Concise report

Gout: an independent risk factor for all-cause and cardiovascular mortality

Chang-Fu Kuo1,2,3, Lai-Chu See4,5, Shue-Fen Luo3, Yu-Shien Ko6,7, Yu-Sheng Lin2,6, Jawl-Shan Hwang2, Chi-Ming Lin2, Hung-Wei Chen5 and Kuang-Hui Yu3

Abstract

Objective. The relation of gout and hyperuricaemia to cardiovascular diseases has been well documented. This study investigates the survival impact of both gout and hyperuricaemia.

Methods. The subjects of this study comprised participants of a health screening programme conducted by the Chang Gung Memorial Hospital in Taiwan from 2000 to 2006. The status and causes of death were ascertained by the Taiwan National Death Registry 2000–07. Cox proportional hazard model was performed to examine the association.

Results. Among 61,527 subjects, 1,383 deaths (198 cardiovascular deaths) were identified, corresponding to a crude mortality rate of 4.86 deaths per 1000 person-years. Crude mortality rates were 4.50, 5.61 and 10.46 deaths per 1000 person-years for subjects with normouricaemia, hyperuricaemia and gout, respectively. Compared with subjects with normouricaemia, the hazard ratios (HRs) of all-cause mortality were 1.46 (95% CI 1.12, 1.91) for individuals with gout and 1.07 (95% CI 0.94, 1.22) for those with hyperuricaemia, respectively, after adjustments were made for age, sex, component number of metabolic syndrome and proteinuria. The adjusted HRs of cardiovascular mortality were 1.97 (95% CI 1.08, 3.59) for individuals with gout and 1.08 (95% CI 0.78, 1.51) for those with hyperuricaemia. Moreover, the risk of all-cause or cardiovascular mortality for gout remained unchanged when limiting the data to those with an estimated glomerular filtration of >60 ml/min/1.73 m².

Conclusion. This study demonstrates a link of gout, not hyperuricaemia, with a higher risk of death from all causes and cardiovascular diseases.

Key words: Gout, Hyperuricaemia, Mortality, Uric acid, Metabolic syndrome, Glomerular filtration rate, Proteinuria, Dyslipidaemia, Atherosclerosis, Epidemiology.

Introduction

Individuals inflicted with gout often have long-lasting hyperuricaemia and intense inflammatory episodes, as well as a high prevalence of metabolic syndrome [1]. Epidemiological studies indicate that gout and hyperuricaemia patients often have clinical and biochemical abnormalities of metabolic syndrome, including insulin resistance, obesity and hyperlipidaemia [2]. Recent studies have closely linked gout with diabetes mellitus [3] and chronic kidney disease [4]. All these associated conditions are linked to atherosclerosis and tend to reduce long-term survival.

Despite the well-documented link of gout and hyperuricaemia with atherosclerosis-related conditions, the independent survival impact of gout and hyperuricaemia has seldom been addressed. Although reporting significant cardiovascular mortality risk among subjects inflicted with gout, the Health Professionals Follow-up Study [5] and the Multiple Risk Factor Intervention Trial [6] did not...
evaluate how renal function affects mortality in individuals inflicted with gout; in addition, only male subjects were included.

Therefore, this study examines how gout or hyperuricaemia is related to all-cause or cardiovascular mortality by merging data from health screening participants at Chang Gung Memorial Hospital (CGMH) from 2000 to 2006 with that of the Taiwan Death Registry from 2000 to 2007.

Methods
Study population and measurement
The Institutional Review Board of CGMH approved this study (approval number: 97-1564C). Health screening participants in a programme at CGMH from 2000 to 2006 were enrolled in the study. Demographic data and disease history were recorded in a structured questionnaire. Serum urate levels were determined by the colorimetric uricase method. The coefficient of variation was 1.8% for urate measurement in CGMH. For subjects with more than one visit during the study period, data from the first visit were used for analysis.

