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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

Tatiana Yakovleva PharmD[1] | Victor Sokolov MSc[1] | Lulu Chu PhD[2] | Weifeng Tang PhD[3] | Peter J. Greasley PhD[5] | Helena Peilot Sjögren PhD[6] | Susanne Johansson MSc[4] | Kirill Peskov PhD[1,7] | Gabriel Helmlinger PhD[2] | David W. Boulton PhD[3] | Robert C. Penland PhD[2]

[1]M&S Decisions, Moscow, Russian Federation

[2] Clinical Pharmacology & Safety Sciences, R&D BioPharmaceuticals, AstraZeneca, Waltham, Massachusetts

[3] Clinical Pharmacology & Safety Sciences, R&D BioPharmaceuticals, AstraZeneca, Gaithersburg, Maryland

[4] Clinical Pharmacology & Safety Sciences, R&D BioPharmaceuticals, AstraZeneca, Gothenburg, Sweden

[5]CVRM, R&D BioPharmaceuticals, AstraZeneca, Gothenburg, Sweden

[6]Discovery Biology, Discovery Sciences, R&D BioPharmaceuticals, AstraZeneca, Gothenburg, Sweden

[7]I.M. Sechenov First Moscow State Medical University, Moscow, Russian Federation

Correspondence
Robert C. Penland, PhD, Astrazeneca Pharmaceuticals LP, 35 Gatehouse Ln, Waltham, MA 02451.
Email: chris.penland@astrazeneca.com

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Abstract

Aim: To develop a quantitative drug-disease systems model to investigate the paradox that sodium-glucose co-transporter (SGLT)2 is responsible for >80% of proximal tubule glucose reabsorption, yet SGLT2 inhibitor treatment results in only 30% to 50% less reabsorption in patients with type 2 diabetes mellitus (T2DM).

Materials and methods: A physiologically based four-compartment model of renal glucose filtration, reabsorption and excretion via SGLT1 and SGLT2 was developed as a system of ordinary differential equations using R/IQRtools. SGLT2 inhibitor pharmacokinetics and pharmacodynamics were estimated from published concentration-time profiles in plasma and urine and from urinary glucose excretion (UGE) in healthy people and people with T2DM.

Results: The final model showed that 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 (eGFR) and that their consideration is critical for interpreting clinical UGE findings.

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. Importantly, we found that the findings of lower than expected UGE with SGLT2 inhibition are explained by the shift to SGLT1, which recovered additional glucose (~30% of total).

KEYWORDS

glucose reabsorption, quantitative drug-disease systems modelling, SGLT2 inhibitors, urinary glucose excretion

1 | INTRODUCTION

Type 2 diabetes mellitus (T2DM) is the most common form of diabetic metabolic disorder (>90% of all cases), characterized by abnormally high plasma glucose concentrations, resulting from resistance to insulin, defects in insulin synthesis and secretion, or both.[1] The World Health Organization estimates that diabetes will be the seventh leading cause of death in 2030, driven by cardiovascular and renal sequelae accompanying the disease.[2]

Treatment of T2DM includes diet, exercise and medications that restore sensitivity to insulin, stimulate insulin secretion by pancreatic β cells, or decrease glucose absorption from the gastrointestinal tract. Sodium-glucose co-transporter (SGLT) inhibitors (gliflozins) are a recently approved class of antidiabetic medication that inhibit renal glucose reabsorption, reduce plasma glucose and lower glycated haemoglobin (HbA1c) at all stages of diabetes.[3] The gliflozin mechanism of action is independent of incretin and insulin regulatory pathways and therefore may be used in combination with other antidiabetic drugs with low risk of hypoglycaemia.

In healthy people with normoglycaemia, glucose filtered in the kidney is fully reabsorbed by sodium-dependent glucose co-transporters 1 (SGLT1) and 2 (SGLT2). SGLT2 transporters located in the upper proximal tubule (S1 and S2 segments) are responsible for 80% to 90% of renal glucose reabsorption, while SGLT1 reabsorbs the residual 10% to 20% of glucose reaching the distal S3 segment.[4]

Despite its large contribution (~80%) to renal glucose reabsorption in healthy individuals, complete inhibition of SGLT2 only results in a 30% to 50% renal glucose reabsorption decrease in people with T2DM. Simple hypotheses explaining this phenomenon have been proposed, for example, insufficient drug concentration in the tubular lumen to completely inhibit SGLT2,[5] or enhancement of SGLT1-dependent glucose reabsorption.[6] The underlying drivers may, however, be more complex.

The transport maximal renal glucose reabsorption capacity (TmG) and the glucose reabsorption threshold (lowest plasma glucose level at which complete glucose reabsorption is saturated and glucosuria is observed) are markedly increased in people with T2DM compared with healthy individuals, contributing to the maintenance of hyperglycaemia.[7] Differences in the relative contributions from SGLT1- and SGLT2-mediated renal reabsorption probably exist between healthy individuals and those with T2DM. In addition, the maximal glucose reabsorption capacity of SGLT1 itself may be underestimated[8]; a recent examination of renal mRNA levels for glucose transporters (including SGLTs) from human kidney biopsies show SGLT1 expression is markedly higher in people with T2DM.[9]

Accurate estimation of SGLT1 and SGLT2 contributions to renal glucose reabsorption, in both healthy individuals and those with T2DM is fundamental to understanding the pharmacological mechanism of gliflozins, but the relative role of each SGLT in renal glucose reabsorption has not been quantified clinically. To address this, we developed a drug-disease quantitative systems pharmacology (QSP) model, which integrates the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of the three most commonly used gliflozins, dapagliflozin, canagliflozin and empagliflozin, in a mechanistic framework of renal physiology calibrated with experimental data. Model simulations with and without SGLT2 inhibitor treatment characterized the role of SGLT1-dependent glucose reabsorption in both healthy individuals and those with T2DM.

