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Original Paper

Relationship Between Serum Uric Acid Levels and Intrarenal Hemodynamic Parameters

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Key words
Uric acid • Inulin clearance • Para-aminohippurate clearance • Afferent arteriolar resistance

Abstract
Background/Aims: Hyperuricemia has been reported to affect renal hemodynamics in rat models. We evaluate the relationship between serum uric acid and intrarenal hemodynamic parameters in humans, utilizing the plasma clearance of para-aminohippurate (C_{PAH}) and inulin (C_{in}). ***Methods:*** Renal and glomerular hemodynamics were assessed by simultaneous measurement of C_{PAH} and C_{in} in 58 subjects. Of these, 19 subjects were planned to provide a kidney for transplantation; 26 had diabetes without proteinuria; and 13 had mild proteinuria. Renal and glomerular hemodynamics were calculated using Gomez`s formulae. ***Results:*** C_{in} was more than 60 ml/min/1.73m^2 in all subjects. Serum uric acid levels correlated significantly with vascular resistance at the afferent arteriole (R_a) (r = 0.354, p = 0.006), but not with that of the efferent arteriole (R_e). Serum uric acid levels (β = 0.581, p = <0.001) were significantly and independently associated with R_a after adjustment for several confounders (R^2 = 0.518, p = <0.001). ***Conclusions:*** These findings suggest, for the first time in humans, that higher serum uric acid levels are associated significantly with R_a in subjects with C_{in} > 60 ml/min/1.73m^2. The increase in R_a in subjects with higher uric acid levels may be related to dysfunction of glomerular perfusion.

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Introduction

It is well known that higher uric acid levels are associated with reduced glomerular filtration rate (GFR) [1-4]. The mechanism underlying renal dysfunction induced by higher uric acid levels has been explained in rats as occurring through endothelial dysfunction, which causes a decrease in nitric oxide synthesis, leading to an increase in the resistance of renal artery [5, 6]. In a rat model, glomerular ischemia was induced by hyperuricemia [7]. Increases in resistance of the renal artery and decreases in renal plasma flow have been reported to be caused by hyperuricemia [8]. However, to date, there are no data supporting a relationship between serum uric acid levels and intrarenal hemodynamic parameters in humans with normal renal function. In humans, it is not possible to measure glomerular hemodynamic variables directly. However, Gomez published a series of formulae for the indirect evaluation of glomerular hemodynamics in humans [9]. These formulae have been used to calculate glomerular hemodynamics in various conditions, including untreated and treated essential hypertension [9, 10], renovascular hypertension in human [11], primary aldosteronism [12], and supraventricular tachycardia [13], and diabetic and non-diabetic subjects by us [14, 15]. The aim of the present study was to evaluate the relationship between serum uric acid levels and renal hemodynamic parameters in humans, utilizing clearance of para-aminohippurate (C_{PAH}) and inulin (C_{in})

Subjects and Methods

Subjects

The study protocol was approved by the Ethics Committee of Osaka City University Graduate School of Medicine (# 1444). The study was performed as a single-center study at Osaka City University Hospital between January 2010 and August 2014. Subjects with preserved renal function were consecutively included after written informed consent to precisely examine the renal function was obtained. Subjects with GFR measured by C_{in} as being less than 60 mL/min/1.73m^2 were excluded from the analysis, since these subjects were considered to have severely impaired renal hemodynamics and would be inappropriate for the application of Gomez formulae.

Fifty-eight subjects (55.6 ± 13.2 years old, 25 males and 33 females) were examined in the present study. Of these, 19 subjects were planned to provide a kidney for transplantation; 26 had diabetes without proteinuria; and 13 had mild proteinuria (urine protein ≤ 1+ by the dipstick test, no hematuria). They were admitted to Osaka City University Hospital for the evaluation of renal function.

Measurement of C_{in} and C_{PAH}, and calculation of intrarenal hemodynamic parameters

Renal plasma flow (RPF) and glomerular filtration rate (GFR) were determined by the constant input clearance technique using PAH and inulin, respectively, as previous reported by us [14, 15]. Continuous intravenous infusion of 1% inulin and 0.5% PAH via the antecubital vein was performed in the morning after an overnight fast, based on the method of Horio *et al.* [16]. C_{PAH} and C_{in} were measured simultaneously using a simple method based on a single urine collection. In brief, subjects received 500 ml of water orally 15 min before infusion. After a priming dose of PAH and inulin, the rates of infusion were set a 300 ml/h for the first 30 min and 100 ml/min for the remaining time. To maintain hydration, 180 ml of water was given orally. Subjects completely emptied their bladder at 45 min after the start of the test and urine was collected for measurement of urinary PAH and inulin. The urine collection period was set at 90 min to increase the accuracy of the clearance study. Blood samples for the measurement of serum PAH and inulin were taken at the beginning and end of the clearance period.

