Gout and mortality

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ABSTRACT
This review provides an update on the most recent data on mortality in people with gout. A large prospective study among men found that those with gout have a higher risk of death from all causes. Among men who did not have pre-existing coronary heart disease, the increased mortality risk is due primarily to an elevated risk of cardiovascular death, particularly from coronary heart disease. Also, an extension study of a large clinical trial among men with above-average risk for coronary heart disease found that a diagnosis of gout accompanied by an elevated uric acid level is associated with increased long-term (approximately 17 years) risk of all-cause mortality that arises largely from an increased risk of cardiovascular disease (CVD) mortality. Although limited, these emerging data suggest that men with gout have a higher risk of death from all causes and the increased mortality risk is primarily due to an elevated risk of CVD death. These findings would provide support for the aggressive management of cardiovascular risk factors in men with gout. More data that adjust comprehensively for various associated CVD markers are needed to reinforce this concept. Furthermore, given apparent potential sex differences in gout epidemiology and its risk factors, prospective studies specifically among women would be valuable.

Introduction
Gout is a type of inflammatory arthritis that is triggered by the crystallization of uric acid crystals within the joints and is often associated with hyperuricemia (1). Gout constitutes one of the most common forms of inflammatory arthritis, particularly among males (2-4); the overall disease burden of gout remains substantial and may be growing (1). Furthermore, gout may be associated with premature death, similar to other inflammatory rheumatic disorders (e.g., rheumatoid arthritis [RA] (5), giant cell arteritis (6), systemic lupus erythematosus [SLE] (7), and ankylosing spondylitis (8)). While common comorbidities of gout (e.g., insulin resistance syndrome, obesity, and hypertension) may lead to premature mortality among gout patients, emerging data also suggest that gout itself may have an independent impact on the risk of mortality, particularly cardiovascular death.

In this review, we seek to summarize the available data concerning the potential mortality impact of gout. Because increased cardiovascular disease (CVD) risk tends to lead to increased cardiovascular mortality, we first review earlier studies on the overall cardiovascular impact of gout. Studies of mortality outcomes in gout patients are subsequently discussed in detail separately.

Studies of gout and CVD
While many studies investigated the link between serum urate levels and cardiovascular outcomes, fewer studies have examined the relation between clinical gout and cardiovascular outcomes as summarized in Table I. In early 1980s, Yu et al. (9) and Nishioka et al. (10) described several major causes of death in gout patients, including CVD, but the authors did not calculate mortality risk estimates compared to an appropriate control group of non-gout patients. Darlington et al. (11) conducted a mortality study in 180 gout patients with their families, and observed no significant increase in coronary or cerebrovascular disease deaths rates when compared to expected rates in the general population. However, this study used a small sample size and there was no appropriate control group to allow for the evaluation of association of gout with study outcomes (11).

In the prospective Framingham Study, serum urate levels were not independently associated with the risk of
coronary heart disease (CHD) (12) but clinical gout was associated with an increased risk of CHD (12). Abbott and colleagues observed 37 CHD events among 94 men (39%) with gout unrelated to diuretic use, compared with 509 CHD events in 1,764 men without gout (29%). After risk adjustment, they found an excess risk of 60% for CHD among subjects with clinical gout as compared with those who did not have clinical gout (13). In their analyses, the investigators excluded cases of diuretic-induced gout and adjusted for potential confounding by age, systolic blood pressure, total cholesterol level, alcohol intake, body mass index (BMI), and diabetes mellitus, but no adjustment was made for possible effect of smoking. The association was observed only in men and was primarily due to excess cases of angina pectoris. Although significant associations between clinical gout and CHD were not observed in women, only 3 observed events occurred in females with gout over the study period.

