Serum Uric Acid Levels and Nephrosclerosis in a Population-Based Autopsy Study: The Hisayama Study

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Keywords

Uric acid · Nephrosclerosis · Autopsy · Population-based study

Abstract

Introduction: Information regarding the influence of serum uric acid (SUA) levels on pathological changes in the kidney is limited. In this study, we examined the association between SUA levels and pathological findings of nephrosclerosis in population-based autopsy samples. **Methods:** A total of 923 deceased individuals in a Japanese community underwent autopsy examinations between 1974 and 1994. Of these, 547 individuals with available kidney tissues and health examination data within a median of 3 years before death were eligible for the present study. SUA levels were categorized into quintiles (Q1, 107–237; Q2, 238–279; Q3, 280–326; Q4, 327–380; Q5, 381–755 $\mu\text{mol/L}$). Advanced degrees of glomerular sclerosis, kidney arteriolar hyalinosis, and kidney arteriosclerosis were defined as the 90th percen-

tile or more of a glomerular sclerosis index and an arteriolar hyalinosis index, and the 10th percentile or less of a wall-lumen ratio, respectively. A logistic regression model was used to evaluate odds ratios (ORs) and their 95% confidence intervals (CIs) of SUA levels on each kidney lesion. **Results:** Higher SUA levels were significantly associated with higher values of the age- and sex-adjusted glomerular sclerosis index and lower values of the wall-lumen ratio (both p for trend <0.01). Individuals in the Q5 group had a significantly greater likelihood of advanced glomerular sclerosis (OR 7.19, 95% CI 2.42–21.38) and advanced kidney arteriosclerosis (OR 5.28, 95% CI 1.77–15.80) than individuals in the Q1 group after adjusting for potential covariates. There was no evidence of significant associations of SUA levels with either the arteriolar hyalinosis index or the presence of advanced arteriolar hyalinosis. **Conclusions:** Elevated SUA levels were significantly associated with advanced glomerular sclerosis and advanced kidney arteriosclerosis, but not with advanced arteriolar hyalinosis in community-based autopsy samples of Japanese.

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Introduction

Nephrosclerosis is one of the underlying diseases of chronic kidney disease (CKD), which is pathologically characterized by the sclerosis of kidney arterioles and small arteries [1]. The vascular changes cause the glomerulosclerosis and subsequently kidney failure [1]. Therefore, it is important to identify the risk factors for nephrosclerosis in order to prevent the deterioration of kidney function.

Several epidemiological studies have shown that elevated serum uric acid (SUA) levels are significantly associated with the development of CKD [2–4]. Hospital-based pathological studies with kidney biopsy samples have reported a significant association between SUA levels and pathological changes of nephrosclerosis among CKD patients with urinary abnormalities and kidney transplant donors [5, 6]. However, because the small tissues from kidney biopsies contain only limited numbers of glomeruli and vessels, autopsy samples are preferable for the assessment of glomeruli and vessels. In addition, any pathological changes in the kidneys of CKD patients with urinary abnormalities are likely to be affected by the primary disease. Therefore, the findings from a population-based autopsy study could provide valuable information on this research area. However, there have been few pathological studies investigating the risk factors for nephrosclerosis among community-dwelling populations [7–10].

The Hisayama Study is an ongoing community-based observational study of cardiovascular disease begun in 1961 in the town of Hisayama, a suburban community adjacent to Fukuoka city in Japan [11]. In conjunction with this study, autopsies have been performed among approximately 80% of deceased individuals in a community to determine the causes of deaths and evaluate pathological changes in various organs [9, 10, 12–17]. This study previously reported that cardiovascular risk factors such as aging, hypertension, prehypertension, glucose intolerance, and dyslipidemia are associated with pathological changes of nephrosclerosis [9, 10]. The present study aimed to examine the association between SUA levels and pathological changes of glomeruli and vessels using cross-sectional data from population-based autopsy cases.

Methods

Study Population and Autopsy

A total of 923 individuals underwent autopsy examinations among 1,146 deceased residents of all age-groups in the town of Hisayama from January 1974 to December 1994 (autopsy rate

80.5%). Among these consecutive autopsy individuals, 768 individuals had participated in at least one of the four health examinations in 1974, 1978, 1983, and 1988. At each of these examinations, the participation rate among Hisayama residents aged ≥ 40 years exceeded more than 80%. We excluded 92 individuals for whom kidney tissues were not available (e.g., those for whom kidney tissues were not preserved, those with degenerated or small kidney tissues, and those who underwent autopsy examination at other hospitals), 72 individuals who had no health examination data within 7 years before death, and 57 individuals who were missing health examination data. The remaining 547 individuals were included. The median period from the most recent health examination to death was 3 years.

