Urinary Albumin Excretion Rate Is Associated With Increased Ambulatory Blood Pressure in Normoalbuminuric Type 2 Diabetic Patients

Cristiane B. Leitão, MD1
Luís H. Canani, MD1
Patrícia B. Polson1
Marcel P. Molon1
António F. Pinotti, MD2
Jorge L. Gross, MD4

OBJECTIVE — To evaluate the 24-h blood pressure profile in normoalbuminuric type 2 diabetic patients.

RESEARCH DESIGN AND METHODS — A cross-sectional study was conducted in 90 type 2 diabetic patients with a urinary albumin excretion rate (UAER) <20 μg/min on two occasions, 6 months apart (immunoturbidimetry). Patients underwent clinical and laboratory evaluations. Ambulatory blood pressure monitoring and echocardiograms were also performed.

RESULTS — UAER was found to correlate positively with systolic doctor’s office blood pressure measurements (r = 0.243, P = 0.021) and ambulatory blood pressure (24 h: r = 0.280, P = 0.008) and left ventricular posterior wall thickness (r = 0.359, P = 0.010). Patients were divided into four groups according to UAER (<5, ≥5–10, ≥10–15, and ≥15–20 μg/min). Systolic blood pressure parameters for the 1st, 2nd, 3rd, and 4th groups, respectively, were 123.0 ± 10.6, 132.5 ± 15.0, 139.0 ± 23.4, and 130.7 ± 8.0 mmHg for 24-h blood pressure (ANOVA P = 0.004) and 48.4 ± 6.0, 54.5 ± 11.2, 58.8 ± 15.6, and 57.6 ± 8.0 mmHg for 24-h pulse pressure (ANOVA P = 0.003). A progressive increase in the prevalence of diabetic retinopathy was observed from the 1st to the 4th UAER group: 27.3, 43.8, 45.5, and 66.7% (P = 0.029 for trend).

CONCLUSIONS — In type 2 diabetic patients, UAER in the normoalbuminuric range is positively associated with systolic ambulatory blood pressure indexes, left ventricular posterior wall thickness, and diabetic retinopathy, suggesting that intensive blood pressure treatment may prevent diabetes complications in these patients.

From the 1Endocrine Division, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil, and the 2Cardiology Division, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil.

Address correspondence and reprint requests to Jorge L. Gross, Serviço de Endocrinologia do Hospital de Clínicas de Porto Alegre, Rua Ramiro Barcelos 2350, Prédio 12, 4º andar, 90035-003, Porto Alegre, RS, Brazil. E-mail: jorgegross@terra.com.br.

Received for publication 10 December 2004 and accepted in revised form 4 April 2005.

Abbreviations: UAER, urinary albumin excretion rate.

© 2005 by the American Diabetes Association.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
Health Organization criteria (i.e., >30 years of age at onset of diabetes, no previous episode of ketoacidosis or documented ketonuria, and treatment with insulin only after 5 years of diagnosis) (15). Patients with other renal diseases, cardiac arrhythmia, or postural hypotension were excluded. Normoalbuminuric patients were selected based on UAER values <20 μg/min on at least two occasions over the preceding 6 months while on their usual antihypertensive drugs. Patients using ACE inhibitors had these medications suspended for 1 week, after which a 3rd UAER measurement was performed. Of the 92 patients recruited, 2 had UAER >20 μg/min and were not included in the study. Therefore, UAER was consistently within the normoalbuminuric range for all of the patients included. The study protocol was approved by the hospital’s research ethics committee, and informed consent was obtained from all patients.

Clinical, blood pressure, and echocardiographic evaluation
Demographic and anthropometric data were collected by means of an interview and clinical examination, as previously described (16). Indirect ophthalmoscopy was performed through dilated pupils by an ophthalmologist. For the purpose of this study, patients were classified only according to the presence or absence of any degree of diabetic retinopathy.