Another prospective observational study that examined the link between gout and CVD was based on the Meharry and Johns Hopkins Precursors cohorts of male physicians (14). The former group was composed entirely of African American subjects, and the latter group was composed entirely of white subjects. The possible confounding variables adjusted for in analyses for this study were cholesterol level, smoking, BMI, alcohol use, hypertension, and diabetes mellitus. However, the effect of other powerful potential confounders, such as family history and aspirin use, was not addressed. Furthermore, information on diuretic use and renal function was not available. The results were contradictory to those of the Framingham Heart Study, with a pooled, risk-adjusted relative risk (RR) for cardiovascular disease of 0.59 and a 95% confidence interval (CI) ranging from 0.24 to 1.46. The Meharry-Hopkins study, however, was underpowered, with just 3 CHD events among the 31 subjects in the gout group of the Meharry cohort and 4 CHD events in the corresponding group of 62 subjects of the Johns Hopkins Precursors cohort. Of note, both profession as physicians and accompanying higher socioeconomic status have been noted to have an inverse association with CVD, and thus provide potential explanation for the relatively small number of CHD events among gout patients in these cohorts.

Analysis of 170 cases of gout in a general practice database in The Netherlands (15) showed that the cumulative incidence of CVD (a pooled outcome combining angina pectoris, myocardial infarction [MI], heart failure, cerebrovascular accident, transient ischemic attack, and peripheral vascular disease) was higher in individuals with gout (26%) than in controls (21%) matched for age, sex, and physician practice. In a multivariate Cox proportional hazards regression model which was adjusted for potential confounding effects of hypertension, diabetes mellitus, and hyperlipidemia, the RR for gout was

Table I. Studies of gout, CVD and mortality.

<table>
<thead>
<tr>
<th>Study (ref.)</th>
<th>Population</th>
<th>Study design</th>
<th>No. subjects</th>
<th>Follow-up Years</th>
<th>Outcomes</th>
<th>No. Subjects with outcome</th>
<th>Adjusted effect size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yu, 1980 (USA) (18)</td>
<td>A gout research clinic</td>
<td>Case Series</td>
<td>2,000</td>
<td>30</td>
<td>Mortality</td>
<td>382</td>
<td>N/A (Descriptive data)</td>
</tr>
<tr>
<td>Nishioka, 1981 (Japan) (10)</td>
<td>Gout patients</td>
<td>Case Series</td>
<td>104</td>
<td>8</td>
<td>CVD</td>
<td>28</td>
<td>N/A (Descriptive data)</td>
</tr>
<tr>
<td>Darlington, 1983 (UK) (11)</td>
<td>A rheumatology institute</td>
<td>Case Series</td>
<td>180</td>
<td>6</td>
<td>CVD mortality</td>
<td>5</td>
<td>N/A (O/I ratio, ns)</td>
</tr>
<tr>
<td>Abbot, 1988 (USA)* (13)</td>
<td>Framingham cohort</td>
<td>Cohort</td>
<td>94 (1,858)</td>
<td>32</td>
<td>CHD</td>
<td>37 (509)</td>
<td>1.60 (1.10-2.50) ns</td>
</tr>
<tr>
<td>Gelber, 1997 (USA)* (14)</td>
<td>Meharry-Hopkins cohort</td>
<td>Cohort</td>
<td>93 (1,624)</td>
<td>30</td>
<td>CHD</td>
<td>7 (182)</td>
<td>0.59 (0.24-1.46) ns</td>
</tr>
<tr>
<td>Janssens, 2003 (Netherlands)** (15)</td>
<td>Continuous morbidity Registration cohort</td>
<td>Case-control</td>
<td>170 (510)</td>
<td>11</td>
<td>CVD</td>
<td>44 (114)</td>
<td>0.98 (0.65-1.47) ns</td>
</tr>
<tr>
<td>Krishnan, 2006 (USA) (16)</td>
<td>Multiple Risk Factor Intervention Trial cohort</td>
<td>Cohort</td>
<td>1,123 (12,866)</td>
<td>6.5</td>
<td>a. Fatal MI</td>
<td>22 (246)</td>
<td>a. 0.96 (0.66-1.44) ns</td>
</tr>
<tr>
<td>Chen, 2007 (Taiwan) (20)</td>
<td>Ho-Ping Gout database</td>
<td>Cross-sectional</td>
<td>22,572</td>
<td>N/A</td>
<td>QWMI</td>
<td>393</td>
<td>1.18 (1.03-1.38) s</td>
</tr>
<tr>
<td>Choi, 2007 (USA) (21)</td>
<td>Health professionals Follow-up cohort</td>
<td>Cohort</td>
<td>2,773 (51,297)</td>
<td>12</td>
<td>a. All-cause mort. b. CVD mortality c. CHD mortality</td>
<td>304 (2132)</td>
<td>b. 1.38 (1.15-1.66) s</td>
</tr>
<tr>
<td>Krishnan, 2008 (USA) (19)</td>
<td>Multiple Risk Factor Intervention Trial cohort</td>
<td>Cohort</td>
<td>655 (9,105)</td>
<td>17</td>
<td>a. Fatal MI b. CHD mortality c. CVD mortality</td>
<td>36 (360)</td>
<td>a. 1.35 (0.94-1.93) ns</td>
</tr>
<tr>
<td>Cohen, 2008 (USA) (23)</td>
<td>US Renal Data System dialysis patients</td>
<td>Cohort</td>
<td>24,415 (234,794)</td>
<td>5</td>
<td>a. All-cause mort. b. CHD mortality</td>
<td>22 (246)</td>
<td>a. 0.94 (0.63-1.43) ns</td>
</tr>
</tbody>
</table>