Measurements of SUA Concentration

In this study, we used the data of SUA concentrations from the last health examination. Blood samples were collected after an overnight fast. SUA concentrations were measured using the phosphotungstic acid method in 1978, and the enzymatic method in 1983 and 1988. In 1974, SUA concentrations were probably measured by the phosphotungstic acid method used in most of Japan at that time, but no confirmatory information was available. Individuals were categorized into 5 groups according to the quintiles of SUA levels (Q1, 107–237; Q2, 238–279; Q3, 280–326; Q4, 327–380; Q5, 381–755 $\mu\text{mol/L}$). For the sensitivity analysis, individuals were categorized according to the sex-specific SUA quintiles (Q1, 107–261; Q2, 262–308; Q3, 309–350; Q4, 351–398; Q5, 399–684 $\mu\text{mol/L}$ for men; Q1, 137–213; Q2, 214–243; Q3, 244–285; Q4, 286–344; Q5, 345–755 $\mu\text{mol/L}$ for women).

Morphologic Examination of Kidney Tissue

The methods of morphologic examination of kidney tissue have been described in detail, elsewhere [9, 10]. Briefly, for light microscopic study, paraffin-embedded kidney tissues obtained by standard autopsy methods were cut at 2- μm thickness and stained with periodic acid-Schiff. The semiquantitative score was used to evaluate the severity of glomerular sclerosis by the method of Raij et al. [18]. Specifically, a score of 0 represented a complete absence of sclerotic lesion of the glomerulus, 1+ represented 1% to 25% involvement of sclerotic lesion of the glomerulus, and 2+, 3+, and 4+ represented 26%–50%, 51%–75%, and 76%–100% involvement of the glomerulus, respectively. The glomerular sclerosis index was calculated by the following formula: glomerular sclerosis index = $(n_0 \times 0 + n_1 \times 1 + n_2 \times 2 + n_3 \times 3 + n_4 \times 4)/4$, where the variables n_0 , n_1 , n_2 , n_3 , and n_4 indicate the number of glomeruli showing sclerotic lesion scores of 0 to 4+, respectively.

The severity of arteriolar hyalinosis was assessed semiquantitatively by the method of Bader et al. [19]. For each tissue specimen, 50 arterioles were examined and the severity of the lesion in each arteriole was graded from 1+ to 4+ according to the extent of arteriolar hyalinosis as follows: 1+, absence of any conspicuous alteration of the arteriolar wall; 2+, arteriolar wall hyalinosis comprising less than 50% of the arteriolar circumference; 3+, arteriolar wall hyalinosis of more than 50% but less than 100% of the arteriolar circumference; and 4+, hyalinization of the entire arteriolar wall. The arteriolar hyalinosis index was calculated by the following formula: arteriolar hyalinosis index = $(n_1 \times 1 + n_2 \times 2 + n_3 \times 3 + n_4 \times 4)/50$, where the variables n_1 , n_2 , n_3 , and n_4 indicate the number of arterioles showing hyalinosis scores of 1+ to 4+, respectively.

Table 1. Age- and sex-adjusted baseline characteristics according to the SUA levels

Characteristics	SUA, $\mu\text{mol/L}$					<i>p</i> value for trend
	quintile 1 107–237 (<i>n</i> = 106)	quintile 2 238–279 (<i>n</i> = 109)	quintile 3 280–326 (<i>n</i> = 113)	quintile 4 327–380 (<i>n</i> = 111)	quintile 5 381–755 (<i>n</i> = 108)	
Age at death, * years	76 $\pm$ 1.2	75 $\pm$ 1.1	76 $\pm$ 1.1	75 $\pm$ 1.1	73 $\pm$ 1.1	0.08
Men [†]	24	51	61	73	67	<0.001
Systolic blood pressure, mm Hg	142 $\pm$ 2.7	145 $\pm$ 2.6	148 $\pm$ 2.5	148 $\pm$ 2.6	149 $\pm$ 2.6	0.04
Diastolic blood pressure, mm Hg	78 $\pm$ 1.3	82 $\pm$ 1.2	80 $\pm$ 1.2	82 $\pm$ 1.3	82 $\pm$ 1.3	0.07
Antihypertensive agents	14	23	27	28	39	<0.001
Hypertension	56	63	64	67	73	0.003
Diabetes	18	12	13	17	16	0.83
Serum total cholesterol, mmol/L	4.6 $\pm$ 0.1	4.8 $\pm$ 0.1	4.8 $\pm$ 0.1	4.9 $\pm$ 0.1	4.9 $\pm$ 0.1	0.08
eGFR, mL/min/1.73 m ²	80 $\pm$ 1.2	78 $\pm$ 1.1	74 $\pm$ 1.1	69 $\pm$ 1.1	62 $\pm$ 1.1	<0.001
Proteinuria [‡]	12	14	13	18	20	0.15
BMI, kg/m ²	20.3 $\pm$ 0.3	20.4 $\pm$ 0.3	20.9 $\pm$ 0.3	21.2 $\pm$ 0.3	21.4 $\pm$ 0.3	0.003
ECG abnormalities	24	24	30	35	40	0.002
History of cardiovascular disease	9	11	14	15	24	0.004
Smoking habits	44	44	35	38	36	0.18
Alcohol intake	25	29	28	37	36	0.003

Data are presented as mean $\pm$ standard error or percentage. ECG, electrocardiogram; BMI, body mass index. * Adjusted for sex. [†] Adjusted for age at death. [‡] Proteinuria data were not available in 13 subjects.

