

Mild Hyperuricemia and Subclinical Renal Damage in Untreated Primary Hypertension

Francesca Viazzi, Giovanna Leoncini, Elena Ratto, Valeria Falqui, Angelica Parodi, Novella Conti, Lorenzo E. Derchi, Cinzia Tomolillo, Giacomo Deferrari, and Roberto Pontremoli

Background: Subclinical renal damage and hyperuricemia are not uncommon in patients with primary hypertension. Whether mild hyperuricemia reflects a subclinical impairment of renal function or contributes to its development is currently debated. We investigated the relationship between serum uric-acid levels and the occurrence of early signs of kidney damage.

Methods: Four hundred eighteen patients with primary hypertension were studied. Albuminuria was measured as the albumin-to-creatinine ratio, and creatinine clearance was estimated by the formula of Cockcroft and Gault. Interlobar resistive index and renal abnormalities, ie, the renal volume-to-resistive index ratio, were evaluated by renal Doppler and ultrasound.

Results: Uric acid was directly related to resistive index ($P = .007$) in women and to albuminuria ($P = .04$) in men, and was inversely related to the renal volume-to-resistive index ratio in both men ($P = .005$) and women ($P = .02$). Patients with uric-acid levels above the median

showed a higher prevalence of microalbuminuria (14% v 7%, $P = .012$) and of renal abnormalities (41% v 33%, $P = .007$). Moreover, when creatinine clearance was taken as a covariate, patients with increased uric-acid levels showed higher albuminuria and resistive indices, and a lower renal volume-to-resistive index ratio. Even after adjustment for several risk factors, each standard deviation increase in serum uric acid entailed a 69% higher risk of microalbuminuria, and a 39% greater risk of ultrasound detectable renal abnormalities.

Conclusions: Mild hyperuricemia is associated with early signs of renal damage, ie, microalbuminuria and ultrasound-detectable abnormalities, regardless of the glomerular filtration rate in primary hypertension. Am J Hypertens 2007;20:1276–1282 © 2007 American Journal of Hypertension, Ltd.

Key Words: Hypertension, microalbuminuria, renal abnormalities, serum uric acid, renal resistive index.

Subclinical renal abnormalities, such as a slight decrease in glomerular filtration rate (GFR) or microalbuminuria, are not uncommon findings in patients with primary hypertension (PH).¹ These signs of renal involvement were reported in up to 30% of hypertensive patients, and are usually regarded as unfavorable prognostic markers. Mild hyperuricemia is another relatively common feature of patients with high blood pressure,² although its independent prognostic value was recently debated.³ As a matter of fact, chronic hyperuricemia was shown to induce several potentially unfavorable effects, both experimentally and clinically. These effects may include vascular smooth muscle cell hyperplasia,⁴ endothelial dysfunction,^{5,6} and intrarenal activation of the renin-angiotensin-aldosterone system,⁷ thus making

it a likely candidate for linking hypertension to cardiovascular (CV) and renal damage.⁸

A better understanding of the relationship between serum uric acid (SUA) and subclinical renal abnormalities in patients with PH might help clarify the mechanisms underlying the development of hypertensive kidney damage. The present investigation tested the hypothesis that mild hyperuricemia may be related to early renal damage in subjects with uncomplicated essential hypertension.

Methods

Study Population

Between January 2000 and March 2006, all patients with primary hypertension who were attending the outpatient

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Department of Internal Medicine and Cardio-Nephrology, Azienda Universitaria Ospedale San Martino, University of Genoa, and Department of Radiology-Dipartimento di Discipline Chirurgiche, Morfologiche e Metodologie Integrate (DICMI), University of Genoa, Genoa, Italy.

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Address correspondence and reprint requests to Dr. Roberto Pontremoli, Department of Internal Medicine and Cardio-Nephrology, Azienda Universitaria Ospedale San Martino, University of Genoa, Viale Benedetto XV 6, 16132 Genoa, Italy; e-mail: roberto.pontremoli@unige.it

