SERUM URIC ACID IS NOT ASSOCIATED WITH DIABETIC NEPHROPATHY IN PATIENTS WITH TYPE 2 DIABETES

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ABSTRACT

Introduction: Although epidemiologic studies suggest a link between serum uric acid (SUA) and vascular complications in diabetes, the relationship of uric acid with diabetic nephropathy remains unclear. We aimed to investigate the relationship between SUA and the degree of albuminuria in patients with type 2 diabetes (T2D).

Materials and methods: The cross-sectional study included 223 T2D patients. Nephropathy was graded as follows: normoalbuminuria, urinary albumin excretion (UAE) less than 30 mg per gram of creatinine (mg/g Cr); microalbuminuria, 30 to 300 mg/g Cr; or macroalbuminuria, more than 300 mg/g Cr. SUA was measured using a uricase-peroxidase enzymatic method.

Results: The degree of nephropathy was as follows: normoalbuminuria in 163 subjects, microalbuminuria in 45 subjects, and macroalbuminuria in 15 patients. SUA did not differ significantly according to the degree of albuminuria. In addition, multivariable analysis demonstrated that hyperuricemia was not an independent predictor of neither microalbuminuria nor macroalbuminuria in T2D patients.

Conclusion: Hyperuricemia does not reflect the severity of nephropathy in T2D patients.

Key words: Microalbuminuria, Serum uric acid, Diabetes, Nephropathy.

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Introduction

Cardiovascular disease (CVD) is the primary cause of mortality and morbidity in patients with type 2 diabetes (T2D), and several risk factors including smoking, hypertension, and dyslipidemia have been shown to accelerate the progression of CVD in this patient population1-3. Microalbuminuria - defined as excretion of albumin in the urine above the normal level but less than gross proteinuria – is considered as a T2D4-6. Recently, an increased level of serum uric acid (SUA) has been shown to have a significant impact on the risk of early progressive renal function loss in these patients4-11.

Elevated SUA is a highly prevalent condition. Over 38 million adults meet criteria for hyperuricemia (>416 μmol/L in men and >357 μmol/L in women) in the US alone12. Nevertheless, the implications of an elevated SUA in the pathogenesis of micro- and macrovascular complications are incompletely elucidated13. Uric acid has been viewed as a potent antioxidant with protective effects toward inflammation and circulating free radicals, but there is also evidence pointing-out how this molecule may act as a pro-oxidant14. Although some observational studies have demonstrated that elevations in SUA are associated with albuminuria, it is still unclear whether demographic or clinical-related risk factors can modify the relationship between SUA and diabetic nephropathy4-11.

Therefore, the aim of this cross-sectional study was to investigate the relationship between SUA and...
the degree of albuminuria, which is a useful marker for diabetic nephropathy, in Turkish T2D patients.

Materials and methods

Patients and study design
In this cross-sectional study, we measured SUA in 223 consecutive T2D patients recruited from the outpatient endocrinology clinic at the Uludag University School of Medicine, Bursa, Turkey. T2D was diagnosed according to the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus\(^{(15)}\). Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Abdominal obesity was estimated measuring the waist/hip ratio. Measurements of systolic and diastolic blood pressure were obtained using a mercury sphygmomanometer. Patients were classified as nonsmokers, past smokers, or current smokers according to a self-administered questionnaire. Nephropathy was graded as follows: normoalbuminuria, urinary albumin excretion (UAE) less than 30 mg per gram of creatinine (mg/g Cr); microalbuminuria, 30 to 300 mg/g Cr; or macroalbuminuria, more than 300 mg/g Cr\(^{(16)}\). Patients with advanced renal dysfunction (serum Cr more than 2.0 mg/dL) or malignancy were excluded from this study. This study was approved by the local Research Ethics Committee and was conducted in accordance with Declaration of Helsinki. Written informed consent was obtained from all participants.

Laboratory measures
Blood samples were taken in the morning. Serum total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride concentrations were assessed using standard enzymatic methods. Fasting plasma glucose was measured by the hexokinase enzymatic method. Hemoglobin A1c was assayed using high-performance liquid chromatography. Urinary albumin and Cr concentration were determined in an early morning spot urine. UAE was measured with an immunoturbidimetric assay. A mean value for UAE was determined from three urine collections.

