COMMENT ON LOVSHIN ET AL.

Dipeptidyl Peptidase 4 Inhibition Stimulates Distal Tubular Natriuresis and Increases in Circulating SDF-1$\alpha^{1\text{-}67}$ in Patients With Type 2 Diabetes. Diabetes Care 2017;40:1073–1081

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We read with interest the study by Lovshin et al. (1) investigating the natriuretic effect of the dipeptidyl peptidase 4 (DPP-4) inhibitor sitagliptin in patients with type 2 diabetes (T2D). The authors report that 1 month of sitagliptin therapy increases creatinine-based fractional sodium excretion (FE_{Na}) compared with placebo, which is in line with our previous observation (2). As lithium clearance and (intra)renal hemodynamics were not affected, the authors suggest that sitagliptin inhibits tubular sodium reabsorption at a level that is likely downstream of the macula densa. In parallel with enhanced FE_{Na}, DPP-4 inhibition increased intact stromal cell–derived factor (SDF)-1$\alpha^{1\text{–}67}$ levels, suggesting a relevant natriuretic role for this DPP-4 substrate. We agree with the authors that their mechanistic findings are of potential clinical relevance, particularly when hypothesizing about the added natriuretic effect of combined pharmacological DPP-4/sodium–glucose cotransporter 2 (SGLT2) inhibition in T2D. However, we believe some comments and suggestions for future research are important to explore this issue in more detail.

We note that sitagliptin only increased FE_{Na} 3 h after the second liquid meal test, in the setting of a concomitant euglycemic clamp, after 1 month of treatment. Sitagliptin had no effect on urinary sodium excretion at baseline (~4.5 h after the first meal, prior to sitagliptin intake), nor did it affect the sodium/creatinine ratio in 24-h urine collections. This result may suggest that DPP-4 inhibitors potentiate natriuresis particularly in the early postprandial state, or it could have been due to the complex study design.

Although the investigators attempted to stabilize dietary sodium intake 7 days prior to testing (i.e., minimum intake 150 mmol/day), the substantial FE_{Na} variability in the placebo arm suggests incomplete adherence to these instructions. It will be of paramount importance to control, or at least closely monitor, sodium intake in future human studies that aim to investigate effects of pharmacological compounds on long-term sodium balance.

One-third of the study population (33.3% on placebo, 27.8% on sitagliptin) used concomitant diuretics, which may have affected FE_{Na}, lithium clearance, and/or tubuloglomerular feedback. We request that the authors provide details on the type of diuretics used (e.g., loop diuretics directly block macula densa signaling [3]) as well as their potential influence on FE_{Na} (e.g., by performing a sensitivity analysis).

To enable full appreciation of the current results, the authors might also provide data on fasting and postprandial (clamped) glucose and insulin (i.e., endogenous/exogenous) concentrations, as both influence tubular functions (e.g., insulin-mediated distal sodium reabsorption).

Finally, we echo the raised possibility that SDF-1$\alpha^{1\text{–}67}$ is a mediator in the association between DPP-4 inhibition and urinary sodium excretion, perhaps via blockade of thiazide-sensitive epithelial sodium channels in the distal tubule. However, we point out that multiple DPP-4 substrates are linked to tubular sodium handling (e.g., glucagon-like peptide 1, substance P, peptide YY, neuropeptide Y) (4), which may be of natriuretic relevance in the setting of DPP-4 inhibition, especially when ACE is concomitantly inhibited (5). As such, it would be of high interest to further scrutinize the relationship between FE_{Na} and SDF-1$\alpha^{1\text{–}67}$ in exploratory subgroup and correlation analyses.

The study by Lovshin et al. (1) suggests an important mechanism underlying the natriuretic properties of sitagliptin in T2D. To further investigate the clinical relevance of their findings, particularly the suggested added value of combined DPP-4/SGLT2 inhibitor use, we call for additional dedicated sodium balance studies. Investigators are encouraged to closely monitor or fully control dietary sodium intake, collect multiple acute and chronic 24-h urine samples, and assess FE_{Na} in both the fasting and postprandial state.

Duality of Interest. D.H.v.R. serves on advisory boards for AstraZeneca, Merck Sharp & Dohme,

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