Blood pressure evaluations were performed 1 week after withdrawal from all antihypertensive medications. Office blood pressure was measured with a mercury sphygmomanometer, using the left arm and with the patient in a sitting position, after a 5-min rest. The mean of two measurements was considered. The patient was classified as hypertensive based on use of antihypertensive drugs and/or office blood pressure ≥140/90 mmHg. Ambulatory 24-h blood pressure monitoring was performed by oscillography (Spacelabs 90207), with a 15-min interval during the daytime and a 20-min interval during the nighttime. Patients were advised to maintain their usual daily activities. Sleep time was recorded as the period between the time when the patient went to bed and the time when the patient woke up the next morning. The means of 24-h, daytime, and nighttime systolic and diastolic blood pressure were recorded. Blood pressure load was defined as the percentage of 24-h and daytime blood pressure ≥140/90 mmHg and of nighttime blood pressure ≥120/80 mmHg. Pulse pressure was the difference between the systolic and diastolic blood pressure means. Patients with a night/day blood pressure ratio >0.9 were considered to be nondippers.

Echocardiograms (n = 60) were obtained according to the recommendations of the American Society of Echocardiography (17), using standard parasternal and apical views with subjects in the partial left decubitus position and using a commercially available instrument (Sonus 1000; Hewellet Packard). Left ventricular mass was calculated based on wall thickness (end-diastolic ventricular internal diameter, end-diastolic interventricular septum, and posterior wall) and was adjusted to body surface area. The cardiologist who performed the echocardiograms was unaware of the subjects’ clinical and laboratory characteristics.

Laboratory methods
UAER was measured in sterile 24-h timed urine samples by immunoturbidimetry (Microlab; Ames, Tarrytown, NY). HbA1c (AIC) was measured by a high-performance liquid chromatography system (normal range 2.7–4.3%, Merck-Hitachi 9100). Fasting plasma glucose was measured by the glucose-peroxidase colorimetric enzymatic method (Biodiagnostic). Creatinine was measured by the Jaffe method and the lipid profile by a colorimetric method. The glomerular filtration rate was determined in 67 patients by the single-injection 131Cr-EDTA technique (18).

Statistical analysis
One-way ANOVA or the χ² test were used to compare clinical and laboratory data. The Bonferroni test was used to determine differences between groups. Quantitative variables without normal distribution were submitted to logarithmic transformation. Data are expressed as the means ± SD, except for triglycerides, serum creatinine, and blood pressure loads, which are expressed as the median (range). Correlations were performed with the Pearson’s χ² (log-UAER versus blood pressure means and left ventricular posterior wall thickness) or Spearman’s rank correlation (log-UAER versus blood pressure loads) tests, depending on the distribution of variables. Multiple linear regression was performed with log-UAER as the dependent variable. P values <0.05 (two tailed) in the univariate analysis were considered to be significant.

RESULTS — There was a positive and significant correlation found between log-UAER and systolic office (r = 0.243, P = 0.021), systolic 24-h (r = 0.280, P = 0.008) (Fig. 1), systolic daytime (r = 0.264, P = 0.013) and systolic nighttime (r = 0.261, P = 0.013) blood pressure, as well as for log-UAER and systolic blood pressure loads (24-h: r = 0.353, P =
Table 1—Clinical and laboratory characteristics of type 2 diabetic patients according to UAER