* Results reported for males only; **Results reported for gout cases with no prevalent CVD; • Effect size for frequency of gout attack on outcome; s No. of outcomes not reported.

CVD: cardiovascular disease; CHD: coronary heart disease; MI: myocardial infarction; O/I ratio: ratio of observed vs. expected deaths; QWMI: Q-wave myocardial infarction; s: gout is independent predictor of outcome; ns: gout is not independent predictor of outcome.
0.98 (95% CI, 0.65–1.47). Other possible confounding factors, such as diuretic use, smoking, family history, aspirin use, etc., were not accounted for in that analysis. Notably, the RR for the presence of hyperlipidemia (0.56; 95% CI, 0.20–1.56) was lower than that for gout.

In 2006, Krishnan and colleagues first reported on their prospective cohort study of men in the Multiple Risk Factor Intervention Trial (MRFIT) (16). The MRFIT was a randomized clinical trial designed to examine the efficacy of a coronary risk reduction program among men at high risk of adverse coronary events. Subjects were eligible if scores for the combination of three risk factors (smoking, hyperlipidemia, and hypertension) were sufficiently high to place them in the upper 15% of a risk score distribution based on data from the Framingham Heart Study. Among the 12,866 subjects during the 6 year intervention phase of the MRFIT, gout was associated with an increased risk of nonfatal acute myocardial infarction (AMI) (multivariate odds ratio [OR] 1.26; 95% CI, 1.14–1.40; p < 0.001) but not with an increased risk of fatal AMI (multivariate OR 0.96; 95% CI, 0.66–1.44; p = 0.83) (16). In their analyses, investigators adjusted for age, diastolic blood pressure, total serum cholesterol, BMI, fasting blood glucose, smoking, serum creatinine, diuretic use, aspirin use, alcohol use, incident diabetes mellitus, and family history of AMI. This was the first of two reports based on MRFIT data and focused primarily on CVD outcomes; a subsequent report that provided greater focus on CVD mortality in a subset of MRFIT subjects is discussed in further detail below.

Compared to the Framingham study (13) and initial MRFIT trial report (16), some of these previous studies that attempted to evaluate a possible association between gout and CVD were too small (11, 17), selected inappropriate controls (18), or used administrative data with limited data on other CVD risk factors. (15). A recent large study that included some form of diagnostic validation was a Taiwanese report on the relationship between clinical gout and electrocardiographic evidence of MI using the Ho-Ping Gout Database (20). Among the 22,572 patients with established gout, 393 demonstrated positive findings for Q-wave myocardial infarction (QWMI). Independent variables of gout that were shown to be associated with QWMI in models adjusted for covariates (age, gender, smoking, drinking, diuretic use, total cholesterol, triglycerides, hypertension, diabetes, BMI) and serum urate level, were joint count (OR 1.09; 95% CI, 1.01–1.19) and frequency of gout attack (OR 1.18; 95% CI, 1.02–1.38) (20).