Serum uric acid
Serum was separated within two hours and immediately analyzed for uric acid. SUA was measured using a uricase-peroxidase enzymatic method on a Cobas Bio centrifugal analyzer. The inter-batch coefficient of variation was <4% and intra-batch was <1%. Hyperuricemia was defined as a SUA >416 (7 mg/dL) μmol/L in men and >357 μmol/L (6 mg/dL) in women\(^{(17)}\).

Data analysis
Analyses were performed using the SPSS software version 17.0 (Statistical Package for the Social Sciences Inc., Chicago, IL, USA). To test the distribution pattern, the Kolmogorov–Smirnov test was used. Continuous data were presented as median and interquartile range (skewed data) or mean ± SD (normally distributed variables). Categorical variables were summarized as percentages and compared with chi-square test. The study population was divided into three groups according to the degree of nephropathy (normoalbuminuria, microalbuminuria, or macroalbuminuria)\(^{(16)}\). Comparisons of continuous variables across the three groups were carried out by Kruskal-Wallis tests or analysis of variance, as appropriate. Spearman correlation coefficients were computed to examine the association between continuous variables. The effect of SUA and the general characteristics of the study participants on the risk of nephropathy was calculated in multivariable analysis. Variables for which the unadjusted P value was <0.10 in univariate analysis were identified as potential risk factors and included in the multivariable model. A P value <0.05 (two-tailed) was considered statistically significant and the confidence interval (CI) was 95%.

Results
The general characteristics of the 223 T2D patients according to the degree of nephropathy (normoalbuminuria, microalbuminuria, or macroalbuminuria) are shown in Table 1. The three study groups were found to be significantly different in terms of duration of diabetes, total cholesterol, and LDL cholesterol. Specifically, subjects with micro- and macroalbuminuria had a greater duration of diabetes and higher total and LDL cholesterol levels than those with normoalbuminuria.

Serum uric acid and diabetic nephropathy
SUA did not differ significantly according to the degree of albuminuria (Table 1 and Figure 1), although there was a trend toward higher levels of SUA in patients with micro- and macroalbuminuria compared to those with normoalbuminuria. Similarly, the prevalence of subjects with hyper-
uricemia did not differ significantly in the three study groups (Table 1).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normoalbuminuria</th>
<th>Microalbuminuria</th>
<th>Macroalbuminuria</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>51 ± 12</td>
<td>55 ± 11</td>
<td>53 ± 15</td>
<td>0.25</td>
</tr>
<tr>
<td>Sex</td>
<td>52/111</td>
<td>19/26</td>
<td>6/9</td>
<td>0.39</td>
</tr>
<tr>
<td>BMI &gt; 25</td>
<td>133 ± 18</td>
<td>134 ± 18</td>
<td>134 ± 18</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Current smoking</td>
<td>33/130</td>
<td>7/58</td>
<td>2/12</td>
<td>0.71</td>
</tr>
<tr>
<td>Systolic blood</td>
<td>126 ± 15</td>
<td>128 ± 13</td>
<td>130 ± 16</td>
<td>0.59</td>
</tr>
<tr>
<td>Diastolic blood</td>
<td>78 ± 10</td>
<td>78 ± 9</td>
<td>80 ± 10</td>
<td>0.86</td>
</tr>
<tr>
<td>Fasting plasma</td>
<td>158 ± 66</td>
<td>163 ± 58</td>
<td>156 ± 56</td>
<td>0.89</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>8.1 ± 1.9</td>
<td>8.3 ± 1.8</td>
<td>8.2 ± 1.6</td>
<td>0.52</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>192 ± 38</td>
<td>188 ± 28</td>
<td>228 ± 46</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>116 ± 36</td>
<td>112 ± 30</td>
<td>118 ± 40</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>133 (95–217)</td>
<td>128 (97–208)</td>
<td>181 (119–290)</td>
<td>0.15</td>
</tr>
<tr>
<td>Serum uric acid, mg/dl</td>
<td>3.9 (3.1–4.8)</td>
<td>4.4 (3.5–5.7)</td>
<td>4.9 (3.5–6.1)</td>
<td>0.08</td>
</tr>
<tr>
<td>Prevalence of hypertension</td>
<td>28/143</td>
<td>18/35</td>
<td>4/11</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Table 1: General characteristics of the 223 T2D patients according to the degree of nephropathy (normoalbuminuria, microalbuminuria, or macroalbuminuria).

