Clinical Rheumatology (2019) 38:1385–1391
https://doi.org/10.1007/s10067-019-04520-6

ORIGINAL ARTICLE

Crystal-proven gout patients have an increased mortality due to cardiovascular diseases, cancer, and infectious diseases especially when having tophi and/or high serum uric acid levels: a prospective cohort study

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Received: 11 July 2018 / Revised: 6 March 2019 / Accepted: 14 March 2019 / Published online: 30 March 2019

Abstract

Objective To investigate the cause-specific mortality and the possible involved clinical characteristics with increased mortality in a cohort of 700 patients with crystal-proven gout. The cause-specific mortality of gout was compared to the mortality of the general population.

Methods Patients with arthritis referred for diagnosis were consecutively included in the Gout Arnhem-Liemers Cohort (GOAL). Joint fluid analysis was performed in all patients and only *crystal-proven* gout patients were included in this study. At inclusion clinical characteristics and laboratory values were collected. At follow-up patients who died were identified. Standardized mortality ratios (SMRs) were calculated for all-causes, cardiovascular diseases, cancer, and infectious diseases using indirect standardization methods for mortality outcomes and compared with the general population. The clinical characteristics of the patients who died were compared with those of the survivors and were analyzed by a logistic regression analysis to identify any associations with mortality.

Results The study population at inclusion contained 573 (81.9%) men and 127 (18.1%) females with an average age of 62.0 (SD 13.4). During 3500 person-years from inclusion visit till 31 May 2016, in 700 gout patients, 66 deaths (27 cardiovascular deaths, 15 cancer-related deaths, 8 infectious deaths, 16 various other causes) occurred in this cohort. The all-cause standardized mortality ratio in gout patients was 2.21 (95% CI 1.68–2.74). In this cohort, gout patients had a higher SMR for death attributed to cardiovascular diseases (6.75; 95% CI 4.64–8.86), infectious diseases (4.66; 95% CI 1.51–7.82) and cancer (3.58; 95% CI 1.77–5.39). Corrected for confounders high serum uric acid levels (SUA; > 0,56 mmol/L), tophaceous gout, a history of peripheral vascular disease, myocardial infarction, and heart failure at the inclusion visit were associated with increased mortality during follow-up.

Conclusion Compared to the general population, gout patients have an increased association with all-cause disease mortality, especially attributed to cardiovascular diseases, cancer, and infectious diseases. This association is strongest in hyperuricemic (uric acid levels > 0,56 mmol/l) and tophaceous patients and in those with a history of peripheral vascular disease, myocardial infarction, and heart failure. Preventive measures like treatment of high SUA levels and treatment of cardiovascular risk factors need to be considered and evaluated.

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Keywords Cancer · Cardiovascular diseases · Crystal-proven gout · Infectious diseases · Mortality · Standardized mortality ratios (SMR)

Introduction

Cardiovascular disease (CVD), cancer, and infectious diseases are the leading global cause of death [1]. In gout, several studies showed also an increased risk of death from cardiovascular diseases, cancer, and also from all causes of death [2–6], especially when tophaceous and hyperuricemic [5] . These studies were based on the clinical diagnosis of gout, although the gold standard for diagnosing gout is the identification of monosodium urate (MSU)-crystals in joint fluid by polarization microscopy. We could not identify studies considering the impact on mortality of *crystal-proven gout* in secondary care populations. In addition, European studies assessing mortality among gout patients as compared with the general population could not be identified. In this study, we investigated the all-cause mortality and especially of cardiovascular diseases, cancer, and infectious diseases among patients with crystal-proven gout and compared these results with data from the general population of the Netherlands. In addition, we studied which clinical characteristics are associated with increased mortality in gout.