The wall-lumen ratio was evaluated as the severity of kidney arteriosclerosis by the method of Kernohan et al. [20]. For each tissue specimen, all arteries with an outer diameter exceeding 60 μm were examined using an eyepiece micrometer. The outer diameter and the lumen diameter of least axis of the elliptic profile were directly measured. The wall-lumen ratio was calculated in each artery as lumen diameter/([outer diameter–lumen diameter]/2), and the mean value among all arteries in each individual was used as the index of kidney arteriosclerosis. A small wall-lumen ratio indicates progressive narrowing of the vessel lumen.

The cutoff limits for the advanced degree of each lesion were defined as the 90th percentile value for the glomerular sclerosis index and arteriolar hyalinosis index and the 10th percentile value for the wall-lumen ratio; that is, advanced glomerular sclerosis, advanced arteriolar hyalinosis, and advanced kidney arteriosclerosis were defined as a glomerular sclerosis index >28.0, an arteriolar hyalinosis index >1.70, and a wall-lumen ratio <2.18, respectively.

Measurements of Other Risk Factors

Details of the measurement of the other risk factors are provided in the online supplementary materials (for all online suppl. material, see www.karger.com/doi/10.1159/000521426).

Statistical Analysis

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Two-tailed *p* < 0.05 was considered significant in all analyses. Trends in the means and the frequencies of risk factors across the quintiles of SUA levels were tested by a linear and a logistic regression analysis, respectively.

The glomerular sclerosis index, arteriolar hyalinosis index, and wall-lumen ratio were log-transformed to remove skewness. The trends in the age- and sex-adjusted means of the glomerular sclerosis index, arteriolar hyalinosis index, and wall-lumen ratio across the quintiles of SUA levels were tested by a linear regression analysis, and differences in the values among SUA levels were tested using the Dunnett's *t* test. The similar analysis was performed for eGFR and systolic blood pressure as for SUA. The age- and sex-adjusted or multivariate-adjusted odds ratios (ORs) and 95% confidence intervals were calculated by a logistic regression analysis. Clinically or biologically plausible risk factors for atherosclerosis – namely, age at death, sex, systolic blood pressure, the use of antihypertensive agents, diabetes, serum total cholesterol, body mass index, electrocardiogram abnormalities, history of cardiovascular disease, smoking habits, and alcohol intake – were included in the multivariable-adjusted model. eGFR was not included in the multivariable-adjusted model, since the reduced kidney function was the result, not the cause, of glomerular sclerosis and vascular changes. For advanced kidney arteriosclerosis, the outer diameter was also adjusted to account for the effect of the outer diameter on the wall-lumen ratio. We used restricted cubic splines to show the shape of associations between SUA levels and each advanced lesion with 4 knots placed at the 5th, 35th, 65th, and 95th percentiles of SUA levels (184, 268, 333, and 464 $\mu\text{mol/L}$, respectively); 238 $\mu\text{mol/L}$ (= 4 mg/dL of SUA) was set as the reference value. The heterogeneity in the association between subgroups was tested by adding a multiplicative interaction term to the relevant statistical model. As a sensitivity analysis, we addressed the association between SUA levels and the five degrees of each kidney lesion using an ordinal logistic regression model.

Fig. 1. Age- and sex-adjusted mean values of the log-transformed glomerular sclerosis index, arteriolar hyalinosis index, and wall-lumen ratio (solid line) and age- and sex-adjusted frequencies of advanced glomerular sclerosis, advanced arteriolar hyalinosis, and advanced kidney arteriosclerosis (bar graph) according to SUA levels. * $p < 0.05$ versus Q1. † p for trend < 0.01 .

Results

Baseline Characteristics

The age- and sex-adjusted baseline characteristics of the study population according to the SUA levels are shown in Table 1. Individuals with higher SUA levels were likely to be male. The mean values of systolic blood pressure and body mass index, and the frequencies of individuals with antihypertensive agents, hypertension, electrocardiogram abnormalities, history of cardiovascular disease, and alcohol intake increased significantly with elevating SUA levels, whereas the mean values of eGFR decreased significantly.

Mean Values of Lesion Indices and Frequencies of Nephrosclerotic Lesions according to SUA Levels

Figure 1 presents the age- and sex-adjusted means of the log-transformed glomerular sclerosis index, arteriolar hyalinosis index, and wall-lumen ratio according to the SUA levels. The mean values of the log-transformed glomerular sclerosis index increased linearly and those of the log-transformed wall-lumen ratio decreased gradually with elevating SUA levels (both p for trend < 0.01). In contrast, the mean values of the log-transformed arteriolar hyalinosis index increased slightly, but not significantly (p for trend = 0.08). Likewise, the age- and sex-adjusted frequencies of advanced glomerular sclerosis and advanced kidney arteriosclerosis – but not those of advanced arteriolar hyalinosis – increased significantly with elevating SUA levels. The similar analysis was performed for eGFR and systolic blood pressure in online supplementary Figures 1 and 2. The age- and sex-adjusted frequencies of each advanced kidney lesion increased significantly with decreasing eGFR levels. On the other hand, only the age- and sex-adjusted frequency of advanced kidney arteriosclerosis increased significantly with the elevating systolic blood pressure levels.

