Original

Association between serum uric acid, metabolic syndrome and microalbuminuria in previously untreated essential hypertensive patients

Enrique Rodilla \textsuperscript{a,b}, Francisco Pérez-Lahiguera \textsuperscript{a,b}, José A. Costa \textsuperscript{a}, Carmen González \textsuperscript{c}, Amparo Miralles \textsuperscript{d}, Desamparados Moral \textsuperscript{d} and José María Pascual \textsuperscript{a,b,e,*}

\textsuperscript{a} Unidad de Hipertensión, Servicio de Medicina Interna, Hospital de Sagunto, Agencia Valenciana de Salud, Sagunto, Valencia, España
\textsuperscript{b} CIBER 03/06 Fisiopatología de la Obesidad y Nutrición, Instituto de Salud Carlos III, Madrid, España
\textsuperscript{c} Servicio de Medicina Preventiva, Hospital de Sagunto, Agencia Valenciana de Salud, Sagunto, Valencia, España
\textsuperscript{d} Servicio de Análisis Clínicos, Hospital de Sagunto, Agencia Valenciana de Salud, Sagunto, Valencia, España
\textsuperscript{e} Departamento de Medicina, Universidad de Valencia, Valencia, España

\textbf{ABSTRACT}

Background and objective: The aim of the study was to assess the association of serum uric acid levels with microalbuminuria —urinary albumin excretion (UAE) ≥ 30 mg/24 h—.

Patients and method: Cross-sectional study in 429 (220 women) hypertensive, non diabetic, never treated patients (mean age: 47 years) with glomerular filtration rate ≥ 60 ml/min/1.73 m\textsuperscript{2}.

Results: The prevalence of microalbuminuria was 20.5%; 18% had hyperuricemia and 47% fulfilled the criteria for metabolic syndrome (MS). Baseline UAE correlated in the unvaried analysis to diastolic blood pressure, waist circumference, high-density lipoprotein cholesterol and uric acid. In multiple linear regression models, only MS (beta = 0.113; p = 0.03), and serum uric acid values (beta = 0.04; p = 0.05) were independently associated with logUAE, after adjustment for age and sex. Hyperuricemia (serum uric acid level ≥ 7.0 mg/dl for men and ≥ 6.5 mg/dl for women; odds ratio = 2.18; 95% confidence interval, 1.21–3.92; p = 0.010), and MS (odds ratio = 2.16; 95% confidence interval, 1.32–3.53; p = 0.002) were independently associated with a higher risk of microalbuminuria in multiple logistic regression analyses. The prevalence of microalbuminuria was 45.8% in patients with coexistent MS and hyperuricemia, as compared to 13.6% in hypertensive patients without it (p < 0.001). In patients with concomitant MS and hyperuricemia the probability of being microalbuminuric was 3.7 times higher than in patients without those factors.

Conclusion: Serum uric acid level is associated with microalbuminuria. Coexistence of MS and hyperuricemia in hypertensive patients increases almost 4 times the odds of being microalbuminuric.

\textcopyright 2008 Elsevier España, S.L. All rights reserved.

---

Asociación entre el ácido úrico y el síndrome metabólico con la presencia de microalbuminuria en hipertensos no tratados

\textbf{RESUMEN}

Fundamento y objetivo: valorar la relación de la microalbuminuria —excreción urinaria de albúmina (EUA) ≥ 30 mg/24 h— con los valores de ácido úrico y la presencia de síndrome metabólico (SM).

Pasientes y método: se ha realizado un estudio transversal de 429 pacientes hipertensos (220 mujeres), con una edad media de 47 años, sin tratamiento previo ni diabetes, y con filtrado glomerular igual o mayor que 60 ml/min/1.73 m\textsuperscript{2}.

Resultados: la prevalencia de microalbuminuria fue del 20.5%. El 18% presentaba hiperuricemia y el 47% SM. La EUA se correlacionó con la presión arterial diastólica, el perímetro de la cintura, los valores de colesterol unido a lipoprotenas de alta densidad y el ácido úrico. En un modelo de regresión lineal múltiple, sólo el SM (beta = 0.113; p = 0.03) y el ácido úrico (beta = 0.04; p = 0.05) se asociaron de forma independiente al logEUA. La hiperuricemia (ácido úrico ≥ 7.0 mg/dl en varones y ≥ 6.5 mg/dl en mujeres; odds ratio = 2.18; intervalo de confianza del 95%, 1.21–3.92; p = 0.010) y la presencia de SM...
The amount of urinary albumin excretion (UAE) is considered to be a reflection of generalized endothelial dysfunction associated with a variety of risk factors. Therefore, microalbuminuria is a useful biological marker for the identification of people who are at high risk of cardiovascular events. Microalbuminuria is associated with an increased risk of cardiovascular morbidity in the general population as well as in patients with diabetes and hypertension.