2 | MATERIALS AND METHODS

2.1 | Data used for model calibration

Data from clinical and in vitro studies were collected to estimate SGLT2 inhibitor concentrations along the proximal tubule, and the resulting impact on glucose filtration/reabsorption processes in healthy people and those with T2DM. A summary of the clinical data used for model development and calibration is presented in Table S1.

Available clinical data on healthy individuals and individuals with T2DM without treatment or treated with gliflozins were collected. For dapagliflozin, published and internal AstraZeneca data were used. For canagliflozin and empagliflozin, a literature search was conducted using various resources (PubMed, Google Scholar, ClinicalTrials.gov, Citeline). Databases containing summary PK and PD endpoints from dose-ranging clinical studies for dapagliflozin (n = 5, 1-100 mg), canagliflozin (n = 7, 10-800 mg) and empagliflozin (n = 12, 0.5-800 mg) were assembled. The following information was collected for each study, when available: (a) number of individuals per study arm, treatment regimen and dosages, (b) drug exposure time profiles in plasma and 24-hour urinary excretion of unchanged drug, (c) 24-hour urinary glucose excretion (UGE), and (d) population characteristics of patients, including disease status (healthy or T2DM), mean plasma glucose and renal status (creatinine clearance [CrCl] rate or estimated glomerular filtration rate [eGFR] value).

The PK parameters were estimated using data on drug exposure-time profiles in plasma and 24-hour urinary drug excretion. Renal status and mean plasma glucose concentrations were extracted to calculate glucose fluxes through the kidney. When a trial reported only CrCl and not eGFR, a correction factor eGFR = 0.9 × CrCl was used, acknowledging that CrCl overestimates actual GFR by 10% to 20% due to tubular secretion of creatinine.[10,11] Missing mean plasma glucose or eGFR values were imputed with the typical value for the corresponding patient population (healthy or T2DM).

Capacities of SGLT1 and SGLT2 transporters in renal glucose reabsorption as well as the affinity of the inhibitors (K_i) were estimated based on cumulative 24-hour UGE in healthy individuals and those with T2DM treated with gliflozins, and guided by results from in vitro SGLT-mediated glucose uptake assays in cultured cell lines (AstraZeneca internal data).

2.2 | SGLT-mediated glucose uptake assay

SGLT1 and SGLT2 both mediate sodium-dependent uptake of D-glucose or α-methyl-glucopyranoside, a non-metabolizable glucose analogue specific for sodium-dependent glucose transporters. Dapagliflozin, canagliflozin and empagliflozin were profiled in a ^{14}C α-methyl-glucopyranoside assay for inhibition of SGLT-mediated sodium-dependent glucose uptake in HEK293 cells transiently expressing human SGLT1 or

SGLT2 (Supporting Information) with a range of glucose concentrations (0 to 5 mM). At each glucose concentration, the half maximal inhibitory concentration values against each transporter were calculated using empirical four-variable model fitting in Genedata software (Screener 14). The K_i for each compound/transporter was calculated using the Cheng-Prusoff equation, assuming the K_m for glucose was 0.4 mM for SGLT1 and 2 mM for SGLT2.[12] The SGLT1/SGLT2 ratio from the uptake assay was used as a fixed variable for each compound in the systems model.

2.3 | Biological rationale for the proposed mathematical model structure

The drug-disease QSP model structure was guided by exploratory analyses of the published experimental data on renal glucose excretion, as well as by a review of renal physiology.

Data on glucose filtration, reabsorption and excretion showed the following:

- Plasma glucose is filtered by the kidney at the rate of glomerular filtration, that is, the rate of fluid filtration from renal glomerular capillaries into the Bowman's capsule.[13]
- The filtered glucose load is proportional to the plasma glucose concentration. Glucose is co-transported with sodium from the proximal tubule S1/S2 segment into the proximal convoluted tubule wall via SGLT2, and from the proximal tubule S3 segment into the proximal straight tubule wall via SGLT1.[13]
- Glucose not reabsorbed in the kidney accumulates in the bladder and is excreted in urine. Once filtered glucose load exceeds the TmG, additional glucose in excess of the TmG is excreted.[7]
- TmG is greater in people with T2DM patients than in healthy people (140 vs 105.6 mmol/h), based on the stepwise hyperglycaemic clamp procedure.[7]

Data on the mechanism of action of SGLT inhibitors show the following:

- SGLT inhibitors block reabsorption of glucose in the kidney via competitive inhibition.[14]
- Gliflozins are absorbed through the intestine after oral administration. The unbound fraction in plasma is filtered through the kidney and then excreted in urine with the same fluid flux as that for glucose.[5]
- Selectivity and potency to SGLT1/2 and the PK profile differ amongst members of the SGLT inhibitor class.[15]

2.4 | Structural model

The proposed model emulates the physiological structure of the kidney (Figure 1) where glucose is filtered by the kidney, distributed along the proximal tubules, and accumulates in the bladder. The proximal tubules are segmented into two compartments: the S1 and S2 segments comprising the proximal convoluted tubules (PCT, V_{lumen1}) and the S3 segment comprising the proximal straight tubules