C_{PAH} and C_{in} were calculated by the UV/P method (U: concentration in urine, V: urine volume [ml/min], P: concentration in plasma) using the mean serum PAH and inulin concentrations at the beginning and end of the clearance period. Plasma PAH and inulin concentrations were determined colorimetrically using the N-1 naphthylethylenediamine and anthrone method, respectively, with a Corning 258 spectrophotometer [17-19].

While direct measurement of glomerular hemodynamics parameters in humans is not feasible, the formulae introduced by Gomez [9] allow indirect assessment of glomerular hemodynamics, as recently discussed in detail by Guidi *et al.* [20]. These formulae were designed for quantitative estimation of filtration pressure across the glomerular capillaries (ΔPF), glomerular hydrostatic pressure (P_{glo}), and afferent and efferent arteriolar resistances (R_a and R_e, respectively) using measured blood pressure, GFR, as measured by C_{in}, RPF, as measured by C_{PAH}, hematocrit, and plasma protein concentrations under the assumptions that (1) intrarenal vascular resistances can be divided into three compartments: afferent, efferent and venular; (2) hydrostatic pressures in the venules, interstitium, renal tubules and Bowman's space (P_{Bow}) are in equilibrium at a value of approximately 10 mmHg; (3) the gross filtration coefficient (K_{FG}) is 0.0406 ml/s per mmHg per kidney; and (4) filtration disequilibrium is postulated along the glomerular capillaries [9, 20].

The Gomez formulae were calculated from the original paper as follows:

$\Delta P_F = GFR/K_{FG}$

$P_{glo} = \Delta P_F + P_{Bow} + \pi G$

$\pi G = 5 \cdot (C_M - 2)$

$C_M = TP/FF \cdot \ln (1/(1-FF))$

In the above, ΔP_F was the filtration pressure across the glomerular capillary. K_{FG} (the gross filtration coefficient) was estimated as 0.0406 mL/sec·mm Hg per kidney. P_{Bow} (the hydrostatic pressure in Bowman's space) was estimated as 10 mm Hg; πG (the oncotic pressure within the glomerular capillaries) can be obtained from C_M (plasma protein concentration within the glomerular capillaries), and calculated from the TP (total protein concentration) and filtration fraction (FF).

From Ohm's law:

$R_a = ((MBP-P_{glo})/RBF) \cdot 1328$

$R_e = (GFR/K_{FG} \cdot (RBF-GFR)) \cdot 1328$

RBF can be calculated from RPF and hematocrit (Ht) using the standard formula:

$RBF = RPF/(1-Ht)$

In the above, 1328 is the conversion factor to dyne·sec·cm^{-5}; GFR (glomerular filtration rate), RPF (renal plasma flow), and RBF (renal blood flow) are expressed in mL/sec; and the mean blood pressure (MBP) is calculated as (2 x diastolic BP + systolic BP)/3. In the present study, Gomez formulae were applied in subjects with C_{in} > 60 ml/min/1.73m^2.

Statistical analysis

Results are expressed as the mean ± standard deviation (SD). Correlations between two variables were examined using Pearson's correlation coefficient. Multiple regression analyses were performed to evaluate the relationships between R_a and other parameters. All analyses were performed using StatView 5 for Windows (SAS Institute Inc., Cary, NC, USA). The level of significance was set at $p < 0.05$.

Results

Baseline characteristics

Baseline characteristics of the subjects are shown in Table 1. The mean age was 55.6 ± 13.2 years old, and 25 subjects (43.1%) were male. The mean serum creatinine level was 0.7 ± 0.2 mg/dl. GFR measured by C_{in} was 86.0 ± 20.2 ml/min/1.73m^2, being > 60 ml/min/1.73m^2 in all subjects.

The mean blood pressure was 92 ± 11 mmHg, and 22 subjects (37.9%) were receiving antihypertensive therapy with an angiotensin receptor blocker (ARB) and/or angiotensin converting enzyme (ACE) inhibitor (n=20), and/or a calcium channel blocker (n=10). Antihyperuricemia agents (allopurinol) were prescribed in three subjects.

