Association Between Uric Acid and Renal Hemodynamics: Pathophysiological Implications for Renal Damage in Hypertensive Patients

Giulio Geraci, MD; Giuseppe Mulè, MD; Manuela Mogavero, MD; Calogero Geraci, MD; Emilio Nardi, MD; Santina Cottone, MD

From the Dipartimento Biomedico di Medicina Interna e Specialistica (DIBIMIS), Unit of Nephrology and Hypertension, European Society of Hypertension Excellence Center, University of Palermo, Palermo, Italy

The role of vascular renal changes in mediating the association between serum uric acid (SUA) and renal damage is unclear. The purposes of this study were to investigate the relationship between SUA and renal resistive index (RRI), assessed by duplex Doppler ultrasonography, and to assess whether hemodynamic renal changes may explain the association between SUA and renal damage in hypertensive patients. A total of 530 hypertensive patients with and without chronic kidney disease were enrolled and divided into SUA tertiles based on sex-specific cutoff values. RRI and albuminuria were greater and glomerular filtration rate (GFR) was lower in the uppermost SUA tertile patients when compared with those in the lowest tertiles (all $P<.001$). Moreover, SUA strongly correlated with RRI ($P<.001$) in all patients. However, RRI did not seem to explain the relationship between SUA and renal damage, and GFR significantly related with SUA in the overall population ($P<.001$) even after adjustment for RRI. *J Clin Hypertens (Greenwich).* 2016:1–8. © 2016 Wiley Periodicals, Inc.

The link between uric acid and hypertension is not fully understood. Epidemiological studies, as well as experimental data, reveal a strong association between increased serum uric acid (SUA) and high blood pressure (BP) both in animal models and humans, even if the causal connection remains to be clarified.[1–3] Likewise, the relationship between SUA and kidney damage is controversial. Although hyperuricemia is associated with decreased renal function, it is unclear whether the increased SUA is the cause or the expression of renal injury itself in hypertensive patients.[2–7]

In order to explain these intricate relationships, some authors hypothesize hyperuricemia as a prime mover in kidney damage through its modulatory action on intrarenal vasculature.[8–10] However, this assumption mainly arises from histological and pathophysiological studies performed in animal models,[8–11] whereas few clinical studies assess the independent relationship between SUA and renal hemodynamics in humans.[12–14] Furthermore, there are currently no studies that analyze the different role of intrarenal vascular impedance, as assessed by ultrasonographic renal resistive index (RRI), in mediating the association between SUA and kidney damage in subsets of hypertensive patients with different renal impairment.

Therefore, the purposes of our study were to: (1) investigate the relationship between SUA and RRI in hypertensive patients, (2) evaluate the influence of renal function on this relationship, and (3) assess whether hemodynamic renal changes may explain the association between SUA and renal damage in this population.

Address for correspondence: Giulio Geraci, MD, Via del Vespro, 141, 90127 Palermo, Italy
E-mail: giulio.geraci@unipa.it

Manuscript received: December 17, 2015; **revised:** January 30, 2016; **accepted:** February 1, 2016
DOI: 10.1111/jch.12812

MATERIALS AND METHODS

Patients

The study population was selected from Caucasian hypertensive patients consecutively attending our unit of nephrology and hypertension for specialist advice between May 2014 and July 2015.

Exclusion Criteria

- Age younger than 18 years and older than 70 years.
- Renovascular, malignant, endocrine hypertension, or hypertension associated with obstructive sleep apnea syndrome.
- Treatment with xanthine oxidase inhibitors.
- Severe obesity, defined as a body mass index (BMI) $\geq$40 kg/m^2.
- Rapid deterioration of renal function, defined as a reduction in estimated glomerular filtration rate (eGFR) >25% within 7 days.
- Abnormal renal anatomy (difference in renal length >1.5 cm between the two kidneys, the presence of solitary or supernumerary kidneys, congenital renal abnormalities, and polycystic kidney disease).
- Hydronephrosis grade 2 or higher.
- Renal replacement therapy (patients with transplant or undergoing dialysis).
- Heart failure.
- Permanent atrial fibrillation.
- Moderate to severe aortic/mitral valve disease.
- Previous coronary or cerebrovascular events.
- Major noncardiovascular diseases.

- Low-quality renal sonographic recordings.

Endocrine hypertension and renovascular hypertension were ruled out by clinical examination, by duplex Doppler assessment of intrarenal and extraparenchymal renal arteries and by laboratory determination of serum electrolytes, plasma renin activity, and plasma aldosterone concentration. When appropriate, plasma catecholamine level was determined and renoscintigraphy was performed. To screen for obstructive sleep apnea, we used the Berlin questionnaire and the Epworth Sleepiness Scale, followed by polysomnography when appropriate.

Written informed consent was obtained from each patient. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the local review board.