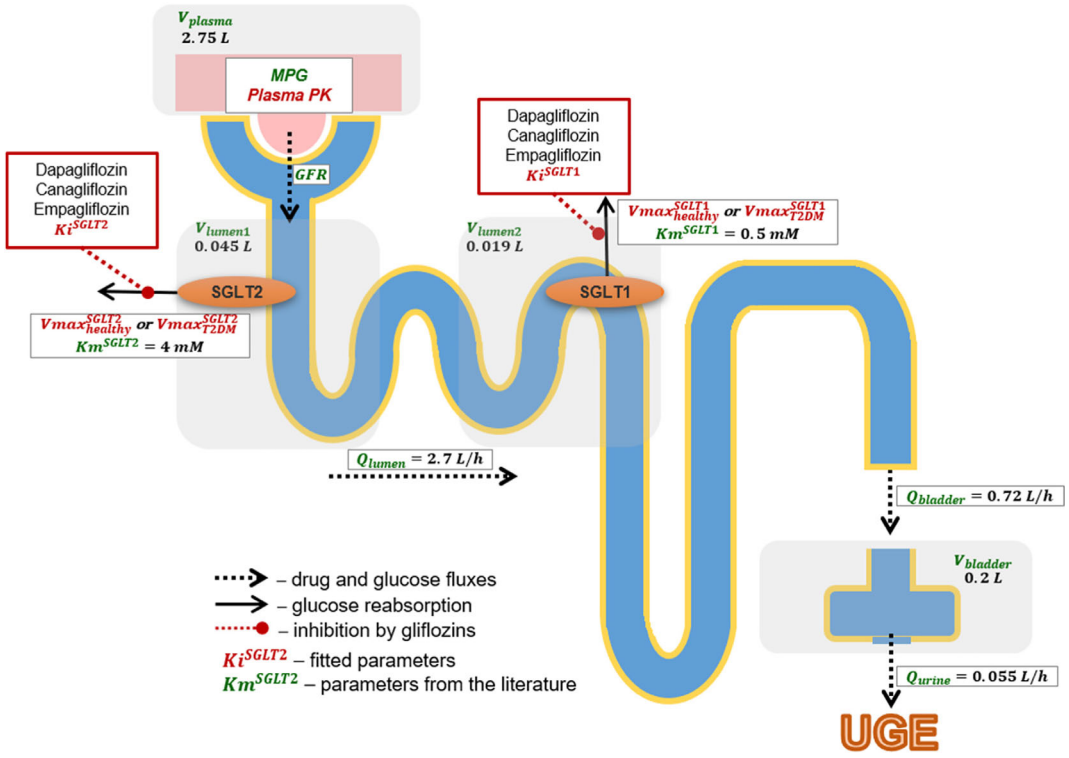

FIGURE 1 Schematic of drug-disease quantitative systems pharmacology model for glucose filtration, reabsorption and excretion. Ki, inhibition constant for SGLT1 or 2; Km, Michaelis-Menten constant for glucose affinity for SGLT1 or 2; MPG, mean plasma glucose; PK, pharmakinetics; Q, physiological fluxes; SGLT, sodium-glucose co-transporter; T2DM, type 2 diabetes; UGE, urinary glucose excretion; Vbladder, bladder volume; Vlumen 1,2, volume of proximal convoluted tubules and proximal straight tubules, respectively; Vmax; transporter capacity; Vplasma, plasma volume

(PST, V_{lumen2}), each being the sites for SGLT2- and SGLT1-mediated glucose reabsorption, respectively.

The rate of glucose filtration ($V_{GFR}^{glucose}$) is constant and defined by the product of mean plasma glucose and GFR:

$$V_{GFR}^{glucose} = GFR * mean\ plasma\ glucose \quad (1)$$

The glucose fluxes passing through the proximal tubules and excreted into the bladder are first-order processes[16]:

$$V_{flux}^{glucose} = Q * Glucose_{conc} \quad (2)$$

where Q is the appropriate volumetric fluxes and $Glucose_{conc}$ is the glucose concentration in the compartments; proximal convoluted tubules ($Glucose_{lumen1}$), proximal straight tubules ($Glucose_{lumen2}$) or bladder ($Glucose_{bladder}$), respectively.

The total glucose reabsorption rate is the sum of contributions from both cotransporters, each governed by Michaelis--Menten kinetics:

$$GRR = \frac{V_{max}^{SGLT2} * Glucose_{lumen1}}{K_m^{SGLT2} + Glucose_{lumen1}} + \frac{V_{max}^{SGLT1} * Glucose_{lumen2}}{K_m^{SGLT1} + Glucose_{lumen2}} \quad (3)$$

where GRR is glucose reabsorption rate, V_{max}^{SGLT2}, V_{max}^{SGLT1} are maximal rates of reabsorption by SGLT2 and SGLT1, respectively; and K_m^{SGLT2} and K_m^{SGLT1} denote corresponding glucose affinity constants.

The PK characteristics for each SGLT2 inhibitor were estimated using the physiologically based kidney model and the pooled dataset containing drug plasma concentration-time profiles, as well as data on urinary excretion of unchanged drug in healthy individuals and those with T2DM treated with different doses and regimens. Dapagliflozin pharmacokinetics were best described by a model having central and peripheral distribution compartments, while canagliflozin and empagliflozin were well characterized without the peripheral compartment.[17]

The absorption delay of each drug appearing in plasma was described using transit compartments (five for dapagliflozin and empagliflozin, four for canagliflozin) and a corresponding k_{tr} value. The unbound fraction (*fup*) of the compounds is filtered through the kidney and considered available to inhibit glucose reabsorption:

$$V_{GFR}^{Drug} = GFR * fup * Drug_{plasma}, \quad (4)$$

where V_{GFR}^{Drug} is the rate of drug filtration and $Drug_{plasma}$ denotes compounds concentration in plasma. Coefficients for fraction unbound in plasma are 0.22,[18] 0.086,[19] and 0.01[20] for empagliflozin, dapagliflozin, and canagliflozin, respectively.

