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Association between serum uric acid level and renal arteriolar hyalinization in individuals without chronic kidney disease

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ABSTRACT

Background and aims: Recent studies have reported an association between serum uric acid (SUA) and renal arteriolar changes in patients with chronic kidney disease (CKD). However, the association in individuals without CKD remains unclear. In this study, we investigated the relationship between SUA and renal arteriolar lesions in individuals without CKD from our living kidney donor cohort.

Methods: Between January 2006 and May 2016, 393 living kidney donors underwent "time-zero" biopsy at Kyushu University Hospital. Patients were divided into sex-specific quartiles of SUA before donation: Q1, Q2, Q3, and Q4 (male: <5.2,5.2–5.8,5.9–6.4, and ≥6.5 mg/dL, female: <3.8,3.8–4.3,4.4–5.0, and ≥5.1 mg/dL). Renal arteriolar hyalinization and wall thickening were assessed using a semiquantitative grading system. Predictive performance was compared between models with and without SUA by calculating the net reclassification improvement (NRI).

Results: In total, 158 (40.2%) patients had arteriolar hyalinization, and 148 (37.6%) had wall thickening. High SUA was significantly associated with arteriolar hyalinization in multivariable logistic analysis (odds ratio [OR] per 1-mg/dL increase in SUA, 1.24; 95% confidence interval [CI], 1.00–1.53; $p = 0.048$. OR for Q4 *vs.* Q2, 2.22; 95% CI, 1.17–4.21; $p = 0.01$). We found no association between SUA and wall thickening. When SUA was incorporated into a predictive model with conventional atherosclerotic factors, the NRI was 0.21 ($p = 0.04$).

Conclusions: High SUA was an independent risk factor for arteriolar hyalinization in individuals without CKD. SUA provided additional predictive value beyond conventional atherosclerotic factors in predicting arteriolar hyalinization.

1. Introduction

Increasing evidence suggests that high serum uric acid (SUA) is a significant risk factor for several clinical conditions in the general population, including hypertension [1,2], cardiovascular disease [3,4], and chronic kidney disease (CKD) [5,6]. Furthermore, high SUA is associated with atherosclerotic changes, namely coronary atherosclerosis [7,8], carotid atherosclerotic plaques [9], increased carotid intima-media thickness [10,11], atrial stiffness [12], and cardio-ankle vascular index [13]. Several studies also demonstrated an association between SUA and microvascular diseases. In patients with type 2 diabetes mellitus, high SUA is associated with worsening of peripheral neuropathy [14], retinopathy [15,16], and nephropathy [17,18], which are typical findings associated with microangiopathy. A recent renal biopsy-based clinicopathological study showed that a high level of SUA was associated with renal arteriolar hyalinization and arteriolar wall thickening in patients

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with various glomerular and tubulointerstitial diseases [19]. These studies indicate that SUA plays an important role in the progression of microvascular lesions in patients with diabetes mellitus and CKD. However, diabetes mellitus and CKD themselves can influence the progression of microvascular changes. Therefore, the pathological mechanisms in these patient populations may differ from those in the general population. To determine the specific effects of uric acid on microvascular injuries, studies of the general population are required. Further understanding of the effects of high SUA levels on subclinical microvascular damage could improve therapeutic strategies for reducing microvascular injury in the general population.

In both living- and deceased-donor kidney transplantation (KT), many transplant centers perform a wedge biopsy ("time-zero" biopsy) of the donated kidney during transplant surgery to investigate baseline pathological changes. In living-donor KT, patients with CKD are excluded as donor candidates. Therefore, time-zero biopsy provides a unique and valuable opportunity to observe kidney morphology in individuals without CKD. We hypothesized that observations from time-zero biopsies would further clarify the relationship between SUA and microvascular damage.

In the present study, we examined the relationship between SUA and renal pathological changes, especially microvascular changes, in our time-zero biopsy-based cohort of individuals without CKD.

2. Patients and methods

2.1. Study design and population

This was a cross-sectional study of individuals who donated a kidney for living-donor KT at Kyushu University Hospital, from January 2006 to May 2016. During the study period, we performed 623 living-donor KTs; time-zero biopsy was not performed in 106 donors because of factors such as bleeding tendency, the use of antiplatelet therapy, or capsular injury of the donated kidney. Sixty-five donors were excluded because of inadequate biopsy samples containing fewer than 10 glomeruli. Another 59 donors were excluded because relevant laboratory findings were missing. The remaining 393 donors were enrolled in this study. This study was performed in adherence to the guidelines of the Declaration of Helsinki. The study protocol was approved by the Human Ethics Committee of Kyushu University Hospital (protocol #24–54). The ethics committee of all participating institutions granted approval to waive the requirement for written informed consent because of the retrospective nature of the study, and the database was accessed for analytical purposes only. Researchers did not access the personal information of patients.