Study Design

Careful clinical history and physical examination were performed in all subjects. Patients who reported smoking cigarettes regularly during the past year were considered current smokers. Body weight and height were measured by a nurse. Clinic BP was recorded by a doctor, following the recommendations of the 2013 European Society of Hypertension/European Society of Cardiology guidelines[15]; furthermore, 24-hour ambulatory BP monitoring (ABPM) was carried out. Main laboratory tests were performed, including SUA determination, and a 24-hour urine sample was collected on nonworking days to evaluate albumin excretion rate.

Moreover, a B-mode and duplex Doppler ultrasonographic examination of intrarenal vasculature was alternatively performed by two different well-trained operators (MM and CG) unaware of the clinical data of patients. The reproducibility of RRI recordings by two investigators was assessed in a subgroup of 30 patients, in whom measurements were performed within 1 hour by both operators in a blinded fashion. The intraobserver and interobserver coefficients of variation for the measurements were 2.8% and 3.6%, respectively.

Measurements

Clinic BP was considered as the mean of three consecutive measurements obtained at 2-minute intervals by an electronic oscillometric validated device (WatchBP Office, Microlife Corporation, Taipei, Taiwan) after 5 minutes of rest in a sitting position. A portable, noninvasive SpaceLabs 90207 recorder (Redmond, WA) was used to perform 24-hour ABPM. BP was recorded automatically at 15-minute intervals during the day and at 20-minute intervals during nighttime resting. Only records with more than 80% of valid data were accepted.

Routine biochemical parameter determination was performed with standard techniques using an autoanalyzer (Hitachi System 911, Boehringer, Mannheim, Germany). SUA was measured using an uricase/peroxidase method. Low-density lipoprotein cholesterol was calculated by the Friedewald formula. The 24-hour albumin excretion rate was assayed by a solid-phase enzyme immunoassay (Microalbumin ELISA kit, DRG Diagnostics, Marburg, Germany). eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[16] Chronic kidney disease (CKD) was defined as eGFR <60 mL/min/1.73 m^2 for 3 months or as a structural abnormality, hematuria, or proteinuria if eGFR was ≥ 60 mL/min/1.73 m^2. All patients with CKD had either eGFR <60 mL/min/1.73 m^2 or albuminuria ≥ 30 mg/d or both.

Intrarenal color duplex ultrasonography was performed through a GE Logiq P5 PRO instrument (General Electric Company, Milan, Italy), with a 4 MHz transducer operating at 2.5 MHz for Doppler analysis. The Doppler signal was obtained from the interlobar arteries by placing the sample volume at the level of the corticomedullary junction. Peak systolic velocity (PSV) and telediastolic velocity (TDV) were measured, and RRI was calculated by the formula: RRI = (PSV − TDV)/PSV. The values were calculated as the average of six measurements from the upper, middle, and lower third of both kidneys. In patients with renal cysts, RRI was determined as the average of at least four measurements performed in renal areas far from the cysts. The Doppler angle chosen was less than 60°, and special care was taken not to compress the kidney and not to have the patient perform a Valsalva maneuver, because both can increase the RRI.[17]

Statistical Analysis

A total of 296 patients met the exclusion criteria. Among these, 10 had abnormal renal anatomy. Therefore, the final analysis involved 530 hypertensive patients. Statistical analyses were performed using SPSS software package, version 21.0 (IBM Corporation, New York, NY). Statistical analysis was initially performed in the whole study population and subsequently carried out in the different subgroups of patients with normal renal function (n=266) and those with chronic kidney disease (CKD) (n=264). Furthermore, the overall study population was divided into SUA tertiles based on sex-specific cutoff values (women: 4.90 mg/dL and 5.95 mg/dL; men: 5.56 mg/dL and 6.40 mg/dL), and analysis was performed in these three subsets of patients.

Normal distribution of the continuous variables was assessed using the Kolmogorov-Smirnov test and assumption of satisfactory Gaussian distribution was met for all of the examined variables, except for albuminuria and triglycerides. Normal distributed continuous variables were given as mean±standard deviation, whereas albuminuria and triglycerides were expressed as median and interquartile range; they were logarithmically transformed (base 10) to better satisfy distributional assumptions before parametric tests were used. Categorical variables were expressed as percentage values.

Differences between groups were evaluated using analysis of variance, Holm-Sidak test for multiple

comparisons, Student *t* test for unpaired data, and chi-square test, as appropriate. Adjustment for potential confounders was performed by analysis of covariance.

The univariate relationships between SUA, RRI, and other variables were tested by simple linear regression analysis in the overall study population, and the strength of the associations between the variables was expressed by Pearson correlation coefficients (*r*). In particular, the univariate relationship between SUA and RRI was also tested in various subsets of patients divided by sex, eGFR (cutoff value: 75 mL/min/m^2), albuminuria (cutoff value: 30 mg/die), or CKD. We chose an eGFR cutoff value of 75 mL/min/m^2 because a large meta-analysis by the Chronic Kidney Disease Prognosis Consortium demonstrated that cardiovascular risk began to rise below this cutoff value.[18] Moreover, we tested the relationship between (Log) albuminuria and eGFR, as dependent variables, with both SUA values unadjusted and adjusted for RRI. In all of these analyses, Fisher *r*-to-*z* transformation was used to compare different correlation coefficients.

