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Inhibiting renal sodium–glucose transport in diabetes: pass the salt

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To the Editor: In their elegant review, Bakris *et al.*[1] explored the role of selective inhibitors of sodium glucose co-transporter 2 (SGLT2) (*SLC5A2*, a sodium–glucose transporter in the renal proximal tubule) in diabetes mellitus type 2 (DM2). Indeed, early studies indicate that dapagliflozin is able to reduce HbA1C levels in DM2.[2] However, based on our experience regarding a patient with a *SLC5A2* mutation, and cases of similar patients from the literature,[3] we feel some caution is warranted. Our patient is a 33-year-old Turkish man with no past medical history, and no medication or parental consanguinity. He has hypotension (90/60 mm Hg) and persistently high serum sodium and bicarbonate levels (150 and 33 mmol/l, respectively).

As massive amounts of glucose are filtered daily, perturbed glucose reabsorption causes profound glucosuria, osmotic diuresis, and subsequent urinary sodium loss. Indeed, patients with *SLC5A2* mutations are often severely volume depleted, as evidenced by orthostatic complaints and a fivefold increase in their plasma renin values.[3] A high angiotensin II level stimulates the sodium–hydrogen exchanger type 3 in the proximal tubule to reabsorb sodium at the expense of alkalosis. Thus, these patients depend on their renin–angiotensin system to stay upright. As many diabetic patients are treated with inhibitors of the renin–angiotensin system, SGLT2 inhibitors may induce unwanted effects, such as hypotension and reduced glomerular filtration, when used in combination with these drugs. However, if one looks at the bright side, the natriuretic effect of the SGLT2 inhibitors may improve the typical volume expansion in DM2. Moreover, reducing proximal sodium reabsorption may even reduce glomerular hyperfiltration.[4] Time alone can tell which of these effects will prevail.

1. Bakris GL, Fonseca VA, Sharma K *et al.* Renal sodium-glucose transport: role in diabetes mellitus and potential clinical implications. *Kidney Int* 2009; **75**: 1272–1277.
2. Wilding JP, Norwood P, T'Joen C *et al.* A study of dapagliflozin in patients with type 2 diabetes on high doses of insulin plus insulin sensitizers: applicability of a novel insulin-independent treatment. *Diabetes Care* 2009; **32**: 1656–1662.
3. Calado J, Sznajer Y, Metzger D *et al.* Twenty-one additional cases of familial renal glucosuria: absence of genetic heterogeneity, high prevalence of private mutations and further evidence of volume depletion. *Nephrol Dial Transplant* 2008; **23**: 3874–3879.
4. Vervoort G, Veldman B, Berden JH *et al.* Glomerular hyperfiltration in type 1 diabetes mellitus results from primary changes in proximal tubular sodium handling without changes in volume expansion. *Eur J Clin Invest* 2005; **35**: 330–336.

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Response to 'Inhibiting renal sodium–glucose transport in diabetes: pass the salt'

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We read with interest the letter by Zietse and Hoorn[1] regarding their patient and the caution with the use of sodium glucose co-transporter 2 (SGLT2) agents in such a setting. We are aware of the fact that these agents have the potential to cause volume depletion if not properly monitored. However, in the more typical clinical setting, it would be unusual to have a patient develop volume depletion simply from this agent. Similar to agents that block the renin–angiotensin system, it is appreciated that changes in volume status can adversely affect kidney function and may occur with any agent, including diuretics as well as the aforementioned classes in any patient.

Given that the increased urine output per day generated by this class of agents is in the range of 400–600 ml, it would be uncommon to predict volume depletion simply on this basis. Moreover, this increase in urine volume does not necessarily continue indefinitely, or else one would get severely dehydrated eventually. There are compensatory mechanisms for this volume loss, thirst being a prominent one. The lack of thirst or a disrupted thirst mechanism may have been a problem in the patient described. Lastly, clinical trials completed to date have not turned up patients with problems such as that described. Thus, clinicians, as always, are required to be vigilant about concomitant medications and diseases that might affect the volume status of patients. The SGLT2 agents will be a welcome adjunct to the armamentarium of agents that help manage the worldwide epidemic of diabetes.

1. Zietse R, Hoorn EJ. Inhibiting renal sodium-glucose transport in diabetes: pass the salt. *Kidney Int* 2009; **76**: 1293.

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