Methods

Patient selection

This was a prospective cohort study of patients with acute arthritis referred by general practitioners (GPs) or secondary care physicians, for diagnosis to the Department of Rheumatology, Rijnstate Hospital, Arnhem, the Netherlands. This Department is a non-academic general Rheumatology practice and is representative for all non-academic hospitals in the Netherlands. Patients with signs and symptoms of acute arthritis were consecutively included in the Gout Arnhem-Liemers (GOAL) cohort, and data were stored in a database of the Rheumatology Department. For this study, we used all newly diagnosed crystal-proven gout patients included from July 2011 until May 2016. During this period, 1036 patients were referred with an arthritis suspected for gout and underwent joint aspiration. In 700 of these patients, the diagnosis "gout" was confirmed by microscopic detection of monosodium urate crystals in the aspirate from the joint or bursal fluid or extra-articular tophi. At the first visit of our outpatient Clinic of Rheumatology, patients gave written informed consent for the anonymous use of their clinical data and for blood sampling. At inclusion, patients had a standardized interview and physical examination. In case of death during follow-up, patient clinical files were evaluated for the directly involved cause of death. When the cause of death was missing in the clinical files, the GP of the patient was consulted and by a standard questionnaire evaluating the cause of death. If any additional information concerning the death cause was needed, the GP was interviewed by telephone by one of the investigators (IJMD). Each death was attributed to a single underlying cause—the cause that initiated the series of events leading to death—according to the International Classification of Diseases (ICD) principles. Ethical approval for this type of study was not required in accordance to the policy of Rijnstate hospital.

Baseline assessment

Referred patients were examined by physicians at the research centre. The affected joint of each patient was aspirated and the joint fluid was analyzed with a polarization microscope for the presence of MSUcrystals. When no joint fluid could be collected during arthrocentesis, the patient was classified as having non-gout. When a non-gout patient had at follow-up another episode of arthritis, the newly affected joint was punctured and the synovial fluid was analyzed by polarization microscopy. When MSU crystals were then present, the diagnosis was changed from non-gout to gout. Only crystal-proven gout patients were included in this study.

At inclusion, the following data were collected: age, gender, race, body mass index (BMI), prevalent cardiovascular disease, family history of cardiovascular disease, smoking, alcohol consumption, diabetes mellitus, hypertension and hypercholesterolaemia, serum creatinine- and urate levels, glomerular filtration rate (GFR) as estimated by renal creatinine clearance. Tophi were defined as typical clinical findings and/or typical radiological findings of gout (e.g., punched-out lesions). Cardiovascular disease was defined as one or more of the following eight diseases: angina pectoris, myocardial infarction, heart failure, transient ischemic attack, cerebrovascular accident, peripheral vascular disease, heart valve abnormality or arrhythmia. The presence of cardiovascular risk factors and cardiovascular diseases were double checked by searching the medical files and asking patients at the inclusion visit. The history of any previous infectious diseases or cancer was not evaluated at the inclusion visit.

Mortality assessment

The survival status and causes of death were determined at 31 May 2016. When a patient dies, this becomes visible in the

Table 1 Clinical characteristics of patients with crystal-proven gout at baseline

Patients' characteristics	Gout ($n = 700$)	95% CI (%)
Age, years, mean (SD)	62.0 (13.4)	61.0–63.0
Male sex, no. (%)	573 (81.9%)	79.1–84.7
Body mass index, kg/m^2, mean (SD)	29.4 (5.6)	29.0–29.8
Family history of CVD, No. (%)	166 (23.7%)	20.4–27.0
Smoking, no. (%)		
No	370 (52.9%)	49.1–56.6
Stopped	211 (30.1%)	26.7–33.6
Yes	119 (17.0%)	14.3–19.9
Alcohol consumption, no. (%)		
> 21 units per week	190 (27.2%)	24.1–30.5
Creatinine level, μmol/L, mean (SD)	102.5 (40.6)[b]	99.5–105.4
Serum uric acid, (mmol/L), mean (SD)	0.50 (0.11)	0,499-0,506
Glomerular filtration rate, mL/min/1.73m^2, mean (SD)	64.3 (21.5)[c]	62.4–66.4
Diabetes mellitus, no. (%)	123 (17.6%)	14.6–20.3
Hypertension, no. (%)	431 (61.6%)	57.9–65.4
Hypercholesterolaemia, no. (%)	203 (29.0%)	25.6–32.3
Cardiovascular diseases (≥ 1[a]), no.(%)	331 (47.3%)	43.6–50.9
Angina pectoris, no. (%)	86 (12.3%)	10.1–14.7
Myocardial infarction, no. (%)	102 (14.6%)	12.0–17.1
Heart failure, no. (%)	98 (14.0%)	11.6–16.7
Transient ischemic attack, no. (%)	47 (6.7%)	5.0–8.6
Cerebrovascular accident, no. (%)	47 (6.7%)	5.0–8.6
Peripheral vascular disease, no. (%)	54 (7.7%)	5.7–9.7
Heart valve abnormality, no. (%)	51 (7.3%)	5.6–9.1
Arrhythmia, no. (%)	117 (16.7%)	14.1–19.4