The independent relationships between SUA with other variables were tested by multiple linear regression analyses. Multiple regression models were built in the overall study population considering SUA as the outcome variable, and including the regressors by a hierarchical (blockwise entry) approach. A block represented by age, sex, and statin treatment was initially introduced, followed by the remaining potential confounders included one by one in the order based on their strength of association in univariate analyses (see also Table S1 and Table II).

To evaluate the influence of CKD on the relationship between SUA and RRI, further multivariate models were built, using the same hierarchical procedure, alternatively in the group of patients with normal renal function and in the group of patients with CKD, considering SUA as the outcome variable. Finally, in order to assess the role of RRI in mediating the relationship between SUA and kidney damage, additional models were planned considering alternatively eGFR and (Log)albuminuria as outcome variables and including into the models as potential explanatory parameters SUA and the same variables of previous linear multiple regression analyses, by using the blockwise method.

In all multiple regression analyses, the strength of the associations between the variables was expressed by the unstandardized (*B*) and standardized (β) multiple regression coefficients. Collinearity was assessed by calculating the variance inflation factor (VIF). Not acceptable collinearity was assumed for a variance inflation factor of two or more, indicating that a variable should not be included in the model.

The null hypothesis was rejected at a two-tailed *P* value of <.05.

TABLE I. Demographic and Clinical Data of the Overall Study Population and of the Two Groups Without and With CKD[a]

	Overall Study Population (n=530)	Patients Without CKD (n=266)	Patients With CKD (n=264)	*P* Value
Age, y	54±16	48±15	59±15	<.001
Men, %	56.2	55.6	56.8	NS
Smokers, %	30.2	29.3	31.1	NS
Diabetic, %	31.4	30.5	32.2	NS
BMI, kg/m^2	28.5±10.5	28.7±14.0	28.2±4.6	NS
Serum glucose, mg/dL	100.6±35.6	95.3±36.6	106.4±33.7	.001
Serum uric acid, mg/dL	5.86±1.53	5.42±1.32	6.31±1.60	<.001
Total cholesterol, mg/dL	189±44	192±41	186±46	NS
HDL cholesterol, mg/dL	49±15	49±13	49±17	NS
LDL cholesterol, mg/dL	119±38	124±36	113±39	.009
Triglycerides, mg/dL	115 (80–155)	107 (73–148)	125 (95–166)	.001
Albuminuria, mg/24 hours	28.9 (14.6–87.5)	15.2 (8.1–23.1)	87.7 (40.9–380.8)	<.001
Serum creatinine, mg/dL	1.17±0.85	0.84±0.16	1.53±1.10	<.001
eGFR, mL/min/1.73 m^2	78.9±27.5	94.2±15.4	63.5±28.4	<.001
Clinic systolic BP, mm Hg	136±16	134±14	139±17	.001
Clinic diastolic BP, mm Hg	81±11	82±10	81±12	NS
Clinic pulse pressure, mm Hg	55±14	52±12	58±15	<.001
Clinic heart rate, beats per min	72±10	74±11	71±10	NS
24-h Systolic BP, mm Hg	130±14	128±13	132±15	.003
24-h Diastolic BP, mm Hg	79±10	79±10	79±11	NS
24-h Pulse pressure, mm Hg	51±10	48±9	53±11	<.001
RRI	0.64±0.07	0.62±0.07	0.65±0.07	<.001

Abbreviations: BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RRI, renal resistive index. [a]We used Student *t* test for independent samples to compare continuous variables between two groups, whereas χ^2 test (or Fisher exact test, when appropriate) was used to compare categorical variables. Not significant (NS): *P*>.05.

RESULTS

A total of 530 hypertensive patients were enrolled (mean age, 54±16 years; men, 56.2%; smokers, 30.2%; CKD, 49.8%; diabetes, 31.4%). Table I summarizes the demographic and clinical data of the overall population and of the two groups with or without CKD. SUA and RRI, as well as albuminuria, were significantly higher in patients with CKD when compared with those with normal renal function, whereas eGFR was lower (all $P<.001$). Similarly, diabetic patients had higher values of SUA and RRI than nondiabetic patients, and greater RRI values were also observed in smokers than in nonsmokers, whereas higher SUA values were noted in men compared with women (Figure S1).

The percentages of patients treated with cardiovascular drugs in the overall study population and in the groups with and without CKD are presented in Table S1. Higher RRI values and lower eGFR values were observed in patients treated with statins (0.67±0.06 and 69.5±27.2 mL/min/1.73 m^2, respectively) than in patients not using these agents (0.64±0.07 and 78.4±29.4 mL/min/1.73 m^2; $P<.001$ and $P=.018$, respectively). Patients treated with other cardiovascular drugs (including diuretics) did not differ in SUA, albuminuria, and the abovementioned parameters when compared with not treated patients.

