EDITORIAL

Gouty Offense in Patients With Obstructive Coronary Artery Disease Despite State-of-the-Art Therapy

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Gout is a painful condition of the joints and affects up to 2% of the world’s population, mainly in industrialized and emerging countries. It is caused by hyperuricemia and triggered by the incorporation of crystallized salts of uric acid (urates) in the joints. However, hyperuricemia is also associated with hypertension, type 2 diabetes mellitus, obesity, chronic kidney disease, and cardiovascular disease (CVD). While earlier studies explained the strong associations between CVD and prevalent hyperuricemia with comorbid conditions such as metabolic syndrome, renal dysfunction, and hypertension, large epidemiological studies have now demonstrated that gout is an independent risk factor for CVD.1–3 Nevertheless, in this issue of the Journal of the American Heart Association (JAHA), Pagidipati et al revisited this paradigm since treatment regimens of CVDs have improved lately and individuals included in earlier investigations were not separated by the type of coronary artery disease (CAD) present or the studies were mainly conducted in men.4 The authors surveyed the long-term association between gout and CVD in a contemporary population of men and women with known CAD from the Duke Databank for Cardiovascular Diseases. The 17,201 patients who were included in this study underwent cardiac catheterization at Duke University Medical Center between 1998 and 2013 and were found to have obstructive CAD. Furthermore, 1,406 of these individuals had a baseline history of gout (8.2%), while 15,795 did not. Notably, from these patients with a history of gout at time of catheterization a majority (66.9%) already received at least 1 gout medication at baseline. Gout-at-baseline individuals were also mostly older, more often male, nonwhite, and more commonly had a history of myocardial infarction (MI), coronary revascularization, congestive heart failure, cerebrovascular disease, peripheral vascular disease, diabetes mellitus, hypertension, and renal disease compared with those without gout. In general, the majority of subjects included in this study received optimal medical therapy for CVD. In this context, Pagidipati et al further revealed that over a median follow-up of 6.4 years after catheterization, a diagnosis of gout at the time of catheterization was not primarily associated with cardiovascular death, MI, or stroke, but significantly correlated with higher overall mortality and was associated with cardiac and noncardiac deaths. An initial (baseline) gout diagnosis was particularly associated with a more than 2-fold increase in the risk of death from heart failure. Overall, these data suggest that long-term cardiovascular mortality is increased despite medical therapy of obstructive CAD in patients with clinical manifestations of gout and that current standard therapies do not address that residual cardiovascular risk.4

As noted before, gout and hyperuricemia have been identified as risk factors for atherosclerosis and CAD (for example, in the Framingham Study or in the US National Health and Nutrition Examination Survey). Both studies report an ≈60% increase in coronary heart disease or cardiovascular mortality in men with gout, but not in women, regardless of traditional risk factors or diuretic medications. The survey also revealed a gradual increase in cardiovascular mortality dependent on blood uric acid levels.5,6 In line with this, a prospective study of the Health Professionals Follow-Up Study confirmed these data by also revealing an ≈60% increase in the risk of fatal coronary heart disease in men with diagnosed gout and a history of CVD.3 Additional new independent meta-analyses have confirmed these correlations of gout and CVD risk.7,8 However, the most conclusive studies have only been conducted in men, most likely because risk factors and development of gout in women follow different patterns since serum estrogen levels play a significant role in the control of uric acid levels. Therefore, extrapolation of data on gout from men to...
women should be done with caution. However, it seems that gradual increase of serum uric acids also increases the risk of gout in a graded manner among women, but the rate of increase is lower than that among men.\(^9\) Studies investigating the association of CVD risk and gout focusing on both sexes reported inconclusive results. While 1 study investigating both sexes found a generally increased risk for CVD in patients with gout without separating by sex,\(^10\) others investigated both sexes individually and reported an increased risk for both sexes but a more pronounced risk for coronary heart disease in Chinese women and for CVD in Taiwanese women.\(^11,12\) Notably, the latter 2 studies were conducted in Asian individuals only, suggesting that besides sex, ethnicity also influences the individual risk profile. Because CVD and coronary heart disease/CAD comprise slightly different diseases and none of the studies described above gave details on the specific type of coronary heart disease, it would have been very interesting to differentially display the data presented by Pagidipati et al for sex and race since \(\approx300\) individuals with a gout history included in this study were women and/or of nonwhite background. Association between MI and gout is less clear; however, recent studies and meta-analysis suggest a correlation of gout and the risk for nonfatal MI in both sexes,\(^13–15\) a finding not supported by data from Pagidipati et al.\(^4\) Yet, comparison between different studies in general has to be viewed with caution. Pagidipati and colleagues, for example, only included individuals who underwent cardiac catheterization, were diagnosed with obstructive CAD, and already received CVD therapy; hence these results should not be generalized to patients without catheterization or CVD therapy.

Keeping in mind these limitations, it is clear that there is an association between gout and cardiovascular risk in patients. This could be at least partly explained by the fact that gout is characterized by clinically apparent inflammation, caused by the accumulation of monosodium urate crystals in the affected joints.\(^2\) It has been demonstrated that monosodium urate crystals can activate the NLRP3 inflammasome, resulting in high levels of IL-18 and IL-1\(\beta\).\(^16\) Interestingly, the presence of crystals does not always elicit symptoms of gout, as seen during asymptomatic periods where subclinical inflammation persists. As an explanation, monocyte-derived macrophages need to be primed by an exogenous signal inducing toll-like receptor activation prompting IL-1\(\beta\) transcription before the cell encounters the crystals.\(^17\) Additionally, this also explains why certain foods trigger acute gout attacks, because fatty acids can act as such second signals for IL-1\(\beta\) transcription.

NLRP3 activation through (cholesterol) crystals has also been shown to be crucial for atherosclerosis development,\(^18\) and much effort has been made to investigate the effectiveness of targeting inflammation in patients with gout, which therefore could also result in a concomitant benefit in cardiovascular outcome. For example, a cross-sectional, retrospective study of 1200 patients with gout demonstrated that treatment with colchicine, a general anti-inflammatory agent, resulted in a significantly lower prevalence of MI and a clear trend towards reduced all-cause mortality compared with patients who did not take colchicine.\(^2\) Additionally, a randomized clinical trial evaluated the effects of canakinumab, an anti-IL-1\(\beta\) monoclonal antibody, on the occurrence and degree of gout symptoms. Canakinumab treatment resulted in significant pain relief, reduced the risk of new flares, and decreased inflammation levels measured by C-reactive protein levels.\(^19\) Although the effects on cardiovascular outcome in patients with gout have not yet been evaluated using canakinumab, results of the recent CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study) trial\(^20\) make it very plausible that canakinumab treatment in patients with gout will also have beneficial effects on their cardiovascular risk.

The recent results from the study by Pagidipati et al clearly confirm the association of gout with cardiovascular risk. Although these results will be of great importance towards future therapeutic applications for patients with gout, where the symptoms of gout as well as the cardiovascular risk have to be targeted simultaneously, results of such studies have to be interpreted with caution. Most studies only examine a very limited and specified patient group, making it challenging to compare results between studies and to extrapolate these results to the general patient pool. Therefore, in the future, efforts should be made to conduct much larger studies including a mixed and thus general representation of patients in order to produce conclusions that are universally valid.

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Disclosures

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