Figure 1: Scatter diagram for SUA levels in the 223 T2D patients according to the degree of nephropathy (normoalbuminuria, microalbuminuria, or macroalbuminuria). Horizontal lines across the scatter diagram represent mean values.

Multivariable analysis after adjustment for factors associated with the risk of micro- and macroalbuminuria with unadjusted P value was <0.10 in univariate analysis demonstrated that hyperuricemia was not an independent predictor of neither microalbuminuria (odds ratio = 1.98, 95% CI = 0.84-4.57, P = 0.10) nor macroalbuminuria (odds ratio = 2.45, 95% CI = 0.70–8.12, P = 0.18) in our T2D patients.

Discussion

The present study demonstrates that SUA is not independently associated with the degree of albuminuria in patients with T2D and does not reflect the severity of diabetic nephropathy.

Numerous lines of evidence have suggested that increased SUA may be potentially involved in the pathogenesis of diabetic nephropathy. Kosugi et al. have reported that hyperuricemia has a pathogenic role in the mild tubulointerstitial injury associated with diabetic nephropathy but not glomerular damage in type 2 db/db mice(18). In a cross-sectional study conducted in 60 patients with T2D without a history of gout, Behradmanesh et al. reported a significant positive association of serum uric acid with level of proteinuria(7). In a larger study, Bonakdaran and coworkers showed a stepwise increase of SUA for normoalbuminuric, microalbuminuric, and macroalbuminuric patients(8). In a study of 343 men with T2D, Fukui et al. reported that SUA correlated positively with the logarithm of urinary albumin excretion(9). Similarly, Resl et al. have shown that SUA correlates to albuminuria in a prospective observational study of 494 patients with diabetes(10). Zoppini et al. reported that hyperuricemia seems to be an independent risk factor for the development of incident nephropathy in type 2 diabetic individuals with preserved kidney function(11).

Despite such evidences and experimental studies providing unequivocal evidence that elevated SUA led to increased oxidative stress and kidney function deterioration, there is an ongoing debate as to whether uric acid itself, free oxygen radicals produced while generating uric acid or both are the main culprits responsible for these effects(13, 14). Despite experimental data demonstrating and clinical data suggesting a relationship between uric acid and kidney function, the precise mechanisms and even the presence of true causality are still a matter of debate(7-11, 18).

A few factors have been put forward to argue against uric acid as a causal factor for nephropathy.

First, and somewhat ambiguously, uric acid acts both as a pro-oxidant and antioxidant molecule(14). Second, while uric acid is being produced, cells concurrently produce significant amounts of free oxygen radicals as well(19). This increased
 oxidative stress may in turn cause endothelial dysfunction. Thus, this close coupling with oxidative system makes it difficult to attribute observed detrimental effects associated with hyperuricemia solely to uric acid. To reconcile this, Sautin and Johnson proposed that uric acid behaves differently in intra- and extracellular environments, serving as a pro-oxidant in the former and antioxidant in the latter. Currently a randomized controlled trial is underway and testing efficacy of allopurinol to prevent nephropathy development in type 1 diabetes mellitus patients. However, our data argue against a major role of SUA in the pathogenesis of albuminuria, at least in patients with T2D. Considering potentially severe allergic reactions to allopurinol in the context of other medications and strategies available for treatment of microvascular disease, it will be important to establish which line therapy allopurinol will represent in the treatment of diabetic nephropathy.

There are two main limitations inherent in this report. First, our study was cross-sectional and therefore does not elucidate the causal relationships between SUA and the degree of albuminuria in patients with T2D. Second, the relatively small sample size limits the generalizability of our conclusions.

In conclusion, our data suggest that SUA does not reflect the severity of nephropathy in T2D patients. The use of allopurinol to prevent or slow nephropathy development in these patients does not seem to be entirely justified.

References


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