Familial Hypertension and Albuminuria in Normotensive Type I Diabetic Patients

Maria Beatriz Sayeg Freire, Sandra Roberta Gouvea Ferreira, Marco Antonio Vivolo, José Mário Oliveira, Maria Teresa Zanella

Abstract An inherited predisposition to hypertension may increase susceptibility to nephropathy in type I diabetes. We evaluated the influence of a family history of essential hypertension on albuminuria in normotensive, normoalbuminuric type I diabetic patients. Forty-two diabetics (12.9±2.04 years) were divided into three groups according to tertiles of albumin excretion rate (group 1, 1.27±0.35; group 2, 2.43±0.49; group 3, 6.37±3.43 μg/min; P<.001). Familial hypertension was considered to be present if the patient had one parent or grandparent on antihypertensive therapy. The three groups did not differ concerning age, diabetes duration, insulin requirement, body mass index, blood pressure, and urinary glucose excretion. Albumin excretion rate did not correlate with any parameter studied. The frequency of hypertension was significantly lower among the relatives of the patients from group 1 compared with those from groups 2 and 3 (28.6% versus 64.3% versus 78.6%, P<.03). Our data suggest that a familial antecedent of hypertension in normoalbuminuric type I diabetic patients is associated with a high normal albumin excretion rate not related to increases in blood pressure. Early changes in renal hemodynamics, seen in patients with a predisposition to hypertension, may contribute to increments in albuminuria even within the normal range. (Hypertension. 1994;3(2 suppl):I-256-I-258.)

Key Words • diabetes mellitus, insulin-dependent • hypertension, essential • albuminuria • diabetic nephropathies

Recent studies have suggested that an inherited predisposition to essential hypertension (EH) may increase susceptibility to nephropathy in insulin-dependent diabetes mellitus (IDDM) based on the following arguments: (1) Nondiabetic parents of IDDM patients with nephropathy have higher blood pressure than parents of patients without proteinuria; (2) the rates of sodium-lithium countertransport, a marker of risk for EH, have been found to be elevated in IDDM patients in whom the renal disease was developing; and (3) hyperactivity of Na-Li countertransport is also observed in diabetic patients even before the onset of nephropathy and is associated with hyperfiltration. In fact, the influence of familial antecedents for EH on renal hemodynamics and sodium handling was evidenced by the comparison of normoalbuminuric IDDM offspring of hypertensive and nonhypertensive parents. However, possible influences on urinary albumin excretion in those patients without nephropathy were not investigated.

This study evaluated the influence of a familial predisposition to EH on the albumin excretion rate (AER) in normoalbuminuric IDDM patients.

Methods

Fifty-two IDDM patients (23 boys, 19 girls) who attended the 13th Camp for Diabetic Youngsters, São Paulo, Brazil, aged 12.9±2.04 years, participated in this study after their parents' consent was obtained. IDDM duration ranged between 1.5 and 12 years. All patients were normoalbuminuric (as defined by AER<15 μg/min) and normotensive. Blood pressure was considered normotensive when systolic levels were less than 130 and diastolic levels less than 85 mm Hg over three recordings using a standard sphygmomanometer and adequate cuffs after 15 minutes of sitting rest. Patients were receiving a normal sodium diet and no medication other than insulin. The 42 AER values were arranged in increasing order and tertiles were determined. Three groups of 14 patients were created according to these tertiles. Patients from group 1 presented the minimum values of AER and from group 3 the maximum values. Besides blood pressure recordings and AER, body mass index, insulin requirement, and urinary glucose excretion were also assessed.

