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Preliminary Communication

Serum uric acid levels show a 'J-shaped' association with all-cause mortality in haemodialysis patients

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Abstract

Background. Although elevated serum levels of uric acid are common in patients with kidney disease or in those receiving maintenance dialysis therapy, the clinical impact of uric acid on mortality in haemodialysis (HD) patients remains unclear. This work was designed to explore the predictive value of serum uric acid levels on all-cause mortality of HD patients.

Methods. We retrospectively analysed mortality rates in 146 chronic HD patients that were treated with HD three times per week at our HD unit for a period of one full year. The analysed parameters included demographic characteristics, aetiology of end-stage renal disease, co-morbid conditions, duration (at least 1 year) and delivered dose of HD, normalized protein catabolic rate, serum albumin concentration, haematocrit, serum uric acid (UA) levels and other laboratory parameters. A multivariate Cox proportional hazards model, which included adjustment for the above factors, was applied to identify the predictive value of UA levels on patient mortality.

Results. A Cox proportional hazards model revealed that decreased serum albumin, underlying diabetic nephropathy (DMN) and UA groups ($\leq$20th, 20–80th and $\geq$80th percentiles; $P = 0.016$) were all significant, independent predictors of all-cause mortality in HD patients. The hazard ratios of death were: serum albumin (per 0.5 g/dl decrease), 3.10 [95% confidence interval (95% CI), 1.80–5.34, $P < 0.001$]; DMN (*vs* non-DMN), 3.47 (95% CI, 1.25–9.59, $P = 0.017$); and UA groups (*vs* 20th to 80th percentile): $\leq$20th percentile, 2.98 (95% CI, 0.82–10.90, $P = 0.099$); $\geq$80th percentile, 5.67 (95% CI, 1.71–18.78, $P = 0.004$).

Conclusions. These preliminary observations suggest that HD patients in the lowest and highest quintiles of UA levels would face higher risk of mortality. Further studies with larger sample sizes will be needed to confirm these findings.

Keywords: albumin; diabetes mellitus; haemodialysis; mortality rate; serum uric acid

Introduction

Uric acid is the final product of purine metabolism in humans. The kidneys excrete approximately two-thirds of the uric acid that is produced daily. For an individual, the serum uric acid concentration is determined largely by the rate of purine metabolism and the efficiency of renal clearance. Therefore, significant amounts of uric acid may accumulate in patients approaching end-stage renal disease (ESRD). The mean uric acid removal is ~1 g per haemodialysis (HD) session, even with high-flux haemodialysers [1]. Nevertheless, hyperuricaemia is still common in HD patients following HD therapy. After the suggestion of Gertler *et al*. [2] of a complex interaction between uric acid and coronary heart disease, several large prospective cohort studies have demonstrated associations between serum uric acid levels and cardiovascular disease as well as all-cause mortality in the general population [3–5]. However, to our knowledge, there is no information on the clinical impact of serum uric acid levels on prognosis of HD patients. This study was therefore designed to explore possible associations between serum uric acid and mortality in HD patients.

Subjects and methods

Patients

We set December 2001 as the starting point for this retrospective study. A total of 183 patients had been receiving HD three times a week at our HD unit for at

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least 3 months. However, to minimize the confounding effect of residual renal function on serum uric acid levels, we only included 146 patients who had been undergoing HD for at least 1 year. Patient demographics, aetiology of ESRD, duration of maintenance HD, and co-morbid conditions on enrolment were obtained from charts and from a computerized database at our unit. Smokers, including ex- and current smokers, made up ~10% of the population and were evenly distributed in the whole patient group. Body length and body mass indices of the patients were not available from the records. All patient outcomes were followed through to December 2002 for a period of 1 full year. Patient mortality during this observation period was recorded. Patients were surveyed at the time of transfer to other out-patient HD units, at hospitalization for transplantation or at the end of the observation period.

Definitions of co-morbidity

Co-morbidities were determined with the following criteria: diabetes mellitus (DM), by documented medical history and/or underlying diabetic nephropathy; hypertension, by documented medical history and/or taking antihypertensive drugs; congestive heart failure, by documented medical history or proven by ultrasonic cardiography with left ventricular ejection fraction $<40\%$; ischaemic heart disease, by documented medical history of coronary artery disease, myocardial infarction, coronary artery bypass surgery, angioplasty or abnormal angiography; cerebrovascular accidents, by documented episodes of neurological deficits; liver cirrhosis, diagnosed by abdominal ultrasonographic findings; malignancy, by documented medical history and/or pathological reports; and tuberculosis infection, by documented medical history and/or taking anti-tuberculosis therapy.

