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COMMENTARY

Lowering the risk of gout: Another benefits from the use of sodium–glucose cotransporter 2 inhibitors

Hyperuricemia and the risk of gout are commonly seen in patients with type 2 diabetes. It has also been reported that chronically elevated circulating uric acid concentrations are associated with an increased risk of hypertension, cardiovascular disease and chronic kidney disease, all of which are known diabetes-associated complications[1,2].

By analyzing the USA nationwide commercial insurance database, Fralick *et al.*[3] reported a lower risk of gout in new users of sodium–glucose cotransporter 2 (SGLT2) inhibitors, as compared with new users of glucagon like peptide-1 (GLP-1) receptor agonists (with 1:1 propensity score matched), in patients with type 2 diabetes. Several features of this study should be taken into consideration. It involved real-time data and enrolled nearly 300,000 adults with type 2 diabetes who had received SGLT2 inhibitors or GLP-1 receptor agonists. Additionally, the study collected information regarding the diagnosis of gout, as well as the prescribed medication used for treatment from March 2013 to December 2017. What the authors discovered was that new users of SGLT2 inhibitors experienced a 64% lower risk of gout, as compared with new users of GLTP-1 agonists (4.9 vs 7.8 events per 1,000 person years) in patients with type 2 diabetes. Data obtained from this study are particularly welcome for two reasons. First, there are a limited number of drugs that have been shown to safely lower uric acid levels. As a matter of fact, there have been concerns raised in a recent report that the use of febuxostat, a relatively new uric acid-lowering agent, caused a higher risk for cardiovascular death and all-cause mortality as compared with allopurinol, a traditional uric acid lowering drug. Second, the US Food and Drug Administration is encouraging the use of applications of real-world data to evaluate supplemental indications for already approved medications.

Presumably, the glycosuria caused by the use of SGLT2 inhibitors helps uric acid to be secreted into the urine. The most likely mechanism postulated was that, through SGLT2 inhibitors, an increase in uricosuria occurred by suppressing the activity of glucose transporter 9b, a hexose/urate transporter located at the proximal tubular cells across the basolateral membrane[1]. However, the exact mechanisms have not been fully illustrated. It is estimated that the increased uric acid elimination through the use of SGLT2 inhibitors usually lowers circulating uric acid concentrations by approximately 35–45 μmol/L (0.60–0.75 mg/dL) in individuals with a baseline uric acid value in the normal concentration range of approximately 200–400 μmol/L (~3.3–6.7 mg/dL)[1]. In the Empagliflozin Reduced Mortality and Hospitalization for Heart Failure Across the Spectrum of Cardiovascular Risk (EMPA-REG OUTCOME) trial, patients who received empagliflozin showed a lower serum uric acid level of approximately 30 μmol/L compared with those who had been assigned a placebo[4]. Alternatively, it was shown that the use of GLP-1 agonists in patients with type 2 diabetes did not show any effect on serum uric acid levels, when compared with a placebo or comparator medication. To confirm their observations, the authors also examined those who had undergone up to 1 year of index medication exposure, and found that adults with type 2 diabetes who had received SGLT2 inhibitors had a 73% lower risk of gout, as compared with those who had received GLP-1 agonists (5.6 vs 7.7 events per 1,000 person years). The authors also clearly showed that the users of SGLT2 inhibitors had a reduced risk of gout with a hazard ratio of 0.66 (95% confidence interval 0.58–0.75) compared with a group of new users who were prescribed dipeptidyl peptidase-4 inhibitors, which is one of the most commonly prescribed second-line medications for adults with diabetes, without lowering serum uric acid levels.

Previous observational and interventional studies have shown that uric acid acts as a modifiable risk factor in the progression of chronic kidney disease for type 2 diabetes[1,2]. This is also true for those diabetes patients with lesser degrees of hyperuricemia. Several potential benefits are listed from the use of SGLT2 inhibitors in Table 1. One item of note that should be pointed out is that the authors particularly excluded patients with a history and diagnosis of gout at baseline. Those with prevalent gout and those with a higher baseline risk for gout (such as the elderly, and those diagnosed with chronic renal diseases and established cardiovascular disease) were not enrolled. Thus, the benefits from the use of SGLT2 inhibitors might be underestimated.

