RESPONSE TO 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

Julie A. Lovshin,[1,2] Leif E. Lovblom,[3] and David Z.I. Cherney[2,4,5]

Diabetes Care 2017;40:e159–e160 | https://doi.org/10.2337/dci17-0033

We thank van Baar et al. (1) for their interest in our study (2). We agree that the chronic natriuretic effect(s) of the dipeptidyl peptidase 4 (DPP-4) inhibitor sitagliptin occurred in the early postprandial state (3 h after a standardized liquid meal during a euglycemic clamp). We cannot, however, rule out that DPP-4 inhibitor–mediated effect(s) on natriuresis persisted for several hours after this sampling period. Recognizing feasibility concerns around having research participants in a highly controlled research setting for prolonged periods, we limited our fractional sodium excretion (FE_{NA}) and renal hemodynamic function measurements to 3 h. This was in addition to the 4–5 h that patients had already been in the lab for baseline testing.

We agree that clinical studies focused on natriuresis should attempt to control for dietary sodium intake, and we emphasize the importance of including a placebo-controlled arm. In our study, patients fasted for up to 12 h prior to all study visits. Then they were administered two standardized liquid meals composed of identical quantities of calories and electrolytes, including sodium. Accordingly, FE_{NA} end points were measured approximately 16–20 h after the study subjects' last ad libitum meal, thereby attenuating the potential impact of heterogeneity in dietary sodium intake.

We confirm that approximately one-third of study subjects were taking stable doses (>3 months or more) of diuretic therapies, which is similar to real-world diuretic use in patients with type 2 diabetes. All subjects receiving diuretics in this study were taking thiazide-type diuretics only, and none of the participants were taking loop diuretics. Since the sample size was limited ($n = 32$), performing sensitivity analyses based on the type of thiazide diuretic used would not be informative. Neither would subgroup analyses stratified by baseline thiazide use.

We confirm that there were no statistically significant differences observed between the two treatment groups for maintenance, insulin, or glucose solutions administered for the euglycemic clamp.

While several DPP-4 substrates have been associated with sodium handling, preclinical studies have provided robust experimental evidence identifying stromal cell–derived factor (SDF)-1$\alpha^{1\text{–}67}$ as the candidate DPP-4 substrate stimulating natriuresis (3). We agree with the comments by van Baar et al. (1) that the identification of SDF-1$\alpha^{1\text{–}67}$ as a mediator linking DPP-4 inhibition to distal tubular natriuresis in patients with type 2 diabetes is clinically relevant. We also agree that research examining the combinatorial use of DPP-4 inhibitors with sodium–glucose cotransporter 2 (SGLT2) inhibitors is needed. We suggest that mechanistic studies evaluating natriuresis with combined glucagon-like peptide 1 receptor agonists and SGLT2 inhibitors are also warranted. Drugs from both of these classes are preferred therapies for patients with clinical cardiovascular disease and type 2 diabetes, and both have renal protective effects (4,5). Interestingly, both are proximal tubular natriuretic agents. Hence, mechanistic studies with glucagon-like peptide 1 receptor agonists and SGLT2 inhibitors would best inform us about the combined clinical use of these drug classes from a sodium balance and cardiorenal perspective.

Duality of Interest. J.A.L. has received either consulting fees or speaking honoraria or both from Novo Nordisk, Eli Lilly & Co., Merck Sharp & Dohme, and AstraZeneca. D.Z.I.C. has received consulting fees or speaking honoraria or both from Janssen, Boehringer Ingelheim-Eli Lilly, AstraZeneca, Merck, and Sanofi, and has received operating funds from Janssen, Boehringer Ingelheim-Eli Lilly, AstraZeneca, and Merck. No other potential conflicts of interest relevant to this article were reported.

[1]*Division of Endocrinology and Metabolism, Department of Medicine, University of Toronto, Toronto, Ontario, Canada*
[2]*Division of Nephrology, Department of Medicine, University Health Network, University of Toronto, Toronto, Ontario, Canada*
[3]*Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada*
[4]*Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada*
[5]*Department of Physiology, University of Toronto, Toronto, Ontario, Canada*

Corresponding author: Julie A. Lovshin, lovshin@lunenfeld.ca.

References

1. van Baar MJB, van Raalte DH, Muskiet MHA. Comment on Lovshin et al. Dipeptidyl peptidase 4 inhibition stimulates distal tubular natriuresis and increases in circulating SDF-1α^{1-67} in patients with type 2 diabetes. Diabetes Care 2017;40:1073–1081 (Letter). Diabetes Care 2017;40:e157–e158. https://doi.org/10.2337/dc17-1258

2. Lovshin JA, Rajasekeran H, Lytvyn Y, et al. Dipeptidyl peptidase 4 inhibition stimulates distal tubular natriuresis and increases in ciculating SDF-1α^{1-67} in patients with type 2 diabetes. Diabetes Care 2017;40:1073–1081

3. Takashima S, Fujita H, Fujishima H, et al. Stromal cell-derived factor-1 is upregulated by dipeptidyl peptidase-4 inhibition and has protective roles in progressive diabetic nephropathy. Kidney Int 2016;90:783–796

4. Neal B, Perkovic V, Mahaffey KW, et al.; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017; 377:644–657

5. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311–322