<table>
<thead>
<tr>
<th></th>
<th>1st group (&lt;5 µg/min)</th>
<th>2nd group (≥5–10 µg/min)</th>
<th>3rd group (≥10–15 µg/min)</th>
<th>4th group (≥15–20 µg/min)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>37</td>
<td>32</td>
<td>11</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>56.7 ± 10.1</td>
<td>57.1 ± 10.5</td>
<td>57.8 ± 7.5</td>
<td>58.5 ± 11.3</td>
<td>0.962</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>9.0 ± 6.2</td>
<td>11.3 ± 7.0</td>
<td>11.8 ± 5.3</td>
<td>16.8 ± 8.8</td>
<td>0.021*</td>
</tr>
<tr>
<td>Male subjects</td>
<td>35.1</td>
<td>25.0</td>
<td>45.5</td>
<td>50.0</td>
<td>0.402</td>
</tr>
<tr>
<td>Caucasians</td>
<td>83.3</td>
<td>80.6</td>
<td>72.7</td>
<td>100.0</td>
<td>0.395</td>
</tr>
<tr>
<td>Smokers</td>
<td>16.2</td>
<td>9.7</td>
<td>9.1</td>
<td>0.0</td>
<td>0.686</td>
</tr>
<tr>
<td>Hypertension</td>
<td>56.8</td>
<td>62.5</td>
<td>72.7</td>
<td>80.0</td>
<td>0.510</td>
</tr>
<tr>
<td>Office blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>136.4 ± 17.5</td>
<td>139.7 ± 21.7</td>
<td>143.6 ± 20.6</td>
<td>145.9 ± 8.6</td>
<td>0.446</td>
</tr>
<tr>
<td>Diastolic</td>
<td>83.8 ± 10.9</td>
<td>86.5 ± 11.2</td>
<td>93.2 ± 14.8</td>
<td>82.3 ± 9.4</td>
<td>0.084</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.6 ± 3.8</td>
<td>28.1 ± 4.3</td>
<td>28.5 ± 4.9</td>
<td>27.6 ± 6.2</td>
<td>0.927</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>27.3</td>
<td>43.8</td>
<td>45.5</td>
<td>66.7</td>
<td>0.029†</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dl)</td>
<td>152.5 ± 57.5</td>
<td>167.3 ± 65.6</td>
<td>170.2 ± 62.8</td>
<td>138.1 ± 39.0</td>
<td>0.477</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>6.04 ± 2.40</td>
<td>6.31 ± 1.92</td>
<td>6.94 ± 1.54</td>
<td>5.82 ± 1.21</td>
<td>0.631</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>181.6 ± 44.9</td>
<td>218.6 ± 48.8</td>
<td>218.8 ± 52.4</td>
<td>199.8 ± 55.1</td>
<td>0.011†</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>44.6 ± 9.2</td>
<td>48.3 ± 13.7</td>
<td>46.9 ± 17.4</td>
<td>46.1 ± 13.3</td>
<td>0.686</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>120 (54–421)</td>
<td>131 (39–1115)</td>
<td>197 (50–392)</td>
<td>115 (68–609)</td>
<td>0.152</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.8 (0.5–1.2)</td>
<td>0.8 (0.3–1.3)</td>
<td>0.9 (0.7–1.0)</td>
<td>0.9 (0.5–1.1)</td>
<td>0.204</td>
</tr>
<tr>
<td>GFR (ml · min⁻¹ · 1.73 m⁻²)</td>
<td>107.5 ± 33.8</td>
<td>109.7 ± 34.3</td>
<td>81.5 ± 25.6</td>
<td>120.3 ± 38.9</td>
<td>0.472</td>
</tr>
</tbody>
</table>

Data are means ± SD, %, or median (range). *P < 0.05 for 1st vs. 4th group; †P for trend; ‡P < 0.05 for 1st vs. 2nd group. §glomerular filtration rate data available for 27, 23, 9, and 8 patients in the 1st, 2nd, 3rd, and 4th groups, respectively. GFR, glomerular filtration rate.

0.001; daytime: r = 0.351, P = 0.001; and nighttime: r = 0.229, P = 0.031).

A positive and significant correlation between the log-UAER and left ventricular posterior wall thickness (r = 0.359, P = 0.010) was also observed. This supports the hypothesis that UAER is associated with target-organ injury, even if it is within the normal range, probably because of higher blood pressure levels. There was no association between log-UAER and the other echocardiographic parameters analyzed, such as left ventricular mass, septum thickness, and left atrium size.

Patients were divided into four groups according to UAER (1st group: <5 µg/min; 2nd group: ≥5–10 µg/min; 3rd group: ≥10–15 µg/min; and 4th group: ≥15–20 µg/min) (Table 1). Patients in the 4th UAER group had longer diabetes duration than patients in the 1st group. In terms of laboratory characteristics, patients in the 1st group of UAER had the lowest levels of total cholesterol. The prevalence of diabetic retinopathy increased progressively from the 1st to the 4th UAER group (27.3, 43.8, 45.5, and 66.7%; P = 0.029 for trend). Mean age, BMI, proportion of male sex, smokers, and hypertensive patients were similar in the four groups, as was the ethnic group distribution.

