Uric acid and left ventricular hypertrophy: another relationship in hemodialysis patients

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ABSTRACT

Background. The impact of serum uric acid (UA) on morbidity and mortality in hemodialysis (HD) patients is quite controversial in relation to the general population. The aim of this study was to evaluate the association of serum UA with both mortality and left ventricular hypertrophy (LVH) in HD patients.

Methods. This longitudinal study enrolled 225 prevalent HD patients who were classified into three groups according to their follow-up-averaged UA (FA-UA) levels: low FA-UA (FA-UA < 400 μmol/L), intermediate/reference FA-UA (FA-UA between 400 and 450 μmol/L) and high FA-UA (FA-UA > 450 μmol/L). Echocardiography was performed on a nondialysis day and the presence of LVH was defined based on a left ventricular mass index (LVMI) > 131 and > 100 g/m² for men and women, respectively. The patients were followed during a 60-month period.

Results. The mean FA-UA level was 425 ± 659 μmol/L (range 294–620). There was a consistent association of higher FA-UA with better nutritional status (higher body mass index, normalized protein catabolic rate, creatinine, albumin and phosphorus), higher hemoglobin, but lower C-reactive protein and LVMI. During the 5-year follow-up, 81 patients died (36%) and the main causes of death were cardiovascular (CV) related (70%). When compared with the reference group, the hazard ratio for all-cause mortality was 1.75 [95% confidence interval (CI) 1.02–2.98; P = 0.041] in the low FA-UA group, but there was no significant association with the high FA-UA group. In contrast, FA-UA did not show an association with CV mortality neither with the lower nor with the high FA-UA group. The unadjusted odds ratio (OR) of LVH risk in the low FA-UA compared with the reference FA-UA group was 3.11 (95% CI 1.38–7.05; P = 0.006), and after adjustment for age, gender, diabetes and CV disease, ORs for LVH persisted significantly only in the low FA-UA group [OR 2.82 (95% CI 1.16–6.88); P = 0.002].
**INTRODUCTION**

Uric acid (UA) is the end product of purine metabolism in humans, and despite being a major antioxidant in human plasma, it both correlates and predicts development of conditions associated with oxidative stress. Thus, in the general population, an elevation of serum UA has been shown to be associated with an increased risk of hypertension [1], diabetes mellitus [2], coronary heart disease [3], cardiovascular disease (CVD) [4], stroke [5] and all-cause and CV mortality [6]. An elevated UA level is commonly observed in chronic kidney disease (CKD) patients, and although two meta-analyses showed that higher serum UA levels were associated with higher all-cause mortality [7, 8], the role of UA in higher serum UA levels was associated with higher all-cause and CV mortality in patients with CKD [7, 8], the role of UA in CKD progression is still under debate [9, 10].

However, regarding hemodialysis (HD) patients, the impact of UA level on their morbidity and mortality remains more obscure and quite controversial. Serum UA levels have a wide variation in the general population, there is an inverse association in relation to oxidative stress, which may be due to different physiology of UA in HD patients [14]. Many studies involving HD patients have shown an inverse association between serum UA and CV and/or all-cause mortality [11, 12, 15], however, some studies have reported either increased or no difference in mortality [16, 17]. In the HD population, the higher UA concentrations represent better nutritional status [11, 12, 18], and concentrations were inversely correlated with markers of malnutrition and inflammation. In this association, UA shows a paradoxical correlation with some traditional CV risk factors and uremia-related factors.

Left ventricular hypertrophy (LVH) with multifactorial etiology is an important predictor of CV mortality and morbidity in HD patients. In the last decade, numerous cross-sectional clinical studies have investigated the association between UA and LVH in the general population, hypertensive cohorts and patients with diabetes and renal failure [19–21]. The Pressioni Arteriose Monitorate E Loro Associazioni 10-year follow-up study [22] is the first study that showed UA is a predictor of long-term echocardiographic changes from normal left ventricular mass index (LVMI) to LVH in a community sample. However, to our knowledge, there is no information in the literature on the clinical effect of longitudinal changes in serum UA levels on LVH in HD patients, and hence this is the first clinical study to assess the relationship between serum UA level and LVH in HD patients.

