Modeling & Simulation Decisions

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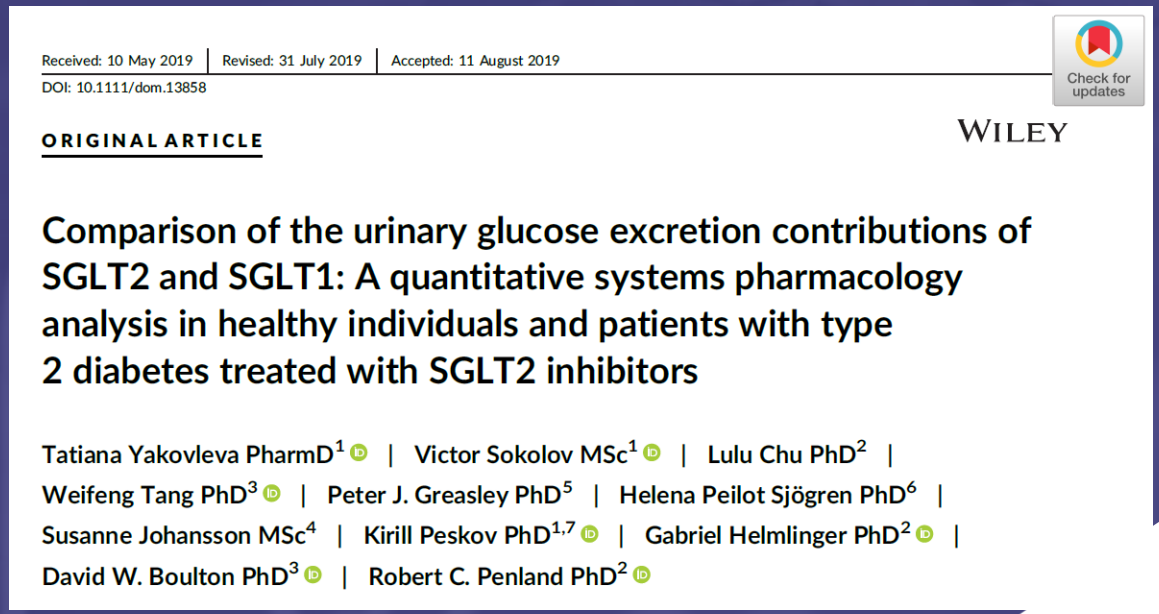

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ORIGINAL ARTICLE

WILEY

Comparison of the urinary glucose excretion contributions of SGLT2 and SGLT1: A quantitative systems pharmacology analysis in healthy individuals and patients with type 2 diabetes treated with SGLT2 inhibitors

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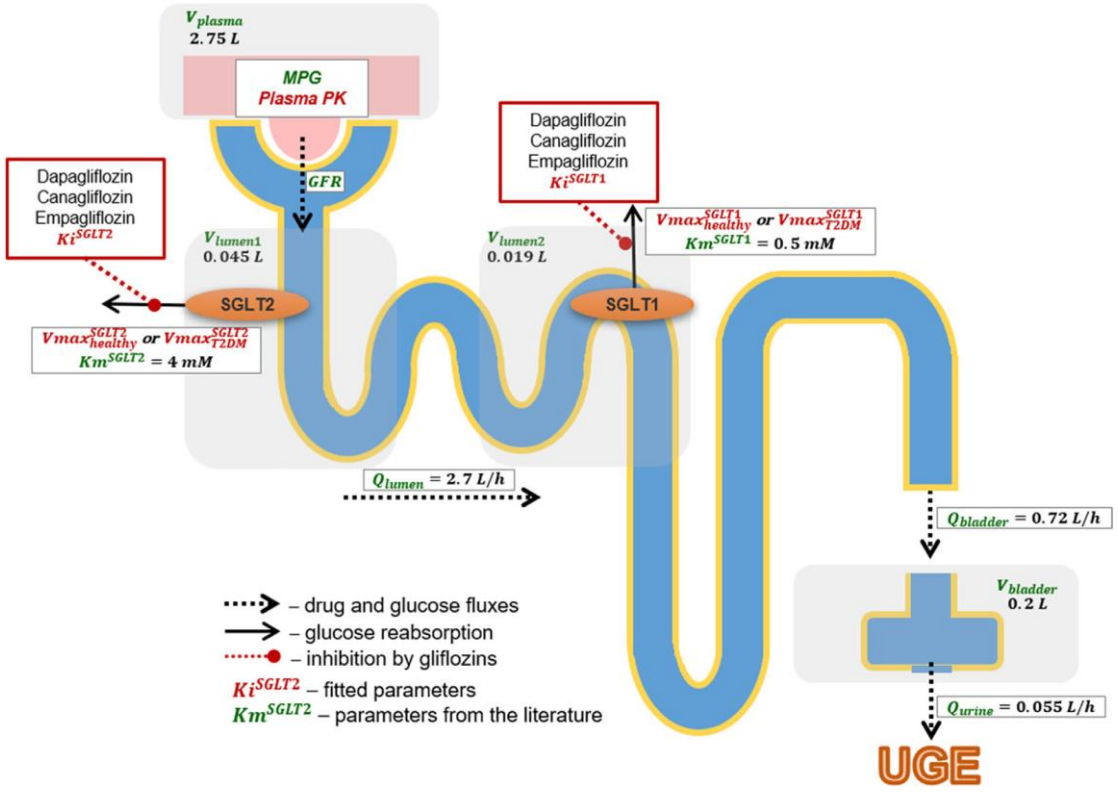
Contribution and regulation of SGLT1 and SGLT2 in healthy and type 2 diabetes subjects: a drug-disease modeling study

