Objectives: Sodium-glucose cotransporter 2 inhibitors (SGLT2i) may improve renal function through changes in tubular sodium (Na) reabsorption. We aimed to determine the quantitative contribution of SGLT2 to Na reabsorption in healthy and type 2 diabetes mellitus (T2DM) subjects, and the impact of SGLT2i on Na reabsorption.

Methods: A published model of glucose dynamics (1,2) was extended to include prediction of urinary glucose excretion (UGE). System parameters describing the normal and diabetic states (including the renal capacity for glucose reabsorption [RC]) were estimated by fitting published plasma glucose and UGE data (3,4). We then simulated glucose and Na filtration, reabsorption, and excretion in healthy and T2DM subjects, and in T2DM subjects treated with SGLT2i canagliflozin 100 mg (modeled by changing only RC).

Results and Discussion: 24 hour glucose reabsorption was estimated to be 811 and 1618 mmol for healthy and T2DM subjects respectively. SGLT2 reabsorbs Na and glucose at a 1:1 molar ratio, and these amounts correspond to 4.6% and 9.1% of total PT Na reabsorption. Thus, PT Na reabsorption through SGLT2 is more than doubled in diabetes, an increase that is likely sufficient to drive pathologic changes in renal hemodynamics (5). Treatment with SGLT2i canagliflozin returned total PT Na reabsorption to the healthy range (851 mmol, or 4.8% of total PT Na reabsorption) (Figure 1).

Conclusions: This study provides critical quantitative information for understanding the role of SGLT2 in renal Na handling and hemodynamics, the potential mechanisms of renoprotection through SGLT2 inhibition, and the impact of SGLT2i on PT Na reabsorption.

References: