Drug-disease modeling of renal glucose reabsorption in healthy and diabetes subjects: Investigating differences in SGLT2 inhibitors efficacy

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Objectives: Gliflozins inhibit renal glucose reabsorption (RGR) mediated by sodium-dependent glucose cotransporters (SGLT) and are used to treat hyperglycaemia in type 2 diabetes mellitus patients (T2DM). Experimental data suggests that there is an apparent discrepancy in stimulation of urinary glucose excretion (UGE) by SGLT2 inhibitors in T2DM vs. healthy subjects [1]. To investigate observed differences, we developed a mechanistic drug-disease model of RGR that incorporates dapagliflozin, canagliflozin and empagliflozin.

Methods: A physiologically-based 4-compartment model of glucose filtration, reabsorption and excretion was developed as a differential equation system (Fig.1). SGLT-mediated glucose reabsorption was described by Michaelis-Menten kinetics. The mechanism of action of SGLT2 inhibitors was described by competitive inhibition of glucose reabsorption with compound specific Ki values. The model was developed and analysed using the IQM toolbox for MATLAB 2013b [2].

Results: The model adequately described the body of experimental data, without the need for auxiliary compartments, and includes additional covariates of mean plasma glucose (MPG) and eGFR for each study, which were necessary for precise UGE predictions. The model adequately described the 24-hour UGE data following gliflozin administration in healthy subjects. In T2DM, V_{max} for SGLT1 and SGLT2 were re-estimated, resulting in a 50% increase of V_{max} SGLT1 and 10% increase of V_{max} SGLT2 vs. healthy subjects, in full agreement with experimental data [3,4].

Conclusions: According to model predictions, increased SGLT1 contribution to RGR causes an apparent drop in gliflozin efficacy in T2DM. Incorporation of individual MPG and eGFR data were necessary to correctly predict UGE, given the high sensitivity towards these characteristics.


Figure 1: Model scheme