All participants were categorized as normouricaemia, hyperuricaemia and gout based on the level of serum urate or gout definition as described in the following paragraph. Hyperuricaemia was defined as serum urate of >7.7 mg/dl in males or >6.6 mg/dl in women [7]. Case definitions of gout in this study were: (i) records of the presence of IA MSU in SF; (ii) one or more visits to CGMH outpatient department due to gout, with an International Classification of Diseases, Ninth revision (ICD-9) code of 2740 or 2749; (iii) self-report by participants of the health screening programme. Metabolic syndrome was defined by modified Adult Treatment Panel III criteria according to recommendations by the Department of Health in Taiwan [8]. Hypertension was defined as systolic blood pressure (SBP) of >140 mmHg or diastolic blood pressure (DBP) of >90 mmHg [9]. Estimated glomerular filtration rate (eGFR) was calculated by the Modification of Diet in Renal Disease equation, modified for Chinese [10]. Low eGFR was defined as having an eGFR <60 ml/min/1.73 m².

The National Death Registry in Taiwan determined the survival status and causes of death, through the survival status and causes of death, through 31 December 2007. Causes of death consisted of all causes (ICD-9 codes, 001–998), cancer-related (ICD-9 codes, 140–239) and cardiovascular mortality (ICD-9 codes, 390–459). A death was attributed to a cardiovascular disease if the cause of death contained ICD-9 codes between 390 and 459. The ICD-9 codes for coronary heart disease, stroke, hypertensive heart diseases and heart failure were 410–414, 430–438, 401–405 and 428, respectively.

Statistical analysis
Summary statistics were expressed as percentages for categorical data; mean (s.d.) for normally distributed continuous variables, as well as median and inter-quartile range for skewed continuous variables. A two-sided P < 0.05 was considered statistically significant. Differences in baseline characteristics among groups were tested using the chi-square test for categorical data, analysis of variance for continuous data with normal distribution and the Kruskal–Wallis test for skewed continuous data. When a finding was deemed significant, Scheffe’s multiple comparison for normal continuous data was made to identify the group that had a different mean. For categorical data or skewed continuous data, pairwise comparisons were made with Bonferroni adjustment with respect to the significant level to determine the groups that differed from each other.

All-cause mortality or cardiovascular mortality among groups was compared by using log-rank test univariately. How normouricaemia, hyperuricaemia and gout groups affected all-cause and cardiovascular mortality with consideration of other explanatory variables was examined by using Cox proportional hazards model. Four models used in this study had different sets of explanatory variables. Model 1 included only the study groups (normouricaemia, hyperuricaemia and gout), while Model 2 included the study group, age and gender as explanatory variables. In Model 3, explanatory variables were the study groups, age, gender and component numbers of metabolic syndrome. In addition to the explanatory variables in Model 3, Model 4 included proteinuria. To prevent misclassification of gout, the entire analysis was performed again by excluding the case definition criteria (iii). Hazard ratios (HRs) and 95% CIs were computed for gout or hyperuricaemia by treating the normouricaemia group as the reference group. All these analyses were performed using SPSS statistical software, version 17.0 (SPSS, Chicago, IL, USA).

Results
From 2000 to 2006, 67 570 subjects with age ranging from 30 to 74 years participated in the health screening programme at CGMH. After subjects (n = 6043) with incomplete data or repeated visits were excluded, 61 527 [men: 34 126 (55.5%); women: 27 401 (44.5%)] subjects were used for analysis. The study population was an average 49.1 (11.0) years old for males and 50.8 (10.8) years old for females. Among them, 78.1% (n = 48 021) of the subjects were normouricaemic, 19.8% (n = 12 195) had hyperuricaemia and 2.1% (n = 1311) had gout. The mean serum urate was 6.9 (1.5) mg/dl in males and 5.4 (1.4) mg/dl in females.

