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[4]) 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

Table I. Studies of gout, CVD and mortality.

Study (ref.)	Population	Study design	No. subjects Gout (Total)	Follow-up Years	Outcomes	No. Subjects with outcome Gout (Total)	Adjusted effect size (95% CI)
Yu, 1980 (USA) (18)	A gout research clinic	Case Series	2,000	30	Mortality	382	N/A (Descriptive data)
Nishioka, 1981 (Japan) (10)	Gout patients	Case Series	104	8	CVD	28	N/A (Descriptive data)
Darlington, 1983 (UK) (11)	A rheumatology institute	Case Series	180	6	CVD mortality	5	N/A (O/I ratio, *ns*)
Abbot, 1988 (USA)* (13)	Framingham cohort	Cohort	94 (1,858)	32	CHD	37 (509)	1.60 (1.10-2.50) *s*
Gelber, 1997 (USA) (14)	Meharry-Hopkins cohort	Cohort	93 (1,624)	30	CHD	7 (182)	0.59 (0.24-1.46) *ns*
Janssens, 2003 (Netherlands)** (15)	Continuous morbidity Registration cohort	Case-control	170 (510)	11	CVD	44 (114)	0.98 (0.65-1.47) *ns*
Krishnan, 2006 (USA) (16)	Multiple Risk Factor Intervention Trial cohort	Cohort	1,123 (12,866)	6.5	a. Fatal MI b. All MI	22 (246) 118 (1108)	a. 0.96 (0.66-1.44) *ns* b. 1.26 (1.14-1.40) *s*
Chen, 2007 (Taiwan) (20)	Ho-Ping Gout database	Cross-sectional	22,572	N/A	QWMI	393	1.18 (1.01-1.38) • *s*
Choi, 2007 (USA) (21)	Health professionals Follow-up cohort	Cohort	2,773 (51,297)	12	a. All-cause mort. b. CVD mortality c. CHD mortality	645 (5825) 304 (2132) 238 (1576)	a. 1.28 (1.15-1.41) *s* b. 1.38 (1.15-1.66) *s* c. 1.55 (1.24-1.93) *s*
Krishnan, 2008 (USA) (19)	Multiple Risk Factor Intervention Trial cohort	Cohort	655 (9,105)	17	a. Fatal MI b. CHD mortality c. CVD mortality	36 (360) 78 (833) 110 (1241)	a. 1.35 (0.94-1.93) *ns* b. 1.35 (1.06-1.72) *s* c. 1.21 (0.99-1.49) *ns*
Cohen, 2008 (USA) (23)	US Renal Data System dialysis patients	Cohort	24,415 (234,794)	5	a. All-cause mort. b. CVD mortality	◆ ◆	a. 1.49 (1.43-1.55) *s* b. 1.47 (1.26-1.59) *s*

* Results reported for males only; **Results reported for gout cases with no prevalent CVD; • Effect size for frequency of gout attack on outcome;
◆ 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.

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

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 non-fatal 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. Nonethe-

less, 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.

The MRFIT study population consisted of men who were at high risk for CHD, and thus, the potential generalizability of these results to women or to individuals without CHD risk factors should be interpreted with caution (19). Subsequent data on uric acid levels, gout medications, aspirin use, and other potential risk factors for cardiovascular mortality were not available after the baseline visit for this study. Finally, the study did not have information on the risk factor status of individuals after the end of the intervention phase of the study, and individuals could have changed their lifestyle behaviors. This could potentially influence associations between gout and long-term mortality, but the nature of the effect is not likely to be great unless there was a systematic adoption of healthier lifestyles by either those with gout or those without gout

US Renal Data System study
A recent study by Cohen *et al.* evaluated the independent association between incident gout and mortality among patients with end-stage renal disease (ESRD) and on dialysis therapy in the United States Renal Data System (23). Using Cox regression models adjusted for gender, race, chronic pulmonary disorder, peripheral vascular disease, diabetes, ischemic heart disease, congestive failure, albumin levels, and smoking status, authors reported that gout was independently associated with mortality (HR 1.49; 95% CI, 1.43-1.55) and CVD-mortality (HR 1.47; 95% CI, 1.26-1.59) (23).
One of the limitations of this study was use of national registry data that did not include information on other potential risk factors for mortality among ESRD patients including malnutrition, infection, and social circumstances (23). There was also potential for misclassification of gout status and outcomes which could not be confirmed by investigators. However, findings from this study are consistent with results reported by Krishnan (19) and Choi (21) as well as reports of CVD as the primary cause of death in patients with ESRD.

