Renal Failure

ISSN: 0886-022X (Print) 1525-6049 (Online) Journal homepage: informahealthcare.com/journals/irnf20

Association between serum uric acid and mortality in a Chinese population of hypertensive patients

Jian Wang, Yong Wang, Dongdong Zhao, Xiaoyan Guo & Jing-quan Zhong

To cite this article: Jian Wang, Yong Wang, Dongdong Zhao, Xiaoyan Guo & Jing-quan Zhong (2015) Association between serum uric acid and mortality in a Chinese population of hypertensive patients, Renal Failure, 37:1, 73-76, DOI: 10.3109/0886022X.2014.964148

To link to this article: https://doi.org/10.3109/0886022X.2014.964148

RENAL FAILURE

http://informahealthcare.com/rnf
ISSN: 0886-022X (print), 1525-6049 (electronic)

Ren Fail, 2015; 37(1): 73–76
 DOI: 10.3109/0886022X.2014.964148

informa
healthcare

CLINICAL STUDY

Association between serum uric acid and mortality in a Chinese population of hypertensive patients

Jian Wang[1,2]*, Yong Wang[3]*, Dongdong Zhao[4], Xiaoyan Guo[5], and Jing-quan Zhong[1]

[1]Department of Cardiology, Key Laboratory of Cardiovascular Remodeling and Function Research, Qilu Hospital of Shandong University, Chinese Ministry of Education and Chinese Ministry of Health, Jinan, China, [2]Department of Cardiology, Weifang People's Hospital, Weifang, China, [3]Department of Cardiology, Shanghai First People's Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China, [4]Department of Cardiology, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai, China, and [5]Department of Gastroenterology, Shanghai Pudong Gongli Hospital, Shanghai, China

Abstract

Objectives: To investigate the association between serum uric acid and mortality in a Chinese population of hypertensive patients. *Methods and results*: A total of 2757 Chinese hypertensive patients from department of cardiology of several hospitals in Shanghai in China were followed up for about six years in this prospective study. Mortality was recorded and related factors were evaluated. Hyperuricemia was diagnosed by serum uric acid levels of >420 μmol/L in males or >357 μmol/L in females. A total of 2585 hypertensive patients with complete data were included in the final statistical analysis. Totally 709 deaths (27.4%) occurred during the six-year follow-up, of which 475 deaths were attributable to cardiovascular disease (CVD). All-cause and CVD mortality of hypertensive patients with hyperuricemia was significantly higher than that of patients without hyperuricemia. The Cox regression analysis indicated that hazards ratios (HRs) of hyperuricemia for all-cause and CVD mortality were 1.206 (95% CI: 1.002–1.453) and 1.085 (95% CI: 1.002–1.271) respectively. All-cause and CVD mortality of hypertensive patients was significantly increased (both $p < 0.05$) when uric acid levels increased. HRs of uric acid levels >536 μmol/L to all-cause and CVD mortality of hypertensive patients were 2.115 (95% CI: 1.596–2.801) and 1.861 (95% CI: 1.296–2.673), respectively, compared with those of uric acid levels ≤357 μmol/L. *Conclusions*: The data from this cohort study indicate that hyperuricemia can predict increased all-cause and CVD mortality in hypertensive patients.

Keywords

Cardiovascular disease, hypertension, hyperuricemia, mortality, risk factors

History

Received 3 June 2014
Revised 9 August 2014
Accepted 3 September 2014
Published online 26 September 2014

Introduction

Hypertension is one of the leading causes of disease burden worldwide.[1] The incidence of hypertension is increasing in China.[2] Hypertension can cause severe target organs damage, and increase the mortality in those patients as well. The association between high blood pressure and cardiovascular disease (CVD) and mortality is established in many studies.[3–5] Several million premature deaths can be attributed directly or indirectly to hypertension in the world per year.[6]

Hyperuricemia is prevalent in patients with cardiovascular disease, along with other chronic conditions related to increased cardiovascular risk, such as hypertension, insulin resistance, and metabolic syndrome.[7–9] Several previous studies have reported a positive association between serum uric acid levels and cardiovascular events.[10–12]

However, very few studies to date have examined the association of serum uric acid with mortality in patients with hypertension in China. In this report, we present the six-year prospective study aimed to assess the association of uric acid on the outcomes of all-cause mortality and cardiovascular mortality in Chinese hypertensive patients.