Furthermore, several large epidemiological studies have reported that elevated serum uric acid levels are associated with cardiovascular disease. The association of uric acid with cardiovascular disease appears to be stronger in individuals with hypertension than in the general population, and seems to be further increased when blood pressure (BP) is higher and the target organ damage is more evident. Whether uric acid plays a significant role in the development of cardiovascular disease or merely reflects other concomitant risk factors, such as hypertension, insulin resistance, obesity, or lipid abnormality, has been a matter of debate for years.

The relationship between uric acid and microalbuminuria has been observed previously in hypertensive and pre-hypertensive subjects, mostly related to BP values. However, the pathophysiological mechanism underlying this association remains elusive. In fact, obesity, lipid abnormalities and insulin resistance are related to hyperuricemia as well as to microalbuminuria.

The aim of the present study was to evaluate the association between uric acid levels and the presence of microalbuminuria in a group of middle-aged, non-diabetic subjects, with no history of cardiovascular disease, renal dysfunction or prior treatment for hypertension.

Patients and method

Patient population and selection of study participants

Over a 2 year period, between 1 January 2005 and 31 December 2006, all previously untreated adult patients (>18 years) with suspected primary hypertension attending the outpatient hypertension clinic at Sagunto Hospital (Sagunto, Spain) were asked to participate. All participants gave informed written consent to participate in the study, which was approved by the Ethical Committee of the Sagunto Hospital. Exclusion criteria were: the presence of secondary hypertension, neoplastic, hepatic and/or renal disease, chronic heart failure (New York Heart Association class III and IV), positive history or clinical signs of ischemic heart disease, and diabetes mellitus. Patients with a previous history of gout, renal stones, or use of uric acid-lowering agents, as well as a present history of fever, or urinary tract infection were also excluded.

Diagnosis of essential hypertension was made by the attending doctor following a complete medical history, physical examination and routine biochemical analyses. Further investigations were performed if abnormalities were found in the initial analyses, or if other symptoms or signs suggesting secondary hypertension were present.

In total, 660 untreated hypertensive patients (96% Caucasian) were screened at the clinic during the study period. Of these, 7 were excluded for overt proteinuria, 34 for suspected secondary hypertension, 24 for diabetes, 42 for systemic disorders and 124 for a glomerular filtration rate of <60 ml/min/1.73 m². Hence, the cohort of the present study included 429 patients (65%).

Procedures

A thorough clinical history and physical examinations were performed in all patients. Anthropometric measurements included body mass, height and waist circumference, and the body mass index (BMI) was calculated as weight (kg)/height (m²). Family history, lifestyle habits and other possible cardiovascular risk factors were assessed by means of a standard questionnaire. BP was measured using a mercury sphygmomanometer following the recommendations of the British Hypertension Society. Systolic BP and diastolic BP were the average of 3 readings measured at 5 min intervals. The BP categories of the European Society of Hypertension-European Society of Cardiology 2003 guidelines were considered.

Blood samples were obtained in the morning after a minimum of 12 h fasting. Fasting plasma glucose and serum total cholesterol, triglycerides, uric acid, and creatinine were measured by an automatic biochemistry analyzer (Roche Diagnostics). High-density lipoprotein cholesterol (HDL-C) was measured directly by an enzymatic in vitro assay that uses poly-ethylene-glycol-modified enzymes in the presence of magnesium sulfate and dextran sulfate to get a selective catalytic activities of lipoprotein fractions (Roche Diagnostics). Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation: LDL-C = total cholesterol – (HDL-C + triglycerides/5). Hyperuricemia was defined as a serum uric acid level ≥7.0 mg/dl for men and ≥6.5 mg/dl for women. The glomerular filtration rate was estimated by the MDRD (Modification of Diet in Renal Disease) abbreviate formula. Two urine samples were collected over a 24 h period and stored in sealed glass tubes at 4 °C and analyzed within 7 days after collection. UAE was measured from both samples using a nephelometric immunoassay (Behring Institute). For each patient, UAE was considered as the mean of values obtained from the 2 separate 24 h urine collections. Microalbuminuria was defined as a UAE ≥30 mg/24 h.