2.2. Pathological interpretation of time-zero biopsies

Wedge biopsy samples were obtained from the outer cortex of donated kidneys during bench surgery. The samples were fixed in formalin solution and then embedded in paraffin. Next, 2-μm sections of the samples were stained with hematoxylin and eosin, periodic acid-Schiff (PAS), methenamine silver, and Masson trichrome staining. Atherosclerotic changes in the renal biopsy samples were evaluated, namely % global glomerulosclerosis (%GGS), arteriolar hyalinization, and wall thickening. Light microscopy was used to determine %GGS. Pathological changes of arterioles were evaluated semiquantitatively with the grading system reported by Kohagura et al. [19]. Arteriolar hyalinization was scored as follows: no PAS-positive hyaline deposit, Grade 0 (G0); hyaline deposit <25% of the circumference, Grade 1 (G1); hyaline deposit between 25% and 50% of the circumference, Grade 2 (G2); and hyaline deposit >50% of the circumference, Grade 3 (G3). Based on these findings, the arteriolar hyalinization index was calculated for each patient as the mean grade of renal arteriolar hyalinization according to the following formula: arteriolar hyalinization index = $(n0 \times 0 + n1 \times 1 + n2 \times 2 + n3 \times 3)/N$. Here, n0, n1, n2, and n3 indicate the number of arterioles with hyalinization scores of G0–G3, respectively, and N indicates the total number of arterioles. Arteriolar wall thickening was defined as follows: no thickening, Grade 0 (G0); mild thickening, Grade 1 (G1); moderate thickening without definite narrowing of the lumen, Grade 2 (G2); and severe thickening with definite narrowing of the lumen, Grade 3 (G3). Based on these findings, the arteriolar wall thickening index was calculated for each patient as the mean grade of renal arteriolar wall thickening according to the following formula: arteriolar wall thickening index = $(n0 \times 0 + n1 \times 1 + n2 \times 2 + n3 \times 3)/N$. Here, n0, n1, n2, and n3 indicate the number of arterioles with wall thickening scores of G0–G3, respectively, and N indicates the total number of arterioles. Each biopsy specimen was evaluated by two observers (AT and KM), who were blinded to the donors' clinical data.

2.3. Covariates

Information regarding medical history, current medications, and smoking habits was obtained from each donor before kidney donation. No donor was a current smoker at the time of surgery; therefore, donors were classified as past smokers or non-smokers. Baseline clinical data were collected from medical records. Hypertension was defined as blood pressure ≥140/90 mmHg or current use of antihypertensive agents. Diabetes mellitus was defined as fasting blood glucose concentration ≥126 mg/dL, hemoglobin A1c ≥ 6.5%, and/or current use of oral glucose-lowering agents. In donors whose hemoglobin A1c was measured according to the Japanese Diabetes Society Japanese Society of Clinical Chemistry guidelines, the values were standardized by adding 0.4% to the estimate to obtain the National Glycohemoglobin Standardization Program equivalent value [20]. Dyslipidemia was defined as total cholesterol ≥220 mg/dL or the use of lipid-modifying agents. Hyperuricemia was defined as an SUA concentration ≥7.0 mg/dL in males and ≥6.0 mg/dL in females. Obesity was defined as body mass index (BMI) ≥25 kg/m^2. SUA and serum creatinine (SCr) levels were measured with enzymatic assays. Because all donors were 18 years or older, estimated glomerular filtration rate (eGFR) was calculated using the following Chronic Kidney Disease Epidemiology Collaboration equation with a Japanese coefficient of 0.813 [21]: eGFR (mL/min/1.73 m^2) = $0.813 \times 141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{Age}$ (if female, × 1.018), where SCr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min (SCr/κ, 1) indicates the minimum of SCr/κ or 1, and max (SCr/κ, 1) indicates the maximum of SCr/κ or 1.

2.4. Statistical analyses

In the present donor population, serum SUA levels between males and females differed significantly (males: 5.8 ± 1.2 mg/dL *vs.* females: 4.4 ± 1.0 mg/dL, $p < 0.001$). Therefore, the study population was divided into four groups according to sex-specific quartiles of SUA level: Quartile 1 (Q1), male, SUA <5.2 mg/dL, female, <3.8 mg/dL; Q2, male, SUA 5.2–5.8 mg/dL, female, SUA 3.8–4.3 mg/dL; Q3, male, SUA 5.9–6.4 mg/dL, female, SUA 4.4–5.0 mg/dL; and Q4, male, SUA ≥6.5 mg/dL, female, SUA ≥5.1 mg/dL. Data are presented as mean ± standard deviation, median and interquartile range, or percentage for categorical variables, as appropriate. To evaluate trends in continuous and categorical values across the quartiles of SUA, we used the Jonckheere-Terpstra and Cochran-Armitage tests, respectively. Furthermore, we tested the