Therefore the aim of the current 5-year follow-up study was not only to evaluate the association between serum UA level and all-cause or CV mortality, but also with LVH in patients treated at a single HD center.

**MATERIALS AND METHODS**

**Study design**

This observational 5-year prospective longitudinal study was conducted at a single outpatient dialysis center. The study was approved by our institutional ethics committee. All patients were informed about the aim of the study and participated voluntarily after providing written consent.

**Study population, comorbidity index and follow-up**

A total of 225 prevalent HD patients on regular HD treatment for at least 3 months were recruited for the study. Patient demographics, etiology of ESRD, duration of maintenance HD and comorbid conditions on enrolment were obtained from the medical records at our unit. We determined the comorbidity index for atherosclerotic CVD using the scoring system for each of these diseases, namely coronary heart disease, cerebrovascular disease and peripheral vascular disease. The comorbidity index of individual patients is scored with a value ranging from 0 to 3, with 0 indicating the absence of disease and increasing values indicating an increasing severity of disease [23, 24]. The follow-up period of patients was from January 2010 to December 2014. Patients transferred to alternative renal replacement therapies (kidney transplantation or peritoneal dialysis) were censored from the survival analysis. CV mortality was defined as death resulting from coronary heart disease, sudden death, stroke or complicated peripheral vascular disease.

**Laboratory measurements, dialysis parameters and echocardiography**

All patients were on 4–4.5 h standard thrice-weekly HD at a blood flow rate of 250 mL/min and a dialysis solution flow rate of 500 mL/min. Dialysis treatments were performed with high-flux biocompatible dialyzer membranes with surface areas of 1.4–1.8 m². None of the patients was receiving UA-lowering agents such as allopurinol during the follow-up period.

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured routinely before each dialysis session. Pulse pressure (PP) was evaluated by the formula (SBP – DBP).

Echocardiography was performed in all of these patients prior to starting the study, on a nondialysis day. Left ventricular end-diastolic diameter, left ventricular end-systolic diameter, interventricular septal thickness, left atrial diameter and left ventricular posterior wall thickness were measured. LVMI was calculated by dividing LVM by the body surface area. LVM was defined as an LVMI > 131 g/m² in men and > 100 g/m² in women. Left ventricular mass was calculated using the Devereux modified method [i.e. LVM = 1.04(IVSTd + LVIDd + LVPWTd)3 – LVIDd3] – 13.6 g], where IVSTd is interventricular septal thickness in diastole, LVIDd is the left ventricular internal dimension in diastole and LVPWT is the left ventricular posterior wall thickness in diastole [25].

**Conclusions.** Low serum UA is a mortality risk factor and is associated with LVH in HD patients. These results are in contrast with the association of UA in the general population and should be the subject of further research.

**Keywords:** chronic hemodialysis, left ventricular hypertrophy mortality, uric acid
Venous blood samples collected pre- and postdialysis at the start of the study and then on the first Monday or Tuesday of each month during the follow-up period were used for analysis and included hemoglobin, albumin, creatinine, serum calcium, phosphorus, potassium, UA, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and C-reactive protein (CRP). For all these monthly laboratory analyses, an average of 35.7 values were taken per patient. Serum total intact parathyroid hormone was measured at 6 months and ferritin quarterly. Brain natriuretic peptide (BNP) was measured only at the beginning of the study, and blood samples were drawn from vascular access just before HD. Repetitive blood samples of UA during the follow-up period, collected with other laboratory analyses (regular intervals of every month in a period of 60 months for patients who survived and to the last laboratory for patients who died during the follow-up period) were used to calculate the follow-up-averaged UA (FA-UA) to represent the UA level more precisely for HD patients. Dietary protein intake was also estimated by using the normalized protein catabolic rate (nPCR) calculation from patient’s urea generation rate by urea kinetic modeling [26]. Single-pool model urea kinetics were used to estimate the nPCR. The Kt/V was calculated by the Daugirdas method [27]. Postdialysis blood urea nitrogen from the same dialysis session was used to calculate the delivered dose of dialysis (Kt/V) during a treatment session.