clinic of our institution were asked to participate in this study, which was part of a larger trial (Microalbuminuria: A Genoa Investigation on Complications, or MAGIC). Details of the study were previously published.⁹ Exclusion criteria were the presence of neoplastic or hepatic disease, serum creatinine ≥ 1.3 mg/dL in males and ≥ 1.2 mg/dL in females, clinical proteinuria, chronic heart failure (New York Heart Association classes III and IV), and a history or clinical signs of ischemic heart disease, diabetes mellitus, severe obesity (defined as body weight $>150\%$ of ideal body weight), and disabling diseases such as dementia or inability to cooperate. Altogether, 476 hypertensive patients (all Caucasian Europeans), seen at our clinic within the above-mentioned time frame, fulfilled the inclusion criteria. Fourteen patients (3%) had received, or were currently receiving, allopurinol, and were therefore excluded from this analysis, and 44 patients were excluded because of unwillingness to participate or for miscellaneous reasons. Of 418 participating patients, 372 (89%) had never been treated for hypertension, whereas 46 (11%) had received antihypertensive treatment in the past, albeit intermittently and not during the 6 months before the study. The study protocol was approved by the Ethics Committee of our department, and written, informed consent was obtained from each subject. Patients underwent a complete physical examination and routine biochemical blood and urine analyses. Twenty-four hour urine collection was obtained from each subject on the day before the study to assess dietary sodium intake. All patients were on a free, salt-unrestricted diet at the time of the study, and they did not receive any medication until biochemical and ultrasound and Doppler evaluations were completed.

Low-density lipoprotein (LDL) cholesterol was calculated using the formula of Friedewald et al.¹⁰ Metabolic syndrome (MS) was defined according to Adult Treatment Panel III criteria, modified as recommended in the latest American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement.¹¹ Body mass index (BMI) was calculated using the formula $BMI = \text{weight (in kilograms)}/\text{height (in meters)}^2$. A family history of hypertension and cardiovascular disease, the amount of physical activity, smoking habits, and alcohol consumption were assessed by means of a standardized questionnaire.

Renal Damage

Albuminuria Albuminuria was evaluated by measuring the urinary albumin-to-urinary creatinine ratio (ACR). The mean of three nonconsecutive, first morning samples was recorded. Only samples from patients with negative urine cultures were collected. The urine albumin concentration was measured with a commercially available radioimmunoassay kit (Pantec, Turin, Italy). Microalbuminuria was defined as $ACR \geq 22$ mg/g in men and ≥ 31 mg/g in women.¹² The upper cutoff limit for microalbuminuria was 310 mg/g.

Creatinine Clearance Creatinine clearance was estimated by the formula of Cockcroft and Gault.¹³ Ideal body weight was used in the formula.

Renal Ultrasound and Doppler Studies Renal volume (RV) was measured by use of the ellipsoid formula ($\text{volume} = \text{length} * \text{width} * \text{thickness} * \pi/6$). The mean of the two kidney volumes for each patient was taken into consideration and corrected for BMI.¹⁴ Doppler signals were obtained from the interlobar arteries by placing the sample volume at the edge of the medullary pyramids. Mean resistive index (RI), ie, $(\text{peak systolic velocity} - \text{end-diastolic velocity})/\text{peak systolic velocity}$, was calculated by using six measurements (three from each of the two kidneys) taken for each patient. The ultrasound examination of the kidneys and pulsed Doppler of the intrarenal arteries were performed using an AU 450 machine (Hitachi, Tokyo, Japan), with a 3.5-MHz transducer working at 2.5 MHz for Doppler analysis. Renal ultrasound abnormalities were diagnosed when the renal volume-to-resistive index ratio was below the median, ie, $<177 \text{ mL} * \text{m}^2/\text{kg}$.

Statistical Analysis

Data are expressed as mean \pm standard deviation, except for variables not normally distributed, ie, duration of disease, triglycerides, and creatinine clearance, expressed as median (interquartile range). Logarithmically transformed values of skewed variables were used for the statistical analysis. The degree of association between variables was assessed using the Pearson correlation coefficient (r). Comparisons between groups were made by analysis of variance. Creatinine clearance was used in analysis of covariance (ANCOVA) to test the role of uric acid, regardless of renal function in the variations of albuminuria and renal ultrasound (US) abnormalities. Comparisons of proportion among groups were performed using the χ^2 test. Relative risks and 95% confidence intervals were calculated by exponentiation of logistic regression coefficients. Statistical analyses were performed using Statview for Windows (version 5.0.1, SAS Institute, Inc., Cary, NC). $P < .05$ was considered statistically significant.