The magnitude in the reduction of serum uric acid levels in those users of SGLT2 inhibitors was generally modest, and believed to be less potent than xanthine oxidase inhibitors, such as

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Table 1 | Potential benefits on gout in sodium –glucose cotransporter 2 inhibitor users

Benefits
Plasma glucose ↓
Bodyweight ↓
Body fat ↓
Blood pressure ↓
Use of diuretics ↓
Anti-inflammatory effects
Renal protection

allopurinol or febuxostat. However, given that the modes of action are different and might be potentially complementary, it is likely that the use of SGLT2 inhibitors for diabetes with hyperuricemia might offer an additive effect if combined for use with a xanthine oxidase inhibitor. Alternatively, it has been postulated that increased uric acid elimination in the urine through the use of an SGLT2 inhibitor might lead to an increased risk of renal calculi; however, until now, studies have yet to observe this possible long-term risk. It is also hoped that non-diabetic adults with hyperuricemia and/or a history of gout might gain benefits from the use of SGLT2 inhibitors. If proven, this will be useful for adults with hyperuricemia who do not have diabetes.

As with all observational studies, the findings by Fralick *et al.*[3] might be subject to unmeasured confounding, despite many confounders being well balanced by propensity score matched analysis. There are very limited laboratory data regarding hemoglobin A1c and serum creatinine levels available (these values were available for approximately 5% of the patients with a baseline hemoglobin A1c level of 8.6%, and a baseline creatinine level of 78.7 μmol/L (0.89 mg/dL). This greatly devalues the opportunity to examine the effects of the changes in glycemic control and the alterations of renal function on the risk of gout. Additionally, there were no serum uric acid levels available that might enable a comparison with the uric acid-lowering effects of these two glucose-lowering agents. Information with regard to the bodyweight of the participants was not reported in this article. Therefore, it is not known whether the benefits of less frequent gout favored those with a higher or lower body mass index given the known effects of SGLT2 inhibitors on bodyweight[5]. One might argue that the use of a diagnosis code for gout, plus a prescription claim for medication used to treat gout for up to 14 days, would be sufficient to capture all incidences of gout and flare up.

There was 41 days difference in the mean follow-up time (302 days for SGLT2 inhibitor vs 261 days for GLP-1 agonist)[3]. In addition, a sizable number of patients did not refill their medications during the follow-up period. Specifically, 45% of the patients discontinued their SGLT2 inhibitor medication, with 49% discontinuing their GLP-1 agonist. There were also mixed effects in that 9% of the patients who had started GLP-1 agonist treatment and subsequently filled a prescription for an SGLT2 inhibitor, whereas 8% of the patients who had started treatment with an SGLT2 inhibitor subsequently filled a prescription for a GLP-1 agonist. As these phenomena did occur in real-world practice, the data presented should be interpreted cautiously.

In summary, the authors of this real-world observational cohort study reported a relative risk reduction in gout of nearly 40%, and an absolute risk reduction of approximately three fewer adults who experienced gout per 1,000 person-years by new users of SGLT2 inhibitors, as compared with new users of GLP-1 agonists. Given the potential limitations, such as unmeasured confounding, missing data, incomplete laboratory data, clinical information (use of alcohol, dietary patterns, body mass index) and a low baseline risk for gout, the authors' findings are clinically relevant and demand further investigations.

DISCLOSURE

The author declares no conflict of interest.

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REFERENCES

1. Baily CJ. Uric acid and the cardio-renal effects of SGLT2 inhibitors. *Diabetes Obes Metab* 2019; 21: 1291–1298.
2. Sheu WHH, Tseng YH. Uric acid: an additional component of metabolic syndrome? *J Chin Med Assoc* 2006; 69: 99–100.
3. Fralick M, Chen SK, Patorno E, *et al.* Assessing the risk for gout with sodium-glucose cotransporter-2 inhibitors in patients with type 2 diabetes: a population-based cohort study. *Ann Intern Med* 2020; 172: 186–194.
4. Zinman B, Wanner C, Lachin JM, *et al.* Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; 373: 2117–28.
5. Sheu WHH, Chan SP, Matawaran BJ, *et al.* Use of SGLT-2 inhibitors in patients with type 2 diabetes mellitus and abdominal obesity: an Asian perspective and expert recommendations. *Diabetes Metab J* 2020; 44: 11–32.

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