When we grouped the study population into three tertiles on the basis of sex-specific cutoff values of SUA, the levels of RRI and albuminuria were greater in patients in the uppermost tertile when compared with those in the lowest tertiles, whereas eGFR was lower (all $P<.001$) (Figure 1). The differences in RRI among tertiles also remained statistically significant after adjustment for age, eGFR, and albuminuria in the whole population ($P<.001$).

Table S2 shows the univariate correlations of SUA, RRI, albuminuria, and eGFR with other variables in the entire study population. SUA strongly correlated with RRI in all patients as well as in women and men separately considered, without significant differences between the two groups (Figure 2). Moreover, it was associated with RRI in the groups with albuminuria ≥30 mg/d, eGFR<75 mL/min/1.73 m^2, and CKD, whereas in patients with lower albuminuria, higher eGFR, or without CKD, this relationship was not statistically significant (Figure 2). Furthermore, eGFR and albuminuria were significantly associated with SUA in the entire study population ($P<.001$), even after SUA adjustment for RRI (Figure S2).

In the overall study population, the association between SUA and RRI also remained after correction for various confounding factors in multiple linear regression analyses (Table IIA). When we built further multivariate models in patients with normal renal function or in CKD patients, different results were obtained: the relationship between SUA and RRI remained statistically significant only in the CKD group, whereas it lost significance in hypertensive individuals with normal renal function (Table IIB and IIC). In all of these analyses, VIF was <2.

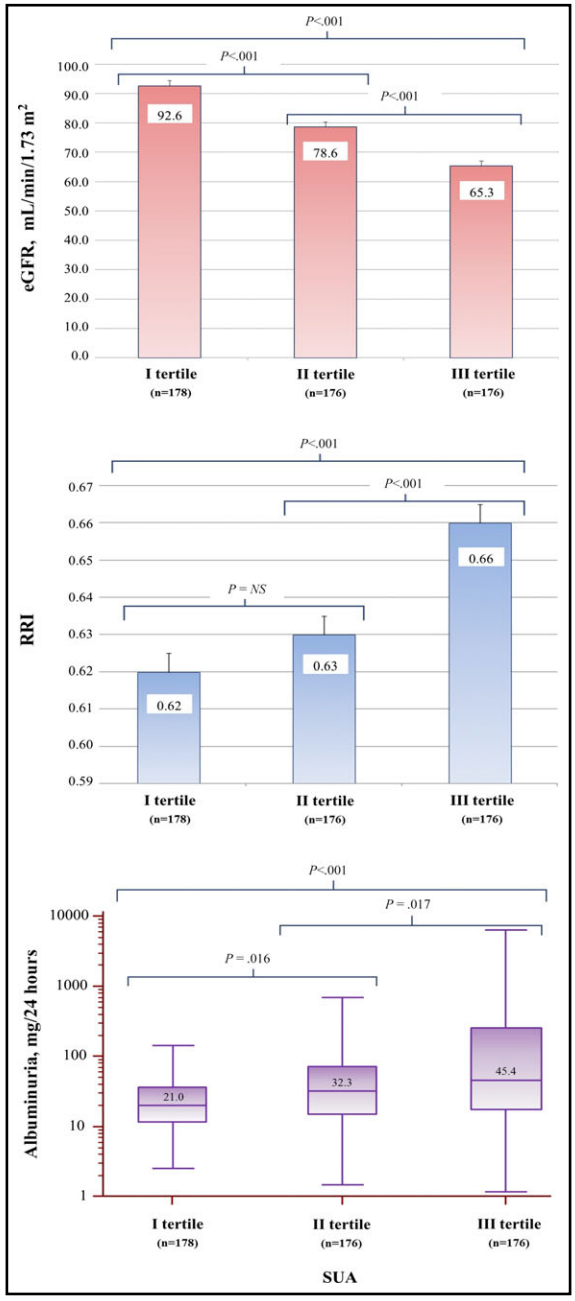

FIGURE 1. Values of renal resistive index (RRI) (mean±standard error of the mean [SEM]), estimated glomerular filtration rate (eGFR) (mean±SEM), and albuminuria (medians and interquartile ranges) in the study population divided into serum uric acid (SUA) tertiles.