Results

The overall prevalence of moderate reduction in renal clearance (creatinine clearance <60 mL/min), of microalbuminuria, of increased renovascular resistance (above the median, ie, $RI \geq 0.59$), and of renal US abnormalities (renal volume-to-resistive index ratio below the median, ie, $\leq 177 \text{ mL} * \text{m}^2/\text{kg}$) was 6%, 11%, 41%, and 37%, respectively.

The main clinical characteristics of our study patients (260 men, 158 women) are reported in Table 1. As expected, men showed significantly higher SUA levels compared with women (5.8 ± 1.2 mg/dL v 4.1 ± 1.0 mg/dL, $P < .0001$). Therefore, we analyzed the study population on the basis of sex-specific median of SUA. Overall,

Table 1. Descriptive characteristics of study patients according to SUA levels and gender (*n* = 418)

Variable	All			Females			Males		
	Low SUA	High SUA	<i>P</i>	Low SUA	High SUA	<i>P</i>	Low SUA	High SUA	<i>P</i>
Number	418	203	215	73	85		130	130	
Sex, males (%)	260 (62%)	130 (31%)	130 (31%)			NS			
Age (y)	48 ± 9	47 ± 9	48 ± 9	46 ± 8	50 ± 9	.015	48 ± 10	47 ± 9	NS
Duration of disease (months)	30 (60)	30 (58)	24 (72)	30 (59)	24 (72)	NS	30 (55)	36 (76)	NS
BMI (kg/m ²)	26 ± 3	26 ± 3	27 ± 4	25 ± 4	26 ± 4	.01	26 ± 2	28 ± 3	>.0001
Smoking habits (%)	108 (26%)	51 (25%)	71 (33%)	22 (31%)	26 (31%)	NS	29 (22%)	44 (34%)	NS
Office systolic BP (mm Hg)	156 ± 15	156 ± 15	157 ± 14	157 ± 16	158 ± 14	NS	155 ± 15	156 ± 15	NS
Office diastolic BP (mm Hg)	100 ± 8	100 ± 8	101 ± 8	100 ± 8	100 ± 9	NS	100 ± 8	101 ± 8	NS
Office mean BP (mm Hg)	119 ± 9	119 ± 9	119 ± 9	119 ± 9	120 ± 9	NS	118 ± 9	119 ± 8	NS
Office pulse pressure (mm Hg)	56 ± 14	55 ± 14	57 ± 14	56 ± 13	58 ± 12	NS	54 ± 15	55 ± 14	NS
Serum glucose (mg/dL)	90 ± 11	90.2 ± 11	90.2 ± 12	86 ± 11	88 ± 12	NS	92 ± 11	91 ± 11	NS
Serum uric acid (mg/dL)	5.1 ± 1.4	4.3 ± 1.0	5.9 ± 1.2	3.3 ± 0.5	4.7 ± 0.8	<.0001	4.8 ± 0.8	6.7 ± 0.6	>.0001
Cholesterol (mg/dL)	211 ± 43	207.8 ± 43	214.4 ± 43	207 ± 41	212 ± 40	NS	208 ± 45	216 ± 45	NS
HDL cholesterol (mg/dL)	53 ± 15	54.2 ± 14	52.8 ± 16	59 ± 13	60 ± 16	NS	51 ± 13	48 ± 13	.04
LDL cholesterol (mg/dL)	136 ± 40	133.1 ± 40	138.7 ± 40	128 ± 40	133 ± 37	NS	136 ± 39	142 ± 43	NS
Triglycerides (mg/dL)	104 (69)	99 (65)	109 (78)	85 (47)	89 (53)	NS	108 (63)	126 (93)	.003
Serum creatinine (mg/dL)	0.9 ± 0.2	0.90 ± 0.2	0.92 ± 0.2	0.8 ± 0.1	0.8 ± 0.1	NS	1.0 ± 0.1	1.0 ± 0.1	NS
Creatinine clearance (mL/min)	84 (26)	86 (24)	82 (28)	83 (30)	75 (17)	NS	90 (25)	88 (27)	NS

BMI = body mass index; BP = blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SUA = serum uric acid.

Data are mean ± SD or percentage, except for duration of disease, triglycerides, and creatinine clearance, which are expressed as median (interquartile range). Low SUA indicates patients with SUA levels below the sex-specific median; high SUA indicates patients with SUA levels above or equal to the sex-specific median.