The plasma glucose and HbA1c values were 107 ± 29 mg/dL and 6.7 ± 1.8%, respectively, with 26 subjects diagnosed as having type 2 diabetes mellitus based on a history of diabetes or the criteria in the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus [21].

Table 1. Clinical characteristics of the subjects

	Mean ± SD	range
age (years)	55.6 ± 13.2	22 - 77
male / female	25 / 33	
body mass index (kg/m^2)	24.9 ± 4.5	17.0 - 36.0
mean blood pressure (mmHg)	92 ± 11	65 - 114
systolic blood pressure (mmHg)	126 ± 16	97 - 162
diastolic blood pressure (mmHg)	74 ± 10	50 - 98
hemoglobin (g/dL)	13.8 ± 1.4	10.6 -1 7.2
serum albumin (g/dL)	4.2 ± 0.4	3.0 - 4.9
serum uric acid (mg/dL)	5.2 ± 1.2	3.2 - 7.5
plasma glucose (mg/dL)	107 ± 29	73 – 176
hemoglobin A1c (%)	6.7 ± 1.8	4.6 - 12.1
serum creatinine (mg/dL)	0.7 ± 0.2	0.4 - 1.2
C_{in} (mL/min/1.73m^2)	86.0 ± 20.2	60.2 - 153.3
renal plasma flow (mL/min)	415 ± 150	169 – 873
renal blood flow (mL/min)	688 ± 242.	265 – 1451
afferent arteriolar resistance (dyne · sec · cm^{-5})	7468 ± 3680	872 – 20184
efferent arteriolar resistance (dyne · sec · cm^{-5})	2659 ± 1299	1013 – 7422

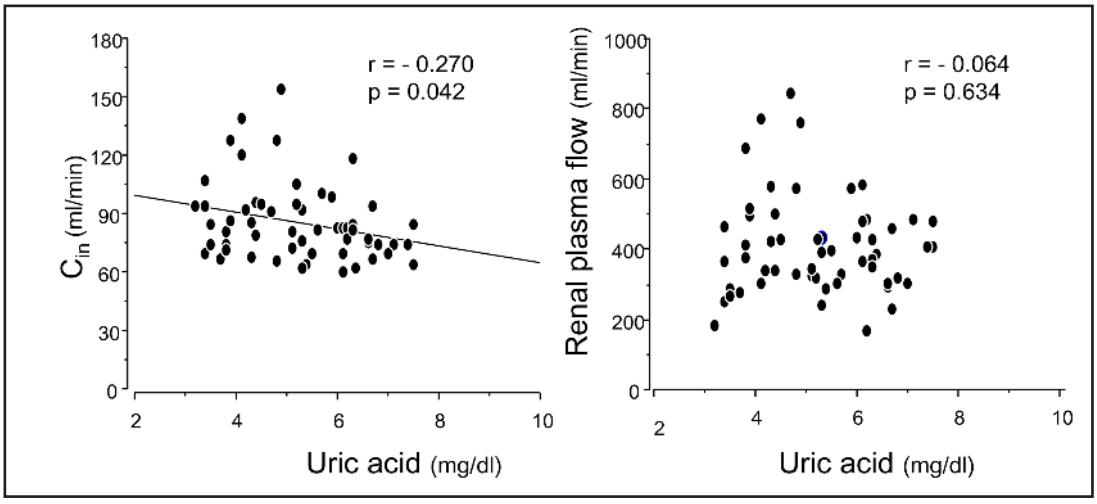

Fig. 1. Relationship between serum uric acid levels and inulin clearance (C_{in}) and renal plasma flow. There was a significant, negative correlation between serum uric acid levels and C_{in}.

Relationship between serum uric acid and each of the renal hemodynamic parameters

We examined the relationship between serum uric acid levels and renal hemodynamic parameters. Serum uric acid showed a significant negative correlation with C_{in} (r = - 0.270, p =0.0421). However, there were no significant correlations between serum uric acid levels and renal plasma flow, or renal blood flow (r = - 0.064, p = 0.634, r = - 0.0018, p = 0.892, respectively) (Figure 1).

Multiple regression analyses were performed to examine whether serum uric acid levels were associated with C_{in} after adjustment for age, gender, body mass index, blood pressure and serum albumin. Serum uric acid levels were not associated with decreasing C_{in} (Table 2).

The relationships between serum uric acid levels and the resistance of the afferent (R_a) and efferent (R_e) arterioles were examined. As shown in Figure 2, serum uric acid levels correlated positively with R_a (r = 0.354, p = 0.0064), but not with R_e (r = - 0.250, p = 0.158).