Moreover, in order to better assess the role of RRI in mediating the association between SUA and kidney damage, additional models were planned considering eGFR (or [Log]albuminuria) as outcome variables (Table III). RRI was independently associated with

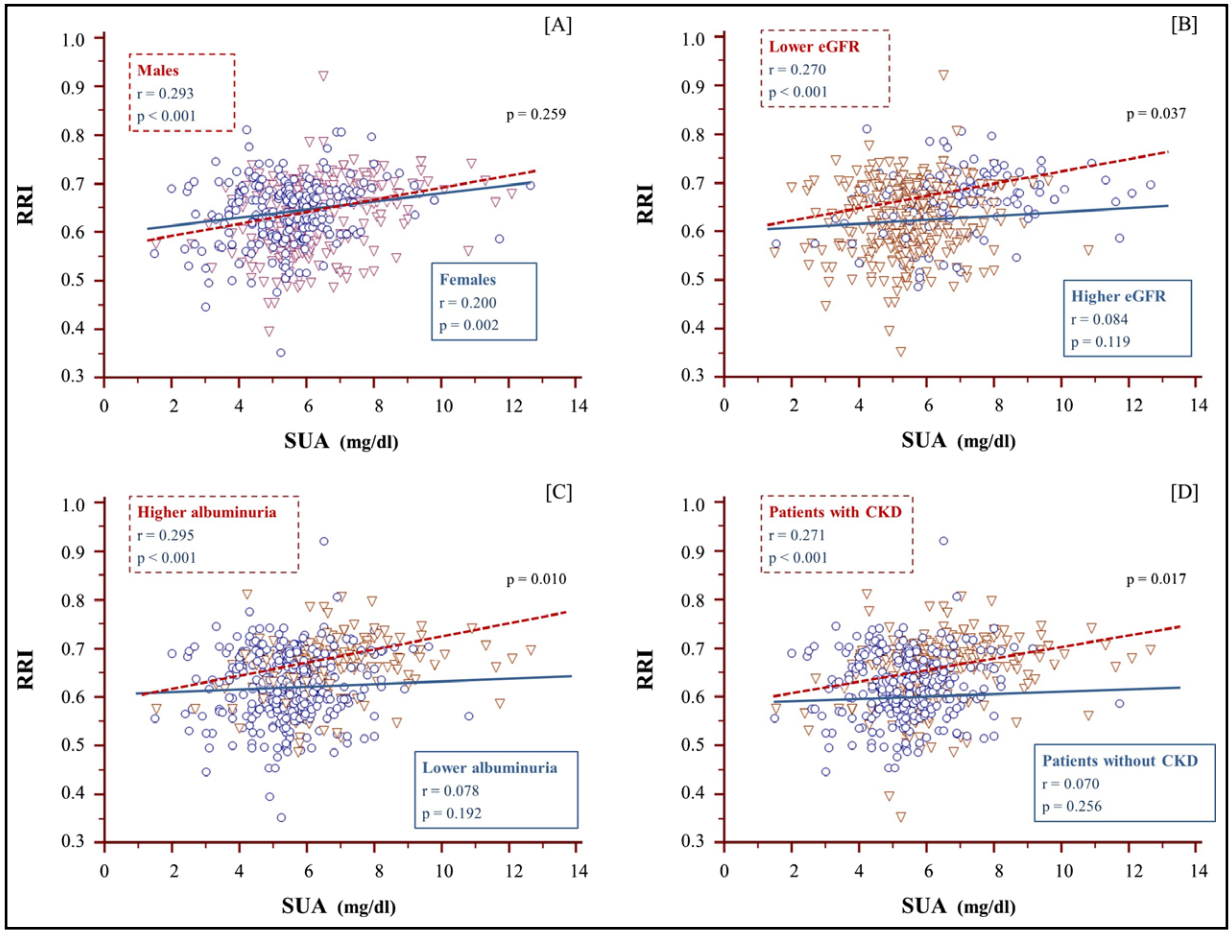

FIGURE 2. Relationship between serum uric acid (SUA) and renal resistive index (RRI) in the study population divided by sex (female or male) (A) by eGFR (> or <75 mL/min/1.73 m^2) (B), albuminuria (> or <30 mg/24 hours) (C), and chronic kidney disease (CKD) (absent or present) (D).

albuminuria (*P*=.032) but not with eGFR (*P*=.326), even in a further multiple regression model built without SUA as a potential explanatory parameter (β=−0.059; *P*=.071). On the other hand, SUA showed a strong independent association with eGFR (*P*<.001), whereas it did not significantly correlate with albuminuria (*P*=.325), even after a further model was built without RRI as a potential confounding factor (β=0.049; *P*=.217). In all of these analyses, VIF was <2.

DISCUSSION

An important finding of our study was that, in hypertensive patients, SUA strongly correlated with intrarenal hemodynamics, assessed noninvasively by RRI, and that this relationship remained significant after adjustment for multiple confounders, including eGFR and albuminuria.