SD standard deviation, *CI* confidence interval

[a] Angina pectoris, myocardial infarction, heart failure, transient ischemic attack, cerebrovascular accident, peripheral vascular disease, heart valve abnormality, or arrhythmia

[b] $n = 684$

[c] $n = 452$

Electronic Patient Dossier via a report from the civil registry which is automatically sent to the hospital. We also controlled the living status of the patients from reports of Dutch family physicians and hospital specialists. Causes of death consisted of all-causes (ICD-9 codes, 001-999), infectious diseases (ICD-9 codes, 001-139), cancer-related (ICD-9 codes, 140-239), and cardiovascular diseases (ICD-9 codes, 390-459).

Statistical analysis

Descriptive statistics were conducted to summarize background characteristics of the crystal-proven gout population. The national population of the Netherlands has been chosen as reference population. The expected deaths for all-cause mortality and cause-specific mortality in the general population were calculated using crude mortality rates, by applying indirect standardization method [7, 8]. We calculated the standardized mortality ratios (SMRs) after adjustment for age and sex for all-cause of mortality and cause-specific mortality, by dividing the total number of observed deaths by the total number of expected deaths for each mortality outcome. For all SMRs, we calculated 95% confidence intervals (CIs). To analyze which factors were associated with mortality, patients' characteristics of survivors were compared with deaths using multiple logistic regression analysis, and odds ratios (ORs) were calculated. All statistical tests were performed using SPSS software (version 20.0; SPSS Inc., Chicago, IL, USA).

Results

From July 2011 until May 2016, 700 crystal-proven gout patients were enrolled in this study. The study population at inclusion contained 573 (81.9%) men and 127 (18.1%) females with an average age of 62.0 (SD: 13.4). Table 1 lists the clinical characteristics for the gout patients at baseline. In

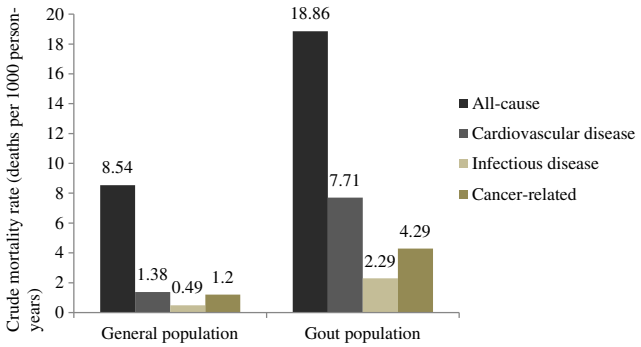

Fig. 1 Crude mortality rates of all-cause, cardiovascular disease, infectious disease and cancer in the general population and the crystal-proven gout population

total, 93% of the population was Caucasian. Table 1 also shows the high prevalence of cardiovascular diseases in gout patients.