- A physiologically based model of renal glucose filtration, reabsorption and excretion via SGLT1/2 was developed based on published data on SGLT2 inhibitors pharmacokinetic and urinary glucose excretion (UGE) in healthy people and people with T2DM under the treatment

- Quantitative drug-disease system modelling revealed mechanistic differences in renal glucose reabsorption and UGE between healthy people and those with T2DM, and clearly showed that SGLT2 inhibition significantly increased glucose available to SGLT1 downstream in the tubule.

- Higher renal glucose reabsorption in people with T2DM versus healthy people was associated with 54% and 28% greater transporter capacity for SGLT1 and SGLT2, respectively.

- Additionally, the analysis showed that UGE is highly dependent on mean plasma glucose and estimated glomerular filtration rate and that their consideration is critical for interpreting clinical UGE findings.



Modeling & Simulation Decisions

Compact work review

Background and objectives

- SGLT2 inhibitors are a class of oral glucose lowering compounds for type 2 diabetes treatment work by preventing renal reabsorption of filtered glucose.
- The renal glucose reabsorption threshold (plasma glucose level at which the proximal tubule can no longer reabsorb all filtered glucose and begins to excrete glucose in the urine) is higher in T2DM subjects compared to healthy subjects
- Despite a large contribution (>80%) by SGLT2 to renal glucose reabsorption, clinical observations show only 30-50% reduction in reabsorption when subjects are treated with potent SGLT2 inhibitors

The aim of this work was to develop a quantitative drug-disease systems model to:

1) Investigate differences in renal glucose reabsorption and UGE between healthy and T2DM subjects treated with SGLT inhibitors
2) Explain the paradox that SGLT2 is responsible for >80% of proximal tubule glucose reabsorption, yet SGLT2 inhibitor treatment results in only 30% to 50% less reabsorption in patients with T2DM