This result is in agreement with previous data in the literature and adds to previous evidence. Mazzali and colleagues[8] observed that mild hyperuricemic rats developed renal arteriolopathy and greater renal vascular damage than normouricemic rats, and the allopurinol administration prevented these changes. In addition, Sanchez-Lozada and colleagues[9,10] showed, through tubular micropuncture studies on animal models of hyperuricemia, a uric acid–induced vasoconstriction of the intrarenal vessels resulting in hypertension and glomerular hyperfiltration. Similar results were observed in humans. Messerli and colleagues[12] showed a correlation between increased SUA and changes in renal blood flow and in renal vascular resistance, assessed using an invasive method. Most recently, positive correlations between hyperuricemia and renal hemodynamics, noninvasively evaluated by Duplex ultrasound, were found in hypertensive patients.[13,14] In these studies, however, hyperuricemia significantly correlated with renal volume/RRI ratio and hybrid and heterogeneous index of intrarenal hemodynamics, whereas the association between SUA and RRI was not observed in the general population and in men, reaching statistical significance only in women. Consistent with these studies, SUA might contribute to renal microcirculation changes and endothelial dysfunction by inducing various pro-oxidant effects in vascular cells

TABLE II. Independent Multivariate Correlates of SUA in the Overall Study Population (A) in the Subgroup of Hypertensive Patients With Normal Renal Function (B) and in the Subgroup of Patients With CKD (C)[a]

	Regression Coefficients				
	Not Standardized		Standardized		
Outcome Variable: SUA	*B*	Standard Error	β	*t*	*P* Value
(A) Model (R^2=0.32)					
Constant	2.478	1.006	–	2.464	.014
eGFR	−0.019	0.002	−0.350	−9.054	<.001
(Log)triglycerides	1.532	0.340	0.181	4.512	<.001
Sex	0.642	0.115	0.208	5.593	<.001
RRI	2.603	0.862	0.115	3.020	.003
HDL cholesterol	−0.014	0.005	−0.108	−2.744	.006
BMI	0.015	0.006	0.095	2.545	.011
(B) Model (R^2=0.17)					
Constant	2.967	0.958	–	3.098	.002
Sex	0.720	0.153	0.271	4.698	<.001
(Log)Triglycerides	1.417	0.416	0.202	3.409	.001
eGFR	−0.013	0.005	−0.147	−2.527	.012
BMI	0.013	0.006	0.127	2.143	.033
(C) Model (R^2=0.32)					
Constant	1.990	1.595	–	1.247	.213
eGFR	−0.018	0.003	−0.327	−5.747	<.001
(Log)triglycerides	1.941	0.523	0.203	3.713	<.001
HDL cholesterol	−0.019	0.007	−0.165	−2.964	.003
Sex	0.519	0.170	0.161	3.058	.002
RRI	3.184	1.390	0.129	2.292	.023

Abbreviations: SUA, serum uric acid; CKD, chronic kidney disease. [a]The variables included in the multiple regression models were renal resistive index (RRI), estimated glomerular filtration rate (eGFR), log(albuminuria), age, sex (0=female, 1=male), smoking habit (0=nonsmokers, 1=smokers), clinic pulse pressure, serum glucose levels (or diabetes as dichotomous variable), body mass index (BMI), high-density lipoprotein (HDL), (log)triglycerides, clinic heart rate, and therapy with statins (0=no treatment, 1=treatment)

TABLE III. Independent Multivariate Correlates of eGFR (A) and (Log)Albuminuria (B) in the Overall Study Population[a]

	Regression Coefficients				
	Not Standardized		Standardized		
Outcome Variable	*B*	Standard Error	β	*t*	*P* Value
(A) eGFR					
Model (R^2=0.56)					
Constant	168.064	5.009	–	33.552	.000
Age	−0.786	0.056	−0.437	−14.026	.000
(Log)albuminuria	−13.123	1.164	−0.349	−11.277	.000
SUA	−3.956	0.548	−0.220	−7.222	.000
Clinic PP	−0.151	0.066	−0.070	−2.294	.022
BMI	0.184	0.084	0.064	2.190	.029
(B) (Log)albuminuria					
Model (R^2=0.31)					
Constant	2.315	0.326	–	7.104	.000
eGFR	−0.015	0.001	−0.574	−12.530	.000
Age	−0.005	0.002	−0.114	−2.456	.014
Serum glucose	0.002	0.001	0.089	2.396	.017
RRI	0.893	0.416	0.083	2.146	.032

[a]The variables included in the multiple regression models were serum uric acid (SUA), renal resistive index (RRI), estimated glomerular filtration rate (eGFR), log(albuminuria), age, sex (0=female, 1=male), smoking habit (0=nonsmokers, 1=smokers), clinic pulse pressure (PP), serum glucose levels (or diabetes as dichotomous variable), body mass index (BMI), high-density lipoprotein cholesterol, (log)triglycerides, clinic heart rate, and therapy with statins (0=no treatment, 1=treatment).

and by impairing nitric oxide production, leading to vasoconstriction and a proliferative effect on vascular smooth muscle cells.[19–21] It is also conceivable that increased SUA might be an expression of a primitive renal vasculature damage, perhaps through an impaired mechanism of uric acid tubular reabsorption.[22,23]