Patients were diagnosed of metabolic syndrome (MS) on the basis of the Adult Treatment Panel III criteria, i.e. when 3 out of the following 5 criteria were fulfilled: a) abdominal obesity (waist circumference ≥102 cm for men and ≥88 cm for women); b) triglycerides ≥150 mg/dl; c) HDL-C <40 mg/dl for men and <50 mg/dl for women; d) BP ≥130/85 mmHg; and e) fasting blood glucose ≥110 mg/dl.

Statistical analysis

The results are expressed as mean and standard deviation for continuous variables and as percentages for categorical variables.
Those data with skewed distribution are expressed as the median and inter-quartile interval. Variables found to deviate from normality were log-transformed (decimal logarithm) before the statistical analysis was carried out. Differences in parameters of interest between patients with or without microalbuminuria were sought by the U Mann-Whitney test or Student t test. Comparison of proportion among groups was performed using the χ² test. Relations among variables were assessed using linear regression analysis with Pearson or Spearman correlation coefficients. Linear regression models were created using UAE as a dependent variable; an analysis of covariance was performed to detect significant interaction between MS and uric acid values in UAE after the adjustment for the number of covariates. Logistic regression models were created to estimate the odds ratios for abnormal microalbuminuria. All of the statistical analyses for this study were conducted with SPSS 11.0 for Windows. Statistical significance was assumed if p < 0.05 (2-tailed).

Results

The general characteristics of the 429 patients (220 women) included in the study (age: 47 years; range: 24–69 years) are shown in Table 1. The prevalence of microalbuminuria was 20.5%, and 23% of patients were smokers. Two hundred and two subjects (47%) fulfilled the criteria for MS. Seventy seven (18%) had hyperuricemia. Unvaried correlation analysis of various parameters used for the definition of MS were significantly related to logUAE, after the adjustment for age and gender. The standardized regression coefficients obtained from the multiple linear regression models for logUAE are shown in Table 3; only MS (beta = 0.113; p = 0.03), and serum uric acid values (beta = 0.040; p = 0.05) were independently associated with logUAE, after adjustment for age and gender.

No interaction between MS and uric acid was evident by covariance analysis (p = 0.32). In addition, the characteristics of subjects with microalbuminuria (UAE ≥30 mg/24 h) were compared with those with normoalbuminuria (UAE <30 mg/24 h), and the results are shown in Table 4. Subjects with microalbuminuria had significantly higher waist circumferences (6.1 cm higher; 95% confidence interval [CI], 9.0–3.2), weight (6.1 kg; 95% CI, 9.7–2.4), BMI (2.3 kg/m²; 95% CI, 3.4–1.1), systolic (BP 5 mmHg; 95% CI, 9–1), diastolic BP (3 mmHg; 95% CI, 5–1), serum glucose (2.9 mg/dl; 95% CI, 5.4–0.5), uric acid (0.6 mg/dl; 95% CI, 1.0–0.2), LDL-C (9.3 mg/dl; 95% CI, 18.1–0.4), and serum creatinine (0.045 mg/dl), and lower values of HDL-C (−5.8 mg/dl), than subjects with normoalbuminuria. As most of these factors are related to MS, the prevalence of MS in subjects with microalbuminuria was higher than in those without microalbuminuria (65% vs 44%; p < 0.001), and the same trend was observed with regard to the prevalence of hyperuricemia (31% vs. 15%; p < 0.001).

We also evaluated, by multiple logistic regression analyses, whether the presence of hyperuricemia and MS were independently associated with a higher risk of microalbuminuria (Table 5). The odds ratio of being microalbuminuric in the presence of hyperuricemia was 2.18 (95% CI, 1.21–3.92; p = 0.010), and in the presence of MS it was 2.16 (95% CI, 1.32 to 3.53; p = 0.002), after adjusting for age and sex. In subjects with coexisting MS and hyperuricemia the probability for being microalbuminuric was 3.7 times higher than in patients without them. The prevalence of microalbuminuria was greater in patients with coexisting MS and hyperuricemia when compared with those without it (45.8% vs. 13.6%; p < 0.001) (Fig. 1).
and pre-hypertensive patients;

Table 4: Descriptive characteristics of study population on the basis of albuminuric state