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Table 2. Factors associated with C_{in} and R_a. (Multiple regression analysis)

	C_{in}		R_a	
	β	p	β	p
age (year)	- 0.105	0.477	0.106	0.3566
gender (male=0, female=1)	0.031	0.834	0.309	0.0078
body mass index (kg/m^2)	- 0.037	0.807	-0.237	0.0477
systolic blood pressure (mmHg)	- 0.095	0.482	0.480	<0.0001
serum albumin (g/dL)	0.204	0.130	- 0.192	0.0713
hemoglobin A1c (%)	0.232	0.115	0.069	0.544
serum uric acid (mg/dL)	0.256	0.104	0.581	<0.0001
R^2	0.225		0.518	
P	0.0753		< 0.0001	

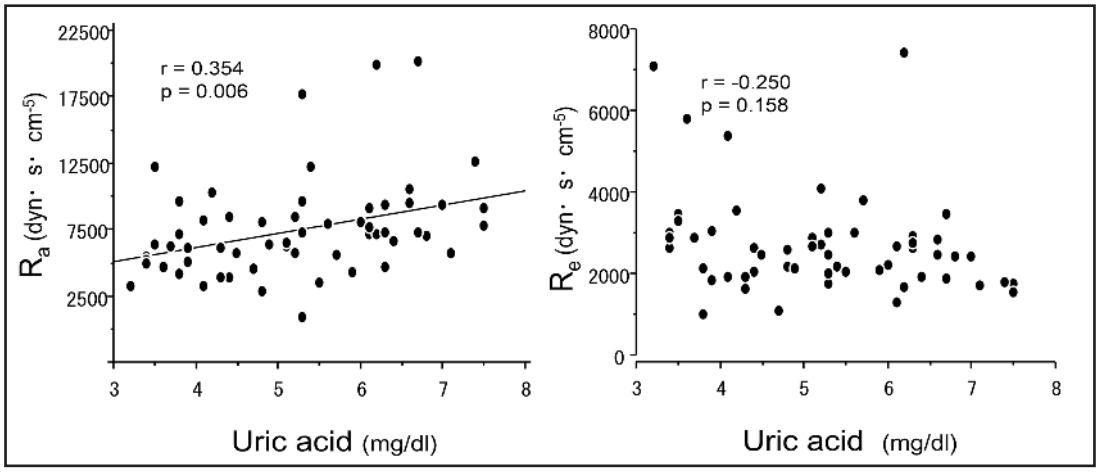

Fig. 2. Relationship between serum uric acid levels and resistance of the afferent (R_a) and efferent (R_e) arterioles. There was a significant positive correlation between R_a and serum uric acid levels, but not between R_e and serum uric acid levels.

As shown in Table 2, multiple regression analysis was performed to examine whether serum uric acid levels were associated with R_a after adjustment for age, gender, body mass index, blood pressure, serum albumin and hemoglobin A1c. Female gender, hypertension, hypoalbuminemia and higher serum uric acid levels were significantly and independently associated with increased R_a.

Discussion

In the present study, we examined the relationship between serum uric acid levels and renal hemodynamic parameters in subjects with C_{in} > 60 ml/min/1.73m^2.

We demonstrated that serum uric acid levels correlated significantly and positively with R_a, but not with R_e. Multiple regression analysis also showed that R_a was associated significantly and independently with serum uric acid levels after adjustment for several confounders.

Sanchez-Lozada *et al.* reported that afferent arterial thickening with increased α-smooth muscle actin staining of the media was seen in hyperuricemic rats [22]. Further, the authors also reported that hyperuricemia-induced arteriolopathy in preglomerular vessels, which possibly impairs the autoregulatory response of afferent arterioles, produces renal hypoperfusion [23]. In addition, lumen obliteration induced by vascular wall thickening results in severe vasoconstriction, decreasing renal plasma flow, GFR, and perfusion to peritubular

capillaries [23]. The resulting ischemia is a potent simulus that induces tubulointerstitial inflammation and fibrosis, as well as arterial hypertension [23]. Khosla *et al.* reported that nitric oxide was reduced in hyperuricemic rats [6]. Uric acid has also been reported to inhibit nitric oxide production in endothelial cells [6]. These experimental results in rats indicate that hyperuricemia induced endothelial dysfunction, i.e., impaired nitric oxide production, and hyperuricemia-induced arteriolopathy, particularly in the afferent arteriole. Increased resistance of the afferent arteriole, as seen with higher serum uric acid levels in the present study, is considered to be consistent with these experimental results.