Materials and methods

Study design and study population

All the participants were recruited from hypertensive patients hospitalized in department of cardiology of several hospitals in Shanghai in China from July to November 2004. Informed consent was obtained from all the participants prior to enrollment. Hypertension was diagnosed when systolic blood pressure ≥140 mmHg, or diastolic blood pressure ≥90 mmHg, or being treated with antihypertensive agents. Subjects with diseases, such as severe heart failure, liver failure, pregnancy, mental disorder, or cancer were excluded from the study. Totally 2757 hypertensive patients aged over

*Jian Wang and Yong Wang are co-first authors and have contributed equally to this work.

Address correspondence to Jing-quan Zhong, Department of Cardiology, Key Laboratory of Cardiovascular Remodeling and Function Research, Qilu Hospital of Shandong University, Chinese Ministry of Education and Chinese Ministry of Health, 107 Wen Hua Xi Lu, Jinan, China. E-mail: gilman_zhong@hotmail.com

35 years were enrolled in this cohort study. The patients or their families were contacted twice at the first year and once a year subsequently. They were followed up until the endpoint (death) was reached or until November 2010. The study complied with the Declaration of Helsinki and was approved by the ethics committee of Tongji University.

Data collection and definition of related clinical conditions

Clinical data, such as the general characteristics, risk factors, comorbidities, and medical treatment were collected. They were obtained according to the medical records of those patients from the department of cardiology of several hospitals. Definition of clinical conditions is as follows. The uric acid levels were usually measured by the colorimetric method. Hyperuricemia was diagnosed by serum uric acid levels >420 μmol/L in males, or >357 μmol/L in females. Smoking history was defined as smoking more than one cigarette per day for at least one year. Lipid disorders were diagnosed when total cholesterol ≥5.7 mmol/L, or LDL ≥3.6 mmol/L, or HDL <1.04 mmol/L, or being treated with antihyperlipidemic drugs. Type 2 diabetes was diagnosed by a fasting plasma glucose ≥7.0 mmol/L, or by a random plasma glucose ≥11.1 mmol/L, or if patients received hypoglycemic therapy. Coronary heart disease (CHD) was diagnosed when stenosis in diameter was more than 50% in at least one main coronary artery, a history of myocardial infarction, or a history of revascularization by percutaneous coronary intervention or coronary artery bypass graft. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2. Peripheral arterial disease (PAD) was diagnosed when ABI ≤0.90 in either leg, or peripheral revascularization or amputation because of PAD. Ischemic stroke was defined as atherosclerotic cerebral infarction or cerebral embolism. Medical treatment was recorded including the use of antiplatelet drugs, angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor antagonists (ARB), calcium antagonists, diuretics, and beta-blockers.

Identification of mortality

Death was identified from records in hospital or by contacting subjects' families. Deaths due to CVD were classified according to Codes 400 to 444, including CHD, stroke, and others using the International Classification of Disease, 9th Revision, Clinical Modification.[13]

Statistical analysis

Continuous variables were expressed as the mean ± standard deviation. Categorical variables were expressed as the percentage. The independent-sample *t*-test was used to compare continuous variables between two groups. The chi-square test was used to compare categorical variables. The Cox regression analysis was used to evaluate the relationship between the possible related factors and mortality, while hazards ratios (HRs) were calculated. Statistical analysis was done using the software program SPSS 13.0 (SPSS Inc., Chicago, IL). $p < 0.05$, which is two-sided, was considered significant.

Results

During a median follow-up time of 69 months (range: 66–75 months), 172 participants (6.2%) were lost because they changed their telephone number or address. Finally, 2585 hypertensive patients with complete data during the six-year follow-up were included in the final statistical analysis.

Baseline characteristics

Baseline characteristics of the hypertensive patients are shown in Table 1. The average age of the subjects was

Table 1. Baseline characteristics of hypertensive patients with and without hyperuricemia.

