CORRESPONDENCE

Gout

TO THE EDITOR: The Clinical Practice review on gout by Mikuls (Nov. 17 issue)[1] underscores the importance of hyperuricemia as a necessary risk factor and mentions the high heritability of serum urate levels.[2] Serum urate levels are mostly controlled by the kidney, as confirmed by genetic studies implicating both rare and common variants in transporters and transcriptional regulators that mediate the tubular transport of urate.[3,4] The latter can be assessed by the fractional excretion of urate, which is approximately 10% under normal conditions.

The genetic influence on serum urate levels has clinical consequences. Patients with monogenic disorders such as autosomal dominant tubulointerstitial kidney disease caused by mutations in the gene encoding uromodulin (*UMOD*) may have early-onset hyperuricemia and gout, with a dramatic reduction in the fractional excretion of urate, despite a normal glomerular filtration rate.[5] Moreover, common susceptibility variants for higher urate levels throughout the genome may be combined in a genetic risk score associated with a variation in the risk of gout by a factor of 100.[4] Genetic factors may explain the limited success of dietary measures in patients with gout[1] and may help to focus preventive measures among persons at risk.[4]

Olivier Devuyst, M.D., Ph.D.
University of Zurich
Zurich, Switzerland
olivier.devuyst@uzh.ch

Eric Olinger, M.D., Ph.D.
Saint-Luc Academic Hospital
Brussels, Belgium

Anna Köttgen, M.D., M.P.H.
University of Freiburg
Freiburg, Germany

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TO THE EDITOR: Mikuls points out the potential of sodium–glucose transporter 2 (SGLT2) inhibitors in gout management owing to the uricosuric properties of these drugs. In this context, the growing evidence of the effect of SGLT2 inhibitors on gout outcomes in patients with type 2 diabetes mellitus deserves a mention.

In our recent meta-analysis, we found that SGLT2 inhibitors improved adverse gout outcomes in a cohort of 568,010 patients with type 2 diabetes, as compared with incretin-based therapies or placebo.[1] A significant relative reduction of 26% in incident gout was also noted in the subgroup analysis involving 17,162 patients who were enrolled in the CANVAS and EMPA-REG OUTCOME randomized, controlled trials. A similar observation was made in the recent post hoc analysis of the EMPEROR-Reduced trial.[2] As compared with patients who received placebo or active comparators such as metformin, dipeptidyl peptidase-4 inhibitors, and glimepiride, patients who received SGLT2 inhibitors had a reduction from baseline in the mean serum urate level of approximately 0.6 mg per deciliter.[3] Despite this modest urate-lowering potential, the significant improvement in clinical gout end points with SGLT2 inhibitors[1,2,4] can be explained by the attenuation of NLRP3 inflammasome activation and subsequent reduction in the release of interleukin-1β.[5] As reported by Kim et al.,[5] ex vivo experiments on human macrophages showed that exposure to SGLT2 inhibitors led to the inhibition of both NLRP3 and interleukin-1β. Thus, SGLT2 inhibition has the potential to play an important role in gout management. Additional preclinical studies and randomized, controlled trials with predefined gout end points are warranted.

Mainak Banerjee, M.D., D.M.
Satinath Mukhopadhyay, M.D., D.M.

Institute of Post Graduate Medical Education and Research
Kolkata, India
mainak18y@gmail.com

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