Laboratory parameters

All biochemical analyses were performed with a Hitachi 747 Automatic Analyzer. Results from routine monthly midweek, pre-dialysis, venous blood samples at the initiation of this study (December 2001) were used for analysis, and included: serum electrolytes, creatinine, albumin (bromocresol green method), uric acid, iron profiles (iron, transferrin and ferritin), lipid profiles (total cholesterol and triglyceride concentrations) and blood urea nitrogen (BUN) concentrations. Post-dialysis BUN from the same dialysis session was measured to calculate the delivered dose of dialysis (Kt/V) during a treatment session. The Kt/V was calculated by the Daugirdas method. The pre-dialysis BUN from the next dialysis was measured and was applied to calculate a normalized protein catabolic rate [nPCR, normalized to body weight derived from the urea distribution space (V_{urea}/0.58)]. Serum calcium was corrected (cCa) for serum albumin according to the formula: cCa (mg/dl) = serum calcium (mg/dl) + $0.8 \times$ [4.0 − serum albumin (g/dl)].

Dialysis prescription

All patients were managed by nephrologists and were dialysed with bicarbonate-based dialysate, volumetric ultrafiltration control and single-use cellulose-based membranes. Average session times were 4.0 ± 0.3 h (range, 3.0–4.5). Erythropoietin was prescribed via a standardized algorithm. Antihypertensive drugs were prescribed for patients having post-dialysis or inter-dialysis blood pressures persistently $>150/95$ mmHg at dry weight. None of the patients took uric acid-lowering drugs upon enrolment or during the observation year.

Statistical analysis

Continuous variables are presented as means ± SD, and categorical variables are expressed as percentages unless otherwise stated. For comparisons of continuous variables between two groups, the Student's *t*-test was used. Correlations were tested by the Pearson correlation method. Mortality rates between the quintiles of serum uric acid levels were examined by a 2×5 table with Pearson χ^2 test. To calculate the relative risk of death, hazard ratios (HRs) and 95% confidence intervals (95% CI) were obtained by Cox proportional hazards models. 'Enter' and 'conditional forward stepwise' methods were used for univariate and multivariate analyses, respectively. The possible independent variables taken into account included age, gender, duration of HD therapy, dry weight, aetiology of ESRD, co-morbid conditions, Kt/V, nPCR, serum albumin concentration, serum uric acid levels and other biochemical parameters. Separate binary variables were constructed for each aetiology and co-morbid condition. Age, duration of HD therapy, dry weight, serum albumin, Kt/V, nPCR and other biochemical parameters were treated as continuous variables. A two-tailed *P*-value of <0.05 was considered statistically significant, and values between 0.05 and 0.10 were marginally significant. All computations were performed by SPSS 10.0 for Windows (SPSS Inc., Chicago, IL).

Results

Demographics

Among the study patients, 78 (53.4%) were women and 68 (46.6%) were men. The mean age was 60 ± 15 years. The duration on HD therapy ranged between 12 and 246 months. Chronic glomerulonephritis (35.6%) and diabetic nephropathy (30.8%) were the main causes of ESRD. Co-morbid conditions included 49.3% with hypertension, 36.3% with DM and 13.7% with pre-existing heart disease (congestive heart failure and ischaemic heart disease). Further demographic characteristics, duration of HD, aetiology of ESRD, co-morbid conditions, delivered doses of dialysis, nPCR and laboratory characteristics of the patients are shown in Table 1.

During the 1-year period, three patients were transferred to different out-patient HD units, two patients received renal transplantation and 16 patients died. The total mortality rate was 11.0% (16/146). Of these, six patients died of cardiovascular disease (including one with a ruptured aortic aneurysm and one with peripheral vascular disease), four died of sepsis, one died of liver failure and the other five patients died at home of unknown causes.