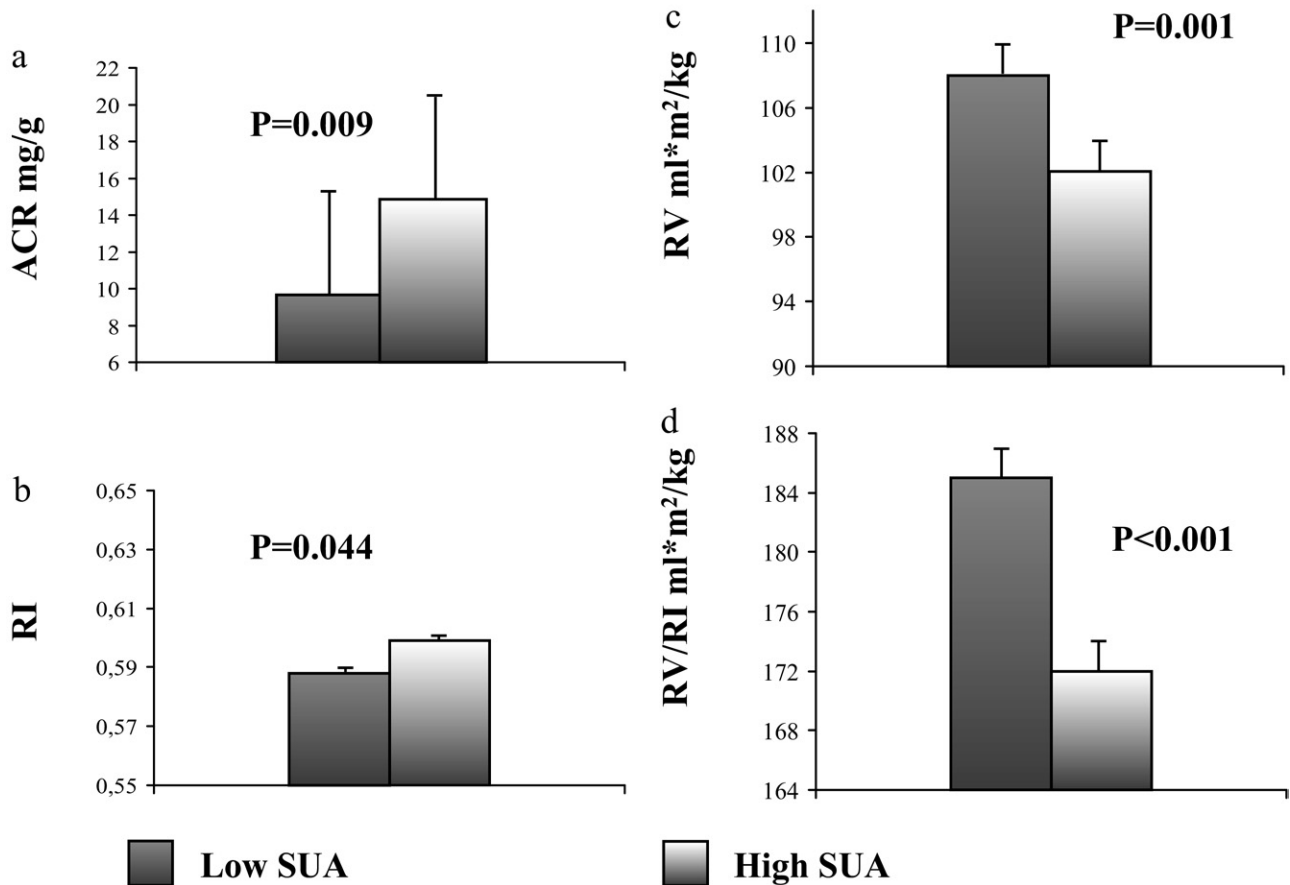


FIG. 1. Albuminuria (a), resistive index (b), renal volume (c), and renal volume to resistive index ratio (d) values on the basis of sex-specific median of serum uric acid (SUA) levels in the whole study population ($n = 418$). Low SUA indicates patients with SUA levels below the sex-specific median. High SUA indicates patients with SUA levels above or equal to sex specific median. ACR = albumin/creatinine ratio expressed as mg/g (conversion factor to mg/mmol, 0.113); RI = resistive index; RV/RI = renal volume-to-resistive index ratio. Data are expressed as mean \pm SD.

patients with higher SUA levels showed a higher BMI and triglycerides. Females with SUA levels above the median showed a higher BMI and were older, whereas males whose SUA levels were above the median showed a higher BMI and triglycerides, and lower HDL cholesterol. There was no difference in creatinine clearance on the basis of SUA levels and sex.