Association between SUA Levels and Each Nephrosclerotic Lesion

Age- and sex-adjusted ORs for the presence of advanced glomerular sclerosis were significantly greater in both Q4 and the Q5 groups than in the Q1 group (Table 2). Likewise, the Q5 group had significantly greater age- and sex-adjusted ORs for the presence of advanced kidney arteriosclerosis than the Q1 group. There were no significant associations between SUA levels and advanced arteriolar hyalinosis. These associations remained substantially unchanged even after a multivariable adjustment. In the analysis of the association between SUA and advanced kidney arteriosclerosis, outer diameter was additionally adjusted, with the result that the association was still significant (Table 2, model 3). The sensitivity analysis using the sex-specific quintiles of SUA levels did not alter the findings substantially (online suppl. Table S1). In addition, we performed an ordinal logistic regression as a sensitivity analysis of the cutoff values for determining each advanced lesion; the results showed significant positive associations of SUA levels with the degree of glomerular sclerosis and kidney arteriosclerosis (online suppl. Table S2). Moreover, we also performed the analysis after excluding individuals with eGFR of < 60 mL/min/1.73 m² in order to exclude the influence of reduced kidney function on the association between SUA levels and advanced kidney lesions. As a con-

Fig. 2. Multivariable-adjusted cubic spline analyses of the association between SUA concentrations and the likelihoods of advanced glomerular sclerosis, advanced arteriolar hyalinosis, and advanced kidney arteriosclerosis. The risk estimates were adjusted for age at death, sex, systolic blood pressure, the use of antihypertensive agents, diabetes, serum total cholesterol, BMI, ECG abnormalities, history of cardiovascular disease, smoking habits, and alcohol intake. BMI, body mass index; ECG, electrocardiogram.

Table 2. Age- and sex-adjusted or multivariable-adjusted ORs of advanced glomerular sclerosis, advanced arteriolar hyalinosis, and advanced kidney arteriosclerosis according to the SUA levels

	SUA, $\mu\text{mol/L}$					<i>p</i> value for trend
	quintile 1 107–237 (<i>n</i> = 106)	quintile 2 238–279 (<i>n</i> = 109)	quintile 3 280–326 (<i>n</i> = 113)	quintile 4 327–380 (<i>n</i> = 111)	quintile 5 381–755 (<i>n</i> = 108)	
Advanced glomerular sclerosis						
Lesions, <i>n</i> (%)	6 (6)	7 (6)	10 (9)	13 (12)	18 (17)	
OR (95% CI)						
Model 1	1.00 (ref)	1.57 (0.50–4.92)	2.40 (0.82–7.04)	4.08 (1.41–11.81)	6.37 (2.29–17.74)	<0.001
Model 2	1.00 (ref)	1.50 (0.46–4.88)	2.45 (0.80–7.47)	4.66 (1.52–14.27)	7.19 (2.42–21.38)	<0.001
Advanced arteriolar hyalinosis						
Lesions, <i>n</i> (%)	10 (9)	7 (6)	11 (10)	12 (11)	12 (11)	
OR (95% CI)						
Model 1	1.00 (ref)	0.75 (0.27–2.07)	1.19 (0.47–3.01)	1.46 (0.57–3.73)	1.55 (0.61–3.95)	0.16
Model 2	1.00 (ref)	0.58 (0.20–1.65)	0.89 (0.34–2.35)	1.22 (0.46–3.25)	1.08 (0.40–2.90)	0.45
Advanced kidney arteriosclerosis						
Lesions, <i>n</i> (%)	8 (8)	9 (8)	8 (7)	11 (10)	19 (18)	
OR (95% CI)						
Model 1	1.00 (ref)	1.49 (0.54–4.14)	1.28 (0.45–3.67)	2.22 (0.80–6.14)	4.90 (1.90–12.64)	0.001
Model 2	1.00 (ref)	1.78 (0.58–5.40)	1.20 (0.38–3.77)	2.73 (0.86–8.69)	5.28 (1.77–15.80)	0.002
Model 3	1.00 (ref)	1.99 (0.64–6.20)	1.07 (0.33–3.42)	2.49 (0.76–8.12)	4.66 (1.53–14.22)	0.007

Model 1: adjusted for age at death and sex. Model 2: adjusted for the covariates included in model 1 + systolic blood pressure, the use of antihypertensive agents, diabetes, serum total cholesterol, BMI, electrocardiogram abnormalities, smoking habits, alcohol intake, and history of cardiovascular disease. Model 3: adjusted for the covariates included in model 2 + outer diameter. BMI, body mass index.

sequence, the multivariable-adjusted OR for the presence of advanced glomerular sclerosis was significantly greater with increased SUA levels, whereas there was no significant association for the presence of advanced kidney arteriosclerosis (online suppl. Table S3).

