MATHEMATICAL MODELING OF RENAL SODIUM, POTASSIUM, AND GLUCOSE DYNAMICS IN DIABETIC AND NON-DIABETIC SIMULATED POPULATIONS

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OBJECTIVE

Type 2 diabetic (T2D) patients often exhibit reduced systolic and diastolic functions, which can place them at an increased risk of heart failure[1], but diuretic therapies can mitigate the risk of heart failure in these patients. To enable future efficacy predictions of diuretics, a quantitative systems pharmacology (QSP) model was developed that includes dynamic transport of solutes across different nephron segments, enabling the ability to accurately capture renal sodium, potassium, and glucose reabsorption dynamics and urinary excretion in response to novel treatments.

METHODS

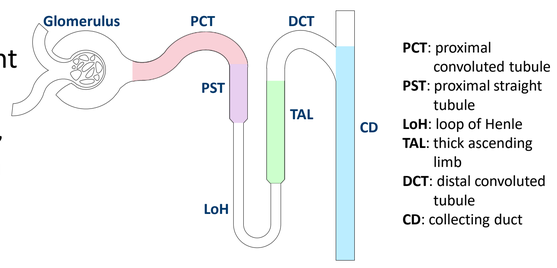
The sodium water regulation model developed by Niederalt et. al[2] was expanded in this work to represent handling of potassium and glucose. This work altered the model to dynamically represent active transport of solutes via explicit inclusion of primary transporters/channels involved in glucose, sodium, and potassium reabsorption (SGLT1, SGLT2, ROMK, NKCC2, Na/K-ATPase, and ENaC) along the nephron. The model was calibrated to a baseline, healthy human using publicly available data for solute reabsorption[3-6] and solute urinary excretion[7,8]. Simulated populations with inter-individual variability in renal physiology and sodium, potassium, and glucose pathways were developed to capture inter-patient variability reported in the literature for nondiabetic and T2D populations[7,9-17]. The model can be used explore potential distributions of key outputs in the simulated populations. Exploratory simulations were conducted to qualitatively assess the impact of transporter inhibition on urinary sodium and potassium excretion and results were qualitatively compared with known effects of on-market diuretics.

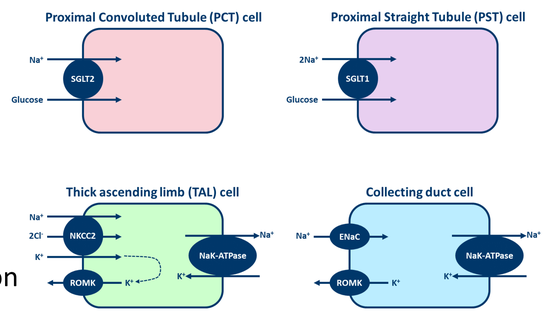
SGLT: sodium-glucose co-transporter
ROMK: renal outer medullary potassium channel
NKCC2: sodium-potassium-chloride co-transporter
NaK-ATPase: sodium-potassium pump
ENaC: epithelial sodium channel

RESULTS

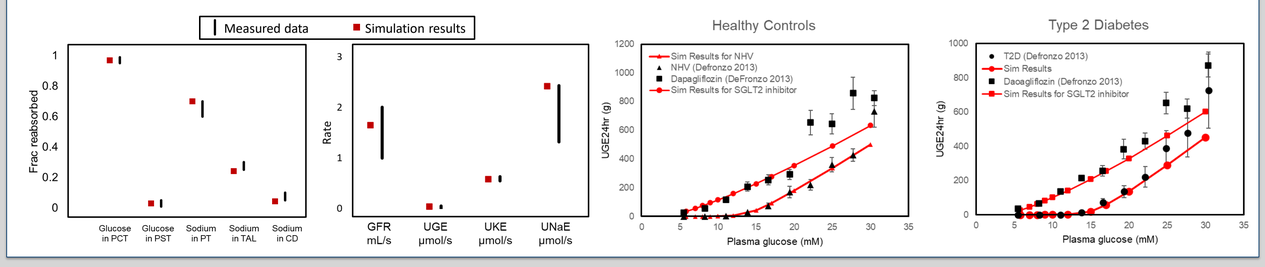
EXPLICIT INCLUSION OF MAJOR GLUCOSE, SODIUM, AND POTASSIUM TRANSPORTERS ALONG NEPHRON