Table 1. Demographic and laboratory characteristics of the patient population ($n = 146$)

Variables	Mean ± SD or % (counts)
Demographics	
Age (years)	60.5 ± 14.7
(range, years)	(19.2–87.0)
Gender (male/female)	68/78
Duration on HD (months)	67.3 ± 50.2
(range, months)	(12.0–245.9)
Dry weight (kg)	53.5 ± 10.2
(range, kg)	(31.3–83)
Aetiology of ESRD	
Chronic glomerulonephritis	35.6 (52)
Diabetic nephropathy	30.8 (45)
Malignant hypertension	4.1 (6)
Obstructive uropathy	4.1 (6)
Lupus nephritis	2.1 (3)
Polycystic kidney disease	2.1 (3)
Chronic pyelonephritis	2.1 (3)
TB kidney	0.7 (1)
Malignancy	0.7 (1)
Undetermined	17.8 (26)
Co-morbid conditions	
Diabetes mellitus	36.3 (53)
Hypertension	49.3 (72)
Congestive heart failure	11.0 (16)
Ischaemic heart disease	2.7 (4)
Cerebrovascular accidents	11.6 (17)
Liver cirrhosis	6.8 (10)
Malignancy	1.4 (2)
Tuberculosis	2.1 (3)
Delivered dose of dialysis	
Kt/V	1.61 ± 0.30
URR (%)	72.5 ± 6.6
Nutrition	
Albumin (g/dl)	3.95 ± 0.45
Transferrin (μg/dl)	212 ± 63
nPCR (g/kg/day)	1.09 ± 0.31
Laboratory data	
Haematocrit (%)	32.3 ± 3.9
Pre-dialysis BUN (mg/dl)	67.7 ± 18.6
Creatinine (mg/dl)	11.0 ± 2.3
AST (IU/l)	18 ± 11
ALT (IU/l)	13 ± 12
ALP (IU/l)	66.6 ± 28.0
cCa (mg/dl)	9.4 ± 0.8
P (mg/dl)	4.8 ± 1.6
cCa × P	44.8 ± 15.3
iPTH (pg/ml)	188 ± 221
Ferritin (ng/ml)	519 ± 277
Uric acid (mg/dl)	7.7 ± 1.4
(range, mg/dl)	(5.2–11.5)
Cholesterol (mg/dl)	190 ± 46
Triglyceride (mg/dl)	199 ± 145

BUN, blood urea nitrogen; URR, urea reduction ratio, equal to [(pre-dialysis BUN – post-dialysis BUN)/pre-dialysis BUN]; nPCR, normalized protein catabolic rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; cCa, calcium corrected by serum albumin; P, phosphate; iPTH, intact parathyroid hormone.

Mortality rate vs serum uric acid level: a 'J-shaped' relationship

Serum uric acid levels in our patients showed a Gaussian distribution (Figure 1). To find a relationship between the mortality rate and serum uric acid, we first grouped patients into quintiles of serum uric acid levels

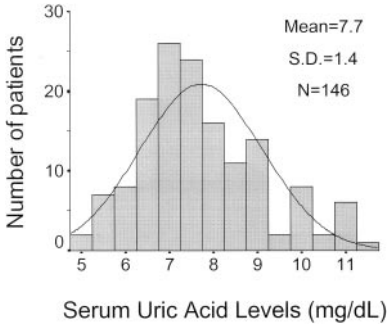

Fig. 1. Frequency distribution of serum uric acid levels in patients.

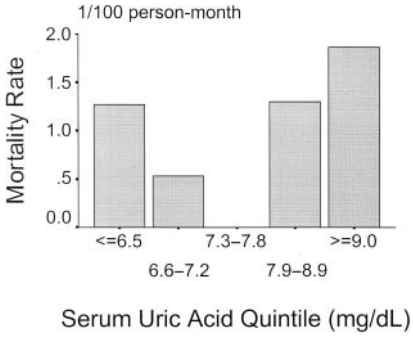

Fig. 2. Mortality rates (per 100 person-month) of patients in the different serum uric acid quintiles. The number of deaths/total patients in each quintile was 4/29, 2/33, 0/26, 4/28 and 6/30, respectively.

(Figure 2). Although there was no significant difference in mortality between the quintiles ($P = 0.136$), we observed the 'J-shaped' relationship between patient mortality and serum uric acid levels. By using curve estimation methods, we found that a quadratic regression model ($P = 0.052$) described the data better than a linear regression model ($P = 0.242$). Therefore, we inferred that patients in the first and fifth quintiles of serum uric acid levels had higher risks of mortality than those in the middle three quintiles. To test this possibility and make it more straightforward, we transformed serum uric acid levels into a categorical variable comprised of three serum uric acid groups (UA groups) that were arbitrarily defined as: 'low level' $\leq$20th percentile of serum uric acid levels; 'average level' 20th to 80th percentile; and 'high level' $\geq$80th percentile. These 'UA groups' were applied in further analyses to predict the risk of mortality of our patients.