Inhibition of SGLT-mediated renal glucose reabsorption is modelled as a simple competitive process characterized by compound-specific Ki values:

$$\text{Renal glucose reabsorption rate} = \frac{V_{max}^{SGLT} * Glucose_{lumen}}{K_m^{SGLT} * \left(1 + \frac{Drug_{lumen}}{Ki^{SGLT}}\right) + Glucose_{lumen}} \quad (5)$$

where $Drug_{lumen}$ denotes SGLT inhibitor concentration in corresponding lumen compartments, and Ki^{SGLT} is the affinity of an inhibitor to a particular SGLT.

The TmG is the sum of the capacities through each of the SGLT cotransporter subtypes:

$$TmG = V_{max}^{SGLT2} + V_{max}^{SGLT1} \quad (6)$$

2.4.1 | Model variables

Twenty-seven of the 44 parameters specified in the model (Table S2) were defined or calculated using values from the literature. The remaining 17 parameters were estimated using a gradient-driven maximum likelihood method and included parameter uncertainty using a combined (additive plus proportional) residual error structure.[21] Model quality was evaluated using multiple criteria: (a) change in the objective function value, (b) inspection of diagnostic plots, (c) precision of parameter estimates (based on estimated relative standard error values), and (d) minimization of residual error estimates.

Parameter estimation for non-linear systems models using global minimization algorithms can be sensitive to initial values chosen to begin the algorithm and subsequently become trapped in local minima. Based on physiological limits available from literature sources, five sets of plausible initial values were randomly generated, and parameter estimation performed for each. Estimated parameter values remained stable regardless of the initial value set used and served to confirm model robustness and identifiability.

2.5 | Software

The model was developed in R (www.r-project.org) version 3.5.0 using the IQRtools package for systems pharmacology and pharmacometrics version 0.9.2 (IntiQuan, Basel, Switzerland). Visualizations of model simulations were created with the ggplot2 package version 2.2.1.

3 | RESULTS

We developed a quantitative drug-disease systems model describing key processes of renal glucose reabsorption. The PK characteristics of the SGLT2 inhibitors dapagliflozin, canagliflozin and empagliflozin, were incorporated into the model to reproduce the gliflozins' mechanism of action and subsequent effects on UGE (Figure 1).

The diagnostics of the model fitting procedure and the model-predicted dose-response curves for dapagliflozin UGE superimposed with the data pooled from the clinical development program confirmed that the model described the curated dataset adequately (Figure 2).

3.1 | Model validation

The predictive power of the model was assessed through an external validation by simulating the outcome of the renal glucose excretion