Restricted Cubic Splines and Association between Low SUA Levels and Each Nephrosclerotic Lesion

Figure 2 shows the shape of the association between SUA levels and each advanced lesion using restricted cubic splines. The likelihoods of advanced glomerular

Table 3. Associations of SUA levels with the presence of advanced glomerular sclerosis, advanced arteriolar hyalinosis, and advanced kidney arteriosclerosis, for which quintile 1 was divided into 2 categories at a SUA of 184 $\mu\text{mol/L}$ (= 5 percentile of SUA)

	SUA, $\mu\text{mol/L}$					
	quintile 1		quintile 2	quintile 3	quintile 4	quintile 5
	107–183 (<i>n</i> = 22)	184–237 (<i>n</i> = 84)	238–279 (<i>n</i> = 109)	280–326 (<i>n</i> = 113)	327–380 (<i>n</i> = 111)	381–755 (<i>n</i> = 108)
Advanced glomerular sclerosis						
Lesions, <i>n</i> (%)	3 (14)	3 (4)	7 (6)	10 (9)	13 (12)	18 (17)
OR (95% CI)						
Model 1	4.09 (0.75–22.33)	1.00 (ref)	2.52 (0.62–10.21)	3.84 (1.00–14.74)	6.53 (1.72–24.76)	10.20 (2.77–37.58)
Model 2	4.42 (0.79–24.75)	1.00 (ref)	2.35 (0.57–9.78)	3.68 (0.93–14.56)	7.26 (1.83–28.90)	10.68 (2.75–41.53)
Advanced arteriolar hyalinosis						
Lesions, <i>n</i> (%)	3 (14)	7 (8)	7 (6)	11 (10)	12 (11)	12 (11)
OR (95% CI)						
Model 1	1.74 (0.41–7.47)	1.00 (ref)	0.85 (0.28–2.57)	1.36 (0.49–3.75)	1.66 (0.60–4.63)	1.78 (0.64–4.92)
Model 2	1.85 (0.41–8.33)	1.00 (ref)	0.65 (0.21–2.02)	1.00 (0.35–2.89)	1.36 (0.47–3.98)	1.20 (0.41–3.55)
Advanced kidney arteriosclerosis						
Lesions, <i>n</i> (%)	4 (18)	4 (5)	9 (8)	8 (7)	11 (10)	19 (18)
OR (95% CI)						
Model 1	4.71 (1.02–21.61)	1.00 (ref)	2.45 (0.71–8.48)	2.10 (0.59–7.44)	3.63 (1.05–12.48)	8.05 (2.47–26.21)
Model 2	5.67 (1.07–30.12)	1.00 (ref)	3.23 (0.83–12.57)	2.14 (0.54–8.51)	5.05 (1.24–20.60)	9.62 (2.49–37.18)

Model 1: adjusted for age at death and sex. Model 2: adjusted for the covariates included in model 1 + systolic blood pressure, the use of antihypertensive agents, diabetes, serum total cholesterol, BMI, electrocardiogram abnormalities, smoking habits, alcohol intake, and history of cardiovascular disease. BMI, body mass index.

sclerosis and advanced kidney arteriosclerosis increased above 238 $\mu\text{mol/L}$. In addition, we divided the Q1 group of SUA levels into 2 groups at 184 $\mu\text{mol/L}$ (= the 5th percentile of SUA) to estimate the influence of low SUA levels on each advanced lesion (Table 3). As a consequence, the multivariable-adjusted ORs for advanced kidney arteriosclerosis were significantly greater in the SUA 107–183 $\mu\text{mol/L}$ group than the SUA 184–237 $\mu\text{mol/L}$ group.

Subgroup Analyses

The subgroup analyses revealed significant heterogeneity in the associations of every 1-SD increment in SUA levels with the presence of advanced glomerular sclerosis between subgroups of history of cardiovascular disease (*p* for heterogeneity = 0.02), with stronger associations being observed in individuals with a history of cardiovascular disease (online suppl. Table S4). Although the SUA concentration measurement methods before 1978 were different from those after 1983, there was no evidence of heterogeneity in the association between the pre-1978 and post-1983 subgroups.

Discussion

The present study clearly demonstrated that elevated SUA levels were significantly associated with the likelihood of advanced glomerular sclerosis and advanced kidney arteriosclerosis based on an analysis of population-based autopsy samples of Japanese. On the other hand, low SUA levels were also significantly associated with advanced kidney arteriosclerosis. There are limited studies addressing the association between SUA levels and nephrosclerotic changes, pathologically [5, 6].