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 level) 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 active 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 active 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

1. CHOI HK, MOUNT DB, REGINATO AM: Pathogenesis of gout. *Ann Intern Med* 2005; 143: 499-516.
2. LAWRENCE RC, FELSON DT, HELMICK CG *et al.*: Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: Parts II. *Arthritis Rheum* 2008; 58: 26-35.
3. ROUBENOFF R, KLAG MJ, MEAD LA, LIANG KY, SEIDLER AJ, HOCHBERG MC: Incidence and risk factors for gout in white men. *JAMA* 1991; 266: 3004-7.
4. CHOI HK, ATKINSON K, KARLSON EW, WILLETT WC, CURHAN G: Purine-rich foods, dairy and protein intake, and the risk of gout in men. *New Eng J Med* 2004; 350: 1093-103.
5. CHOI HK, HERNAN MA, SEEGER JD, ROBINS JM, WOLFE F: Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. *Lancet* 2002; 359: 1173-7.
6. MATTESON EL, GOLD KN, BLOCH DA, HUNDER GG: Long-term survival of patients with giant cell arteritis in the American College of Rheumatology giant cell arteritis classification criteria cohort. *Am J Med* 1996; 100: 193-6.
7. WARD MM: Premature morbidity from cardiovascular and cerebrovascular diseases in women with systemic lupus erythematosus. *Arthritis Rheum* 1999; 42: 338-46.
8. AMANTE EJ, CHOI HK: Mortality Impact of Common Rheumatic Disorders - A Meta-analysis (abstract). *Arthritis Rheum* 2001; 44: 2951.
9. YU KH: Intraarticular tophi in a joint without a previous gouty attack. *J Rheumatol* 2003; 30: 1868-70.
10. NISHIOKA K, MIKANAGI K: A retrospective study on the cause of death, in Japan, of patients with gout. *Ryumachi* 1981; 21 (Suppl.): 29-33.
11. DARLINGTON LG, SLACK J, SCOTT JT: Vascular mortality in patients with gout and in their families. *Ann Rheum Dis* 1983; 42: 270-3.
12. CULLETON BF, LARSON MG, KANNEL WB, LEVY D: Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. *Annals of Internal Medicine* 1999; 131: 7-13.
13. ABBOTT RD, BRAND FN, KANNEL WB, CASTELLI WP: Gout and coronary heart disease: the Framingham Study. *Journal of Clinical Epidemiology* 1988; 41: 237-42.
14. GELBER AC, KLAG MJ, MEAD LA *et al.*: Gout and risk for subsequent coronary heart disease. The Meharry-Hopkins Study. *Archives of Internal Medicine* 1997; 157: 1436-40.
15. JANSSENS HJ, VAN DE LISDONK EH, BOR H, VAN DEN HOOGEN HJ, JANSSEN M: Gout, just a nasty event or a cardiovascular signal? A study from primary care. *Fam Pract* 2003; 20: 413-6.
16. KRISHNAN E, BAKER JF, FURST DE, SCHUMACHER HR: Gout and the risk of acute myocardial infarction. *Arthritis Rheum* 2006; 54: 2688-96.
17. GELBER AC, HOCHBERG MC, MEAD LA, WANG NY, WIGLEY FM, KLAG MJ: Body mass index in young men and the risk of subsequent knee and hip osteoarthritis. *Am J Med* 1999; 107: 542-8.
18. YU T, TALBOTT JH: Changing trends of mortality in gout. *Semin Arthritis Rheum* 1980; 10: 1-9.
19. KRISHNAN E, SVENDSEN K, NEATON JD, GRANDITS G, KULLER LH: Long-term cardiovascular mortality among middle-aged men with gout. *Arch Intern Med* 2008; 168: 1104-10.
