Opinion

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Administration of Sodium-Glucose Co-transporter 2 Inhibitors Could Accelerate Dehydration in Poorly-Controlled Diabetic Patients, Proposing an Option not to Increase Glucosuria but to Decrease Carbohydrate Intake during Hyperglycemia

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ABSTRACT

Sodium-glucose co-transporter 2 (SGLT2) inhibitors, a new class of anti-diabetic agents, have been recently approved for treatment of type 2 diabetes. It was unexpected that possible adverse effects of SGLT2 inhibitors, including fatal events, were reported frequently soon after the first one was marketed in April 2014 in Japan. In poorly-controlled diabetic patients, pre-existing osmotic diuresis is supposed to be augmented by the administration of SGLT2 inhibitors, possibly leading to an acceleration of their dehydration in spite of amelioration of hyperglycemia. It may be reasonable that not only water but a small amount of salt needs to be supplemented with, if necessary, to prevent plasma volume depletion with salt loss. Otherwise, it seems to be a plausible option for such patients to decrease carbohydrate intake by 50 to 100 g of carbohydrate per day during hyperglycemia, instead of excreting a similar amount of glucose into urine with SGLT2 inhibitors.

KEYWORDS: SGLT2 inhibitors; Glucosuria; Osmotic diuresis; Dehydration; Carbohydrate intake.

Sodium-glucose co-transporter 2 (SGLT2) inhibitors, a new class of anti-diabetic agents, have been recently approved for treatment of type 2 diabetes, since dapagliflozin was first approved by the European Medicines Agency in November 2012. SGLT2 inhibitors decrease hyperglycemia independently of insulin by increasing urinary glucose excretion through the inhibition of glucose reabsorption in the proximal renal tubule. They have some advantages including modest weight loss, low risk of hypoglycemia and mild decrease of blood pressure.[1] However, it is reported that Canagliflozin cardiovascular assessment study (CANVAS) showed an increase of cardiovascular events during the first 30 days in patients who received canagliflozin,[2] the first SGLT2 inhibitor approved in the United States in March 2013. In Japan, six SGLT2 inhibitors have been approved since January 2014. It is a matter of concern that the Japan Diabetes Society announced an alert regarding proper use of SGLT2 inhibitors, twice in June and August 2014. It was unexpected that possible adverse effects of SGLT2 inhibitors were reported frequently soon after the first one was marketed in April 2014. Finally, dehydration, which seemed to be occasionally linked to fatal adverse events, was added as a severe adverse effect to a package insert in January 2015.

Familial renal glucosuria with normoglycemia is often referred to as a natural model for SGLT2 inhibition. Plasma volume depletion resulting from osmotic diuresis was indicated by activation of the renin-angiotensin-aldosterone system in cases of severe renal glucosuria (>10 g/1.73m^2/24h) with a favourable prognosis.[3,4] Such activation has been shown after the administration of empagliflozin, another SGLT2 inhibitor, in type 1 diabetic patients.[5] In line

with plasma volume depletion, salt loss is suggested to occur early after the administration of SGLT2 inhibitors,[6,7] reaching to a new balance of total body salt. The diuretic effect of dapagliflozin causes small but significant increases in urine volume, blood urea nitrogen and hematocrit without an increase in serum sodium.[8] As Haas, et al.[9] described, no hypernatremia as a trigger for thirst may explain why, in particular, elderly patients do not develop sufficient thirst to compensate for water loss and consequently tend to have dehydration, unstable pressure or syncope.

In poorly-controlled diabetic patients, pre-existing osmotic diuresis is supposed to be augmented by the administration of SGLT2 inhibitors, possibly leading to an acceleration of their dehydration in spite of amelioration of hyperglycemia. In the case of parenteral administration of mannitol, an osmotic diuretic, initial volume expansion and subsequent hypovolemia is known as one of its adverse effects.[10] From this point of view, it is inferred that hypovolemia is more likely to occur due to osmotic diuresis without an increase in blood glucose (and possibly sodium[8,11]) level to retain water following the administration of SGLT2 inhibitors, even if drinking water is recommended. If this is true, use of SGLT2 inhibitors should be avoided in poorly-controlled diabetic patients. The amelioration of hyperglycemia by treatment with SGLT2 inhibitors might mislead into overestimating the safety of their use. Since familial renal glucosuria with normoglycemia usually has no apparent clinical problems,[3,4] it may need to be determined from which level of HbA1c it becomes safer to use SGLT2 inhibitors for diabetic patients of different ages with the variety of vascular complications.