Although the present study showed that increased SUA levels were significantly associated with the likelihood of advanced glomerular sclerosis, the previous hospital-based studies using kidney biopsy samples failed to reveal a significant association between SUA levels and the proportion of global glomerulosclerosis among kidney transplant donors [6]. The reason for this discrepancy is not clear, but it may be due to differences in the number of glomeruli counted and the type of study samples, such as biopsy versus autopsy. In regard to arteriolar hyalinosis, 2 previous hospital-based studies using kidney biopsy samples from CKD patients with urinary abnormalities and kidney transplant donors showed that increased SUA levels were significantly associated with a

greater likelihood of arteriolar hyalinosis [5, 6]. In the present study, however, there was no evidence of a significant association between SUA levels and advanced arterial hyalinosis, although the arteriolar hyalinosis index increased slightly with higher SUA levels. The discrepancy in findings might be related to differences in the age distribution of study individuals and the definition of arterial hyalinosis between studies. In the present study, almost all individuals had some degree of arterial hyalinosis, probably because most of the autopsied samples were collected from elderly people, with 79.9% of samples derived from individuals aged ≥ 65 years at the time of death. This may have prevented us from detecting an association between SUA levels and the degree of arteriolar hyalinosis. Further pathological studies on the association between SUA levels and the different pathological changes of the kidney are warranted.

In the subgroup analysis, the association between increased SUA levels and advanced glomerular sclerosis was stronger in patients with a history of cardiovascular disease. This may have been a chance finding due to the small sample size, but it may also reflect more advanced systemic arteriosclerosis in individuals with a history of cardiovascular disease.

Several experimental studies have reported on the mechanism underlying the influence of hyperuricemia on vascular lesions. Experimental studies found that hyperuricemia induced by feeding oxonic acid to rats was involved in afferent kidney arteriopathy through activation of the renin-angiotensin-aldosterone system [21] and increased oxidative stress [22]. Moreover, it has been reported that elevated uric acid leads to decreased nitric oxide production and the proliferation of vascular smooth muscle cells [23–25], while the activation of xanthine oxidase induces oxidative stress [26–28]. These changes cause endothelial dysfunction and kidney vascular lesions, likely leading to kidney ischemia and glomerulosclerosis [1]. Conversely, hypouricemia has also been reported to cause endothelial dysfunction [29] and elevate afferent arteriolar resistance [30]. Several epidemiological studies showed that individuals with low SUA levels had an increased risk of CKD [31–34]. The abovementioned study conducted in kidney transplant donors revealed that lower SUA levels tended to be associated with increased ORs of the presence of kidney atherosclerosis [6]. The present study also found that low SUA levels of less than 184 $\mu\text{mol/L}$ were associated with greater risk of the presence of advanced kidney arteriosclerosis, although this association was not significant in the restricted cubic splines. These findings imply that low SUA levels

may confer a risk of kidney vascular lesions, but this is still an area of controversy for several reasons: the sample size of the low SUA group is small; low SUA levels may simply reflect a diabetic condition or malnutrition that is more likely to worsen renal damage; and there may be an influence of residual confounding caused by unmeasured factors such as dietary intake.

Several limitations should be noted. First, causality cannot be inferred from the findings of this study due to its cross-sectional design. Decreased eGFR due to glomerular sclerosis and vascular changes can induce an accumulation of classical and nonclassical risk factors for atherosclerosis and decrease the clearance of uric acid, leading to hyperuricemia. Indeed, the significant association between SUA levels and advanced kidney arteriosclerosis disappeared when we performed an analysis excluding individuals with eGFR of $< 60 \text{ mL/min/1.73 m}^2$. It may be undeniable that the association between SUA levels and kidney atherosclerosis is influenced by the reverse causality derived from low eGFR. Second, only a single measurement of SUA concentration was obtained at the baseline examination. This may have caused the misclassification of study individuals into different SUA categories, likely weakening the association between SUA levels and each kidney lesion. Third, the method used to measure SUA concentrations at health examinations before 1978 differed from that after 1983. However, when we performed a subgroup analysis according to the SUA measurement methods, there was no evidence of heterogeneity in the association between SUA levels and each advanced kidney lesion between the measurement subgroups (online suppl. Table S4). Fourth, this study employed autopsy samples and had an extremely high proportion of elderly people. Therefore, the generalizability of our findings is limited. Fifth, we did not have information about the use of anti-hyperuricemia medication. However, the proportion of patients using anti-hyperuricemia medication was expected to be small in this population over the period studied. We also lacked data on diuretic use, but there were significant positive associations between SUA levels and both advanced glomerular sclerosis and kidney arteriosclerosis in individuals not using antihypertensive medications (online suppl. Table S4). Therefore, the influence of these limitations may have been modest. Sixth, since there was no information on intimal diameter and medial diameter in the present study, it was not possible to distinguish whether advanced kidney atherosclerosis was due to intimal or medial thickening. Finally, we could not examine kidney tubulointerstitial change, since many individuals in our study under-

went autopsy examination more than 24 h after death, and their postmortem interstitial changes were severe.