Statistical analysis
Data were summarized as mean ± SD. Student’s t-test was used to analyze the differences between two mean values. A linear regression analysis was performed to elucidate the associations between FA-UA level and each variable. The strength of the linear correlation between FA-UA and LVH was tested by Pearson’s correlation coefficient. Categorical data were compared between groups by the chi-square test. To compare the characteristics according to FA-UA level, participants were stratified into three groups of FA-UA levels as follows: FA-UA <400 μmol/L (low FA-UA group), FA-UA 400–450 μmol/L (intermediate FA-UA group) and FA-UA >450 μmol/L (high FA-UA group). The intermediate FA-UA group patients served as the reference group. The groups were compared using analysis of variance. Survival curves were assessed using Kaplan–Meier analysis (logrank test) to explore the association between all-cause and CV mortality across three FA-UA categories. Analysis of the receiver operating characteristic (ROC) curves and the area under the ROC curves (AUC) was performed to evaluate the FA-UA levels as a predictor of all-cause mortality in the study populations. To calculate the relative risk of death, hazard ratios (HRs) and 95% confidence intervals (CIs) were obtained by Cox proportional hazards models. The odds ratios (ORs) and their 95% CIs of the risk of LVH according to the three groups of FA-UA levels were calculated by logistic regression, having the intermediate FA-UA group as a reference. Data were adjusted for age and gender, then for age, gender, diabetes and CV diseases. P-values <0.05 were considered statistically significant. SPSS statistical software (version 14.0; SPSS, Chicago, IL, USA) was used for the analysis.

RESULTS
The baseline characteristics of the study population are shown in Table 1. The mean baseline UA level was 414 ± 89 μmol/L and the mean 5-year FA-UA level was 425 ± 59 μmol/L (range 294–620; in our laboratory, the normal value of UA is 150–450 μmol/L). In our study we used the FA-UA to represent the UA level in HD patients. Figure 1 reveals FA-UA as approximately normally distributed, with a mean of 424.0 μmol/L. The mean FA-UA level in male patients (431 ± 58 μmol/L) was higher than that in female patients (415 ± 60 μmol/L, P = 0.048). Patients with diabetes and CVD had significantly lower FA-UA than patients who did not have diabetes and CVD (393 ± 54 μmol/L, P = 0.000; 411 ± 59 μmol/L versus 431 ± 59 μmol/L, P = 0.000).

The FA-UA level of patients with atherosclerotic events (coronary heart disease, cerebrovascular disease and peripheral vascular disease) was compared with that of patients who did not have the condition. A statistically significant difference (present versus absent) was found for coronary heart disease (416 ± 57 versus 441 ± 59 μmol/L, P = 0.002) and peripheral vascular disease (411 ± 61 versus 435 ± 56 μmol/L, P = 0.002), but not for cerebrovascular disease (421 ± 58 versus 426 ± 59 μmol/L, P = 0.616).

Linear regression analysis showed that FA-UA showed a significant positive association with BMI, hemoglobin, creatinine, nPCR, length of HD in hours, ultrafiltration and phosphorus but was negative with age, LDL, BNP and LVH (the table is not shown). Of the patients stratified into three groups, 87 patients (38.7%) were in the low, 67 (29.8%) in the intermediate and 71 (31.6%) in the high FA-UA group. The characteristics of the whole cohort and comparisons across the three FA-UA groups are summarized in Table 2. As the FA-UA level decreased, the participants were older. The low FA-UA level was significantly associated with the lower BMI, nPCR and hemoglobin and higher LDL cholesterol versus the high FA-UA level, but also with lower serum phosphorus and albumin levels and higher CRP versus the intermediate FA-UA level. Ultrafiltration increases with increasing FA-UA levels. Patients in the low FA-UA