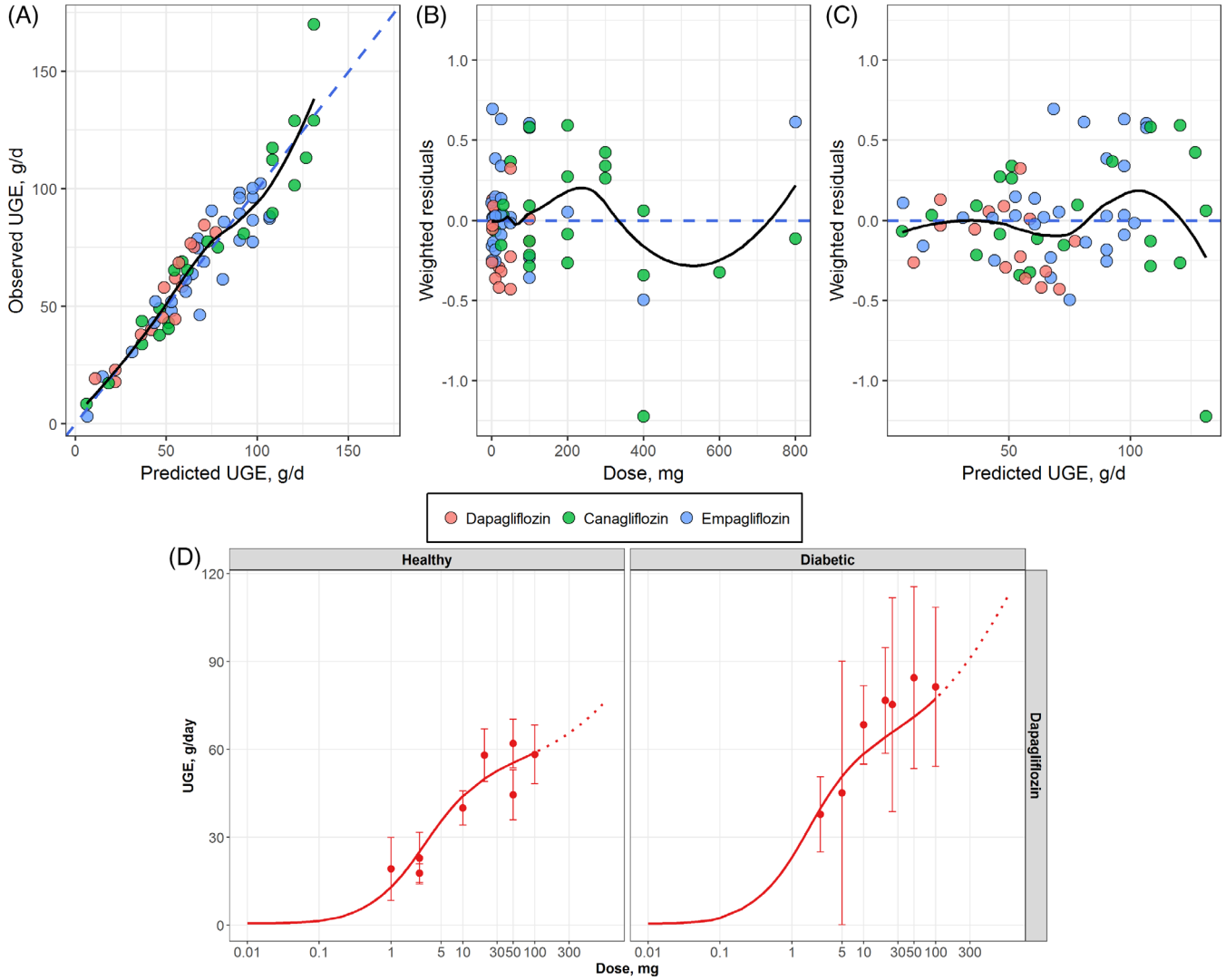

FIGURE 2 Model diagnostic plots. A, Observed versus model-predicted urinary glucose excretion (UGE; g/d) B, Weighted residuals versus compound dose (mg) C, Weighted residuals versus model-predicted UGE (g/d). Symbols represent UGE data from individual treatment cohorts in the pooled clinical dataset; UGE (g/24 h) dose-response relationships for dapagliflozin D. Curves represent the model-predicted dose-response for healthy individuals or those with T2DM treated with dapagliflozin, assuming median mean plasma glucose and eGFR values. Symbols represent experimental 24-hour UGE data pooled for each dose from multiple cohorts (Table S1)

threshold studies which use the stepwise hyperglycaemic clamp procedure.[7,22,23] The model accurately predicted cumulative UGE and total glucose reabsorption rates in healthy individuals and those with T2DM, with and without treatment using 10 mg dapagliflozin (Figure 3A,D) and 25 mg empagliflozin (Figure 3B,E).

3.2 | Glucose reabsorption: Healthy vs T2DM

Differences in renal glucose reabsorption between the healthy individuals and those with T2DM were quantitatively evaluated using the maximal rate of reabsorption for each transporter resulting from the model. Total renal glucose reabsorption capacity can be increased by upregulation of either or both SGLT transporters. Based on knowledge of TmG in untreated healthy individuals and individuals with T2DM,[7] and a pooled dataset of experimental data on 24-hour UGE from individuals treated with SGLT2 inhibitors, we showed that the higher threshold for renal glucose reabsorption in people with T2DM versus healthy people is best explained by the increased transporter capacity of 54% and 28% for SGLT1 and SGLT2 (28.6 vs 18.53 and 111.4 vs 87.07 mmol/h; Figure 3D), respectively.

3.3 | Analysis of model 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 m^2) 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 (Figure 4C). For people with T2DM

