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Gout, just a nasty event or a cardiovascular signal?

A study from primary care

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Objective. Our aim was to examine the relationship between gout on the one hand and cardiovascular diseases and cardiovascular risk indicators on the other.

Methods. A case–control study was carried out in an aggregate primary care population of ~12 000 patients from four Dutch general practices, with follow-up of the cases free of cardiovascular diseases at the time of the first registered episode of gout. The subjects comprised 261 patients with a first episode of gout, 170 of whom were without prevalent cardiovascular diseases, and two control patients for each case matched for age, sex and practice. In the case–control study, the main outcome measures were the prevalence of cardiovascular morbidity (angina pectoris, myocardial infarction, heart failure, cerebrovascular accident, transient ischaemic attack, peripheral vascular disease), hypertension, diabetes mellitus, obesity and hypercholesterolaemia; in the follow-up study, the main outcome measure was the incidence of cardiovascular morbidity.

Results. Thirty-five percent of 261 gout patients and 26% of 522 controls had one or more prevalent cardiovascular diseases. Compared with controls, patients had a higher prevalence of hypertension (43% versus 18%), hypercholesterolaemia (14% versus 6%) and obesity (56% versus 30%). A total of 170 gout patients without prevalent cardiovascular diseases (compared with 340 controls) had a higher prevalence of hypertension (39% versus 14%), hypercholesterolaemia (8% versus 4%), diabetes mellitus (5% versus 1%) and obesity (52% versus 27%). The first occurrence of a cardiovascular disease (real end-point) was seen in 26% of the patients free of cardiovascular morbidity and in 21% of the controls. This difference was not significant. In a Cox proportional hazard model, controlling for the cardiovascular risk indicators, gout did not prove to be an independent determinant for the development of cardiovascular disease.

Conclusion. Gout was found to be associated with cardiovascular diseases and with cardiovascular risk indicators, without evidence of it being an independent risk indicator itself. A gout attack should be an incentive to assess the cardiovascular risk profile, when a patient seeks medical help.

Keywords. Cardiovascular diseases, case–control study, gout, primary health care.

Introduction

Reduction of cardiovascular morbidity and mortality remains one of the top priorities in medicine. Patients at risk of developing cardiovascular diseases and its

complications can be identified by assessing risk indicators (hypertension, hypercholesterolaemia, diabetes mellitus, obesity and smoking habits). Gout has also been proposed as a cardiovascular risk indicator.^{1–3} Should this be true, a most convenient risk indicator would become available, because almost every (first) attack of gout urges patients to seek medical help. Gout is presented to doctors without the efforts of screening or case finding. Physicians easily recognize the diagnostic features, in particular when the metatarso-phalangeal joint of the first toe is affected (podagra). A sudden red, swollen and very painful joint indicating monoarticular arthritis is highly characteristic, as is complete recovery, mostly within 1 or 2 weeks.⁴

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With the exception of studies investigating hyperuricaemia, few studies could be found concerning the association between gout and cardiovascular morbidity and/or mortality.^{3,5-7} These studies had incomparable conclusions and were not based on primary care populations, although most gout patients are diagnosed and treated in primary care.² Studies considering gout and cardiovascular morbidity in primary care populations could not be found.

The following research questions were formulated in this study. (i) Do gout patients have a higher prevalence of cardiovascular morbidity and cardiovascular risk indicators compared with control patients? (ii) Do gout patients without cardiovascular morbidity at the time of diagnosis have a higher incidence of cardiovascular diseases compared with control patients?

Methods

First, a case-control study was performed. Gout patients were compared with control patients for the prevalence of cardiovascular diseases and cardiovascular risk indicators. Then a follow-up was done of those patients with gout who did not have prevalent cardiovascular diseases at the time of the first gout episode. Gout patients were compared with control patients for the incidence of cardiovascular diseases or death. In addition, a survival analysis was carried out with gout as the independent variable, and cardiovascular morbidity or mortality as the dependent variable, controlling for four selected cardiovascular risk indicators (hypertension, diabetes mellitus, obesity and hypercholesterolaemia).

Gout, cardiovascular diseases and risk indicators were diagnosed and reported by Dutch family physicians following consultations that included physical examination and/or following referral from hospital specialists.