- Niederalt et. al[2] developed a mechanistic model of urine concentration by water reabsorption in different segments of kidney tubules using experimental data identifying sodium and urea concentration gradients, water reabsorption, urine flow, and sodium and urea urine concentrations
  - Solute transporters were not explicitly included
- This work expanded the Niederalt model to include renal glucose and potassium transport and explicit representation of primary renal glucose, sodium, and potassium transporters/channels
  - Sodium and potassium dynamics determined by combination of apical (ROMK, NKCC2, ENaC) and basolateral (NaK-ATPase) transporters
- SGLT2 and SGLT1 included to reabsorb glucose in proximal tubule and contribute to sodium reabsorption
  - SGLT2 responsible for >90% glucose reabsorption[3]





INITIAL SIMULATIONS IN BASELINE PATIENT ALIGN WITH REPORTED VALUES FOR SOLUTE REABSORPTION ALONG NEPHRON AND SOLUTE URINARY EXCRETION

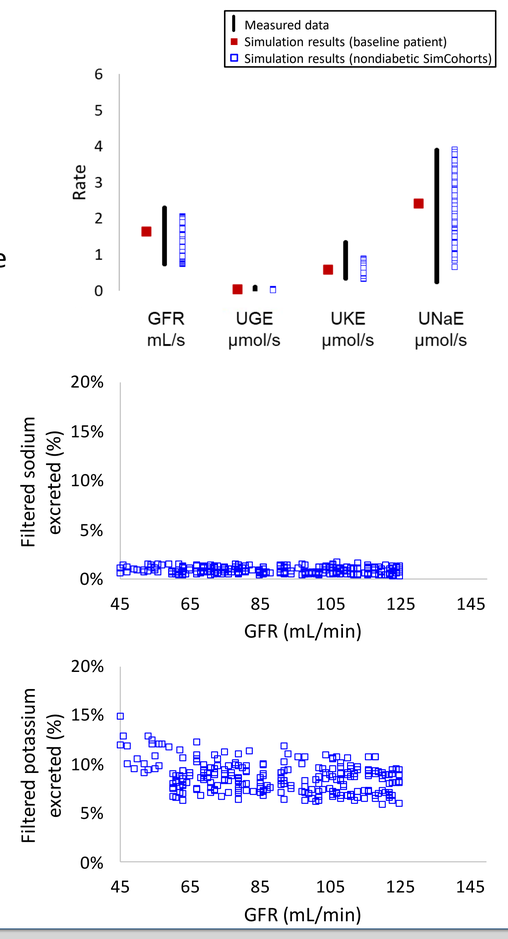


MODEL QUALITATIVELY CAPTURES OBSERVED CLINICAL RESPONSES FOLLOWING TRANSPORTER INHIBITION

Treatment	Clinical Response	Simulated Response
NKCC2 inhibition	↑ urine Na^+ ↑ urine K^+	↑ urine Na^+ ↑ urine K^+
ENaC inhibition	↑ urine Na^+ ↓ urine K^+	↑ urine Na^+ ↓ urine K^+
ROMK inhibition	↑ urine Na^+ ↓ urine K^+	↑ urine Na^+ ↓ urine K^+
SGLT inhibition	↑ urine Na^+ ↑ urine K^+	↑ urine Na^+ ↑ urine K^+