Health professional follow-up study
The Health Professionals Follow-Up Study (HPFS) prospectively examined the relation between a history of gout and the risk of death and MI in 51,297 male participants (21). During the 12 years of follow-up, the study documented 5,825 deaths from all causes including 2,132 deaths from CVD and 1,576 deaths from CHD. Compared with men who did not have a history of gout and CHD at baseline, the multivariate RRs among men with a history of clinical gout were 1.28 (95% CI, 1.15–1.41) for total mortality, 1.38 (95% CI, 1.15–1.66) for CVD deaths, and 1.55 (95% CI, 1.24–1.93) for fatal CHD. The corresponding RRs among men with pre-existing CHD were 1.25 (95% CI, 1.09–1.45), 1.26 (95% CI, 1.07–1.50), and 1.24 (95% CI, 1.04–1.49). In addition, men with gout had a higher risk of nonfatal MI than men without gout (multivariate RR, 1.59; 95% CI, 1.04–2.41). These multivariate RRs were adjusted for age, history of hypertension, history of hypercholesterolemia, history of diabetes, aspirin use, diuretic use, smoking, BMI, physical activity, alcohol intake, family history of MI, total energy intake, trans fat, dietary cholesterol, protein, linoleic fatty acid, and ratio of polyunsaturated fat/saturated fat.

This large study prospectively collected exposure data and covariate information, and thus avoided recall bias (21). However, the study did not validate baseline cases of gout and used self-reported gout diagnosed by a physician as a primary definition, leaving some misclassification inevitable. Nonetheless, the authors have also included this definition for gout as a secondary definition in their previous studies of risk factors for gout (4, 22) and found that suspected associations became even stronger when they used more specific case definitions such as cases meeting the American College of Rheumatology (ACR) criteria or crystal proven or tophaceous gout (4, 22). This notion is further supported by the finding of the significant association with the risk of MI using the incident cases of gout confirmed by the ACR criteria.

Multiple risk factor intervention trial (MRFIT)
Recently, Krishnan and colleagues reported a 17-year follow-up study of 9,105 men, aged 41 to 63 years in the MRFIT who did not die or have clinical or electrocardiographic evidence of coronary artery disease during the 6-year intervention phase of the trial (19). Cox proportional hazards models were used to estimate the risk of CVD death and other causes subsequent to the sixth annual examination associated with gout. Multivariate analyses were adjusted for clinical center, age, systolic blood pressure, diastolic blood pressure, low- and high-density lipoprotein cholesterol levels, plasma triglyceride level, serum creatinine level, fasting glucose level, cigarettes per day, family history of AMI, daily aspirin use at year 6, diuretic use at year 6, alcoholic drinks per day, and BMI. The unadjusted mortality rates from CVD among those with and without gout were 10.3 per 1000 person-years and 8.0 per 1000 person-years, respectively, representing an approximate 30% greater risk (19). After adjustment for traditional risk factors, use of diuretics and aspirin, and serum creatinine level, the hazard ratio (HR) (gout vs. no gout) for CHD mortality was 1.35 (95% CI, 1.06–1.72). The HR for death from AMI was 1.35 (95% CI, 0.94–1.93); for death from CVD overall, 1.21 (95% CI, 0.99–1.49); and for death from any cause, 1.09 (95% CI, 1.00–1.19; p = 0.04). The association between hyperuricemia and CVD was weak and did not persist when analysis was limited to men with hyperuricemia without a diagnosis of gout.
There are several potential mechanisms