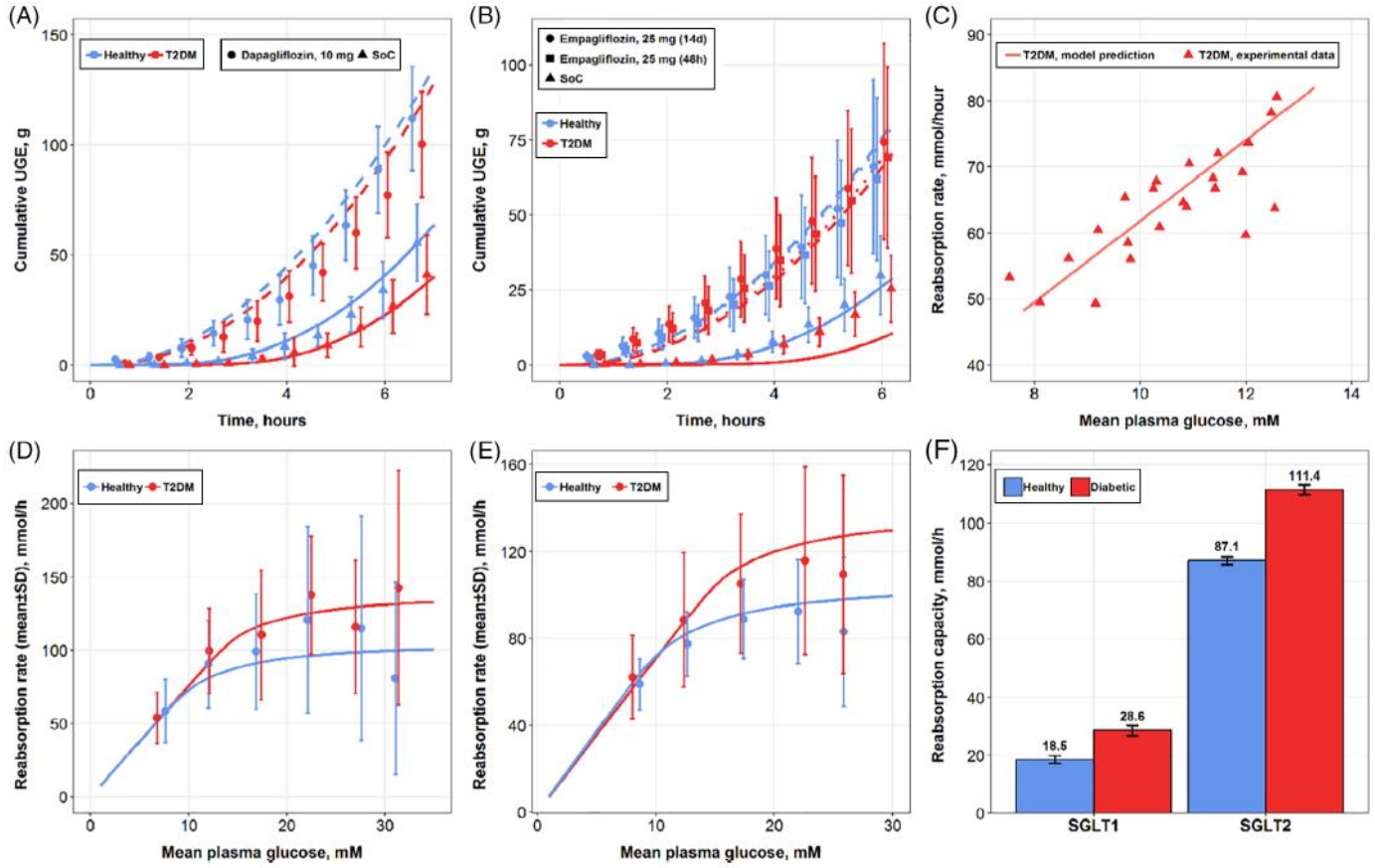
Glucose reabsorption: Healthy vs T2DM

- Using the experimental data on reabsorption rate for healthy and T2DM subjects and 24-hour UGE data during treatment with SGLT2 inhibitors, we show **higher threshold of renal glucose reabsorption observed for T2DM subjects compared with healthy subjects**

- The model accurately describes cumulative UGE and total glucose reabsorption rate for healthy and T2DM subjects untreated and with SGLT2 inhibition by dapagliflozin 10 mg QD during the **stepwise hyperglycemic clamp procedure (panels A-E)**

- The higher threshold for T2DM subjects is explained **by increased transporter Vmax values** of both SGLT1 (↑54%, 28.6 vs. 18.5 mmol/h) and SGLT2 (↑28%, 111.4 vs. 87.1 mmol/h) (panel F)