In conclusion, the risk of the presence of advanced glomerular sclerosis and advanced kidney atherosclerosis increased significantly with elevated SUA levels in autopsies in a Japanese community. Nevertheless, low SUA levels also tended to be associated with greater risk of the presence of advanced kidney atherosclerosis. These findings may suggest that the management of hyperuricemia is important for preventing the deterioration of nephrosclerosis, but extreme lowering of uric acid should be avoided.

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Statement of Ethics

This study was conducted with the approval of the Kyushu University Institutional Review Board for Clinical Research (approval no. 2019-499). Written informed consent was obtained from the relatives of the autopsied individuals at the time of autopsy.

References

- 1 Kumar V, Abbas AK, Aster JC. *Robbins basic pathology*. 10th ed. Philadelphia: Elsevier; 2018.
- 2 Obermayr RP, Temml C, Gutjahr G, Knechtelsdorfer M, Oberbauer R, Klauser-Braun R. Elevated uric acid increases the risk for kidney disease. *J Am Soc Nephrol*. 2008;19(12):2407–13.
- 3 Weiner DE, Tighiouart H, Elsayed EF, Griffith JL, Salem DN, Levey AS. Uric acid and incident kidney disease in the community. *J Am Soc Nephrol*. 2008;19(6):1204–11.
- 4 Takae K, Nagata M, Hata J, Mukai N, Hirakawa Y, Yoshida D, et al. Serum uric acid as a risk factor for chronic kidney disease in a Japanese community: the Hisayama Study. *Circ J*. 2016;80(8):1857–62.
- 5 Kohagura K, Kochi M, Miyagi T, Kinjyo T, Maehara Y, Nagahama K, et al. An association between uric acid levels and renal arteriolopathy in chronic kidney disease: a biopsy-based study. *Hypertens Res*. 2013 Jan;36(1):43–9.
- 6 Matsukuma Y, Masutani K, Tanaka S, Tschimoto A, Haruyama N, Okabe Y, et al. Association between serum uric acid level and renal arteriolar hyalinization in individuals without chronic kidney disease. *Atherosclerosis*. 2017;266:121–7.
- 7 Tracy RE, MacLean CJ, Reed DM, Hayashi T, Gandia M, Strong JP. Blood pressure, nephrosclerosis, and age autopsy findings from the Honolulu Heart Program. *Mod Pathol*. 1988 Nov;1(6):420–7.
- 8 Burchfiel CM, Tracy RE, Chyou PH, Strong JP. Cardiovascular risk factors and hyalinization of renal arterioles at autopsy. The Honolulu Heart Program. *Arterioscler Thromb Vasc Biol*. 1997 Apr;17(4):760–8.
- 9 Kubo M, Kiyohara Y, Kato I, Tanizaki Y, Katafuchi R, Hirakata H, et al. Risk factors for renal glomerular and vascular changes in an autopsy-based population survey: the Hisayama Study. *Kidney Int*. 2003 Apr;63(4):1508–15.
- 10 Ninomiya T, Kubo M, Doi Y, Yonemoto K, Tanizaki Y, Tsuruya K, et al. Prehypertension increases the risk for renal arteriosclerosis in autopsies: the Hisayama Study. *J Am Soc Nephrol*. 2007 Jul;18(7):2135–42.
- 11 Ninomiya T. Japanese legacy cohort studies: the Hisayama Study. *J Epidemiol*. 2018;28(11):444–51.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Data Availability Statement

The datasets generated and analyzed in the present study are not publicly available because they contain confidential clinical and demographic data of the study participants. However, the further information about the datasets is available with permission of the principal investigator of the Hisayama Study (Toshiharu Ninomiya) on reasonable request for purposes of replicating procedures and results.