Survival analysis

By univariate Cox proportional hazards models (Table 2), we found that age, underlying chronic glomerulonephritis or diabetic nephropathy (DMN), co-morbidity with DM or liver cirrhosis, Kt/V, urea reduction ratio (URR), serum albumin, transferrin, creatinine, alkaline phosphatase, ferritin levels and 'UA groups' were potential predictions of mortality ($P < 0.10$). To confirm the independent predictive power of patient mortality, the above data were

Table 2. Predictors of all-cause mortality: univariate Cox proportional hazards model

Variables	Univariate predictors of overall mortality	
	HR (95% CI)[a]	*P*-value
Demographics		
Age (years)	1.06 (1.01–1.10)	0.015[b]
Female (vs male)	0.51 (0.19–1.40)	0.193
Duration of HD (years)	0.99 (0.98–1.00)	0.107
Dry weight (kg)	0.97 (0.92–1.02)	0.267
Aetiology of ESRD		
Chronic glomerulonephritis	0.25 (0.06–1.08)	0.063[b]
Diabetic nephropathy	3.06 (1.14–8.23)	0.026[b]
Undetermined	1.03 (0.29–3.61)	0.963
Co-morbid conditions		
Diabetes mellitus	3.12 (1.13–8.58)	0.028[b]
Hypertension	1.02 (0.38–2.73)	0.962
Heart disease (congestive heart failure and ischaemic heart disease)	0.92 (0.21–4.05)	0.912
Cerebrovascular accidents	1.76 (0.50–6.17)	0.378
Liver cirrhosis	3.30 (0.94–11.6)	0.063[b]
Delivered dose of dialysis		
Kt/V	0.20 (0.03–1.20)	0.077[b]
URR	0.003 (0.000–2.167)	0.084[b]
Nutrition		
Albumin (g/dl)	0.15 (0.06–0.38)	< 0.001[b]
Transferrin (μg/dl)	0.98 (0.97–0.99)	< 0.001[b]
nPCR (g/kg/day)	0.36 (0.06–1.99)	0.240
Laboratory data		
Hct (%)	0.97 (0.86–1.11)	0.665
Pre-dialysis BUN (mg/dl)	1.00 (0.97–1.03)	0.963
Creatinine (mg/dl)	0.80 (0.62–1.02)	0.076[b]
AST (IU/l)	1.02 (0.98–1.05)	0.348
ALT (IU/l)	1.01 (0.98–1.04)	0.649
ALP (IU/l)	1.01 (1.00–1.03)	0.028[b]
cCa (mg/dl)	0.74 (0.40–1.37)	0.339
P (mg/dl)	0.83 (0.60–1.16)	0.276
cCa × P	0.98 (0.95–1.01)	0.248
iPTH (pg/ml)	0.998 (0.995–1.002)	0.320
Ferritin (ng/ml)	1.002 (1.001–1.004)	0.003[b]
Uric acid (mg/dl)	1.22 (0.87–1.70)	0.254
UA groups[c]		0.098[a]
Low level	2.09 (0.69–6.33)	0.154
High level	3.07 (0.99–9.51)	0.052

[a]HR, hazards ratios; 95% CI, 95% confidence interval.
[b]Variables with $P < 0.10$ were entered in the multivariate Cox regression analysis for mortality.
[c]UA groups, serum uric acid level groups: 'low level' ≤20th percentile of serum uric acid levels; 'average level', 20th to 80th percentile; and 'high level', ≥80th percentile. 'Average level' is the reference group.
For other abbreviations, please refer to the footnotes of Table 1.

entered into a multivariate Cox proportional hazards model (Table 3). In this multivariate analysis, 'UA groups' was confirmed as an independent predictor of mortality ($P = 0.016$). When 'average level' was assigned as the reference group, the HR of 'low level' was 2.98 (95% CI 0.82–10.90, $P = 0.099$), and the HR of 'high level', 5.67 (95% CI 1.71–18.78, $P = 0.004$). In addition to uric acid levels, decreased serum albumin levels and the underlying DMN were also identified as independent predictors of patient mortality. The HR of a 0.5 g/dl decrease in serum albumin was 3.10 (95% CI 1.80–5.34, $P < 0.001$), and for DMN *vs* non-DMN was 3.47 (95% CI 1.25–9.59, $P = 0.017$).