Table 1. Clinical and laboratory parameters of the study population

| Parameters          | Mean ± SD     | Range          |
|---------------------|---------------|----------------|
| Age (years)         | 48.9 ± 15.1   | 17–81          |
| Gender (male/female) | 133/90        | –              |
| Diabetes, %         | 38 (17.0)     | –              |
| CVD, %              | 57 (30.8)     | –              |
| HD vintage (months) | 106 ± 72      | 3–311          |
| BMI (kg/m²)         | 24.0 ± 4.3    | 16.2–45.8      |
| SBP (mmHg)          | 136 ± 23      | 84–198         |
| DBP (mmHg)          | 81 ± 15       | 40–120         |
| PP (mmHg)           | 55 ± 15       | 24–106         |
| Hemoglobin (g/L)    | 106.9 ± 12.7  | 62–138         |
| Single-pool Kt/V    | 1.24 ± 0.21   | 0.73–1.76      |
| Follow-up UA (μmol/L) | 425 ± 59     | 294–620        |
| Urea (mmol/L)       | 29.2 ± 3.6    | 17.8–39        |
| Creatinine (μmol/L) | 919.9 ± 203.9 | 450–1670       |
| Albumin (g/L)       | 38.5 ± 3.2    | 26.7–46.9      |
| PCR (g/kg/day)      | 1.03 ± 0.14   | 0.58–1.43      |
| iPTH (pg/mL)        | 216.5 ± 231.1 | 15–1670        |
| HDL cholesterol (mmol/L) | 0.99 ± 0.27  | 0.4–1.80       |
| LDL cholesterol (mmol/L) | 2.66 ± 0.87  | 1.2–7.8        |
| Calcium (mmol/L)    | 2.29 ± 0.14   | 1.89–2.71      |
| Phosphorus (mmol/L) | 1.50 ± 0.34   | 0.63–2.7       |
| Potassium (mmol/L)  | 5.99 ± 0.60   | 4.4–8.0        |
| BNP (pg/mL)         | 1321 ± 1366   | 109.7–8237.6   |
| LVMI (g/m²)         | 138.4 ± 49.7  | 54–438         |
| CRP (mg/L)          | 15.9 ± 23.8   | 0.35–117       |
group had significantly lower creatinine and length of HD but higher LVMI compared with patients in the intermediate and high groups. With regards to BNP in the three groups of FA-UA there was borderline significance.

**Serum FA-UA and mortality**

Of the 225 HD patients during the 5-year follow-up, 81 patients died (36%) and the main causes of death were CV related [57 patients (70%)]. The FA-UA level of survivors ($432 \pm 58 \mu mol/L$)
was higher than that of those who died of all-cause (410 ± 59 μmol/L) and CV causes (407 ± 59 μmol/L) and the difference was statistically significant (P = 0.009 and P = 0.005). But this difference was not statistically significant in terms of baseline UA level (survivors versus died of all-cause and CV causes, 418 ± 95 versus 407 ± 78 and 401 ± 81; P = 0.371 and P = 0.230).

Patients with FA-UA <400 μmol/L had a significantly higher all-cause (logrank, P = 0.003) and CV mortality (logrank, P = 0.004) rate compared with those with FA-UA 400–450 μmol/L and FA-UA >450 μmol/L (Figure 2). The AUC in the ROC was 0.61 (95% CI 0.53–0.68). The cut-off point for FA-UA as a predictor of the 5-year all-cause mortality according to the ROC curve was 379.5 μmol/L (the figure is not shown). When compared with the reference group, the HR for all-cause mortality was 1.75 (95% CI 1.02–2.98, P = 0.041) in the low FA-UA group, but there was no significant association with the high FA-UA group. In contrast, FA-UA did not show an association with CV mortality with the low or the high FA-UA group (Table 3).

Serum FA-UA and LVH

Mean LVMI was 138.4 ± 49.7 g/m² (123.2 ± 42.9 for women and 147.5 ± 51.5 for men). FA-UA showed a significant negative association with LVH (R² = 0.069, β = −0.233, β = −0.262, P = 0.001) (Figure 3). The mean FA-UA level in patients with LVH (417 ± 54 μmol/L) was lower than in those without LVH (448 ± 56 μmol/L, P = 0.000). Compared with patients without

|                | HR  | 95% CI     | P-value |
|----------------|-----|------------|---------|
| All-cause mortality |     |            |         |
| FA-UA 400–450 μmol/L (reference) |   | | |
| FA-UA <400 μmol/L versus 400–450 μmol/L | 1.75 | 1.02–2.98 | 0.041 |
| FA-UA >450 μmol/L versus 400–450 μmol/L | 0.85 | 0.51–1.75 | 0.276 |
| CV mortality |     |            |         |
| FA-UA 400–450 μmol/L (reference) |   | | |
| FA-UA <400 μmol/L versus 400–450 μmol/L | 1.45 | 0.79–2.64 | 0.222 |
| FA-UA >450 μmol/L versus 400–450 μmol/L | 0.61 | 0.28–1.31 | 0.200 |