Data were obtained from the Continuous Morbidity Registration (CMR), Nijmegen. The CMR has been in progress since 1971 in four general practices with an aggregate practice population of ~12 000 patients. The CMR population is highly representative of the Dutch population in terms of socio-demographic characteristics. The family physicians in these practices register every episode of illness whether presented to them, or to a colleague in charge, or reported to them following treatment by a specialist. In the Dutch health care system, most people are registered with a general practice, often remaining in the same practice for many years.

Patient characteristics recorded in the CMR include date of entry; date of departure (death, moved out of area); date of birth; sex; family composition; and social class. All presented morbidity is coded according to the adapted E-list,⁸ using the criteria of the International Classification of Health Problems in Primary Care (ICHPPC-2).⁹ Details of the project, including the quality of the recorded data and diagnoses and the procedures

of classifying and coding, have been described elsewhere.¹⁰

Using the CMR data from the period 1971–1998, an index group could be formed of 261 patients with a first registered episode of gout.

Cardiovascular morbidity was defined as any notifications of one or more of the following six diseases: angina pectoris; myocardial infarction; heart failure; cerebrovascular accident; transient ischaemic attack; or peripheral vascular disease.

For the first step, the case-control study, two control subjects were selected for each patient, matched for age, sex and practice, but without a diagnosis of gout during their total registration time in the CMR. Using the chi-square test, patients and controls were compared for the prevalences of both cardiovascular morbidity and cardiovascular risk indicators at intake.

For the second step, all gout patients without a notification of any cardiovascular disease at the time of their first registered episode of gout were admitted to the follow-up study. For each patient, two controls without gout were selected, matched for age, sex, practice, and without prevalent cardiovascular morbidity at intake. Using the chi-square test, the incidences of the end-points were assessed. The real end-point was the first occurrence of a cardiovascular disease. The censored end-points were non-cardiovascular death, departure from the practice and end of the observation period, i.e. being alive on 31 December 1998. In a Cox proportional hazards analysis of all patients and controls without prevalent cardiovascular diseases, gout was studied as a determinant for cardiovascular morbidity. The predictive power of gout was expressed as a risk ratio with a 95% confidence interval. Age was not added to the model, as patients and controls were matched for this. The cardiovascular risk indicators were added as potential confounders.

Results

All 261 patients from the index group and 522 control persons were admitted to the case-control study. There was a successful matching of cases and controls (Table 1). The characteristics of patients and controls and the prevalences of cardiovascular morbidity and cardiovascular risk indicators are shown in Table 1. Analysis of the data reveals a statistically significant greater prevalence of cardiovascular morbidity, and of three out of four cardiovascular risk indicators in cases as compared with controls.

For the follow-up study, all 91 patients with prevalent cardiovascular morbidity from the index group were excluded, and a cohort of 170 gout patients emerged. A successfully matched cohort of controls was formed. Table 2 shows the results of the matching, the characteristics of patients and controls, the

TABLE 1 *The index group of gout patients and controls: characteristics and the prevalence of cardiovascular morbidity and four risk indicators at intake*

Characteristics	Patients (n = 261)	Controls (n = 522)	Difference in percentages (95% CI)
Male/female	179/82	358/164	
Age			
0–44	18 (48)	18 (95)	
45–64	38 (100)	39 (204)	
65–74	18 (47)	21 (111)	
>75	25 (66)	22 (112)	
Prevalence of cardiovascular morbidity	35 (91)	26 (137)	9 (2–16)
Prevalence of cardiovascular risk indicators			
Hypertension	43 (111)	18 (93)	25 (18–32)
Hypercholesterolaemia	14 (34)	6 (29)	8 (3–12)
Diabetes mellitus	8 (21)	7 (38)	1 (–3 to 5)
Obesity	56 (147)	30 (155)	26 (19–34)

Values are given as percentages, with absolute numbers in parentheses.