In humans, the relationship between uric acid and kidney disease is more complicated because of the many confounding variables. Serum uric acid levels have been reported to be associated with other risk factors for kidney disease, such as hypertension, insulin resistance and microalbuminuria [24, 25]. In the present study examining subjects with preserved renal function, a significant, negative correlation was found between serum uric acid and C_{in} in the univariate analysis, but not in the multivariate analysis, indicating that the association between increased uric acid and decreased GFR was confounded substantially by various risk factors. Potential mechanisms underlying the kidney damage from uric acid have been reported to include induction of afferent arteriopathy, inflammation and activation of the renin–angiotensin system [24, 26]. Kohagura *et al.* demonstrated, by renal biopsy examination, that hyperuricemia was significantly and independently associated with renal arteriolar hyalinosis and higher grade wall thickening, suggesting that higher uric acid may cause progression of chronic kidney disease (CKD) through its effect on arterioles [27]. Weiner *et al.* reported that serum uric acid is a modest independent risk factor for incident CKD in the general population [3]. Bellomo *et al.* also reported that serum uric acid level is an independent risk factor for decreased kidney function [28]. The mechanisms of uric acid on incident CKD have been considered to be the direct toxic effect of uric acid on the kidney, via exacerbation of hypertension [3, 27, 28]. In humans, it has been reported that the highest tertile of serum uric acid levels was associated with incident kidney injury, not associated with progression of kidney injury [29]. However, Iseki et al. reported that hyperuricemia is associated with the progression of CKD to end-stage renal disease [2]. We demonstrated that higher serum uric acid levels were associated with increased R_a in the present study. The increase in R_a with higher uric acid levels may cause impaired or dysregulated perfusion of the glomeruli, which could be related to the decreased renal function in subjects with GFR > 60mL/min/1.73m^2. However, from the present study, it cannot be directly elucidated whether increased R_a with higher serum uric acid levels causes decreased GFR, in part since our study did not show a significant association between serum uric acid levels and GFR (C_{in}) in multiple regression analysis.

In the present study, female gender was a significant, independent factor associated with increased R_a in multiple regression analysis. Iseki *et al.* [1] reported that hyperuricemia was an independent predictor of end stage renal disease (ESRD) in women. In women aged 51 years and older, serum uric acid levels have been shown to be increased, suggesting a role of estrogen [30]. Considering our current results with these previous studies, the risk for ESRD conferred by serum uric acid levels may be greater among women than men.

There are some limitations to the present study. Firstly, the study was performed in a relatively small number of Japanese subjects, and a large-scale study is needed to confirm that hyperuricemia increases R_a. Secondly, some of the subjects took antihypertensive agents, including RAS inhibitors. However, since these inhibitors have been reported to mainly affect efferent arterioles and decrease R_e [31, 32], we consider that the use of RAS inhibitors cannot explain the increase of R_a. Thirdly, we did not directly measured the renal hemodynamics, since it is impossible to measure it in humans. Instead, we used Gomez's formulae to calculate renal hemodynamics. Although the formulae are based on several assumptions, many studies have validated the clinical utility of the formulae [11-13, 15]. Fourthly, our cohort of relatively small number of subjects consisted of rather heterogeneous groups of healthy subjects (n=19), diabetic subjects without proteinuria (n=26), and mild

proteinuria subjects (n=13). This was partly as a result of difficulties in obtaining informed consent to our study; due to the complex infusion techniques and timed blood and urine collection. However, in all subjects, GFR measured by C_{in} was more than 60 mL/min/1.73m^2. Serum uric acid levels were not significantly different between the healthy (5.0 ± 1.5 mg/dL), diabetic (5.3 ± 1.5 mg/dL) and mild proteinuria (5.5 ± 1.7 mg/dL) subjects. Further studies are required to examine renal hemodynamics separately in each of the three groups. Lastly, we did not measure how R_a was affected when serum uric acid levels were reduced with anti-hyperuricemia agents. In the present study, there were only three subjects undergoing treatment with anti-hyperuricemia agents. It is necessary to confirm that R_a is reduced by these agents, in future studies.

Conclusion

The findings of the present study demonstrate, for the first time in humans, that higher serum uric acid levels were associated significantly with increased R_a. The increase in R_a in those subjects with higher uric acid levels may be related to dysfunction of glomerular perfusion.

Disclosure Statement

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the reported research.

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