Office blood pressure was similar in all groups (Table 1). In general, patients belonging to the 1st UAER group (UAER <5 µg/min) had lower ambulatory systolic blood pressure levels than patients with higher UAER levels. Systolic blood pressure values for the 1st, 2nd, 3rd, and 4th UAER groups, respectively, were as follows: 123.0 ± 10.6, 132.5 ± 15.0, 139.0 ± 23.4, and 130.7 ± 8.0 mmHg for 24-h values (ANOVA P = 0.004); 126.09 ± 10.8, 135.0 ± 15.1, 142.5 ± 23.2, and 133.3 ± 9.23 mmHg for daytime values (ANOVA P = 0.004); and 116.2 ± 12.6, 127.2 ± 16.9, 131.9 ± 22.0, and 123.4 ± 14.1 mmHg for nighttime values (ANOVA P = 0.008). The post hoc analyses showing the differences between specific groups are depicted in Fig. 2. The 24-h, daytime, and nighttime pulse pressures also increased across the 1st, 2nd, 3rd, and 4th UAER groups, respectively: 48.4 ± 6.0, 54.5 ± 11.2, 58.8 ± 15.6, and 57.6 ± 8.0 mmHg for 24-h values (ANOVA P = 0.003); 48.1 ± 6.2, 54.7 ± 11.2, 59.9 ± 16.1, and 57.8 ± 7.7 mmHg for daytime values (ANOVA P = 0.001); and 48.6 ± 7.6, 54.5 ± 12.3, 56.0 ± 14.3 and 56.2 ± 11.3 mmHg for nighttime values (ANOVA P = 0.049), reflecting decreased arteriolar compliance. The same pattern was observed for the systolic 24-h blood pressure load values: 14.8% (range 0–95.1), 38.8% (0–96.4), 33.7% (0–100.0), and 34.9% (6.2–81.8); ANOVA P = 0.001. It was also observed for daytime blood pressure load: 7.1% (0–92.5), 35.2% (0–94.6), 29.6% (2.3–100.0), and 22.8% (5.5–73.1); ANOVA P = 0.011. There was a borderline association between UAER groups and nighttime blood pressure load: 23.8% (0–100.0), 66.3% (0–100.0), 53.3% (13.5–100.0), and 49.5% (4.8–100.0); ANOVA P = 0.056.

Nighttime diastolic blood pressure levels were lower in the 1st group (UAER <5 µg/min) compared with the 3rd group (≥10–15 µg/min): 67.5 ± 9.4 vs. 75.9 ± 14.4 mmHg (P = 0.05). However, no difference was observed for the 2nd and 4th groups: 72.7 ± 7.9 and 67.2 ± 10.4 mmHg for 24-h values (P > 0.05). There were no differences among the groups, respectively, regarding the other diastolic blood pressure parameters: 74.5 ± 8.5, 77.9 ± 7.8, 80.2 ± 13.4, and 73.1 ± 7.6 mmHg for 24-h values (ANOVA P = 0.122); 77.9 ± 9.2, 80.3 ± 8.4, 82.6 ± 13.1, and 75.5 ± 8.9 mmHg...
for daytime blood pressure (ANOVA, $P = 0.263$); 7.4% (range 0–73.2), 16.6% (0–89.1), 17.1% (0–94.4), and 7.4% (0–57.4) for daytime blood pressure loads (ANOVA, $P = 0.356$). Analyzing the nocturnal blood pressure descent, there was no difference between this and the 1st group (UAER $<5 \mu g/min$); 2nd group (UAER $\approx 5–10 \mu g/min$); 3rd group (UAER $\approx 10–15 \mu g/min$); 4th group (UAER $\approx 15–20 \mu g/min$).

Multivariate regression analyses were performed with log-UAER as the dependent variable. Diabetes duration, cholesterol, fasting plasma glucose and serum creatinine were included in the model as independent variables. In each regression model, only one blood pressure parameter was included as an independent variable. UAER remained correlated with 24-h systolic blood pressure ($R = 0.45$, $R^2 = 0.16$; $P = 0.004$), daytime systolic blood pressure ($R = 0.45$, $R^2 = 0.15$; $P = 0.003$), nighttime systolic blood pressure ($R = 0.47$, $R^2 = 0.17$; $P = 0.001$), daytime systolic blood pressure loads ($R = 0.47$, $R^2 = 0.17$; $P = 0.001$), nighttime systolic blood pressure loads ($R = 0.42$, $R^2 = 0.13$; $P = 0.014$), 24-h pulse pressure ($R = 0.44$, $R^2 = 0.15$; $P = 0.031$), and daytime pulse pressure ($R = 0.45$, $R^2 = 0.15$; $P = 0.017$). This was not true for mean nighttime pulse pressure ($R = 0.40$, $R^2 = 0.11$; $P = 0.079$). Similar results were obtained with alternative models in which cholesterol levels were replaced by triglycerides (data not shown).