<table>
<thead>
<tr>
<th>Variable</th>
<th>Microalbuminuria (UAE ≥ 30 mg/24 h). N = 88</th>
<th>Normoalbuminuria (UAE &lt; 30 mg/24 h). N = 341</th>
<th>Average variation (CI 95%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46.1 (10)</td>
<td>47.3 (10.3)</td>
<td>−1.20 (−1.1 to −3.6)</td>
<td>0.3</td>
</tr>
<tr>
<td>Sex female (%)</td>
<td>36 (42)</td>
<td>166 (49)</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>100.2 (12.3)</td>
<td>94.1 (12.2)</td>
<td>6.1 (9.0 to 3.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82.4 (15.8)</td>
<td>76.3 (15.3)</td>
<td>6.1 (9.7 to 2.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.5 (5.1)</td>
<td>28.2 (4.8)</td>
<td>2.3 (3.4 to 1.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>155 (17)</td>
<td>150 (15)</td>
<td>5 (9 to 1)</td>
<td>0.005</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>95 (9)</td>
<td>92 (9)</td>
<td>3 (5. to 0.4)</td>
<td>0.018</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>100.74 (10)</td>
<td>97.8 (10.52)</td>
<td>2.94 (5.4 to 0.5)</td>
<td>0.018</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.00 (0.16)</td>
<td>0.95 (0.16)</td>
<td>0.04²</td>
<td></td>
</tr>
<tr>
<td>Glomerular filtration rate (ml/min/1.73 m²)²</td>
<td>78.53 (12.30)</td>
<td>80.53 (14.85)</td>
<td>0.1²</td>
<td></td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>5.86 (1.61)</td>
<td>5.35 (1.47)</td>
<td>0.51 (0.89 to 0.13)</td>
<td>0.003</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>217 (39)</td>
<td>209 (40)</td>
<td>8 (17 to −1)</td>
<td>0.09</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>46.29 (12.21)</td>
<td>52.10 (15.34)</td>
<td>&lt;0.003³</td>
<td></td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>142.11 (36.91)</td>
<td>132.83 (37.65)</td>
<td>9.28 (18.15 to 0.42)</td>
<td>0.040</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>142.11 (93.03)</td>
<td>122.87 (72.23)</td>
<td>0.154³</td>
<td></td>
</tr>
</tbody>
</table>

Values are average (standard deviation). BMI: body mass index; CI: confidence interval; CI: confidence interval; DBP: diastolic blood pressure; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; SBP: systolic blood pressure; UAE: urinary albumin excretion. p value for independent-groups T test.

² Values are median (inter-quartile interval).

Table 5: Multiple logistic regression analyses. Dependent variable: microalbuminuria

<table>
<thead>
<tr>
<th>Variable</th>
<th>Microalbuminuria (UAE ≥ 30 mg/24 h)</th>
<th>ORm</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Woman</td>
<td>18%</td>
<td>1</td>
<td>0.65–1.83</td>
<td>0.74</td>
</tr>
<tr>
<td>Male</td>
<td>22%</td>
<td>1.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>0.99</td>
<td>0.97–1.01</td>
<td>0.42</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not</td>
<td>14%</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>27%</td>
<td>2.16</td>
<td>1.32–3.53</td>
<td>0.002</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not</td>
<td>17%</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>35%</td>
<td>2.18</td>
<td>1.21–3.92</td>
<td>0.011</td>
</tr>
</tbody>
</table>

CI: confidence interval; ORm: odds ratio multivariate; UAE: urinary albumin excretion. Hyperuricemia is considered if serum uric acid ≥7 mg/dl in men, or ≥6.5 mg/dl in women.

Discussion

In this study, we demonstrated the association between serum uric acid levels and MS in the presence of microalbuminuria in previously untreated, non diabetic, hypertensive patients. Increased serum uric acid levels and MS were independent factors for microalbuminuria in this group with normal renal function. It is well known that microalbuminuria is associated with an increased risk of cardiovascular disease and might be an easily detectable marker of generalized vascular dysfunction. Our findings suggest that elevated serum uric acid levels combined with MS can be a strong predictor of the presence of microalbuminuria and, consequently, a sensitive marker for cardiovascular disease. The odds of being microalbuminuric in patients with coexistent MS and hyperuricemia is almost 4 times higher than in subjects without these 2 factors, representing an important clinical finding.

Although several studies have previously shown the association between hyperuricemia and microalbuminuria in hypertensive and pre-hypertensive patients, the relationship has been mainly related to BP values and renal function. The relationship between hyperuricemia and other markers of hypertension and organ damage, such as left-ventricular hypertrophy or carotid alterations, has been equivocal, suggesting that the selection of subjects, BP values, hypertension duration and other concomitant risk factors may affect the results of the analysis. Hypertension is a dominant risk factor for cardiovascular disease that may mask the contributions of other risk factors.