TABLE 2 *A cohort of gout patients and controls without prevalent cardiovascular morbidity at intake: characteristics (including the prevalence of four risk factors) and the incidence of the end-points*

Characteristics.	Patients (n = 170)	Controls (n = 340)	Difference in percentages (95% CI)
Percentage male	91	68	
Age			
0–44	28 (47)	27 (93)	
45–64	45 (77)	47 (160)	
65–74	16 (27)	15 (50)	
>75	11 (19)	11 (37)	
Prevalence of cardiovascular risk indicators			
Hypertension	39 (66)	14 (47)	25 (17–33)
Hypercholesterolaemia	8 (14)	4 (41)	4 (–1 to 9)
Diabetes mellitus	5 (8)	1 (4)	4 (0–70)
Obesity	52 (89)	27 (93)	25 (16–34)
Real end-point			
First occurrence cardiovascular disease	26 (44)	21 (70)	5 (–3 to 13)
Censored end-points			
Death	8 (14)	5 (16)	3 (–1 to 8)
Moved	15 (25)	21 (72)	–6 (–13 to 0)
End of observation period	51 (87)	54 (182)	–3 (–11 to 7)

Values are given as percentages, with absolute numbers in parentheses.

prevalences of risk indicators and the incidences of end-points.

Participants of both cohorts reached their end-points (real or censored) after a mean time of 11.1 years (SD 0.5 year). Forty-four (26%) of the gout patients and 70 (21%) of the controls developed a cardiovascular disease (real end-point). This difference was not statistically significant. The incidences of the censored end-points also did not differ statistically. Hypertension and obesity were statistically more prevalent in the gouty patients.

In the Cox proportional hazards analysis, gout did not turn out to be an independent risk indicator for

cardiovascular disease. Under the conditions of the four selected cardiovascular risk indicators, the risk ratio of gout did not reach statistical significance (Table 3).

Discussion

Gout was strongly associated with prevalent cardiovascular morbidity and with prevalent cardiovascular risk indicators, especially with hypertension and obesity. In agreement with other studies, the association with diabetes mellitus was the weakest.^{11–13} There was no

TABLE 3 The development of cardiovascular morbidity: Cox proportional hazards analysis of gout patients (n = 170) and controls (n = 340) without prevalent cardiovascular diseases

Risk factor	Risk ratio	95% CI
Gout	0.98	0.65–1.47
Hypertension	2.07	1.35–3.18
Obesity	1.56	1.04–2.35
Diabetes mellitus	2.12	0.93–4.79
Hypercholestraemia	0.56	0.20–1.56

statistical evidence that patients free of cardiovascular morbidity at the time of the first episode of gout developed cardiovascular disease more often than control patients. Therefore, the strong relationship between gout and cardiovascular disease did not prove to be a direct causal one. Probably, as illustrated in Table 3, a mediating role in this relationship should be assigned, in particular in hypertension.

Due to a systematic and long-term daily registration, the size of the index group was impressive considering the low gout incidence of 1–2 per 1000 persons per year in general practice. Hence the results do give quite a robust estimation of reality. In contrast to many ailments characterized by the so-called clinical iceberg phenomenon, nearly all gout patients present themselves to their physician, in particular when it is a first attack of gout. The index group therefore contains almost all prevalent cases occurring in the aggregate practice population.

Because of the great deal of attention paid in CMR practices to cardiovascular morbidity and cardiovascular risk indicators (including participation in a screening for cardiovascular risk indicators in 1977/1978 which was repeated in 1994/1995), patients and controls received comparable cardiovascular care.^{14,15} Important misclassification bias concerning the registrations of cardiovascular morbidity and risk indicators was almost certainly excluded for that reason.

A possible confounding influence of treatment regimes could not be excluded, which was a limitation of this study. The CMR did not provide data to adjust for this. Another limitation could be the lack of information about serum uric acid and urate crystals. Serum uric acid, gout related or not, has been associated with atherosclerosis, endothelial cell damage and cardiovascular morbidity, as a symptom or as a causal factor.^{13,16–19} However, a causal role for serum uric acid in the development of cardiovascular morbidity was excluded recently.²⁰

Most gout patients are diagnosed and treated in family practice. This study showed that in Dutch family practice, gout is associated with cardiovascular morbidity and well known cardiovascular risk indicators. Without being

an independent risk indicator itself, gout can function as a marker for a susceptibility to cardiovascular morbidity. Family physicians do not need special efforts of screening or case finding to identify this indicator. It is simply presented to them by almost all patients in whom it occurs. Gout can be seen as an incentive to assess a patient's cardiovascular risk profile, at least including blood pressure and body weight. Gout, a nasty event, but also a cardiovascular signal!

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