External model validation



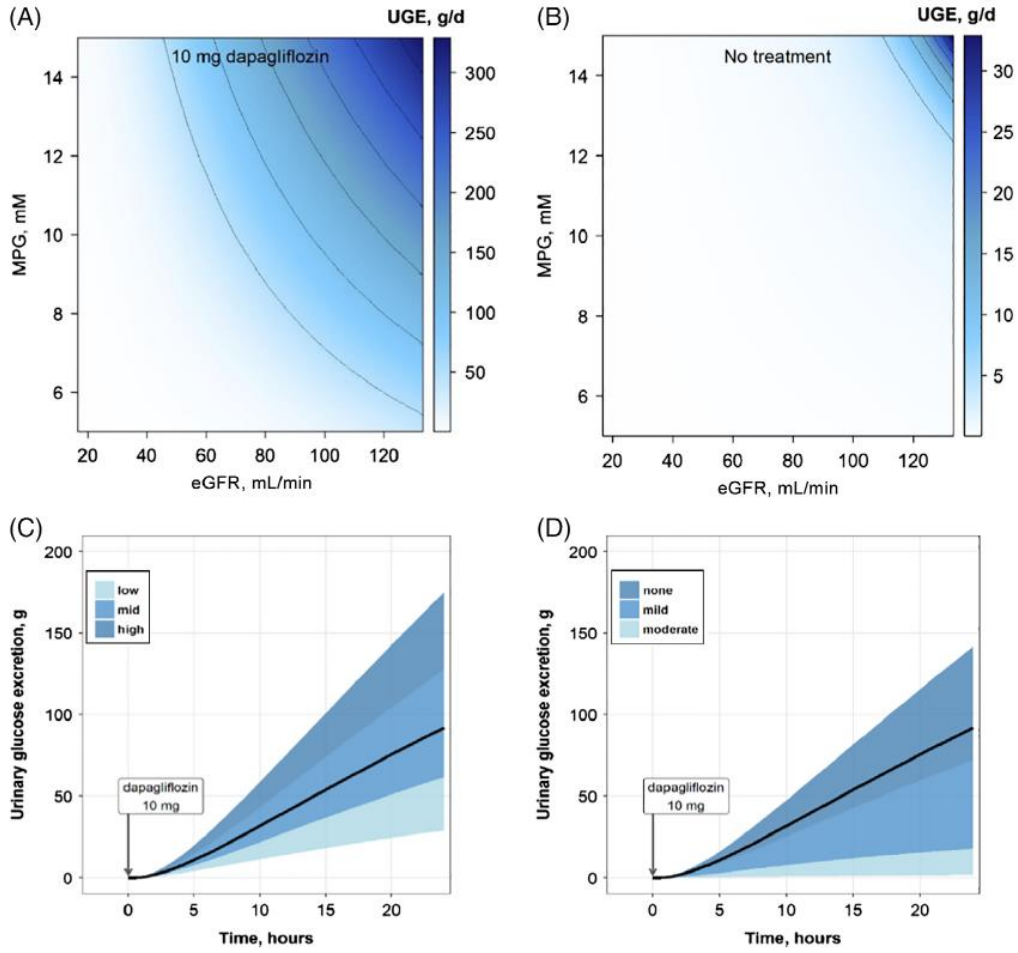
Curves represent model predictions, symbols denote observations: triangles: Standard of Care without SGLT2 inhibitor treatment; circles or squares: treatment with 10 mg dapagliflozin (A), or 25 mg empagliflozin (B)

Sensitivity to mean plasma glucose and eGFR

A sensitivity analysis using the QSP model demonstrated that mean plasma glucose concentrations and GFR were the **primary determinants of UGE in the T2DM group:**

- For those with T2DM and normal renal function (eGFR ≥100 mL/min/1.73 m2) treated with 10 mg dapagliflozin, a change in the mean plasma glucose level from 7.8 to 13.4 mM **increased 24-hour UGE by >100 g** (panel C)

- For people with T2DM and the median mean plasma glucose level (9.3 mM) treated with 10 mg dapagliflozin, a drop in eGFR from 125 to 90 mL/min/1.73m2 **resulted in a >70 g lower 24-hour UGE** (panel D)



Patient categories are based on MPG (low: 6-7.8 mM; mid: 7.8-11.1 mM; and high: 11.1-13.4 mM) and eGFR/renal impairment status (none: 90-125 mL/min/1.73m2; mild: 60-90 mL/min/1.73m2; moderate: 30-59 mL/min/1.73m2)