Laboratory characteristics
Table 1 lists the demographic and laboratory characteristics for the three study groups at baseline. The mean follow-up time was 56 (24) months. Metabolic syndrome and hypertension were significantly more prevalent among those with gout or hyperuricaemia. Subjects with gout and hyperuricaemia had poorer
Mortality rates and causes of death

A total of 1383 deaths (198 cardiovascular deaths) were identified in our cohort. As shown in Fig. 1, all-cause and cardiovascular mortality rates were highest in the gout group (10.46 and 2.09 per 1000 person-years), followed by the hyperuricaemia group (5.61 and 0.87 per 1000 person-years), in comparison with the normouricaemia group (4.13 and 0.59 per 1000 person-years). Log-rank test revealed that gout and hyperuricaemia were associated with a greater all-cause (\(P < 0.001\)) and cardiovascular mortality (\(P < 0.001\)) than normouricaemic subjects. Of the 1383 deaths, 198 (14.3%) were attributed to the circulatory system in the study population. More cardiovascular deaths were found among subjects with gout \(n = 12\) (20.0%); \(P < 0.001\) and hyperuricaemia \(n = 57\); 17.1%; \(P < 0.001\). Stroke, coronary heart disease, heart failure and hypertensive heart diseases accounted for 83 (41.9%), 62 (31.3%), 13 (7.1%) and 10 (5.1%) deaths, respectively.

There were 513 (hyperuricaemia, 121; gout, 26) deaths attributable to cancer. Crude cancer-related mortality rates were 1.67, 2.03 and 2.09 per 1000 person-years for normouricaemia, hyperuricaemia and gout groups, respectively. Log-rank test demonstrated that gout, but not the hyperuricaemia group, was associated with greater cancer-related mortality (\(P < 0.001\)).

Table 1: Demographic and laboratory characteristics among normouricaemia, hyperuricaemia and gout subjects \((n = 61527)\)

<table>
<thead>
<tr>
<th></th>
<th>Normouricaemia ((n = 48021))</th>
<th>Hyperuricaemia ((n = 12195))</th>
<th>Gout ((n = 1311))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>50 (11)</td>
<td>51 (11)*</td>
<td>52 (11)*</td>
</tr>
<tr>
<td>Follow-up, months</td>
<td>55 (24)</td>
<td>59 (22)</td>
<td>53 (23)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>25146 (52.4)</td>
<td>7795 (63.9)*</td>
<td>1185 (90.4)**</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.2 (3.4)</td>
<td>26.3 (3.6)*</td>
<td>26.6 (3.5)*</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>9553 (19.9)</td>
<td>3714 (30.5)*</td>
<td>476 (36.3)***</td>
</tr>
<tr>
<td>Metabolic syndrome, n (%)</td>
<td>6778 (14.5)</td>
<td>3839 (32.2)*</td>
<td>473 (36.8)***</td>
</tr>
<tr>
<td>Component no. of MetS</td>
<td>1 (0, 2)</td>
<td>2 (1, 3)</td>
<td>2 (1, 3)</td>
</tr>
<tr>
<td>Laboratory test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum urate, mg/dl</td>
<td>5.6 (1.1)</td>
<td>8.4 (1.1)*</td>
<td>8.5 (2.0)*</td>
</tr>
<tr>
<td>Fasting sugar, mg/dl</td>
<td>102 (35)</td>
<td>102 (31)</td>
<td>106 (37)**</td>
</tr>
<tr>
<td>Postprandial sugar, mg/dl</td>
<td>119 (62)</td>
<td>122 (54)*</td>
<td>128 (67)*</td>
</tr>
<tr>
<td>Hyperglycaemia, n (%)</td>
<td>13957 (29.1)</td>
<td>4474 (36.7)</td>
<td>523 (39.9)</td>
</tr>
<tr>
<td>Cholesterol, mg/dl</td>
<td>197 (37)</td>
<td>206 (40)*</td>
<td>206 (41)*</td>
</tr>
<tr>
<td>High cholesterol, n (%)</td>
<td>20740 (43.2)</td>
<td>6483 (53.2)*</td>
<td>691 (52.7)*</td>
</tr>
<tr>
<td>Triglyceride, mg/dl*</td>
<td>103 (74, 149)</td>
<td>145 (102, 210)*</td>
<td>158 (111, 234)* **</td>
</tr>
<tr>
<td>High triglyceride, n (%)</td>
<td>11694 (24.4)</td>
<td>5763 (47.3)*</td>
<td>701 (53.5)* **</td>
</tr>
<tr>
<td>HDL, mg/dl</td>
<td>55.0 (14.4)</td>
<td>48.9 (12.4)*</td>
<td>46.3 (11.7)* **</td>
</tr>
<tr>
<td>Low HDL, n (%)</td>
<td>11351 (23.7)</td>
<td>4486 (36.9)*</td>
<td>476 (36.4)*</td>
</tr>
<tr>
<td>LDL, mg/dl</td>
<td>117.2 (32.6)</td>
<td>123.0 (34.7)*</td>
<td>121.7 (34.4)*</td>
</tr>
<tr>
<td>High LDL, n (%)</td>
<td>32896 (68.8)</td>
<td>9079 (74.6)*</td>
<td>947 (72.4)*</td>
</tr>
<tr>
<td>eGFR, ml/min/m²</td>
<td>80.1 (14.7)</td>
<td>72.6 (16.0)*</td>
<td>69.2 (16.7)* **</td>
</tr>
<tr>
<td>Low eGFR, n (%)</td>
<td>1578 (3.3)</td>
<td>1470 (12.1)*</td>
<td>241 (18.4)* **</td>
</tr>
<tr>
<td>Proteinuria, n (%)</td>
<td>2136 (4.4)</td>
<td>947 (7.8)*</td>
<td>129 (9.8)* **</td>
</tr>
</tbody>
</table>

