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Serum uric acid predicts cardiovascular mortality in male peritoneal dialysis patients with diabetes

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Abstract *Background and aims:* Serum uric acid may predict mortality in diabetic patients and dialysis patients. However, the relationship between serum uric acid and prognosis in diabetic peritoneal dialysis (PD) patients is unclear.
Methods and results: We conducted a cohort study of 1278 incident PD patients, (mean age 47.6 years), of which 328 (25.7%) had diabetes and 289 (22.6%) had diabetic nephropathy. During a median follow-up period of 30.7 months, 231 deaths occurred, of which 126 were ascribed to cardiovascular events. Mean serum uric acid was lower for diabetic patients than non-diabetic patients (6.8 ± 1.3 *vs.* 7.4 ± 1.4 mg/dL, respectively; $P < 0.001$). Cox regression models were adjusted for glycated hemoglobin, dialysis-related factors, traditional risk factors, and treatments. After adjustments, the highest sex-specific tertile of uric acid was associated with an increased risk of cardiovascular mortality (HR, 2.26; 95% CI, 1.14–4.48) compared to the lowest tertile in diabetic patients. Adjusted HRs per 1 mg/dL higher uric acid for all-cause and cardiovascular mortality were 1.09 (95% CI, 0.91–1.32) and 1.42 (95% CI, 1.13–1.79) for diabetic men and 1.06 (95% CI, 0.83–1.35) and 1.12 (95% CI, 0.78–1.61) for diabetic women, respectively. Elevated serum uric acid predicted a higher risk of all-cause and cardiovascular mortality in non-diabetic men but not in non-diabetic women.
Conclusions: Elevated serum uric acid is an independent predictor of cardiovascular mortality in diabetic male PD patients.

Introduction

Diabetes mellitus is the leading cause of end stage renal disease (ESRD) in many developed countries and the second most common cause in China [1–3]. The survival rate for diabetic dialysis patients remains much lower than that for non-diabetic dialysis patients [1,4]. Nearly 40% of all deaths in patients with ESRD are due to cardiovascular (CV) diseases [5].

Studies have found that elevated serum uric acid is a potential risk factor for all-cause or CV mortality in patients with diabetes, albeit with conflicting results [6–8]. Similarly, many [9–13], but not all observational studies

Acronyms: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; CV, cardiovascular; ESRD, end stage renal disease; PD, peritoneal dialysis.

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[14,15], found that an elevated serum uric acid was a predictor of all-cause or CV mortality in dialysis patients. However, very few studies have examined the association in diabetic dialysis patients, who constitute a high-risk population. Moreover, the presence of diabetes may modify the predictive role of serum uric acid in dialysis patients. One study demonstrated that elevated serum uric acid was associated with higher all-cause mortality in diabetic hemodialysis patients but not in non-diabetes [16], but another study showed that the prognostic value of serum uric acid in CV and all-cause mortality was weaker for diabetic PD (peritoneal dialysis) patients than for non-diabetes [12]. In our previous study of PD patients, we found that serum uric acid was a predictor of all-cause and CV mortality in men only [13]. Yet another study of overweight/obese individuals, 83.6% of which had diabetes, found an independent association between serum uric acid and mortality in women only [17]. However, no published research has reported the impact of gender on the association between serum uric acid level and mortality in diabetic dialysis patients.

In this study, we examined the association between serum uric acid levels and all-cause and CV mortality in PD patients separately for diabetic and non-diabetic patients and for men and women, accounting for detailed confounding factors.

Methods

Study sample

From January 1, 2006 to December 31, 2011, 1278 consecutive PD patients were recruited from The First Affiliated Hospital of Sun Yat-sen University. The inclusion criteria were all incident patients aged 18–80 years who had received continuous ambulatory peritoneal dialysis for more than 3 months. Patients who had malignant diseases or refused to give written consent were excluded. The study protocol was approved by the Clinical Research Ethics Committee of The First Affiliated Hospital of Sun Yat-sen University, and all enrolled patients provided informed consent.

Baseline investigations

Baseline data were collected within 3 month of the initiation of PD. Patients who reported use of insulin or oral hypoglycemic agents or who had a clinical diagnosis of type 1 or type 2 diabetes mellitus before starting PD were evaluated and those meeting the American Diabetes Association's diagnostic criteria were considered to have diabetes [18]. Renal biopsy was not routinely performed on diabetic patients with renal abnormalities except where we suspected non-diabetic renal diseases [19]. Thus, the diagnosis of diabetic nephropathy was based mainly on clinical experience. CV disease was defined as including coronary heart disease, myocardial infarction, angioplasty, coronary artery bypass, heart failure, or stroke. Laboratory measurements including serum uric acid were obtained using standard methods in the clinical laboratory of The First Affiliated Hospital of Sun Yat-sen University. Residual renal function and total Kt/V were calculated using PD Adequest software 2.0 (Baxter, Deerfield, IL). Residual renal function, in mL/min/1.73 m^2, was estimated from mean values of creatinine clearance and urea clearance and adjusted for body surface area calculated with the Gehan and George equation [20]. Medicine use was recorded based on prescriptions. The patients returned to our center for quarterly evaluation, and trained nurses interviewed the patients by telephone monthly to assess general conditions.

Study outcome

The primary outcome was all-cause mortality, and the secondary outcome was CV mortality. CV events contributing to CV mortality included acute myocardial infarction, cardiac arrhythmia, cardiac arrest, congestive heart failure, cerebrovascular accident, and peripheral vascular disease. If a patient died in any hospital, the death certificate was referred to for the exact cause of death. For out-of-hospital deaths, experts reached a consensus about the cause of death after a comprehensive review of the patient's medical records and descriptions provided by the patient's general practitioner. In this cohort, 160 of 231 (69%) patients died in hospitals. All patients were followed until death, transfer to hemodialysis therapy, kidney transplantation, transfer of care from our center, or censoring on June 30, 2013.

Statistical analysis

Participants were stratified into tertiles of serum uric acid levels, which were calculated separately in diabetic men (tertile 1 [lowest], <6.46; tertile 2 [middle], 6.46–7.38; and tertile 3 [highest], ≥7.38 mg/dL), diabetic women (tertile 1, <5.89; tertile 2, 5.89–7.09; and tertile 3, ≥7.09 mg/dL, respectively), non-diabetic men (tertile 1, <7.00; tertile 2, 7.70–7.89; and tertile 3, ≥7.89 mg/dL), and non-diabetic women (tertile 1, <6.46; tertile 2, 6.46–7.48; and tertile 3, ≥7.48 mg/dL). Summary statistics by sex-specific tertiles of the uric acid level were presented as mean ± standard deviation for approximately normally distributed variables, percentages for categorical data, and median (interquartile range) for skewed variables. Baseline characteristics across uric acid sex-specific tertiles were compared using the χ^2 test for categorical variables, analysis of variance for approximately normally distributed variables, and the Kruskal–Wallis test for skewed variables. Serum uric acid level was analyzed as a continuous variable with hazard ratios (HRs) presented per 1 mg/dL greater and a categorical variable with HRs presented by stratification of tertiles in Cox regression models to evaluate the relationship between uric acid levels and all-cause and CV mortality. Multivariate models included eligible covariates that demonstrated significant or near-significant association with mortality ($P < 0.2$) on bivariable analysis or for clinical significance. The association between sex and serum uric acid levels was examined