist. First, genetic polymorphisms in SLC5A2 encoding SGTL2 leading to increased glucosuria have been described.[46] This phenotype would be expected to increase distal sodium delivery, causing afferent constriction thereby preventing hyperfiltration. Although the present study was not designed to examine between-group genetic differences, future work comprising larger cohorts should consider evaluating the pharmacogenomic influence of SGLT2 polymorphisms. Second, hyperfiltration may be the result of interactions between intrarenal activation of neurohormonal factors, such as the sympathetic nervous system or RAAS, with TGF, which are both known to influence TGF sensitivity.[31,47,48] As a consequence, underlying differences in neurohormonal activation resulting from genetic variability or previous glycemic control may contribute to a predisposition to hyperfiltration. Next, glycemia-related factors could also contribute to the pathogenesis of hyperfiltration. For example, if the daily filtered glucose load was higher in T1D-H, then the resulting increase in SGLT2 activity in this group could promote afferent vasodilatation. Although 24-hour glucose was not different

in T1D-N versus T1D-H at baseline, daily carbohydrate intake did tend to be higher in T1D-H. Adequately powered future studies should therefore examine the interaction between carbohydrate intake, GFR, and SGLT2 inhibition. A final possible mechanism that may contribute to the initiation of hyperfiltration relates to the fetal environment. Previous work in animals and in patients with essential hypertension has suggested that intrauterine abnormalities leading to low birth weight and intrauterine growth restriction may have long-term renal effects, including low nephron number, leading to compensatory hyperfiltration.[49,50] Although speculative, a similar sequence of events could occur in the context of T1D, when the effect on hyperfiltration may be more pronounced because of the additional second hit physiological insults of neurohormonal activation and enhanced proximal sodium-glucose cotransport.

One limitation of our investigational study is the relatively small sample size, potentially leading to heterogeneity in relevant clinical parameters of the study population at baseline, as well as in individual responses to empagliflozin. We attempted to minimize the effect of a small sample size by using homogeneous study groups and by conducting a careful prestudy preparation phase with a particular emphasis on factors that could potentially influence neurohormonal activation, such as dietary sodium intake. We also decreased variability by using a study design that allowed each subject to act as his/her own control. Although this reduction in baseline physiological variability likely improved our ability to detect changes in renal function, the use of homogenous groups of participants did not permit an in-depth analysis of other factors that may inform the research community about the pathobiology of SGLT2 inhibitors such as age, diabetes mellitus duration, degree of proteinuria, or clinical nephropathy, which should be considered in future work. Finally, study participants were not placed on a controlled nitrate diet, and this may have limited the magnitude of the between-group differences in urine NO excretion.

In conclusion, we have demonstrated for the first time in humans that inhibition of SGLT2 is associated with a significant attenuation of renal hyperfiltration. Although several factors may have contributed to the decrease in GFR in T1D subjects with hyperfiltration to near normal levels, it may be hypothesized that activation of TGF by empagliflozin made a large contribution. Future work should focus on the long-term use of SGLT2 inhibitors as potential renoprotective therapies that may reduce intraglomerular pressure thereby reducing the risk of developing overt diabetic nephropathy.

## Acknowledgments

We thank Dr Paul Yip and Jenny Cheung-Hum for their invaluable assistance with biochemical assays included in this work. We acknowledge editorial assistance, supported financially by Boehringer Ingelheim, from Wendy Morris, Fleishman-Hillard Group, Ltd. Finally, we are grateful to the study participants whose time and effort are critical to the success of our research program. Contributions: D.Z.I.C, B.A.P., H.P., M.M., V.L., A.L. researched data, wrote the manuscript. N.F., H.J.W., N.S., O.E.J., U.C.B., M.v.E. contributed to discussion, reviewed/edited manuscript. All authors have approved the final version of this manuscript.

## Sources of Funding

This work was supported by Boehringer Ingelheim (to D.Z.I.C. and B.A.P.) Dr Cherney was also supported by a Kidney Foundation of Canada Scholarship and a Canadian Diabetes Association-KRESCENT Program Joint New Investigator Award and receives operating support from the Heart and Stroke Foundation of Canada.

## Disclosures

These data were presented at the American Diabetes Association Meeting on June 22, 2013. Dr Cherney has received speaker honoraria from Boehringer Ingelheim, and Dr Perkins received operational funding with Dr Cherney for this work. Drs Soleymanlou, Fagan, Woerle, Johansen, Broedl, and von Eynatten are employees of Boehringer Ingelheim. The other authors report no conflicts.

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## CLINICAL PERSPECTIVE

Because of their insulin-independent mechanism of action, sodium-glucose cotransporter (SGLT) 2 inhibitors are being explored as potential adjunctive glucose-lowering agents in type 1 diabetes mellitus. Aside from effects on metabolic parameters, our study is the first to demonstrate beneficial effects of an SGLT2 inhibitor on renal hemodynamic function in type 1 diabetes mellitus patients. The observed improvement in renal hyperfiltration is important because of the association of hyperfiltration with progression of diabetic nephropathy. Moreover, the magnitude of the glomerular filtration rate (GFR) effect is of potential clinical significance, because the change is similar to that expected with angiotensin-converting enzyme inhibition. In the context of experimental work in animals showing reductions in hyperfiltration, proteinuria, and histological nephropathy, our results provide further evidence that SGLT2 inhibitors may exert short-term renal protective effects in humans. Our results may also have implications for primary renal disease prevention in patients with type 1 diabetes mellitus, because the use of angiotensin-converting enzyme inhibitors has failed to show clinical benefit in normotensive, normoalbuminuric individuals. Moreover, because afferent vasoconstrictive responses to SGLT2 inhibition may be additive when combined with the effects of angiotensin-converting enzyme inhibition at the efferent arteriole, future trials should consider combining these 2 drug classes to potentially augment renal protection. Ultimately, prospective clinical trials are required to determine whether changes in renal hyperfiltration with SGLT2 inhibition translate into long-term renal protection.

# Renal Hemodynamic Effect of Sodium-Glucose Cotransporter 2 Inhibition in Patients With Type 1 Diabetes Mellitus

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*Circulation.* 2014;129:587-597; originally published online December 13, 2013;
doi: 10.1161/CIRCULATIONAHA.113.005081
*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539