Consistency of serum uric acid levels

Serum uric acid levels of the patients were routinely checked every 3 months at our HD unit. To test consistency of serum uric acid levels, we analysed the quarterly data within the observation year. We found that serum uric acid levels (mg/dl) were as follows: on enrolment ($n = 146$), 7.7 ± 1.4; the first quarter ($n = 138$), 7.9 ± 1.4; the second quarter ($n = 133$), 7.7 ± 1.4; and the third quarter ($n = 131$), 7.5 ± 1.4. The Pearson correlation method revealed that there were significant correlations between the quarterly results (Table 4).

Discussion

Due to progressive loss of the glomerular filtration rate, patients with renal diseases or ESRD have decreased renal clearance of uric acid and higher serum uric acid levels than in the general population. In the study of Ifudu *et al.* [6], mean serum uric acid levels (mg/dl) of maintenance HD patients ($n = 139$) were 7.6 ± 1.8 in the entire patient group, 7.6 ± 1.8 in men ($n = 85$) and 7.5 ± 1.6 in women ($n = 54$). The mean serum uric acid levels (mg/dl) in our patients were similar, with 7.7 ± 1.4 ($n = 146$) in the total patient group, 7.6 ± 1.2 in men ($n = 68$) and 7.8 ± 1.6 in women ($n = 78$). There was no gender difference in serum uric acid levels in our patients ($P = 0.329$).

For most continuous risk factors, it is anticipated that exposure to the factor increases the risk. However, in the Framingham heart study, the relationship of serum uric acid with coronary heart disease, cardiovascular disease mortality and all-cause mortality appeared to be 'J-shaped' in men [4]. A similar 'J-shaped' relationship was found by Verdecchia *et al.* [7] in patients with hypertension, and by Lehto *et al.* [8] in subjects with type II DM. In the present study, we also found a 'J-shaped' relationship between mortality rates and serum uric acid levels (Figure 2). By multivariate analysis, 'UA groups' was confirmed to be an independent predictor of mortality risk in our patients (Table 3). Specifically, we found that patients in the 'low level' and 'high level' groups had higher risk of mortality than those in the 'average level' group. The precise mechanisms underlying this association remain uncertain. However, when taking causes of mortality into account, we found that the patients ($n = 6$) who died of cardiovascular disease had significantly higher serum uric acid levels than those ($n = 4$) who died of sepsis (9.0 ± 1.0 *vs* 6.7 ± 1.8 mg/dl, $P = 0.031$). We therefore looked for mechanisms to explain the 'J-shaped' relationship between mortality and serum uric acid levels that showed higher mortality risk in patients with relatively higher and lower serum uric acid levels, respectively.

Table 3. Predictors of all-cause mortality: multivariate Cox proportional hazards model with the conditional forward stepwise method ($P > 0.10$ to remove)[a]

Variables	Multivariate predictors of overall mortality	
	HR (95% CI)[b]	*P*-value (2-tailed)
Albumin (per 0.5 g/dl decrease)	3.10 (1.80–5.34)	< 0.001
UA groups[c]		0.016
Low level	2.98 (0.82–10.90)	0.099
High level	5.67 (1.71–18.78)	0.004
Underlying diabetes nephropathy (*vs* non-DMN)	3.47 (1.25–9.59)	0.017

[a]Initially, 13 univariate predictors of mortality (see Table 2, all with $P < 0.10$) were entered for adjustment.
[b]HR, hazards ratios; 95% CI, 95% confidence interval.
[c]See footnotes to Table 2.

Table 4. Correlations between the quarterly data of serum uric acid levels within the study year (Pearson correlation method)

		Q0UA	Q1UA	Q2UA	Q3UA
Q0UA	*r*	1.000	0.632	0.584	0.489
	P-value	–	0.000	0.000	0.000
	n	146	138	133	131
Q1UA	*r*	0.632	1.000	0.628	0.599
	P-value	0.000	–	0.000	0.000
	n	138	138	133	131
Q2UA	*r*	0.584	0.628	1.000	0.624
	P-value	0.000	0.000	–	0.000
	n	133	133	133	131
Q3UA	*r*	0.489	0.599	0.624	1.000
	P-value	0.000	0.000	0.000	–
	n	131	131	131	131

Q0UA, the enrolment data; Q1UA, the first quarterly data; Q2UA, the secondary quarterly data; and Q3UA, the third quarterly data.