Expressed as mean (S.D.) (range), if not specified. \*Not normal distribution, expressed as median (inter-quartile range); \#fasting sugar >100 mg/dl or post-prandial sugar >140 mg/dl; \*cholesterol >200 mg/dl; \*triglyceride >150 mg/dl; \*HDL <40 mg/dl in men or <50 mg/dl in women; \*LDL >100 mg/dl; \*eGFR <60 ml/min/1.73 m²; \*P < 0.05, vs normouricaemia group; \**P < 0.05, vs hyperuricaemia group.
Gout as an independent risk factor for all-cause and cardiovascular mortality

Table 2 summarizes the HRs of death from all causes or cardiovascular diseases according to either hyperuricaemia or gout. Compared with subjects with normouricaemia, individuals with gout had a significantly higher risk of all-cause mortality (HR 1.46; 95% CI 1.12, 1.91, P = 0.005) or cardiovascular mortality (HR 1.97; 95% CI 1.08, 3.59, P = 0.027). Hyperuricaemia was not associated with all-cause (HR 1.07; 95% CI 0.94, 1.22; P = 0.283) or cardiovascular (HR 1.08; 95% CI 0.78, 1.51; P = 0.28) mortality after adjusting for explanatory variables by Model 4. For subjects with an eGFR >60 ml/min/1.73 m², hyperuricaemia was associated with cardiovascular death (HR 1.98; 95% CI 1.03, 3.82), but not all-cause mortality. Gout remained a significant risk factor for all-cause (HR 1.47; 95% CI 1.09, 1.97) and cardiovascular (HR 3.13; 95% CI 2.13, 61) mortality, after being adjusted for explanatory variables in Model 4.

Although gout was associated with an unadjusted HR of 2.26 (95% CI 1.54, 3.30) for cancer-related death, Cox proportional model adjusted by Model 4 revealed an HR of 1.43 without statistical significance (95% CI 0.97, 2.12, P = 0.074). Hyperuricaemia was not associated with increased risk of cancer-related death by all models.

Sensitivity analysis

Misclassification of gout subjects was prevented by implementing Cox’s proportional hazards model according to different gout definitions. For gout subjects diagnosed based on case definition (i) or (ii), 1006 gout subjects had either records of gout treatment at CGMH (n = 667) or IA monosodium urate crystal in the CGMH rheumatology laboratory (n = 339). Following adjustment by Model 4, HRs of gout subjects for all-cause mortality and cardiovascular mortality were 1.51 (95% CI 1.14, 1.99; P = 0.004) and 1.86 (95% CI 1.01, 3.44; P = 0.048), respectively, when comparing with normouricaemia subjects.