The effect of hyperuricemia may become more evident on other risk factors, when BP values are lower. In our untreated hypertensive patients, UAE was related to BP; however, there is a strong correlation with other risk factors of metabolic origin that tend to cluster into the same patients. When the metabolic factors were grouped together into MS, uric acid remained an important independent risk factor of microalbuminuria. It is unknown whether increased uric acid levels and high BP have synergistic effects on microalbuminuria, or whether serum uric acid levels are an alternative marker of renal damage independent of a high BP.

This study has limitations that deserve a mention. The most important is that it was a cross-sectional study which was not

![Figure 1](image-url) Prevalence of microalbuminuria (urinary albumin excretion ≥30 mg/24 h) according to the presence or absence of metabolic syndrome and/or hyperuricemia.
able to measure the impact of hyperuricemia and its modifications over time, in UAE variation, and it may only be assessed in a prospective study. Nevertheless, the present study demonstrates the concomitant and independent association of serum uric acid level and MS with an increased risk for microalbuminuria in subjects with previously untreated hypertension. These findings suggest that increased uric acid values might have some physiopathologic role in renal damage and share a related pathogenic link in relation to microalbuminuria.

Uric acid has for many years been known to be associated with hypertension, and even the Framingham data showed that uric acid values are a prognostic indicator for the development of hypertension. Several mechanisms could lead to hyperuricemia in hypertensive patients. Hypertension leads to vascular disease and increased renal vascular resistance, both resulting in decreased renal blood flow, which in turn stimulates the urate reabsorption. Moreover, microvascular renal disease leads to local ischemia and release of lactate, which compete with the urate transporter in the proximal tubule, thus blocking the urate excretion. In addition, ischemia induces the degradation of adenosine to adenine and xanthine, whereas an increased generation of xanthine oxidase may be observed. The increased generation of the substrate (xanthine) and the enzyme (xanthine oxidase) can lead to increased uric acid production. Furthermore, high uric acid levels have been associated with an increased generation of free radicals and oxidative stress, which may abolish endothelium dependent vasodilatation, induce activation of the renin angiotensin system, and direct actions on endothelial cells and vascular smooth muscle cells, thus leading to hypertension.

On the other hand, the main pathogenic factor of MS is hyperinsulinemia and/or insulin resistance, that eventually results in dyslipidemia, hypertension, impaired carbohydrate metabolism, and other metabolic abnormalities. Several studies have revealed the relationship between hyperuricemia and insulin resistance. Insulin can enhance renal tubular sodium reabsorption in humans and, decrease the renal excretion of uric acid. Furthermore, renal excretion of uric acid is reduced in situations with an increased renal tubular reabsorption of sodium. Therefore, insulin can modify the handling of uric acid by the kidneys, thus leading to hyperuricemia. In addition, there are other metabolic mechanisms connecting increased serum uric acid levels and hyperinsulinemia. Impairment of the glycolytic pathway, caused by insulin resistance, can increase the flux of glucose-6-phosphate through the hexose’s monophosphate shunt, resulting in accumulation of ribose-5-phosphate and other intermediates, which are major substrates for uric acid production.

Uric acid levels are often increased in subjects with MS, further suggesting that uric acid could be included in the definition of MS. Subjects with persistent hyperinsulinemia related to MS may have an additional effect on renal target organ damage and cause both a rise in UAE and uric acid during the early stages. The metabolic impact of high glucose values, even in the non-diabetic range, can add to the deleterious effect of BP in the variation of microalbuminuria in hypertensive patients. The influence of uric acid treatment in UAE, independent of BP treatment, is at present unknown. However, in a recent prospective study, lowering uric acid in individuals with hyperuricemia and renal dysfunction was associated with improved BP control and slower progression of renal disease, which may well constitute a topic open to future investigations.

In summary, this study demonstrates a strong relationship between MS and hyperuricemia for microalbuminuria in untreated hypertensive patients with normal renal function. The concurrence of MS and hyperuricemia increased almost 4 times the odds of being microalbuminuric. This may be a simple, relatively inexpensive and useful means of identifying patients at high risk and is an important clinical finding that deserves attention. Although these findings do not support a causative effect of hyperuricemia in the genesis of microalbuminuria, insulin resistance may be a common mechanism for MS and hyperuricemia which increases the risk of microalbuminuria.

References