Another interesting result of our study was that, when the study population was divided on the basis of renal function, SUA independently correlated with RRI in the CKD group, whereas this relationship lost significance in the group of hypertensive individuals without CKD. To the best of our knowledge, no clinical study has been carried out in humans with impaired renal function. The few studies that have analyzed the association between SUA and renal hemodynamics in humans, in fact, were always performed in hypertensive patients with normal renal function or with eGFR >60 mL/min/1.73 m^2, and this would in part justify the lack of association between the abovementioned variables, in line with our data.[12–14] This is consistent with experimental data obtained in animal models of hyperuricemia, in which intrarenal hemodynamic changes induced by SUA were lower in normal compared with remnant kidney rats.[10]

The most interesting finding of our investigation was that the association between SUA and kidney damage did not appear to be explained by intrarenal vascular changes detected by RRI. In fact, the strong univariate correlations between SUA and eGFR (or albuminuria) remained even after SUA adjustment for RRI values, without significant differences. Moreover, when we ran the full-adjusted multivariate model by using eGFR as an outcome variable, its association with RRI lost statistical significance (P=.326), and a similar result was obtained in a further multiple regression model in which SUA was not introduced as a potential explanatory parameter (P=.071). On the other hand, when we chose albuminuria as an outcome variable, its association with SUA did not attain statistical significance (P=.325), when RRI was not taken into account (P=.217). This also seems to demonstrate that SUA is independently related to eGFR, but not to albuminuria, which, on the contrary, was associated with RRI in an SUA-independent manner.

The evidence that RRI changes do not seem to explain the kidney damage associated with hyperuricemia, despite the presence of a strong independent association between SUA with both RRI and renal damage,[24] suggests the existence of SUA-related underlying mechanisms of which both intrarenal vascular changes and kidney damage could be epiphenomena. In other words, it is conceivable that increased RRI and reduced eGFR might not represent serial steps of a pathophysiological process of consequential events, but they might be independent and parallel expressions of common upstream mechanisms related to hyperuricemia. In this regard, an activation of the intrarenal renin-angiotensin system (RAS) has been reported in animal models of hyperuricemia and in patients with mild hyperuricemia.[25,26] Moreover, morphofunctional systemic vascular alterations have been associated with increased SUA[27–29] as well as with impaired intrarenal hemodynamic changes and worse renal function in hypertensive patients.[17,30,31] These mechanisms, along with others elsewhere described,[32,33] could lead to renal hemodynamic alterations in mild hyperuricemic hypertensive patients, consisting of augmented vascular resistance, as well as to increased albuminuria and reduced eGFR.

CONCLUSIONS

Our investigation seems to suggest that SUA is strongly correlated with RRI, but this latter does not seem to explain the relationship between SUA and renal damage. Because of its cross-sectional design, our study does not allow us to establish a causality relationship. Therefore, the mechanisms provided to explain our data are only speculative, and need to be tested in future studies.

Conflict of Interest: The authors declare no conflict of interest.

References

1. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. *N Engl J Med*. 2008;359:1811–1821.
2. Johnson RJ, Segal MS, Srinivas T, et al. Essential hypertension, progressive renal disease, and uric acid: a pathogenetic link? *J Am Soc Nephrol*. 2005;16:1909–1919.
3. Cirillo P, Sato W, Reungjui S, et al. Uric acid, the metabolic syndrome, and renal disease. *J Am Soc Nephrol*. 2006;17:S165–S168.
4. Sedaghat S, Hoorn EJ, van Rooij FJ, et al. Serum uric acid and chronic kidney disease: the role of hypertension. *PLoS One*. 2013;8:e76827.
5. Ejaz AA, Alquadan KF, Dass B, et al. Effects of serum uric acid on estimated GFR in cardiac surgery patients: a pilot study. *Am J Nephrol*. 2016;42:402–409.
6. Bjornstad P, Lanaspa MA, Ishimoto T, et al. Fructose and uric acid in diabetic nephropathy. *Diabetologia*. 2015;58:1993–2002.
7. Chang YH, Lei CC, Lin KC, et al. Serum uric acid level as an indicator for CKD regression and progression in patients with type 2 diabetes mellitus-a 4.6-year cohort study. *Diabetes Metab Res Rev*. 2015 Nov 21. [Epub ahead of print]
8. Mazzali M, Kanellis J, Han L, et al. Hyperuricemia induces a primary renal arteriolopathy in rats by a blood pressure-independent mechanism. *Am J Physiol Renal Physiol*. 2002;282:F991–F997.
9. Sánchez-Lozada LG, Tapia E, Avila-Casado C, et al. Mild hyperuricemia induces glomerular hypertension in normal rats. *Am J Physiol Renal Physiol*. 2002;283:F1105–F1110.
10. Sánchez-Lozada LG, Tapia E, Santamaría J, et al. Mild hyperuricemia induces vasoconstriction and maintains glomerular hypertension in normal and remnant kidney rats. *Kidney Int*. 2005;67:237–247.
11. Mazzali M, Hughes J, Kim YG, et al. Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. *Hypertension*. 2001;38:1101–1106.
12. Messerli FH, Frohlich ED, Dreslinski GR, et al. Serum uric acid in essential hypertension: an indicator of renal vascular involvement. *Ann Intern Med*. 1980;93:817–821.
13. Viazzi F, Leoncini G, Ratto E, et al. Mild hyperuricemia and subclinical renal damage in untreated primary hypertension. *Am J Hypertens*. 2007;20:1276–1282.
14. Berni A, Boddi M, Fattori EB, et al. Serum uric acid levels and renal damage in hyperuricemic hypertensive patients treated with renin-angiotensin system blockers. *Am J Hypertens*. 2010;23:675–680.
15. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the Management of Arterial Hypertension. The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*. 2013;31:1281–1357.
16. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612.
17. Geraci G, Mulè G, Mogavero M, et al. Renal haemodynamics and severity of carotid atherosclerosis in hypertensive patients with and without impaired renal function. *Nutr Metab Cardiovasc Dis*. 2015;25:160–166.