- 12 Hata J, Ninomiya T, Hirakawa Y, Nagata M, Mukai N, Gotoh S, et al. Secular trends in cardiovascular disease and its risk factors in Japanese: half-century data from the Hisayama Study (1961–2009). *Circulation*. 2013; 128(11):1198–205.
- 13 Nakano T, Ninomiya T, Sumiyoshi S, Fujii H, Doi Y, Hirakata H, et al. Association of kidney function with coronary atherosclerosis and calcification in autopsy samples from Japanese elders: the Hisayama Study. *Am J Kidney Dis*. 2010;55(1):21–30.
- 14 Nakano T, Ninomiya T, Sumiyoshi S, Onimaru M, Fujii H, Itabe H, et al. Chronic kidney disease is associated with neovascularization and intraplaque hemorrhage in coronary atherosclerosis in elders: results from the Hisayama Study. *Kidney Int*. 2013;84(2):373–80.
- 15 Izumaru K, Hata J, Nakano T, Nakashima Y, Nagata M, Fukuhara M, et al. Reduced estimated GFR and cardiac remodeling: a population-based autopsy study. *Am J Kidney Dis*. 2019;74(3):373–81.
- 16 Inaishi J, Saisho Y, Hirakawa Y, Yoshida D, Hata J, Mukai N, et al. Association of glucose tolerance status with pancreatic β - and α -cell mass in community-based autopsy samples of Japanese individuals: the Hisayama Study. *J Diabetes Investig*. 2020;11(5):1197–206.
- 17 Sasaki T, Izumaru K, Hata J, Sakata S, Oishi E, Nagata T, et al. Serum NT-proBNP levels and histopathological myocardial fibrosis in autopsied cases from a Japanese community: the Hisayama Study. *J Cardiol*. 2021;78(3):237–43.
- 18 Raij L, Azar S, Keane W. Mesangial immune injury, hypertension, and progressive glomerular damage in Dahl rats. *Kidney Int*. 1984; 26(2):137–43.
- 19 Bader H, Meyer DS. The size of the juxtaglomerular apparatus in diabetic glomerulosclerosis and its correlation with arteriosclerosis and arterial hypertension: a morphometric light microscopic study on human renal biopsies. *Clin Nephrol*. 1977;8(1):308–11.
- 20 Kernohan JW, Anderson EW, Keith NM. The arterioles in cases of hypertension. *Arch Intern Med*. 1929;44(3):395–423.
- 21 Mazzali M, Kanellis J, Han L, Feng L, Xia YY, Chen Q, et al. Hyperuricemia induces a primary renal arteriolopathy in rats by a blood pressure-independent mechanism. *Am J Physiol Renal Physiol*. 2002;282(6):F991–7.
- 22 Sánchez-Lozada LG, Soto V, Tapia E, Avila-Casado C, Sautin YY, Nakagawa T, et al. Role of oxidative stress in the renal abnormalities induced by experimental hyperuricemia. *Am J Physiol Renal Physiol*. 2008;295(4):1134–41.
- 23 Zharikov S, Krotova K, Hu H, Baylis C, Johnson RJ, Block ER, et al. Uric acid decreases NO production and increases arginase activity in cultured pulmonary artery endothelial cells. *Am J Physiol Cell Physiol*. 2008;295(5):1183–90.
- 24 Sánchez-Lozada LG, Tapia E, López-Molina R, Nepomuceno T, Soto V, Ávila-Casado C, et al. Effects of acute and chronic L-arginine treatment in experimental hyperuricemia. *Am J Physiol Renal Physiol*. 2007;292(4):1238–44.
- 25 Kang DH, Park SK, Lee IK, Johnson RJ. Uric acid-induced C-reactive protein expression: implication on cell proliferation and nitric oxide production of human vascular cells. *J Am Soc Nephrol*. 2005;16(12):3553–62.
- 26 Berry CE, Hare JM. Xanthine oxidoreductase and cardiovascular disease: molecular mechanisms and pathophysiological implications. *J Physiol*. 2004;555(3):589–606.
- 27 Houston M, Estevez A, Chumley P, Aslan M, Marklund S, Parks DA, et al. Binding of xanthine oxidase to vascular endothelium: kinetic characterization and oxidative impairment of nitric oxide-dependent signaling. *J Biol Chem*. 1999;274(8):4985–94.
- 28 George J, Carr E, Davies J, Belch JJ, Struthers A. High-dose allopurinol improves endothelial function by profoundly reducing vascular oxidative stress and not by lowering uric acid. *Circulation*. 2006;114(23):2508–16.
- 29 Sugihara S, Hisatome I, Kuwabara M, Niwa K, Maharani N, Kato M, et al. Depletion of uric acid due to SLC22A12 (URAT1) loss-of-function mutation causes endothelial dysfunction in hypouricemia. *Circ J*. 2015;79(5):1125–32.
- 30 Uedono H, Tsuda A, Ishimura E, Nakatani S, Kurajoh M, Mori K, et al. U-shaped relationship between serum uric acid levels and intrarenal hemodynamic parameters in healthy subjects. *Am J Physiol Renal Physiol*. 2017; 312(6):F992–7.
- 31 Wakasugi M, Kazama JJ, Narita I, Konta T, Fujimoto S, Iseki K, et al. Association between hypouricemia and reduced kidney function: a cross-sectional population-based study in Japan. *Am J Nephrol*. 2015;41(2):138–46.
- 32 Kanda E, Muneyuki T, Kanno Y, Suwa K, Nakajima K. Uric acid level has a U-shaped association with loss of kidney function in healthy people: a prospective cohort study. *PLoS One*. 2015;10(2):e0118031.
- 33 Mun KH, Yu GI, Choi BY, Kim MK, Shin MH, Shin DH. Effect of uric acid on the development of chronic kidney disease: the Korean multi-rural communities cohort study. *J Prev Med Public Health*. 2018;51(5): 248–56.
- 34 Mori K, Furuhashi M, Tanaka M, Numata K, Hisasue T, Hanawa N, et al. U-shaped relationship between serum uric acid level and decline in renal function during a 10-year period in female subjects: BOREAS-CKD2. *Hypertens Res*. 2021;44(1):107–16.