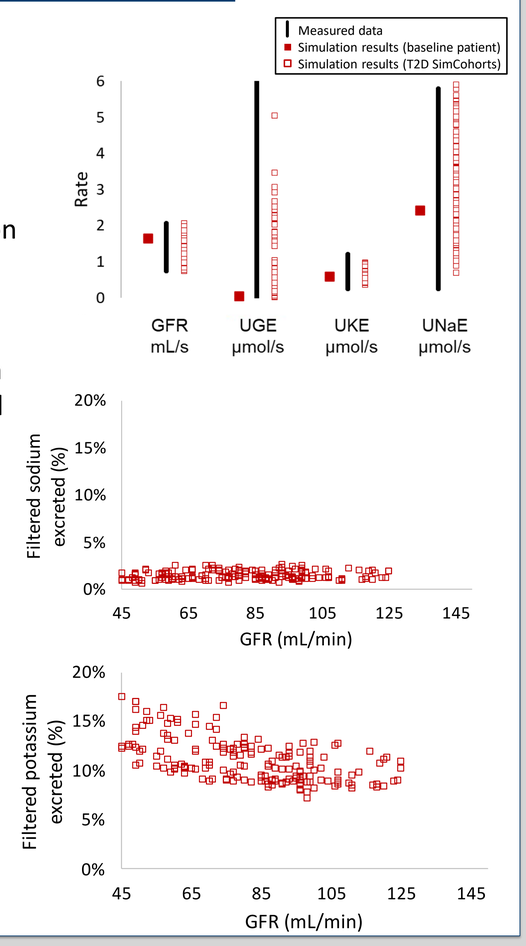
SIMULATED COHORTS OF NONDIABETIC INDIVIDUALS CAPTURES INTER-PATIENT VARIABILITY REPORTED IN LITERATURE

- The nondiabetic cohort (N=247) was simulated with constant glycemia of 5.8 mM[18] and a range of glomerular filtration rates 45 – 125 mL/min[19]
- Nondiabetic simulation results predicted almost complete reabsorption of glucose in the proximal tubule with minimal urinary glucose excretion (UGE, 0 – 0.04 µmol/s)
- Following the baseline individual, sodium and potassium reabsorption along the nephron coincided with reported values in the literature while predicting urinary sodium excretion (UNaE) rate and potassium excretion rate (UKE)[10]
  - Predicted sodium excretion
    - UNaE: 0.65 – 3.90 µmol/s
    - < 3% filtered sodium[11-13]
  - Predicted potassium excretion
    - UKE: 0.32 – 0.88 µmol/s
    - < 15% filtered potassium[14-15]



SIMULATED COHORTS OF TYPE 2 DIABETES PATIENTS CAPTURES INTER-PATIENT VARIABILITY REPORTED IN LITERATURE

- The T2D cohort (N=175) was simulated with constant glycemia in the range of 6.5 – 16 mM[17] and a range of glomerular filtration rates 45 – 130 mL/min[19]
- T2D simulation results predicted incomplete reabsorption of glucose in the proximal tubule, resulting in increased UGE compared to nondiabetic patients[7,9,16]
  - Appreciable increase in UGE when glycemia > 10 mM
- Following the baseline individual, sodium and potassium reabsorption along the nephron coincided with reported values in the literature while predicting UNaE and UKE[20]
  - Predicted sodium excretion
    - UNaE: 0.69 – 5.90 µmol/s
    - < 3% filtered sodium[11-13]
  - Predicted potassium excretion
    - UKE: 0.35 – 0.96 µmol/s
    - < 20% filtered potassium[14-15]



CONCLUSION

- The expanded QSP model accurately captures reabsorption and excretion data for glucose, sodium, and potassium in simulated cohorts of nondiabetic or type 2 diabetes patients.
- Exploratory simulations of transporter inhibition suggest that the model properly captures transporter effects and qualitatively reproduces known clinical responses in potassium and sodium urine output.
- The QSP model of renal potassium and sodium handling provides the ability to simulate responses to diuretic treatments with the aim of predicting reductions in the risk of heart failure.

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