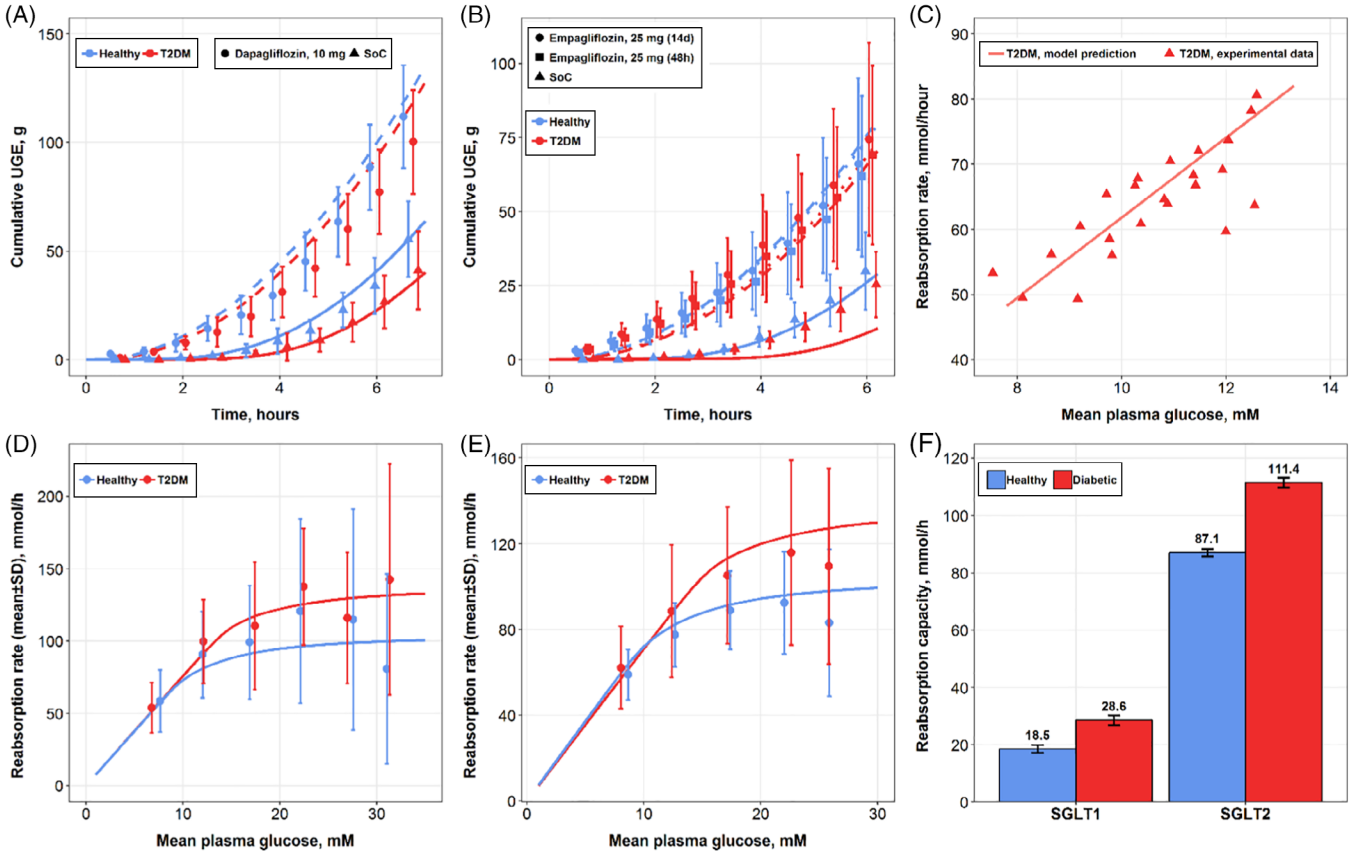

FIGURE 3 External model validation. Curves represent model predictions, symbols denote observations: triangles: Standard of Care without sodium-glucose co-transporter-2 (SGLT2) inhibitor treatment; circles or squares: treatment with 10 mg dapagliflozin A, or 25 mg empagliflozin B. A, B, Cumulative UGE data in healthy individuals (blue) and individuals with type 2 diabetes (T2DM; red) during a stepwise hyperglycaemic clamp procedure with and without SGLT2 inhibitor treatment.[14] C-E, Reabsorption rate dynamics data during a stepwise hyperglycaemic clamp procedure in individuals with T2DM and healthy individuals. Symbols represent experimental data,[7,22,23] line = model predictions. F, Model-predicted maximal SGLT1 and SGLT2 contributions to glucose reabsorption in healthy individuals (blue) and those with T2DM (red)

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/1.73m^2 resulted in a > 70-g lower 24-hour UGE (Figure 4D).

3.4 | Contribution of SGLT1 to renal glucose reabsorption and UGE during SGLT2 inhibition

To explain changes in the reabsorption process and UGE under conditions of SGLT2 inhibition, we simulated dapagliflozin concentration-time profiles in plasma, kidney and urine after a single 10-mg dose (Figure 5).

In people with T2DM, SGLT2 and SGLT1 are responsible for 86% and 14% of the total renal glucose reabsorption, respectively. Following treatment with a single 10-mg dapagliflozin dose, the SGLT2 transporter is quickly and completely inhibited. With no SGLT2-mediated reabsorption greater amounts of glucose flow to the S3 PT segment where the contribution of the SGLT1 transporter to renal glucose reabsorption significantly increases (>90%). Overall, this SGLT1-dependent compensatory effect explains why renal glucose reabsorption is reduced by only 50% (instead of 80%) when SGLT2 is blocked.

After 3 days, dapagliflozin is completely cleared from plasma, but SGLT2 remains partially inhibited due to local compound concentration. UGE and renal glucose reabsorption return to baseline after 5 days.

4 | DISCUSSION

Treatment with SGLT2 inhibitors lowers blood glucose and HbA1c by facilitating UGE through inhibition of glucose reabsorption in the kidney proximal tubules. We studied differences in reabsorption between healthy individuals and individuals with T2DM, based on clinical evidence that the reabsorption threshold is increased in people with T2DM.[2] According to model predictions, people with T2DM would exhibit 54% and 28% increases in maximal reabsorption by SGLT1 and SGLT2, respectively. This represents a compensatory mechanism to retain glucose when renal glucose filtration is increased.

Experimental data comparing SGLT1/SGLT2 expression in diabetic vs wild-type mouse kidneys do not show consistent differences that would explain the changed contribution to reabsorption. Mice with