Univariate analysis showed that in the whole group, SUA was directly related to BMI ($r = 0.31$, $P < .001$), triglycerides ($r = 0.31$, $P < .001$), and LDL cholesterol ($r = 0.12$, $P = .023$), whereas it was inversely related to HDL cholesterol ($r = -0.28$, $P < .001$), renal volume ($r = -0.18$, $P = .001$), and RV/RI ($r = -0.12$, $P = .034$). In women, SUA was directly related to BMI ($r = 0.25$, $P = .002$) and renal resistive index ($r = 0.24$, $P = .007$), and it was inversely related to RV/RI ($r = -0.21$, $P = .02$). In men, SUA was directly related to BMI ($r = 0.22$, $P < .001$), triglycerides ($r = 0.26$, $P < .001$), and ACR ($r = 0.13$, $P = .04$), whereas it was inversely related to HDL cholesterol ($r = -0.16$, $P = .018$), renal volume ($r = -0.23$, $P = .001$), and RV/RI ($r = -0.20$, $P = .005$). Overall, patients whose SUA levels were above the median showed a higher ACR and RI, and lower renal vol-

ume and RV/RI (Fig. 1), as well as a higher prevalence of microalbuminuria (14% v 7%, $P = .012$) and renal US abnormalities (41% v 33% $P = .007$) compared with those who exhibited lower SUA levels.

The relationship between SUA and renal damage persisted even after adjusting for renal function. Patients with increased SUA levels, taken together, and separately by sex (ANCOVA, Fig. 2), showed higher ACR values and RV/RI, even after taking creatinine clearance into consideration.

The independent relationship of SUA to the presence and severity of early renal damage was confirmed by the results of multiple logistic regression analysis (Table 2). In fact, even after adjustment for several known risk factors such as sex and MS, each SD increase in SUA (ie, 1.4 mg/dL) entailed a 69% higher risk of having microalbuminuria, and a 39% greater risk of having decreased RV/RI.

Discussion

The main finding of our report is the strong correlation between early renal abnormalities and mild hyperuricemia,