During 3500 person-years from inclusion visit till 31 May 2016, in 700 gout patients, 66 deaths (mean age 75.5 years (SD 8.7); male $n = 47$; 27 cardiovascular deaths, 15 cancer-related deaths, 8 infectious deaths, 16 various other causes) occurred in this cohort. As shown in Fig. 1, the all-cause, cardiovascular disease, cancer, and infectious disease related crude mortality rates were highest in the gout group in comparison with the general population. Compared with the national population of the Netherlands with a life expectancy of 81.5 years in 2015, the all-cause SMR was 2.21 (95% CI 1.68–2.74). In this cohort, crystal-proven gout patients had a higher SMR for death due to cardiovascular diseases (6.75; 95% CI 4.64–8.86), cancer (3.58; 95% CI 1.77–5.39) and infectious diseases (4.66; 95% CI 1.51–7.82).

The percentage of death ($n = 66$) plotted against classes of uric acid levels are given in Fig. 2. Above the uric acid (SUA) levels of 0.56 mmol/l (vertical line), there was a significant association with mortality ($n = 32$; $p < 0{,}001$). Figure 3 shows predicted probability of death during follow-up plotted against age groups. The continuous line in this figure represents the loess curve of the mean SUA levels ≤ 0.56 mmol/L and the dotted line the loess curve of mean SUA levels > 0.56 mmol/L measured at the inclusion visit. The difference between the lines is $P < 0{,}01$. Table 2 shows the results of multiple logistic regression analysis which includes disease duration (categories: < 2 years, 2–5 years, 5–10 years, > 10 years), past or current smoking, alcohol use (categories 1–7; 8–14, 15–21, > 21 units weekly), BMI > 30, family history of cardiovascular diseases, hypertension, transient ischemic attack, cerebrovascular accident, myocardial infarction, heart failure, heart valve abnormality, peripheral vascular disease, angina pectoris, arrhythmia, hypercholesterolemia, diabetes mellitus. Only peripheral vascular disease, uric acid levels > 0.56 mmol/L, tophaceous gout, myocardial infarction, and heart failure are independently associated with mortality.

Discussion

This study shows that *crystal-proven* gout patients have an increased risk of all-cause disease mortality, especially the mortality for cardiovascular diseases, cancer, and infectious diseases, compared to the Dutch general population. In addition, the study shows that SUA levels > 0.56 mmol/L strongly associates with mortality (Fig. 2)

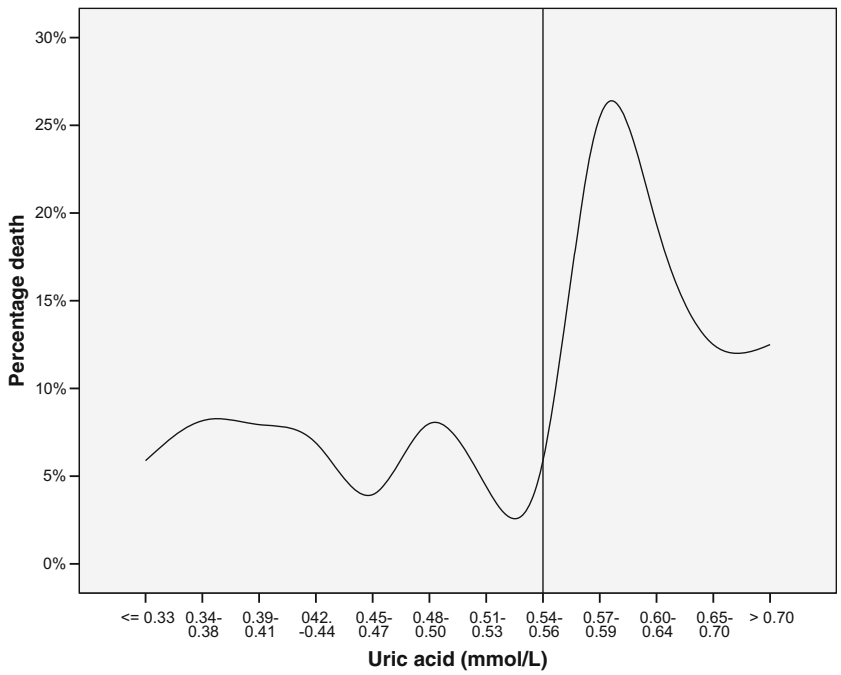

Fig. 2 Percentage of death (total number of death: $n = 66$) of 689 included evaluable patients during follow-up, plotted by classes of serum uric acid levels measured at the inclusion visit of the study. Above the uric acid levels of 0.56 mmol/l (vertical line), there is a significant association with mortality ($n = 32$; $p < 0{,}001$)