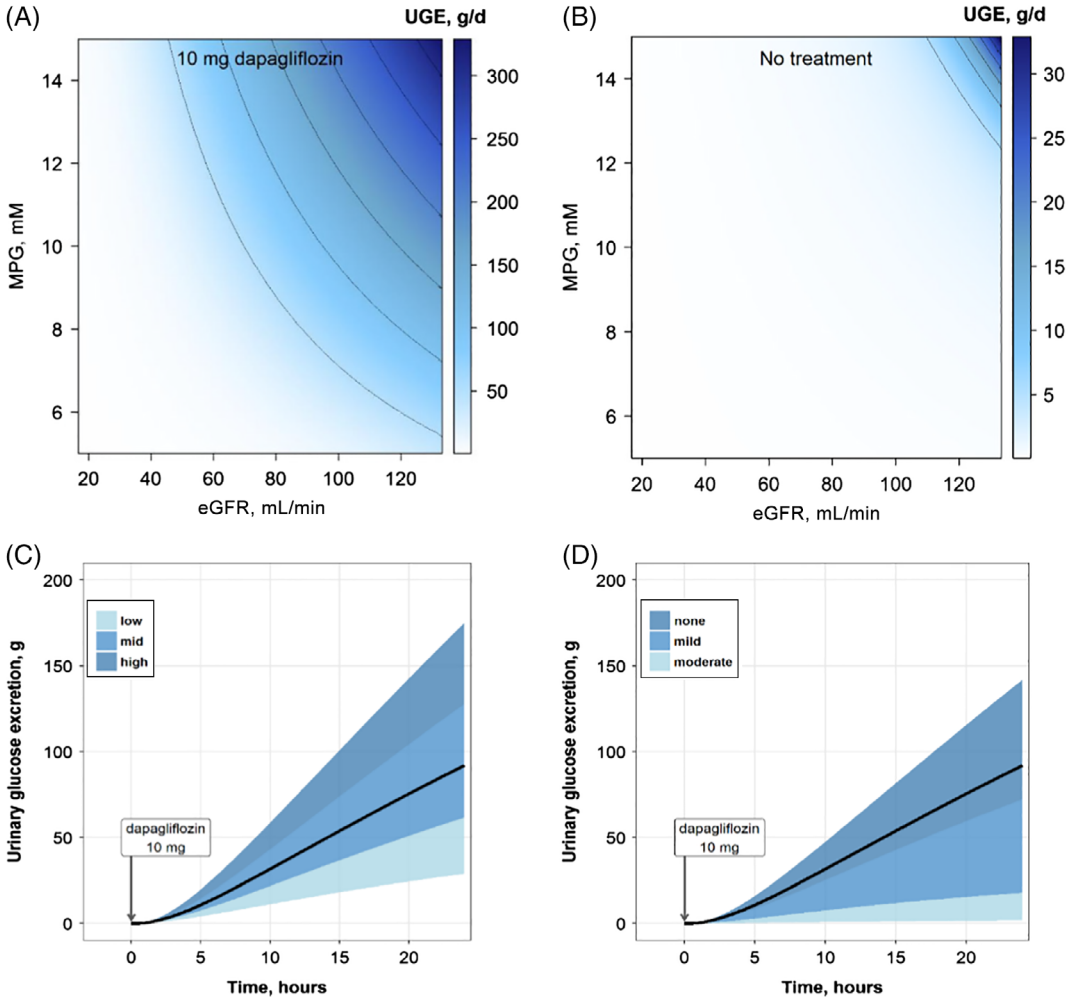

FIGURE 4 Model-based sensitivity analysis: sensitivity of urinary glucose excretion (UGE; g/d) to mean plasma glucose (MPG) and estimated glomerular filtration rate (eGFR) without treatment B, and with 10 mg dapagliflozin (A,C,D). Sensitivity of UGE (g/d) to MPG C, and eGFR D, with 10 mg dapagliflozin. The black line represents an individual with type 2 diabetes (T2DM) with the median eGFR (100 mL/min/1.73m^2) and MPG (9.3 mM). Patient categories are based on MPG (low: 6-7.8 mM; mid: 7.8-11.1 mM; and high: 11.1-13.4 mM)[32] and eGFR/renal impairment status (none: 90-125 mL/min/1.73m^2; mild: 60-90 mL/min/1.73m^2; moderate: 30-59 mL/min/1.73m^2)

streptozotocin-induced diabetes displayed lower renal mRNA and protein expression levels of SGLT2 compared to wild-type controls[24]; however, in the same report, db/db mice and Akita Ins+/C96Y mice (all hyperglycaemic), each had greater renal SGLT2 expression compared to wild-type controls. A more recent study reports no differences in SGLT2 mRNA expression and protein for db/db mice versus wild-type mice.[25]

Human studies are also inconsistent. Wang et al[25] reported increased renal SGLT2 protein in renal biopsies from people with diabetic nephropathy. Recent experimental data on human kidney biopsy specimens demonstrate that renal SGLT1 expression is markedly increased in people with T2DM; SGLT2 expression, however, was not statistically significantly different in healthy individuals versus those with T2DM.[9]

The model-based analysis in the present study shows a significant increase in the maximal reabsorption capacity for SGLT1 and a lower, yet increased reabsorption capacity for the SGLT2 co-transporter.

Despite the greater contribution (>80%) of SGLT2 to proximal tubule glucose reabsorption, clinical observations indicate that SGLT2 inhibitors lead to a maximum decrease in reabsorption of only 30% to 50%. We show that, under conditions of SGLT2 inhibition, contributions from the SGLT1 transporter are increased, leading to a greater SGLT1-mediated contribution to the urinary glucose reabsorption process. SGLT2 inhibition in the proximal tubule increases the availability of glucose for SGLT1 transporters located further downstream. Approximately 30% of glucose is thus reabsorbed by SGLT1 transporters. Although SGLT1 contributions towards the renal glucose reabsorption process are increased under conditions of SGLT2 inhibition, less selective SGLT2 inhibitors may also cause additional SGLT1 inhibition. While this may be beneficial to maximize UGE, it may potentially lead to additional adverse events resulting from increased glucosuria and SGLT1 inhibition in non-renal tissues.

Selectivity of SGLT2 inhibitors should be considered carefully because contributions from SGLT1 inhibition under SGLT2 inhibitor treatment were previously underestimated, particularly in people with T2DM, in whom glucose reabsorption by both transporters is probably upregulated.

