# Acute Effect of Empagliflozin on Fractional Excretion of Sodium and eGFR in Youth With Type 2 Diabetes

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Early markers of diabetic kidney disease (DKD), including hyperfiltration and elevated albumin excretion, are common in youth with type 2 diabetes (T2D) (1). Despite the morbidity associated with the development of future DKD in youth-onset T2D, pharmacotherapeutic options to lower hyperglycemia are limited to metformin and insulin, the only drugs approved for use in pediatric patients.

Sodium–glucose cotransporter 2 (SGLT2) inhibitors reduce blood pressure, weight, and hyperglycemia in adults with T2D. Furthermore, a 38% reduction in cardiovascular death and a 39% reduction in incident or worsening nephropathy have been demonstrated with the selective SGLT2 inhibitor empagliflozin in patients with established cardiovascular disease (2,3). In young adults with type 1 diabetes, treatment with the SGLT2 inhibitor empagliflozin for 8 weeks was associated with natriuresis, increased renal vascular resistance, and reductions in glomerular filtration rate (GFR) (using inulin clearances) and renal blood flow (assessed by *p*-aminohippuric acid clearance) in those with baseline hyperfiltration (4). This renal hemodynamic profile suggested that the 20% reduction in hyperfiltration observed in this trial was due to afferent vasoconstriction and a decline in intraglomerular hypertension (4). In adults with T2D, the reduction in intraglomerular hypertension is typically reflected by a mean reduction in estimated GFR (eGFR) of 2–4 mL/min/1.73 $m^2$ after treatment initiation, followed by a stabilization of eGFR decline compared with placebo during long-term treatment (3). It is, however, not known whether these renal hemodynamic effects occur acutely, if at all, in youth-onset T2D. Accordingly, our aim was to examine whether eGFR effects occur within 24 h of a single exposure to empagliflozin in youth-onset T2D.

In this open-label, randomized, parallel-group study (reg. no. NCT02121483, clinicaltrials.gov), 27 youth with T2D (mean age 14.1 years, 67% girls, mean BMI 35.5 kg/$m^2$) received a single dose of empagliflozin, either 5, 10, or 25 mg. The effects of empagliflozin on fractional sodium excretion ($Fe_{NA+}$) and eGFR (calculated by the Zappitelli combined creatinine and cystatin C equation) were investigated by pooling the three doses of empagliflozin for analyses (to increase the number of observations for meaningful analyses). Two ANCOVA models were fitted to examine change in $Fe_{NA+}$ and eGFR from baseline. Both models included empagliflozin dose and sex as fixed effects and baseline $HbA_{1c}$ and BMI standard deviation score, in addition to baseline $Fe_{NA+}$ or baseline eGFR depending on the dependent outcome, as continuous covariates. Hyperfiltration was defined as eGFR >119.1 mL/min/1.73 $m^2$, namely, 2 SD above mean eGFR by the Zappitelli equation in obese youth in the National Health and Nutrition Examination Survey (NHANES) (5).

At baseline, mean $Fe_{NA+}$ was 0.55 ± 0.46%, and eGFR was 113.4 ± 15.6 mL/min/1.73 $m^2$. After a single dose of empagliflozin, the adjusted mean $Fe_{NA+}$ increased and eGFR decreased ($P = 0.006$ and $P = 0.0006$ vs. baseline, respectively) (Fig. 1). Participants with hyperfiltration ($n = 8$) at baseline experienced a change in adjusted eGFR in response to empagliflozin of −6.7 ± 9.7 mL/min/1.73 $m^2$,

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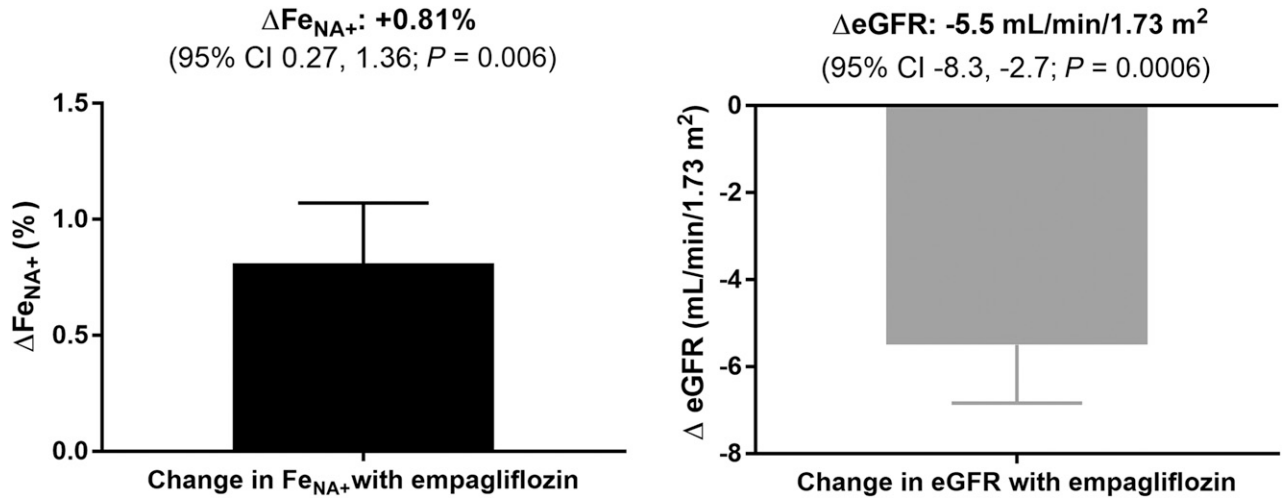


**Figure 1—**Changes from baseline in $Fe_{NA+}$ and eGFR after single-dose administration of empagliflozin ($n = 27$), adjusted for baseline value, age, sex, $HbA_{1c}$, and BMI standard deviation score. Directions of effect on $Fe_{NA+}$ and eGFR were consistent across the three doses of empagliflozin tested.

compared with $-5.0 \pm 6.0$ mL/min/1.73 $m^2$ in those with normofiltration ($n = 19$), although we cannot rule out that this difference reflects regression toward the mean.

There are limitations in this study, including small sample size and calculated rather than measured GFR. Nevertheless, we have shown that SGLT2 inhibition following a single dose of empagliflozin is associated with increased natriuresis and attenuation of elevated GFR in youth with T2D, suggesting a reduction in intraglomerular pressure. These findings are consistent with adult data and may yield potential to reduce the risk of future DKD in youth with T2D. Further mechanistic studies are required to better understand changes in renal function in response to SGLT2 inhibition, and longer-term trials examining renal protective effects in youth with diabetes are warranted.

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**Author Contributions.** P.B., J.M., and D.Z.I.C. wrote the manuscript and researched the data. L.L., W.V.T., S.H., M.v.E., and J.G. reviewed/edited the manuscript and researched the data. G.S. performed the statistical analyses, reviewed/edited the manuscript, and researched the data. The authors were fully responsible for all content and editorial decisions, were involved at all stages of manuscript development, and approved the final version. P.B., J.M., and D.Z.I.C. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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