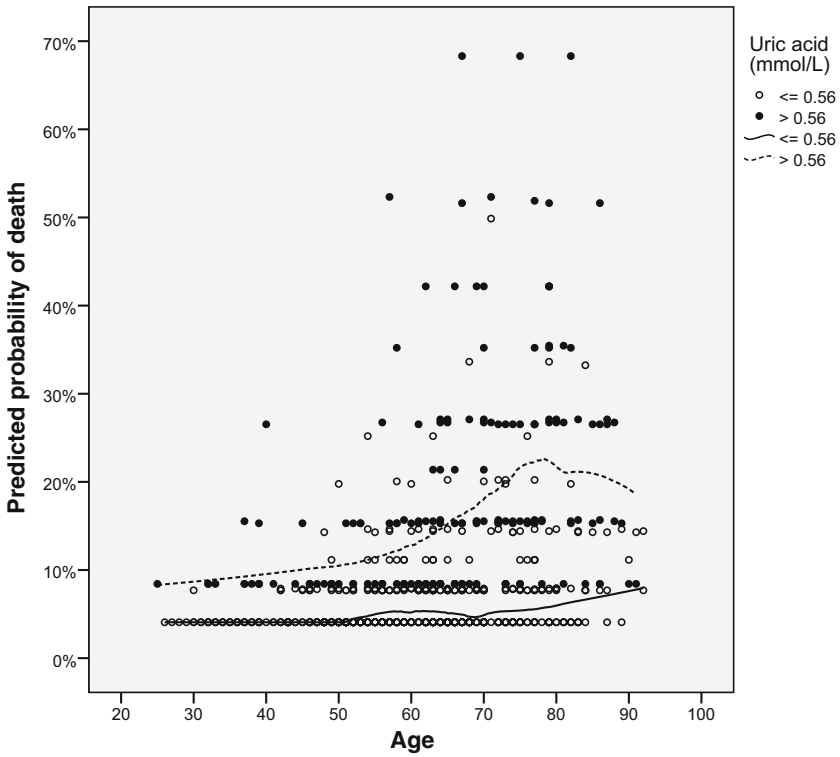

Fig. 3 Predicted probability of death plotted by age groups during follow-up. The continuous line represents the loess curve of the mean serum uric levels ≤ 0.56 mmol/L, and the dotted line > 0.56 mmol/L measured at the inclusion visit

even corrected for age (Fig. 3). SUA levels > 0.56 mmol/L, tophaceous gout, and a history of peripheral vascular disease, myocardial infarction, and heart failure also associates with mortality. Previous studies also showed a high risk of death from all-causes, cardiovascular causes, and cancer in gout patients [2–7] and especially in hyperuricemia and tophaceous gout (5). The finding of an increased mortality risk of infectious diseases in gout is to our knowledge new.

In contrast to other studies, the present study was performed with *crystal-proven gout* patients and showed an even higher risk of all-cause disease mortality in gout patients as compared with the all-cause disease mortality in gout patients in previous clinical studies [2–4]. This supports the notion that the previously reported impact of gout on mortality was underestimated by using less strict diagnostic criteria for gout. In the general Dutch population, 87% is Caucasian while 93% of the study population was Caucasian. Because of the small sample size, it is difficult to conclude whether this difference is clinically meaningful.