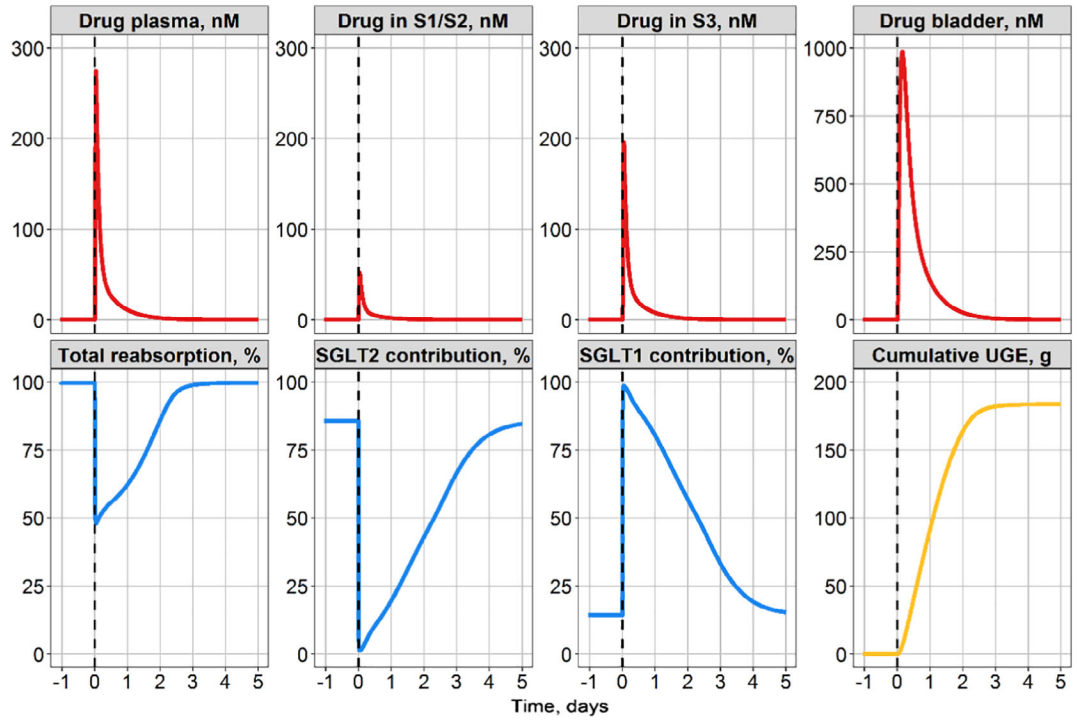

FIGURE 5 Compensatory response of the sodium-glucose co-transporter (SGLT)1 transporter during SGLT2 inhibition by a single 10-mg dose of dapagliflozin in people with T2DM. Model simulations of dapagliflozin concentration-time profiles in plasma, S1/S2 and S3 segments of the proximal tubules and bladder, with total reabsorption rate and contributions from each of the SGLT1 and SGLT2 transporters to renal reabsorption and cumulative urinary glucose

Several mathematical models for SGLT-mediated renal glucose reabsorption have been reported, including: rat models[26]; mice models[27]; a PK/PD model of dapagliflozin in rats[6]; a semi-mechanistic model of SGLT2 inhibitor efficacy[28]; a physiologically based PK/PD model of canagliflozin[29]; and a systems pharmacology model of dapagliflozin and canagliflozin.[14] We reviewed the strengths and shortcomings of these models of renal glucose filtration and SGLT pharmacology to arrive at the structure and parameterization used in the present study. The model we present is a parsimonious but physiologically detailed description of glucose filtration, SGLT-mediated reabsorption and urine excretion. Importantly, the model can reconcile a broad range of clinical UGE dose-response data by incorporating a simple but effective way of scaling filtered glucose by the product of mean plasma glucose and eGFR. We recognize that bespoke models of physiology are targeted at specific research questions and should not be expected to capture every detail of the system. We have used Michaelis-Menten kinetics with simple competitive inhibition to describe the ligand-transporter action, but more detailed mechanistic drug target models may prove useful in differentiating responses of various SGLT2 inhibitors. The present model does not predict mean plasma glucose-lowering resulting from treatment with SGLT2 inhibitors and requires that such data be provided from clinical observations, therefore, no predictions of intraday glycaemic profiles or glucosuria for intervals <24 hours can be reliably made. A logical extension of the model is to couple it with a QSP or semi-mechanistic model of SGLT2 inhibitor-driven glycaemic changes.[30] Finally, renal dysfunction in the model is implemented only through changes in eGFR, although it is possible that progressive renal impairment would impact intrarenal fluxes and require adjustment or additional assumptions.

Throughout the progression of diabetes, the kidney undergoes adaptive changes to accommodate and manage the increased filtered glucose load. These changes not only impact glucose handling but also contribute to the development and progression of renal damage and functional decline.[31] The diabetic kidney is subject to tubular interstitial oxidative stress and inflammation with associated adaptive changes in renal function, biochemistry and pathology. The use of SGLT2 inhibitors ameliorates some of these changes which in turn may indirectly alter the functional behaviour of the proximal tubule glucose reabsorption machinery independently of effects on glomerular filtration and therefore contribute to adaptive changes resulting from SGLT2 inhibition.

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CONFLICT OF INTEREST

L.C., W.T., P.J.G., H.P.S., S.J., G.H., D.W.B. and R.C.P. are employees of AstraZeneca LP, the manufacturer of dapagliflozin. T.Y., V.S. and

K.P. are employees of M&S Decisions LLC, a modelling research consultancy contracting with AstraZeneca.

AUTHOR CONTRIBUTIONS

T.Y., V.S. and R.C.P. contributed to conception and design of the study, data collection and supervision thereof, and data analysis and interpretation. H.P.S. generated the in vitro selectivity data. L.C., P.J.G., G.H., D.W.B. and K.P. contributed to conception and design of the study and data analysis and interpretation. W.T. and S.J. contributed to the data analysis and interpretation. All authors contributed to drafting and critical review of the manuscript and provided approval of the final version for submission.

ORCID

Tatiana Yakovleva https://orcid.org/0000-0002-9715-0931
Victor Sokolov https://orcid.org/0000-0001-7066-0811
Weifeng Tang https://orcid.org/0000-0002-8261-8116
Kirill Peskov https://orcid.org/0000-0003-0678-5729
Gabriel Helmlinger https://orcid.org/0000-0003-4925-2463
David W. Boulton https://orcid.org/0000-0002-0668-7304
Robert C. Penland https://orcid.org/0000-0003-2706-8913

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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