Variables	With hyperuricemia ($n = 600$)	Without hyperuricemia ($n = 1985$)	*p*-Value
Age, yrs	69.6 ± 10.3	67.2 ± 10.6	<0.001
Women (*n*, %)	305 (50.8%)	916 (46.1%)	0.044
Systolic BP (mmHg)	145.9 ± 24.0	145.1 ± 21.7	0.468
Diastolic BP (mmHg)	82.9 ± 13.1	82.8 ± 12.2	0.906
Total cholesterol (mmol/L)	4.79 ± 1.25	4.64 ± 1.13	0.010
LDL-C (mmol/L)	2.83 ± 0.91	2.76 ± 0.85	0.069
HDL-C (mmol/L)	1.17 ± 0.38	1.21 ± 0.37	0.022
Total triglyceride (mmol/L)	1.98 ± 1.59	1.63 ± 1.10	<0.001
Serum creatinine (μmol/L)	133.5 ± 131.5	98.3 ± 89.1	<0.001
Plasma glucose (mmol/L)	6.47 ± 3.03	6.44 ± 2.74	0.829
Smoking (*n*, %)	234 (39.0%)	783 (39.4%)	0.845
PAD (*n*, %)	208 (34.7%)	507 (25.5%)	<0.001
Type 2 diabetes (*n*, %)	254 (42.3%)	891 (44.9%)	0.266
Lipid disorders (*n*, %)	428 (72.2%)	1279 (64.8%)	0.001
CHD (*n*, %)	363 (60.5%)	1086 (54.7%)	0.012
CKD (*n*, %)	370 (62.3%)	775 (39.1%)	<0.001
Ischemic stroke (*n*, %)	203 (33.8%)	757 (38.1%)	0.056
ACEI use (*n*, %)	338 (56.4%)	1011 (51.0%)	0.019
ARB use (*n*, %)	83 (13.8%)	161 (8.1%)	<0.001
Antiplatelet therapy (*n*, %)	413 (68.8%)	1311 (66.1%)	0.215
β-blocker use (*n*, %)	264 (44.0%)	798 (40.2%)	0.101
CCB use (*n*, %)	279 (46.5%)	849 (42.8%)	0.109
Diuretics use (*n*, %)	258 (43.0%)	533 (26.9%)	<0.001

Table 2. All-cause and CVD mortality of hypertensive patients during the six-year follow-up.

Patients	All patients	With hyperuricemia	Without hyperuricemia
Number	2585	600	1985
Person-years (PY) of follow-up	10,856	2364	8492
All-cause deaths			
Number	709	212	497
Mortality (per 1000 PY)	65.3	89.7	58.5
Adjusted HR (95% CI)	–	1.206 (1.002–1.453)	1.00 (Referent)
CVD deaths			
Number	475	135	340
Mortality (per 1000 PY)	43.8	57.1	40.0
Adjusted HR (95% CI)	–	1.085 (1.002–1.271)	1.00 (Referent)

The Cox regression model was used to estimate the independent relationship between hyperuricemia and all-cause and CVD mortality after adjusting for gender, age, smoking, lipid disorders, type 2 diabetes, CKD, CHD, PAD, ischemic stroke, and medical therapy. Adjusted HRs were calculated.

67.8 ± 10.6 years old, and 52.8% of them were male. 600 subjects (23.2%) were diagnosed with hyperuricemia. Hypertensive patients with hyperuricemia were older, and had higher total cholesterol, total triglyceride, and serum creatinine levels than those without hyperuricemia (all $p < 0.05$). More of them were female than those without hyperuricemia ($p < 0.05$). A higher percentage of hypertensive patients with hyperuricemia had lipid disorders, CKD, and CHD than those without hyperuricemia (all $p < 0.05$), and a higher percentage used medications such as ACEI, ARB, and diuretics (all $p < 0.05$).

Mortality of hypertensive patients with or without hyperuricemia

All-cause and CVD mortality of hypertensive patients with or without hyperuricemia was shown in Table 2. A total of 709 deaths (27.4%) occurred during the six-year follow-up, of which 475 deaths were attributable to CVD. Mortality was presented per 1000 patient-years (PY). All-cause and CVD mortality of hypertensive patients with hyperuricemia was significantly higher than that of patients without hyperuricemia. The Cox regression analysis indicated that HRs of hyperuricemia for all-cause and CVD mortality were 1.206 (95% CI: 1.002–1.453) and 1.085 (95% CI: 1.002–1.271), respectively, after adjusting for other potential confounders.