**CONCLUSIONS** — In this sample of normoalbuminuric type 2 diabetic patients, a positive correlation was observed between UAER and systolic blood pressure indexes. Furthermore, these patients had more retinopathy and increased left ventricular posterior wall thickness. Stratification of the patients according to UAER level disclosed that patients with UAER $\approx 5 \mu g/min$ already had a worse cardiovascular risk profile. However, because of the limited number of patients in the 4th group (UAER $\approx 15–20 \mu g/min$, $n = 10$), some of blood pressure differences between this and the 1st group did not reach conventional statistical significance.

In a previous study using office blood pressure measurements and only one morning UAER sample, higher blood pressure levels, as well as an increased prevalence of diabetic retinopathy, were observed in type 2 diabetic patients with high-normal albuminuria ($12.5–30 \text{mg/l}$) (19). A similar association between UAER and blood pressure levels was reported in healthy subjects (13). Previous studies in nondiabetic hypertensive (20) and normoalbuminuric type 1 diabetic (14) patients showed high-normal levels of albuminuria were associated with increased ambulatory blood pressure levels. In nondiabetic hypertensive patients, high-normal UAER was found to be related to left ventricular hypertrophy (20). Furthermore, high-normal levels of albu-
Albuminuria and ambulatory blood pressure

Albuminuria (≥ 4.8 μg/min) have been reported to be an independent risk factor for coronary artery disease and all causes of mortality in a 9-year cohort study of subjects from Copenhagen (21).

The association of UAER with diabetic retinopathy and left ventricular wall thickness was probably related to increased systolic blood pressure in these patients. The increased systolic blood pressure observed could be caused by decreased compliance in the major arteries. In fact, we observed higher pulse pressure levels in this sample of patients. Higher pulse pressure was also reported in type 2 diabetic patients with more advanced diabetic nephropathy (micro- and macroalbuminuria) and proliferative retinopathy (22).

The data concerning the current sample of type 2 diabetic patients, along with previous data on type 1 diabetic patients and nondiabetic healthy and hypertensive subjects, suggest that albuminuria seems to be a continuous risk marker for the development of target organ damage (such as retinopathy, left ventricular hypertrophy, and coronary artery disease) and death. However, clinicians need a precise reference value to adequately guide patients’ treatment. UAER >10 μg/min has been associated with micro- and macroalbuminuria on Cox regression analysis in type 1 and type 2 diabetic patients (8,9). Our data indicate that patients with even lower levels of UAER are at risk.

It is important to point out that our results are based on a cross-sectional study and that our conclusions are limited to the observation of an association between cardiovascular risk factors and UAER. The establishment of a cause and effect relationship will require prospective cohort studies.

In conclusion, normoalbuminuric type 2 diabetic patients with UAER ≥ 5 μg/min should be considered to have a high cardiovascular risk profile for which intense treatment is indicated, especially with regard to blood pressure control, so as to reduce both cardiovascular mortality and progression to more advanced stages of diabetic nephropathy. Prospective intervention studies are needed to confirm whether these patients will in fact benefit from such an aggressive approach.

Acknowledgments—This study was partially supported by the Projeto de Núcleos de Excelência do Ministério de Ciência e Tecnologia (PRONEX), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), and Fundo de Incentivo a Pesquisa (FIP) do Hospital de Clínicas de Porto Alegre.

C.B.L. was the recipient of a scholarship from the Fundação de Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), and L.H.C. was the recipient of a scholarship from the Programa de Apoio à Instalação de Doutores–ProDoc (CAPES).

The authors thank Dr. Sandra P. Silveiro for revising this manuscript.

References


20. Dell’Omo G, Penno G, Giorgi D, Di Bello V, Mariani M, Pedrini L. Association...