As in the statement of "Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach",[12] SGLT2 inhibitors with a diuretic effect should be used cautiously in the elderly, in any patient already on a diuretic, and in anyone with a tenuous intravascular volume status. It may be reasonable that not only water but a small amount of salt needs to be supplemented with, if necessary, to prevent plasma volume depletion with salt loss. Otherwise, it seems to be a plausible option for such patients to decrease carbohydrate intake by 50 to 100 g of carbohydrate per day during hyperglycemia, instead of excreting a similar amount of glucose into urine with SGLT2 inhibitors. Such carbohydrate restriction seems to be readily accepted for diabetic patients educated on carbohydrate counting.[13,14] Despite the inconclusive results of the studies evaluating the effect of differing percentages of carbohydrates, evidence exists that total amount of carbohydrate eaten is the primary predictor of glycemic response.[15] Feinman, et al.[16] claim that evidence supports the use of low-carbohydrate diets as the first approach to treating type 2 diabetes and as the most effective adjunct to pharmacology in type 1 diabetes. Then, conversely, adjunctive use of SGLT2 inhibitors may be also effective in type 1 diabetes.[17] Further studies should be needed towards a better understanding of the benefit to risk ratio of treatment with SGLT2 inhibitors, a unique and anticipated anti-diabetic agent.

CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest.

REFERENCES

1. Mikhail N. Place of sodium-glucose co-transporter type 2 inhibitors for treatment of type 2 diabetes. *World J Diabetes*. 2014; 5: 854-859. doi: 10.4239/wjd.v5.i6.854

2. Vasilakou D, Karagiannis T, Athanasiadou E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. *Ann Intern Med*. 2013; 159: 262-274. doi: 10.7326/0003-4819-159-4-201308200-00007

3. Scholl-Buergi S, Santer R, Ehrich JHH. Long-term outcome of renal glucosuriatype 0: the original patient and his natural history. *Nephrol Dial Transplant*. 2004; 19: 2394-2396. doi: 10.1093/ndt/gfh366

4. 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. doi: 10.1093/ndt/gfn386

5. Cherney DZI, Perkins BA, Soleymanlou N, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation*. 2014; 129: 587-597. doi: 10.1161/CIRCULATIONAHA.113.005081

6. Katsuno K, Fujimori Y, Takemura Y, et al. Sergliflozin, a novel selective inhibitor of low-affinity sodium glucose reabsorption and modulates plasma glucose level. *J Pharmacol Exp Ther*. 2007; 320: 323-330. doi: 10.1124/jpet.106.110296

7. Lin B, Koibuchi N, Hasegawa Y, et al. Glycemic control with empagliflozin, a novel selective SGLT2 inhibitor, ameliorates cardiovascular injury and cognitive dysfunction in obese and type 2 diabetic mice. *Cardiovasc Diabetol*. 2014; 13: 148. doi: 10.1186/s12933-014-0148-1

8. List JF, Woo V, Morales E, Tang W, Fiedorek FT. Sodium-glucose cotransport inhibition with dapagliflozin in type 2 diabetes. *Diabetes Care*. 2009; 32: 650-657. doi: 10.2337/dc08-1863

9. Haas B, Eckstein N, Pfeifer V, Mayer P, Hass MDS. Efficacy, safety and regulatory status of SGLT2 inhibitors: focus on canagliflozin. *Nutr Diabetes*. 2014; 4: e143. doi: 10.1038/nutd.2014.40

10. Shawkat H, Westwood MM, Mortimer A. Mannitol: a review of its clinical uses. *Contin Educ Anaesth Crit Care Pain*. 2012; 12(2): 82-85. doi: 10.1093/bjaceaccp/mkr063

11. Bernstein LM, Blumberg B, Arkin MC. Osmotic diuretic treatment of refractory edema. *Circulation*. 1958; 17; 1013-1020. doi: 10.1161/01.CIR.17.6.1013

12. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centered approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia.* 2015; 58: 429-442.

13. Warshaw HS, Bolderman KM. Practical carbohydrate counting. 2nd ed. Alexandria, VA: American Diabetes Association. 2008.

14. Aoki Y, Onzuka M. Glycemic variations after ingestion of different carbohydrate-containing foods assessed by continuous glucose monitoring in healthy and diabetic individuals in daily life. *Diabetes Res Open J.* 2015; 1(2): 41-47.

15. Evert AB, Boucher JL, Cypress M, et al. Nutrition therapy recommendations for the management of adults with diabetes. *Diabetes Care*. 2013; 36: 3821-3842. doi: 10.2337/dc13-2042

16. Feinman RD, Pogozelski WK, Astrup A, A et al. Dietary carbohydrate restriction as the first approach in diabetes management: critical review and evidence base. *Nutrition*. 2015; 31: 1-13. doi: 10.1016/j.nut.2014.06.011

17. Perkins BA, Cherney DZI, Partridge H, et al. Sodium-glucose cotransporter 2 inhibition and glycemic control in type 1 diabetes: results of an 8-week open-label proof-of-concept trial. *Diabetes Care*. 2014; 37: 1480-1483. doi: 10.2337/dc13-2338