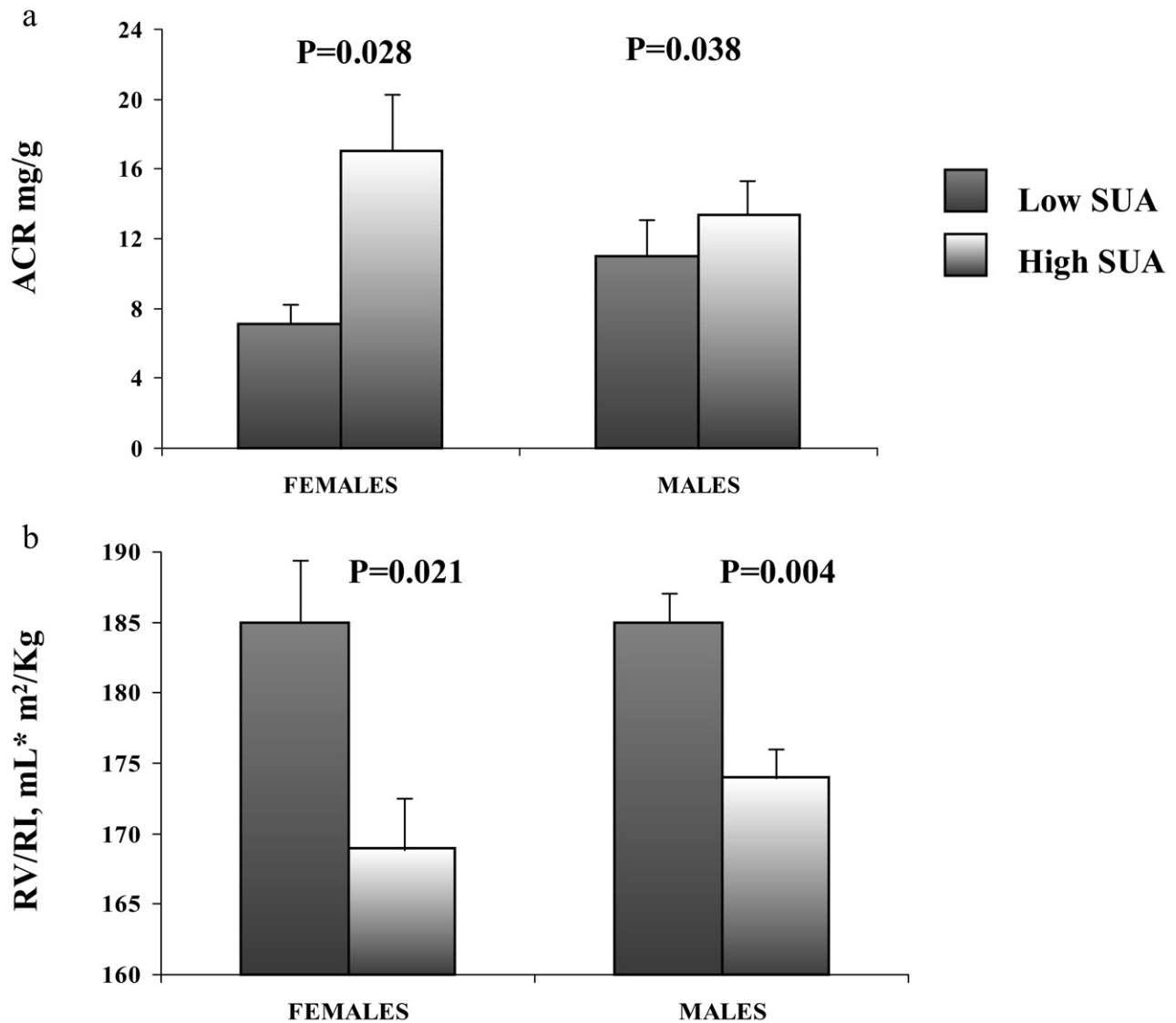


FIG. 2. Albuminuria (**a**) and renal volume-to-resistive index ratio (**b**) values on the basis of serum uric acid (SUA) levels and sex. Data are adjusted for creatinine clearance (ANCOVA). Low SUA indicates patients with SUA levels below the sex-specific median. High SUA indicates patients with SUA levels above or equal to the sex-specific median. ACR = albumin/creatinine ratio expressed as mg/g (conversion factor to mg/mmol, 0.113); RV/RI = renal volume-to-resistive index ratio. Data are expressed as mean \pm SD.

regardless of estimated GFR in patients with primary hypertension.

A great deal of evidence supports the possible role of uric acid as a risk factor for cardiovascular events¹⁵ and as a mediator of subclinical organ damage in diabetic, hypertensive, and prehypertensive subjects.^{16,17,18} Moreover, recent reports suggest that uric acid may also be implicated in the development and progression of renal dysfunction.^{19,20,21} However, whether chronic hyperuricemia by itself is an independent promoter of renal damage is still under debate.

Here, we describe a direct relationship between SUA levels and renal RI in women. Moreover, patients whose SUA levels were above the median showed lower renal volume and a higher resistive index (Fig. 1), even after adjusting for creatinine clearance (ANCOVA, $P < .05$,

data not shown). The intrarenal resistive index is thought to reflect downstream vascular impedance, and therefore was suggested as a measure of renal arterial stiffness. Furthermore, even a slight increase in renal vascular impedance was associated with early signs of cardiovascular damage,²² systemic arterial stiffness,²³ and subclinical abnormalities of renal function in primary hypertension,²⁴ indicating that the renal resistive index should be considered a marker of atherosclerotic processes, at least in this setting. As preclinical chronic ischemia ensues, kidney vascular impedance increases, and kidney size becomes smaller. Therefore, we propose that the renal volume-to-resistive index ratio might be an indicator of intrarenal atherosclerosis. This integration of ultrasound and Doppler findings could help identify patients with preclinical renal ischemia, char-