Mortality of hypertensive patients in various uric acid categories

We observed the mortality of hypertensive patients during six-year follow-up when they were divided into four groups according to uric acid levels $\leq$357 μmol/L, >357 to $\leq$420 μmol/L, >420 to $\leq$536 μmol/L, and >536 μmol/L. Table 3 indicated that all-cause and CVD mortality of hypertensive patients was significantly increased (both $p < 0.05$) when uric acid levels increased. All-cause and CVD mortality of patients with uric acid levels >536 μmol/L was highest (51.5 and 32.4%, respectively). The Cox regression analysis was used to evaluate the independent relationship between uric acid categories and mortality adjusting for other potential confounders (Table 4). HRs of uric acid levels >536 μmol/L to all-cause and CVD mortality of hypertensive patients were 2.115 (95% CI: 1.596–2.801) and 1.861 (95% CI: 1.296–2.673), respectively, compared with those of uric acid levels $\leq$357 μmol/L.

Table 3. Six-year all-cause and CVD mortality of hypertensive patients in various uric acid categories.

Uric acid categories	All-cause mortality (%)	CVD mortality (%)
$\leq$357 μmol/L (*n*, %)	424 (24.5%)	289 (16.7%)
>357 to $\leq$420 μmol/L (*n*, %)	110 (27.2%)	81 (20.0%)
>420 to $\leq$536 μmol/L (*n*, %)	105 (33.3%)	61 (19.4%)
>536 μmol/L (*n*, %)	70 (51.5%)	44 (32.4%)

Table 4. Adjusted HR of various uric acid categories to the six-year all-cause and CVD mortality.

Uric acid categories	All-cause mortality (%)	CVD mortality (%)
$\leq$357 μmol/L (HR, 95% CI)	1.00 (Referent)	1.00 (Referent)
>357 to $\leq$420 μmol/L (HR, 95% CI)	0.974 (0.765–1.239)	1.067 (0.802–1.419)
>420 to $\leq$536 μmol/L (HR, 95% CI)	0.987 (0.766–1.271)	0.813 (0.583–1.136)
>536 μmol/L (HR, 95% CI)	2.115 (1.596–2.801)	1.861 (1.296–2.673)

The Cox regression model was used to estimate the independent relationship between uric acid and all-cause and CVD mortality after adjusting for gender, age, smoking, lipid disorders, type 2 diabetes, CKD, CHD, PAD, ischemic stroke, and medical therapy. Adjusted HRs were calculated.

Discussion

The incidence of hypertension is increasingly high in China, and it is estimated that there are more than 200 million Chinese hypertensive patients.[2] Hypertension is often accompanied by various metabolic disorders, cardiovascular risk factors and target organ damages, and possibly increases the mortality in those patients.[14–17] In this study, 23.2% of Chinese hypertensive patients were accompanied by hyperuricemia which may manifest as increased metabolic disorders and cardiovascular risk.

This study indicates that all-cause and CVD mortality of hypertensive patients with hyperuricemia was significantly higher than that of patients without hyperuricemia. When hypertensive patients were divided into four groups according to uric acid levels $\leq$357 μmol/L, >357 to $\leq$420 μmol/L, >420 to $\leq$536 μmol/L, and >536 μmol/L, all-cause mortality was 24.5, 27.2, 33.3, and 51.5%, respectively, while CVD mortality was 16.7, 20.0, 19.4, and 32.4%, respectively. These data suggest when hypertensive patients suffered hyperuricemia as well; they had increased risk of deaths. Furthermore, risk of deaths was even higher when there is increase in uric acid levels.

The data of this study indicates that hypertensive patients with hyperuricemia were older and had higher total cholesterol, total triglyceride, and serum creatinine than those without hyperuricemia. A higher percentage of hypertensive patients with hyperuricemia were female, and had lipid disorders, CKD, and CHD than those without hyperuricemia. Previous studies have revealed the same tendency that a higher fraction of hypertensive patients with hyperuricemia had lipid disorders, CKD, CHD, and other CVD.[17–20] These clinical features possibly explain why hypertensive patients accompanied by hyperuricemia suffered a higher risk of mortality in this study because they had more CVD risk factors and comorbidities.