Table 2 Regression coefficients and odds ratios (and 95% CIs) for risk factors associated with mortality in patients with crystal-proven gout

Factor	β value	*P* value	Odds ratio (95% CI)
Peripheral vascular disease	1,08	0.004	2.95 (1.40–6.20)
Uric acid (mmol/L) > 0,56	0.773	0.01	2.17 (1.20–3.89)
Tophaceous gout	0.675	0.02	1.96 (1.11–3.47)
Myocardial infarction	0.70	0.03	2.02 (1.08–3.80)
Heart failure	0.693	0.04	1.99 (1.04–3.84)

CI confidence interval

Remarkably, gout is a stronger risk factor for mortality than hyperuricemia alone [4] and in patients with tophaceous disease, the highest mortality is found [5]. There seems to be a biological gradient or a dose-response relationship in the severity of characteristic symptoms of gout patients and the presence of CVD diseases. Disease duration ≥ 2 years, oligo- or polyarthritis, serum urate levels ≥ 0.55 mmol/l at presentation, and joint damage were independently associated with prevalent CVD [9]. Together with the current finding of the increased mortality in gout patients calls us to explanations and solutions to reduce the increased mortality in gout.

Previous clinical gout studies also showed a high prevalence of multiple cardiovascular co-morbidities raising the question whether gout itself or the multiple co-morbidities like hypertension, chronic kidney diseases, myocardial infarction, heart failure, stroke, metabolic syndrome, diabetes, obesity, hyperlipidemia, and sleep apnea contributes to the higher death rate for CVD [10–19]. In the current study we also found a high prevalence of cardiovascular diseases which (partly) explains the high CVD mortality in the gout patients. Therefore, the question remains whether the increased CVD death rate is related to gout itself or to the concomitant diseases.

In acute gout and the intercritical phase, increased levels of circulating interleukin 8 (CXCL8), a proinflammatory cytokine with a pivotal role in the occurrence of CVD were found

which might explain, together with the activator role of urate crystals on the inflammasome, that inflammation and plaque formation contributed to arteriosclerosis and subsequent CVD and premature death [20–23]. A prolonged inflammation, like in the case of gout, is associated with an increased risk of cancer [6, 23]. In turn, telomere length shortening is found in gout patients also associated with increased cardiovascular risk, cancer risk, and increased risk of infectious diseases and subsequent premature death [24]. Therefore, it can be postulated that chronic inflammation might play a pivotal role in the increased cardiovascular diseases, cancer, and infectious disease-related mortality in gout.

The finding that SUA > 0.56 mmol/l is associated with mortality is interesting while there is discussion on the exact level of SUA to be reached in the treatment of gout. The British guideline advised < 0.30 mmol/L, the American College of Rheumatology < 0.36 mmol/L, and the European task force of EULAR formulated a recommendation in between [25–27], therefore well within the threshold < 0.56 mmol/L.

A strength of this study is that the diagnosis of gout in this study was always based on MSU-crystal identification. Another strength is the prospective design with data collection starting at the inclusion visit. In addition, all cardiovascular risk factors and CVD were double checked asking patients for the presence of cardiovascular risk factors and the medical files are searched for CVD at the inclusion visit. Important misclassification bias concerning the registration was minimized because all gout patients were crystal proven, and the death causes were evaluated strictly. Remarkable is the demonstration of the increased CVD (especially peripheral vascular disease, myocardial infarction, and heart failure) in the current gout population where prevention of risk factors and treating hypercholesterolemia is at a high standard of care level in the Netherlands.

A limitation of this study was that the studied group was relatively small compared to other studies. The design of the study was not able to identify whether prompt treatment, or treatment to a strict serum target improves the prognosis in gout patients, nor were we able to investigate whether treatment of the co-morbidities of gout decreased the death rate.

In conclusion, this study showed for the first time that crystal-proven gout patients have an increased risk of all-cause mortality, compared to the general population especially in hyperuricemic and tophaceous patients and in patients with a history with peripheral vascular disease, myocardial infarction, and heart failure. Preventive measures, for example starting empowering networks with GPs to improve the position of all gout patients, similar as has been done for diabetics [25], in combination with a strict adherence to guidelines [26, 27] and treatment of the co-morbidities and evaluation of the effectivity of these measures had to be taken to decrease the excess in mortality. Further studies are needed whether all or subgroups of gout patients are at risk for the increased mortality.

Acknowledgments We wish to thank E.P. Martens (Statisticor) for the assistance by the statistical calculations.

Compliance with ethical standards

Disclosure None.

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