Table 3. HR (95% CI) of all-cause and CV mortality

FIGURE 2: Kaplan–Meier survival curves for all follow-up study patients according to low, intermediate and high FA-UA groups: (A) all-cause and (B) CV mortality.

FIGURE 3: Correlation between serum FA-UA and LVH.
LVH, patients with LVH were older (42.0 ± 13.2 versus 49.5 ± 14.5, P = 0.000) and with lower BMI (24.9 ± 4.4 versus 23.3 ± 3.8, P = 0.013), length of HD (4.1 ± 0.2 versus 4.0 ± 0.2 h, P = 0.008), ultrafiltration (3.5 ± 0.8 versus 3.1 ± 0.8, P = 0.000), hemoglobin (111.7 ± 8.8 versus 107.1 ± 11.9 g/L, P = 0.011), creatinine (104.1 ± 200.8 versus 904.5 ± 175.4 µmol/L, P = 0.000) and albumin levels (39.7 ± 2.4 versus 38.4 ± 3.3 g/L, P = 0.005), but higher SBP (129 ± 21 versus 139 ± 21 mmHg, P = 0.001), DBP (79 ± 14 versus 88 ± 15 mmHg, P = 0.024), PP (50 ± 12 versus 55 ± 14 mmHg, P = 0.011), BNP (1027 ± 1616 versus 2136 ± 3744 pg/mL, P = 0.000) and CRP (9.2 ± 15.4 versus 14.0 ± 16.1 mg/L, P = 0.034) (the table is not shown).

Table 4 shows the OR for the risk of LVH in the lowest and highest tertiles of FA-UA compared with the intermediate FA-UA. In unadjusted analysis, the OR for the risk of LVH in the low FA-UA group compared with the intermediate group was 3.11 (95% CI 1.38–7.05, P = 0.006). After adjusting for age and gender, then by entering diabetes and CV diseases, the OR for LVH remained significant only in the low FA-UA group compared with the intermediate group [OR 3.02 (95% CI 1.29–7.05), P = 0.011 and OR 2.82 (95% CI 1.16–6.88), P = 0.23] (Table 4).

**DISCUSSION**

In this 5-year follow-up study we found an inverse association between UA and all-cause mortality in 225 prevalent HD patients and for the first time it was demonstrated that hypouricemia is associated with LVH in this cohort.

Initially, in our study, we explored the relationship between the FA-UA level and mortality in 225 prevalent HD patients. Until now, in most studies, elevated serum UA levels were associated with lower all-cause and/or CV mortality [11, 12, 15, 18, 28–30], however, some studies reported either increased or no difference [16, 17] in mortality. The principal finding of our results was that when compared with the reference group (FA-UA 400–450 µmol/L), the HR for all-cause mortality was 1.75 in the low FA-UA group, but there was no significant association with the high FA-UA group. In contrast, FA-UA did not show an association with CV mortality in either the low or high FA-UA group. In the ROC curve analysis, FA-UA with a cut-off point of 379.5 µmol/L was identified as a predictor of all-cause mortality, but we think that further analysis with higher sensitivity and specificity may yield better results.

In HD patients, the physiology of UA and its clinical impact is very different from the other types of renal replacement therapy. In HD patients, there is no universally accepted definition of hyperuricemia, so UA levels have a wide range and are significantly different among studies. In our study, the mean FA-UA level was 425 ± 59 µmol/L (range 294–620), and it is quite similar to the value of the Dialysis Outcomes and Practice Patterns Study [11]. Most studies in which elevated serum UA levels were associated with lower mortality relied on the pre-HD serum concentration of UA obtained as a single and baseline measurement of UA. One of the important differences in our study is that we used repeated measurement of UA at regular monthly intervals during the follow-up period. However, the time-averaged UA concentrations, i.e. pre- and post-HD measurements, might be the best predictors of clinical outcomes [31], but the validity of such analyses is still unclear, because the rate of UA rebound after HD has not been evaluated.