In order to exclude the interference of other potential risk factors and comorbidities, we use the Cox regression analysis to evaluate the independent relationship between hyperuricemia and mortality in hypertensive patients. These data indicates that HRs of hyperuricemia for all-cause and CVD mortality were 1.206 (95% CI: 1.002–1.453) and 1.085 (95% CI: 1.002–1.271) respectively. Furthermore, we have found that the relative risks of all-cause and CVD mortality in hypertensive patients with uric acid levels >536 μmol/L increased about two-fold, compared with those of uric acid levels $\leq$357 μmol/L. These data suggest that hyperuricemia can predict mortality in hypertensive patients, independent of other cardiovascular risk factors and comorbidities. This is consistent with the results of the studies in other populations.[10,12]

The data from this six-year cohort study indicate that hyperuricemia can predict higher all-cause and CVD mortality in hypertensive patients. As high blood pressure and hyperuricemia are both modifiable, comprehensive measures to control hypertension and hyperuricemia may help to improve the prognosis of those patients.

Acknowledgments

We are grateful to the subjects who participated in the study, and to the physicians' assistance in this study.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

This study was sponsored by the Natural Science Foundation of China (81270238), the Scientific Research Foundation for the Doctoral Degree, State Education Ministry of China (20100131110059), the Scientific Development Plan of Shandong Province of China (2012G0021850), and Shanghai Natural Science Foundation [13ZR1433500].

References

1. Ezzati M, Lopez AD, Rodgers A, et al. Selected major risk factors and global and regional burden of disease. *Lancet.* 2002;360: 1347–1360.
2. Gao Y, Chen G, Tian H, et al. Prevalence of hypertension in China: A cross-sectional study. *PLoS One.* 2013;8:e65938.
3. Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet.* 2002;360:1903–1913.
4. He FJ, MacGregor GA. Cost of poor blood pressure control in the UK: 62, 000 unnecessary deaths per year. *J Hum Hypertens.* 2003; 17:455–457.
5. He J, Gu D, Chen J, et al. Premature deaths attributable to blood pressure in China: A prospective cohort study. *Lancet.* 2009;374: 1765–1772.
6. Lawes CM, Vander Hoorn S, Rodgers A, et al. Global burden of blood-pressure-related disease, 2001. *Lancet.* 2008;371:1513–1518.
7. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. *N Engl J Med.* 2008;359:1811–1821.
8. Schiffrin EL, Lipman ML, Mann JF. Chronic kidney disease: Effects on the cardiovascular system. *Circulation.* 2007;116:85–97.
9. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med.* 2004;351:1296–1305.
10. Chien KL, Hsu HC, Sung FC, et al. Hyperuricemia as a risk factor on cardiovascular events in Taiwan: The Chin-Shan Community Cardiovascular Cohort Study. *Atherosclerosis.* 2005;183:147–155.
11. Moriarity JT, Folsom AR, Iribarren C, et al. Serum uric acid and risk of coronary heart disease: Atherosclerosis Risk in Communities (ARIC) Study. *Ann Epidemiol.* 2000;10:136–143.
12. 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: 1546–1551.
13. Department of Health and Human Services: The International Classification of Diseases, 9th Revision, Clinical Modification: ICD-9-CM, 3rd edition. Washington, DC: Government Printing Office; 1989.
14. Gu P, Jiang W, Cheng M, et al. Glucose metabolism in outpatients with new-onset hypertension in Chinese Han population. *Clin Exp Hypertens.* 2012;34:474–481.
15. Cao Y, Li W, Yang G, et al. Diabetes and hypertension have become leading causes of CKD in Chinese elderly patients: A comparison between 1990–1991 and 2009–2010. *Int Urol Nephrol.* 2012;44:1269–1276.
16. Zheng L, Sun Z, Zhang X, et al. The association between glomerular filtration rate and stroke in hypertensive patients in rural areas of China. *J Hypertens.* 2012;30:901–907.
17. Tavil Y, Kaya MG, Oktar SO, et al. Uric acid level and its association with carotid intima-media thickness in patients with hypertension. *Atherosclerosis.* 2008;197:159–163.
18. Leoncini G, Viazzi F, Rosei EA, et al. Chronic kidney disease in hypertension under specialist care: The I-DEMAND study. *J Hypertens.* 2010;28:156–162.
19. Keenan RT, Pillinger MH. Hyperuricemia, gout, and cardiovascular disease – An important ''muddle''. *Bull NYU Hosp Jt Dis.* 2009;67: 285–290.
20. Nakagawa T, Cirillo P, Sato W, et al. The conundrum of hyperuricemia, metabolic syndrome, and renal disease. *Intern Emerg Med.* 2008;3:313–318.