Table 2. Multiple logistic regression analysis: relationship of selected variables to the presence of early renal damage

a. Dependent variable: microalbuminuria			
Variable	Odds ratio	95% Confidence interval	P value
SUA (per SD increase, ie, 1.4 mg/dL)	1.69	1.07 to 2.67	.024
MBP (per SD increase, ie, 9 mm Hg)	2.24	1.49 to 3.41	<.001
Log triglycerides (per SD increase, ie, 0.2)	1.59	1.05 to 2.40	.028

b. Dependent variable: ultrasound and Doppler renal abnormalities			
Variable	Odds ratio	95% Confidence interval	P value
SUA (per SD increase, ie, 1.4 mg/dL)	1.39	1.01 to 1.95	.045
Gender (female)	2.41	1.26 to 4.61	.008
MS (presence)	2.87	1.57 to 5.27	<.001

Also included in the model: age, gender, body mass index, log creatinine clearance, LDL cholesterol, pulse pressure, and presence of MS not significantly related to the presence of microalbuminuria.

LDL = low-density lipoprotein; MBP = mean blood pressure; MS = metabolic syndrome; SD = standard deviation; SUA = serum uric acid.

acterized by reduced kidney volume and increased renovascular impedance.

Our finding that even mild hyperuricemia is associated with increased renal vascular impedance and reduced RV/RI supports the hypothesis that increased SUA might be implicated in the development of atherosclerotic lesions at the renal level.

As pointed out by Messerli et al, mild hyperuricemia may simply reflect a decrease in renal blood flow and early hypertensive nephrosclerosis.²⁵ Nevertheless, in our study, patients with creatinine clearance <60 mL/min showed similar SUA levels as those with a preserved GFR (5.10 ± 1.42 , $n = 25$ v 5.13 ± 1.32 , $n = 393$, data not shown). Furthermore, albuminuria and US renal abnormalities were associated with increased SUA levels when creatinine clearance was included as a covariate (Fig. 2b). Finally, in multivariate analyses, the estimation of GFR was not significantly related to the presence of early renal damage (ie, microalbuminuria and RV/RI) (Table 2). Therefore, we hypothesize that mild hyperuricemia, combined with hypertension, might cause endothelial dysfunction and result in glomerular hypertension and arteriolar stiffness, which together may lead to increased albuminuria and reduced kidney size, even before a reduction of creatinine clearance becomes evident.

A recently developed animal model shows that mild hyperuricemia induces endothelial dysfunction⁵ and activation of the renin angiotensin system (RAS),²⁶ thus stimulating vascular smooth muscle cell (VSMC) proliferation.⁴ Similarly, there is increasing evidence of an activated intrarenal RAS in patients with mild hyperuricemia,⁷ and of a functional uric-acid transporter causing VSMC proliferation in humans.²⁷ Chronic inflammation and endothelial dysfunction, as observed in patients with increased SUA, are likely among the mechanisms through which this substance may affect renal function and structure.⁶

Our findings are even more intriguing in the context of the recently reported link between hyperuricemia in pregnant women and the risk of low birth weight in their newborns. In fact, it was postulated that uric acid passes freely into the fetal circulation, where it has the potential to inhibit glomerular endothelial-cell proliferation.²⁸ Low birth weight, an important risk factor for hypertension, is also associated with reduced kidney size and nephron number in children and adults.²⁹ Atherosclerosis is usually a generalized disease which affects the small renal vessels, resulting in decreased intrarenal blood flow and a progressive loss of renal volume.³⁰ Our data show that a slight increase in SUA levels (ie, above the median for our study group) tends to cluster with higher urinary albumin excretion and a lower RV/RI (Fig. 2). This is compatible with the observation that a reduction in renal parenchymal volume in the elderly is often detectable even before serum creatinine levels rise.³¹ These observations, taken together, suggest a possible causal relationship between increased serum uric-acid levels and the development of early renal damage, ie, microalbuminuria, vascular stiffness, and reduced kidney volume. Alternatively, one could speculate that even in the absence of GFR reduction, abnormalities of intrarenal hemodynamics (ie, increased renovascular resistance) could result in greater SUA reabsorption at the tubular level.

Perspectives

The cross-sectional design of our study does not allow us to evaluate the impact of hyperuricemia over time. Therefore, our data should be regarded as hypothesis-generating rather than conclusive. Nevertheless, our finding, that the association between SUA and renal subclinical abnormalities in patients with PH is independent of the glomerular filtration rate, provides a rationale for devising longitudinal, interventional studies to test the role that lowering

SUA levels may play in the development and progression of cardiovascular and renal disease.

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