18. Matsushita K, van der Velde M, Astor BC, et al. Chronic kidney disease prognosis consortium. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet*. 2010;375:2073–2208.
19. Kanellis J, Kang DH. Uric acid as a mediator of endothelial dysfunction, inflammation, and vascular disease. *Semin Nephrol*. 2005;25:39–42.
20. Corry DB, Eslami P, Yamamoto K, et al. Uric acid stimulates vascular smooth muscle cell proliferation and oxidative stress via the vascular renin-angiotensin system. *J Hypertens*. 2008;26:269–275.
21. Kang DH, Han L, Ouyang X, et al. Uric acid causes vascular smooth muscle cell proliferation by entering cells via a functional urate transporter. *Am J Nephrol*. 2005;25:425–433.
22. Rieselbach RE, Steele TH. Intrinsic renal disease leading to abnormal urate excretion. *Nephron*. 1975;14:81–87.
23. Scheven L, Joosten MM, de Jong PE, et al. The association of albuminuria with tubular reabsorption of uric acid: results from a general population cohort. *J Am Heart Assoc*. 2014;3:e000613.
24. Kanda E, Muneyuki T, Kanno Y, et al. Uric acid level has a U-shaped association with loss of kidney function in healthy people: a prospective cohort study. *PLoS One*. 2015;10:e0118031.
25. Eräranta A, Kurra V, Tahvanainen AM, et al. Oxonic acid-induced hyperuricemia elevates plasma aldosterone in experimental renal insufficiency. *J Hypertens*. 2008;26:1661–1668.
26. Ruiz-Hurtado G, Ruilope LM. Hypertension and obesity: correlates with renin-angiotensin-aldosterone system and uric acid. *J Clin Hypertens (Greenwich)*. 2014;16:559–560.
27. Cicero AF, Salvi P, D'Addato S, et al. Association between serum uric acid, hypertension, vascular stiffness and subclinical atherosclerosis: data from the Brisighella Heart Study. *J Hypertens*. 2014;32:57–64.
28. Vlachopoulos C, Xaplanteris P, Vyssoulis G, et al. Association of serum uric acid level with aortic stiffness and arterial wave reflections in newly diagnosed, never-treated hypertension. *Am J Hypertens*. 2011;24:33–39.
29. Mulè G, Riccobene R, Castiglia A, et al. Relationships between mild hyperuricaemia and aortic stiffness in untreated hypertensive patients. *Nutr Metab Cardiovasc Dis*. 2014;24:744–750.
30. Doi Y, Iwashima Y, Yoshihara F, et al. Association of renal resistive index with target organ damage in essential hypertension. *Am J Hypertens*. 2012;25:1292–1298.
31. Geraci G, Mulè G, Geraci C, et al. Association of renal resistive index with aortic pulse wave velocity in hypertensive patients. *Eur J Prev Cardiol*. 2015;22:415–422.
32. Kim IY, Lee DW, Lee SB, Kwak IS. The role of uric acid in kidney fibrosis: experimental evidences for the causal relationship. *Biomed Res Int*. 2014;2014:638732.
33. Ryu ES, Kim MJ, Shin HS, et al. Uric acid-induced phenotypic transition of renal tubular cells as a novel mechanism of chronic kidney disease. *Am J Physiol Renal Physiol*. 2013;304:F471–F480.

Supporting Information

Additional supporting information may be found online in the supporting information tab for this article.

Figure S1. Mean values (±SEM) of SUA (A) and RRI (B) in hypertensive patients divided by sex, diabetes, and smoking habit.

Figure S2. Relationships of eGFR and albuminuria with SUA unadjusted (A and B) and adjusted (C and D) for RRI.

Table S1. Percentage of patients treated with cardiovascular drugs in the overall study population and in the two groups with and without CKD.

Table S2. Correlations of serum uric acid, RRI, eGFR, and (log)albuminuria with other variables in the overall study population.