Potential mechanisms

There are several potential mechanisms for the observed excess cardiovascular deaths in patients with gout. Hyperuricemia, the culprit of gout pathogenesis, is associated with CVD in humans, although whether it is an independent risk factor with a pathogenic role in CVD or only a marker for associated CVD risk factors, such as insulin resistance, obesity, diuretic use, hypertension, and renal disease, remains unclear (24, 25). Approximately two-thirds of previous epidemiologic studies reported an independent link between serum uric acid levels and cardiovascular outcomes after adjusting for various covariates (25). For example, the National Health and Nutrition Examination Survey (NHANES) I Follow-up Study reported that serum uric acid was an independent predictor of cardiovascular mortality in subjects older than 45 years regardless of sex, menopausal status, diuretic use, presence of CVD, or race (26). However, as described above, in the Framingham Study, serum urate levels were not independently associated with the risk of CVD (12). A recent Finnish prospective study of middle-aged men found that the RR of CVD death between extreme tertiles of baseline urate levels was 3.7, after adjusting for various potential confounders, including biomarkers commonly associated with gout, CVD, and metabolic syndrome (27). Further adjustment for markers related to the metabolic syndrome (including triglyceride and HDL cholesterol levels) increased the RR to 4.8. Recently, the aforementioned study based on the MRFIT trial reported that both hyperuricemia (>7.0 mg/dL) and gout were associated with an increased risk of AMI (multivariate OR, 1.11 and 1.26 respectively, both p-values <0.001) (16).

Recently, a novel rodent model of arteriolopathy and hypertension induced by mild hyperuricemia has brought new insight into this possible association (24, 25, 28, 29). The rodent model showed that uric acid could cause renal afferent arteriolopathy and tubulointerstitial disease, leading to hypertension (28, 29). The renal lesions and hypertension were prevented or reversed by lowering uric acid levels (28, 29). Furthermore, hyperuricemia occurring as a complication of diuretic therapy has been implicated as a risk factor for CVD events. The Systolic Hypertension in the Elderly Program (SHEP) trial (30) found that participants who developed hyperuricemia while receiving chlorthalidone therapy sustained CVD events at a rate similar to participants treated with placebo. Data from the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial indicated that treatment with losartan (a uricosuric angiotensin receptor blocker) statistically and significantly attenuated the time-related increase in serum uric acid, and this difference seemed to account for 27% of the total treatment effect on the composite CVD end points (24, 31).

Furthermore, presence of gout per se may pose an increased risk of CVD beyond these potential contributions from hyperuricemia, as suggested by the recent study based on the MRFIT study (16). One possible explanation for this excess risk independent of uric acid levels is that ongoing low-grade inflammation among patients with gout may promote atherogenesis and thrombogenesis, as seen in other inflammatory rheumatic disorders associated with higher risk of CVD (e.g., RA or SLE) (16). The association between higher levels of serum uric acid level and serum markers of inflammation (C-reactive protein, fibrinogen, interleukin [IL]-6, and neutrophil count) demonstrated in previous reports (32-37) may suggest that inflammatory processes provide a potential mechanism for the link between serum urate, gout and atherosclerosis. Locally, the synovial fluid of gout patients have been shown to demonstrate low-grade inflammatory activity even without an episode of acute arthritis (19, 38). While the processes involved in the inflammatory response during an acute gout flare have been studied extensively (39), less is known about the presence or absence of systemic inflammation, especially during periods between gout attacks (19). During an acute gout attack, monosodium urate crystals activate monocytes and stimulate the release of tumor necrosis factor-α, IL-1, IL-6, IL-8, and cyclooxygenase-2 (39). There is also some evidence for continuous, subclinical intra-articular inflammation in these patients with gout (19, 39).
Conclusion

Recently emerging prospective data adjusting for various cardiovascular risk factors suggest that men with gout have a higher risk of death from all causes. This increased mortality risk appears to be primarily due to an elevated risk of CVD death, particularly from CHD. These findings, together with the frequent comorbidities of gout, provide support for the aggressive management of cardiovascular risk factors in men with gout. Nonetheless, compared to other relatively common forms of inflammatory arthritis (e.g., RA), the available data in gout are limited, and more are needed to confirm the independent link between gout and mortality among men. Given the potential sex differences in gout epidemiology and its risk factors, prospective studies specifically among women would also be valuable. Furthermore, it would be critical to evaluate the role of urate-lowering therapy on CVD incidence or mortality in future studies.

References