It has already been confirmed that UA is a good marker of nutrition in HD patients. In line with previous studies [11, 12, 18, 30], we also found that a high UA level is related to higher nPCR, serum levels of creatinine, phosphorus and albumin and greater BMI. The additional significant finding in our study is that, in the survivor patients, there was an increase in serum UA levels from 418 when analyzing only at the baseline level to 432 µmol/L as a result of FA-UA levels. This finding suggests that higher FA-UA levels relative to lower baseline serum UA levels in the survivor patients may be a result of improvement in nutritional status in HD patients. Beberashvili et al. [30] also showed that the longitudinal increase in UA levels over time in HD patients is accompanied by an improvement in nutritional status and lower mortality rates. However, nutritional features of serum UA warrant additional studies, especially after the results of the study of Park et al. [28], where hypouricemia showed a higher mortality risk among incident dialysis patients with low nPCR but not among those with high nPCR. It is known that uremic malnutrition, i.e. ‘protein-energy wasting’, is a very common condition in HD patients, and the question is whether UA belongs to the group of CV risk factors that are paradoxically associated with the outcome in HD patients, such as low BMI and hypcholesterolemia [32].

The link between UA and inflammation in the HD population has not been sufficiently investigated and is still controversial. In a study with an incident HD population, UA was positively associated with serum CRP levels [33], while a retrospective longitudinal study did not observe any association between UA and CRP levels over time [30]. Our study did not find a direct correlation between FA-UA and CRP, but in the grouping analysis we observed that patients in the low FA-UA group had a significantly higher CRP compared with patients in the intermediate and high FA-UA group.

Although this study showed that patients with coronary heart disease and peripheral vascular disease, as well as those who died of CV causes, had significantly lower FA-UA levels, there was no association between serum UA level and CV mortality in the survival analysis. An interesting finding of this study is that contrary to the serum FA-UA, when only the baseline value of UA was analyzed, there was no statistically significant difference between survivors and those who died of all-cause and CV causes. This result confirms the speculation that UA-mediated biological effects are dependent upon the uremic
milieu in HD patients. However, our prevalent cohort was exposed to a very different time period from the initiation of HD to start of the follow-up period. All of this also limits the possibility of analyzing the impact of the HD milieu on changes in UA over time, due to the presence of the temporal bias of this prevalent cohort. Future studies with incident patients may clarify this phenomenon, that is, changes in UA levels over time from the initiation of HD versus baseline levels.

The strength of this study is our finding showing that hyperuricemia is associated with LVH in HD patients, which has not been studied until now, so it is difficult to make a comparative analysis with other studies. It is known that ~70% of patients who start dialysis have LVH [34] and many risk factors are involved in the progression of this condition, such as age, gender, race, diabetes, primary renal disease, BMI, dialysis vintage, hypertension, anemia, inflammation, interdialytic weight gain, left ventricular volume overload and type of vascular access [35–38]. In the last decade, numerous cross-sectional clinical studies in the general population have investigated the association between UA and LVH, with controversial results [19, 20].

Recently, Cuspidi et al. [22] in a 10-year follow-up study, found that each 1 mg/dL increase in UA produced a 26% higher risk of incident LVH in subjects of the general population.

To the best of our knowledge, no information is available from previous studies about the association between UA and LVH in HD patients. Our results showed a significant negative association between LVH and FA-UA and also showed that each 1 mg/dL increase in UA produced a 26% higher risk of incident LVH in subjects of the general population.

In summary, our study shows that prolonged exposure to hyperuricemia is not only associated with higher mortality, but also with LVH in HD patients. This unexpected paradoxical association can only be explained by the hypothesis that the uremic milieu in HD patients changes the influence of UA. However, these results do not prove causality, only association, and should be the subject of further research.
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