20. CHEN SY, CHEN CL, SHEN ML: Severity of gouty arthritis is associated with Q-wave myocardial infarction: a large-scale, cross-sectional study. *Clin Rheumatol* 2007; 26: 308-13.
21. CHOI HK, CURHAN G: Independent impact of gout on mortality and risk for coronary heart disease. *Circulation* 2007; 116: 894-900.
22. CHOI HK, ATKINSON K, KARLSON EW, WILLETT WC, CURHAN G: Alcohol Intake and Risk of Incident Gout in Men - A Prospective Study. *Lancet* 2004; 363: 1277-81.
23. COHEN SD, KIMMEL PL, NEFF R, AGODOA L, ABBOTT KC: Association of Incident Gout and Mortality in Dialysis Patients. *J Am Soc Nephrol* 2008, May 28. [Epub ahead of print].
24. OPARIL S, ZAMAN MA, CALHOUN DA: Pathogenesis of hypertension. *Ann Intern Med* 2003; 139: 761-76.
25. JOHNSON RJ, KANG DH, FEIG D *et al.*: Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? *Hypertension* 2003; 41: 1183-90.
26. FANG J, ALDERMAN MH: Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971-1992. National Health and Nutrition Examination Survey. *JAMA* 2000; 283: 2404-10.
27. NISKANEN LK, LAAKSONEN DE, NYYSSONEN K *et al.*: Uric acid level as a risk factor for cardiovascular and all-cause mortality in middle-aged men: a prospective cohort study. *Arch Intern Med* 2004; 164: 1546-51.
28. MAZZALI M, HUGHES J, KIM YG *et al.*: Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. *Hypertension* 2001; 38: 1101-6.
29. MAZZALI M, KANELLIS J, HAN L *et al.*: Hyperuricemia induces a primary renal arteriolopathy in rats by a blood pressure-independent mechanism. *Am J Physiol Renal Physiol* 2002; 282: F991-7.
30. FRANSE LV, PAHOR M, DI BARI M *et al.*: Serum uric acid, diuretic treatment and risk of cardiovascular events in the Systolic Hypertension in the Elderly Program (SHEP). *J Hypertens* 2000; 18: 1149-54.
31. ALDERMAN M, AIYER KJ: Uric acid: role in cardiovascular disease and effects of losartan. *Curr Med Res Opin* 2004; 20: 369-79.
32. COUTINHO TDE A, TURNER ST, PEYSER PA, BIELAK LF, SHEEDY PF, 2ND, KULLO IJ: Associations of serum uric acid with markers of inflammation, metabolic syndrome, and subclinical coronary atherosclerosis. *Am J Hypertens* 2007; 20: 83-9.
33. KANELLIS J, KANG DH: Uric acid as a mediator of endothelial dysfunction, inflammation, and vascular disease. *Semin Nephrol* 2005; 25: 39-42.
34. RUGGIERO C, CHERUBINI A, BLE A *et al.*: Uric acid and inflammatory markers. *Eur Heart J* 2006; 27: 1174-81.
35. FROHLICH M, IMHOF A, BERG G *et al.*: Association between C-reactive protein and features of the metabolic syndrome: a population-based study. *Diabetes Care* 2000; 23: 1835-9.
36. OLEXA P, OLEXOVA M, GONSORCIK J, TKAC I, KISEL'OVA J, OLEJNIKOVA M: [Uric acid--a marker for systemic inflammatory response in patients with congestive heart failure?] *Wien Klin Wochenschr* 2002; 114: 211-5.
37. LEYVA F, ANKER SD, GODSLAND IF *et al.*: Uric acid in chronic heart failure: a marker of chronic inflammation. *Eur Heart J* 1998; 19: 1814-22.
38. PASCUAL E: Persistence of monosodium urate crystals and low-grade inflammation in the synovial fluid of patients with untreated gout. *Arthritis Rheum* 1991; 34: 141-5.
39. DALBETH N, HASKARD DO: Mechanisms of inflammation in gout. *Rheumatology* (Oxford) 2005; 44: 1090-6.