There are three hypotheses that may explain the higher mortality rates associated with higher serum uric acid levels [9]. First, it is possible that we observed an epiphenomenon reflecting complex interactions between uric acid and other risk factors. It has been well documented that uric acid levels correlate with many cardiovascular risk factors, including older age, male gender and hypertension. However, in our study, we failed to detect significant differences in serum uric acid levels between males and females ($P = 0.329$), as well as between hypertensive and non-hypertensive patients ($P = 0.139$). In addition, there was no correlation ($r = -0.029$, $P = 0.731$) between patient age and serum uric acid levels.

As a second possibility, uric acid may have adverse effects on atherogenesis or on the clinical course of cardiovascular disease. There is evidence that increased serum uric acid promotes oxygenation of low-density lipoprotein cholesterol to then facilitate lipid peroxidation. In addition, increased uric acid levels are associated with increased production of oxygen free radicals. Both of these mechanisms may lead to the progression of atherosclerosis [9]. Furthermore, it has been proposed that elevated uric acid levels are associated with increased platelet adhesiveness [10], an effect that could further potentiate thrombus formation in HD patients. Further studies will be required to clarify these possibilities.

The third possibility is that uric acid *per se* may act as a mediator for the development of other risk factors. Hyperuricaemia itself may predispose towards the development of hypertension or aggravate the deteriorating effect of hypertension on end-organs, including the kidneys, heart, brain or vascular endothelium [9]. However, and as previously mentioned, serum uric acid levels were not different between hypertensive and non-hypertensive patients in this study.

There are three additional hypotheses that may explain the higher mortality rates associated with the lower serum uric acid levels. First, a low serum level of uric acid may have been a surrogate of poor protein intake and malnutrition in the patients. Pre-dialysis BUN is regarded as an indicator of nutritional status in dialysis patients [11], and low BUN levels are often an important clue indicating inadequate protein intake. The nPCR is another well-recognized nutrition parameter. In our study, serum uric acid levels were significantly correlated with both pre-dialysis BUN ($r = 0.518$, $P < 0.001$) and nPCR ($r = 0.317$, $P < 0.001$). These findings suggest that serum uric acid was a surrogate of protein intake.

Secondly, a relatively lower serum uric acid level may merely reflect deficits in daily intake of purines or nucleotides, an essential nutrient [12]. A prospective, randomized, controlled clinical trial showed that patients receiving a nucleotide-supplemented diet had significantly fewer complications and a shorter hospital stay after admission to the intensive care unit due to major trauma, surgical complications or sepsis [13].

Thirdly, lower serum uric acid levels are associated with lower antioxidant capacities. Uric acid has important antioxidant properties *in vivo* [14] and *in vitro* [15]. Indeed, uric acid contributes as much as 60% to free radical scavenging in human serum [16]. Elevated uric acid levels may provide a compensatory mechanism to counteract oxidative damage related to atherosclerosis and ageing in humans [17]. In peritoneal dialysis patients, Kim *et al*. [18] found that total antioxidant capacity was correlated with serum acid levels due primarily to higher levels of uric acid. Therefore, it is possible that lower levels of serum uric

acid result in reduced total antioxidant capacity. However, further studies will be needed to clarify these issues in HD patients.

In summary, high levels of serum uric acid in our HD patients may have contributed to high mortality through direct injury to the endothelium and to alteration of cardiovascular function. Paradoxically, uric acid may also provide protective antioxidant effects in the cardiovascular system, but these benefits may be overwhelmed by the detrimental effects. Lower levels of serum uric acid most probably represent a state of malnutrition that in turn accounts for immunity defects and susceptibility to sepsis.

There were some limitations in the present study. Two vital parameters, body mass index and insulin resistance, were missing from the data. Body mass index has been proposed as a useful predictor of mortality in HD patients [19], and insulin resistance has been shown to be a predictor of cardiovascular mortality in patients with ESRD [20]. However, the small sample size in the present study and the relatively small number of deaths ($n = 16$) would have limited the multivariate analysis and the generalizability of these data. Therefore, further studies in a larger HD population will be necessary not only to confirm the 'J-shaped' relationship between serum uric acid levels and mortality of HD patients, but also to clarify the molecular basis of the relationship.

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Conflict of interest statement. None declared.

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