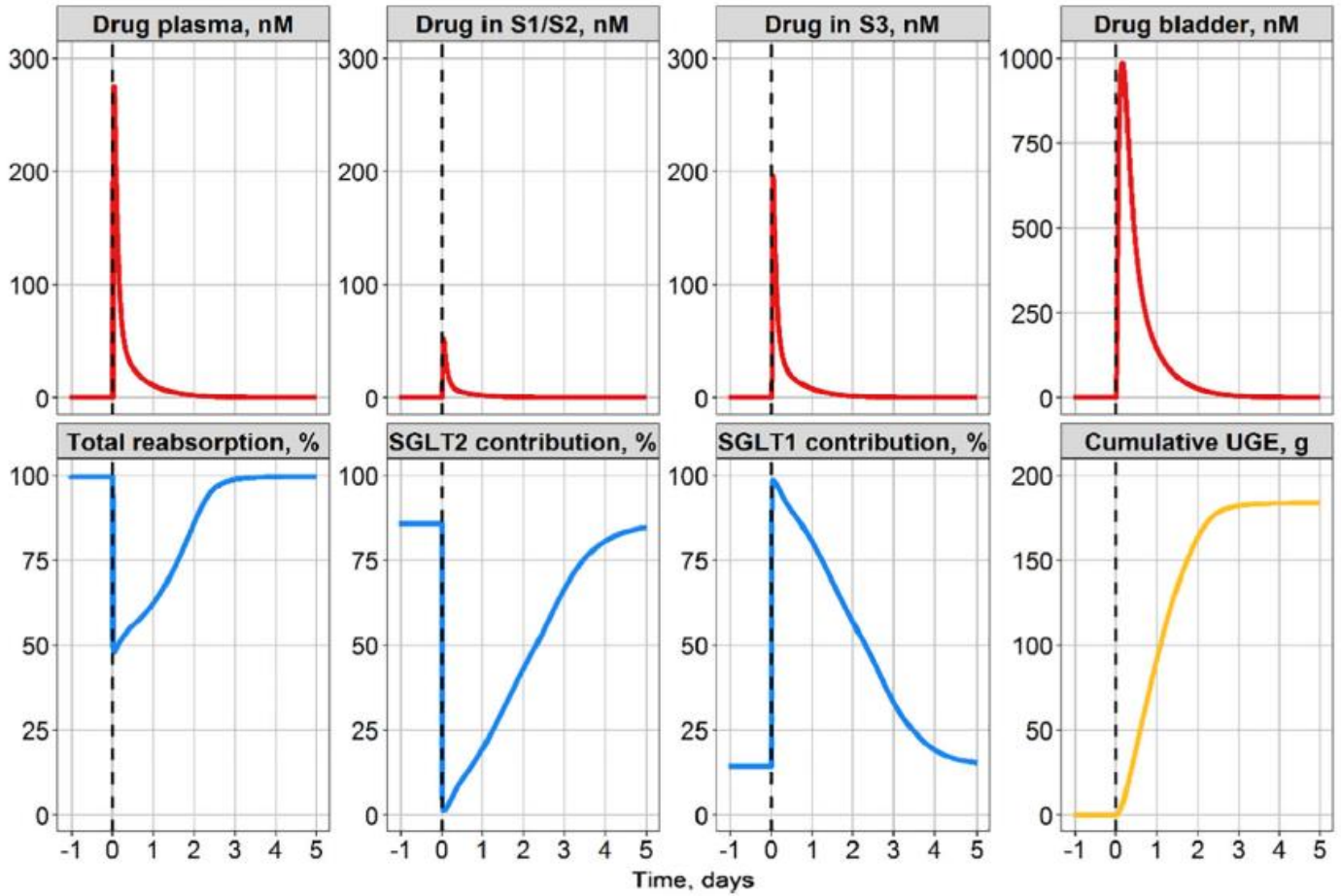
Contribution of SGLT1 to renal glucose reabsorption and UGE

- To explore the role of SGLT1-mediated glucose reabsorption in patients being treated with selective SGLT2 inhibitors, we performed model simulations emulating pharmacokinetic, glucose reabsorption and urinary glucose excretion after dapagliflozin administration

- Inhibition of SGLT2 leads to **increased availability of non-reabsorbed glucose for SGLT1-mediated transport** located down the proximal tubule

- As a consequence, **the contribution of SGLT1 to the total renal glucose reabsorption is increased during SGLT2 inhibition.** Specifically, this greater SGLT1-mediated fraction can rise to nearly 35% of total filtered glucose reabsorbed

Model simulation for typical T2DM subject treated with single dose of dapagliflozin 10 mg (MPG 10 mM, eGFR 110 ml/min)



Conclusions

- Quantitative drug-disease system modelling revealed mechanistic differences in renal glucose reabsorption and UGE between healthy people and those with T2DM, and clearly showed that SGLT2 inhibition significantly increased glucose available to SGLT1 downstream in the tubule

- During treatment with SGLT2 inhibitors, the SGLT1-mediated glucose reabsorption grows to be responsible for up to 35% of total glucose reabsorption following the increase in non-reabsorbed glucose entering the proximal straight tubule

- Higher renal glucose reabsorption in people with T2DM versus healthy people was associated with 54% and 28% greater transporter capacity for SGLT1 and SGLT2, respectively

- Additionally, the analysis showed that UGE is highly dependent on mean plasma glucose and estimated glomerular filtration rate and that their consideration is critical for interpreting clinical UGE findings.