Discussion

Epidemiological studies are limited and inconclusive for the mortality risk of gout. Therefore, this study investigated the link between gout or hyperuricaemia and all-cause or cardiovascular mortality. In this large study with a heterogeneous population of both genders, gout was an independent risk factor for all-cause and cardiovascular mortality independent of age, gender, metabolic syndrome and proteinuria; however, hyperuricaemia alone was not. Gout subjects had higher cancer-related mortality, but the association was not independent after multivariate analysis. In subjects with eGFR of >60 ml/min/1.73 m², the mortality risk of gout remained independent and strong. This study demonstrates that gout is associated with all-cause and cardiovascular mortality, independent of metabolic syndrome and proteinuria.

A positive association between gout and cardiovascular events has been observed previously. The Framingham study found a 60% excess of coronary heart disease in gout patients [11]. A Taiwanese study demonstrated that frequency of gout attack was associated with an odds ratio of 1.18 for myocardial infarction [12]. The MRFIT study found that gout was associated with a 26% increased risk of acute myocardial infarction [21] and an HR of 1.21 for cardiovascular deaths [6]. The Health Professionals Follow-Up Study [5] linked gout to cardiovascular death with a relative risk of 1.38. Notably, both studies were limited to males and did not consider the effects of proteinuria or low eGFR. This study confirms the gout–cardiovascular mortality link, independent of proteinuria in males and extends this finding to females. Importantly, this link remains strong in subjects with an eGFR >60 ml/min/17.3 m².
Whether hyperuricaemia alone contributes to excessive cardiovascular risk remains contentious. Although Framingham’s study found no association between serum urate levels and death from cardiovascular disease [13], the National Health and Nutrition Examination Survey (NHANES) I study, which had a higher number of cardiovascular deaths, revealed an independent role of uric acid and cardiovascular mortality [14]. Hjortnaes et al. [15] demonstrated that hyperuricaemia is associated with the metabolic syndrome, but is not an independent risk factor for vascular disease in patients with metabolic syndrome. A recent study found that hyperuricaemia is likely an independent risk factor for cardiovascular disease in high-risk individuals; however, the magnitude of excess risk attributable to hyperuricaemia is small in healthy individuals [16]. This study, with a low all-cause and cardiovascular mortality rate, found that hyperuricaemia did not contribute to excess risk of all-cause and cardiovascular mortality. Longer observation is needed to confirm this finding.

Although the biological link between gout and cardiovascular disease is still elusive, possible mechanisms have been proposed. Hyperuricaemia, the hallmark of gout, induces endothelial dysfunctioning [17], renal arteriopathy and tubulointerstitial diseases [18]. Gout is also characterized by inflammation, which also contributes to cardiovascular events [19]. Furthermore, other studies have established the role of inflammation in accelerated atherosclerosis in RA [20] and SLE [21].

Certain limitations deserve a mention. First, recall biases may introduce misclassification of gout patients. In this study, gout is defined based on the presence of MSU crystal, outpatient records and self-report by the subjects. Nevertheless, the exclusion of self-reported gout did not affect the results as shown by the sensitivity analysis. Secondly, while inaccuracies or missing data involving causes of death in the Taiwan Death Registry may pose a problem, a satisfactory agreement between death certificates and codes in the Taiwan National Death Registry files was confirmed in a prior study [22]. Thirdly, the follow-up period may not be sufficient to delineate the impact of hyperuricaemia on mortality. As for its contributions, this study analyses data from a large sample of community-dwelling adults, making it relatively easy for findings to be generalized. Moreover, both genders are included and the renal function is adjusted, which previous studies failed to do.

In conclusion, this study demonstrates that gout is associated with a higher risk of death from all causes and cardiovascular diseases, independent of age, gender, metabolic syndrome and proteinuria. The association remains strong and independent in subjects with an eGFR of >60 ml/min/1.73 m².

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References


Rheumatology key messages

- Gout is independently associated with higher risk of all-cause and cardiovascular mortality.
- Whether hyperuricaemia poses an additional risk needs further investigation.