One of the parents of each patient was invited to complete a questionnaire about the presence of EH in the patient's family. Familial history of hypertension was considered to be present if the patient had at least one parent or grandparent in antihypertensive treatment. Hypertension had to be diagnosed by a physician as essential in origin. Such information was collected from the questionnaire, and no further clinical investigation was performed. AER was determined in a 24-hour urine sample using an enzyme-linked immunosorbent technique and is expressed as micrograms per minute; urinary glucose excretion was determined by routine methods. Standard descriptive statistics were used to compare the groups; data are expressed as mean±SD. The significance of differences was assessed by Kruskal-Wallis analysis of variance. For comparison of the frequencies of family history of EH among the three groups of patients, the χ² test was used. Odds ratios were determined together with 95% confidence intervals (CI) to measure the associations between family history of EH and AER level. Correlations between variables were tested using Spearman's coefficient. A value of P<.05 was considered significant.
Results

The IDDM patients from groups 1, 2, and 3 had similar ages, male-female ratio, and duration of diabetes. AER values, used to divide the groups of patients, were significantly different (1.27±0.35, 2.43±0.49, and 6.37±3.43 μg/min, respectively; P<.001). There was no significant difference in body mass index, blood pressure levels, insulin requirements, and metabolic control evaluated by urinary glucose excretion (Table). Twenty-four-hour urinary glucose excretions were not correlated with AER values (r=.24, NS), considering the entire group of 42 patients. In contrast, the frequency of familial antecedents of EH was significantly lower in group 1 compared with patients in groups 2 and 3 (28.6% versus 64.3% and 78.6%, P<.03) (Table). However, the family history of EH did not differ in groups 2 and 3. When the association was expressed as an odds ratio, we found that patients with a hypertensive parent or grandparent had a 6.25-fold (95% CI, 1.26 to 33.80) frequency of hypertensive parents in normoalbuminuric patients than observed in patients who developed microalbuminuria during 6.6 years of follow-up.* Our findings added that even when albuminuria is within its normal range, the association between AER and EH family history of EH exists. How a predisposition to EH would contribute to the onset of diabetic nephropathy is not clear. Several studies have shown that nondiabetic offspring of essential hypertensive parents have abnormalities in renal hemodynamics.10,11 Moreover, hyperglycemia can induce renal hemodynamic changes similar to those seen in individuals with a predisposition to EH.12 It seems reasonable to think that these two factors together may have additive deleterious effects in the diabetic kidney. In fact, it was shown that IDDM patients who were offspring of nondiabetic essential hypertensive parents exhibited an increase in glomerular filtration rate and mean arterial pressure, whereas renal vascular resistance and sodium excretion were nonsignificantly increased and decreased, respectively.6 We speculate that in the presence of a genetic predisposition to EH, critical alterations in the renal microcirculation of IDDM patients would expose their glomeruli to increased intraglomerular pressure, contributing to the development of the diabetic nephropathy. Poor metabolic control has also been considered to be a factor mediating glomerular hyperfiltration in IDDM, and it was hypothesized that both poor metabolic control and hyperfiltration are required for the development of nephropathy, although other factors may be operative.13 In our study, urinary glucose excretion, taken as an index of metabolic control, was not different among the groups of patients. Possible influences of hyperglycemia on AER were not observed in our patients, because no correlation between AER and urinary glucose excretion was detected when the entire group of 42 patients was considered. Prospective studies are necessary to clarify whether our findings are

Discussion

It is unknown why nephropathy develops only in a subset of IDDM patients. Among the determinants of such diabetic complications, hypertension seems to play an important role, because increases in blood pressure have been found before any sign of nephropathy.7 Also, a relation between diabetic renal disease and EH has been suggested by the genetic point of view. Based on the observation that parents of IDDM patients with nephropathy have higher blood pressure than parents of those without nephropathy, it was suggested that an inherited predisposition to EH may increase susceptibility to the renal disease.1 In fact, hyperactivity of the Na-Li countertransport system, considered a genetic marker for EH,2 has also been found in IDDM patients in whom diabetic nephropathy was developing.3,4 Recent reports, using three different qualitative measures of predisposition to hypertension, confirmed that the development of overt proteinuria in the first 20 years of IDDM is closely related to the presence of this major risk factor.8 Our study examined the association between a family history of EH and urinary albumin excretion in IDDM before the occurrence of abnormal albuminuria. We verified that the presence of familial antecedents of EH is associated with high normal AER, without an increase in blood pressure levels. These data are in agreement with other studies that found a lower frequency of hypertensive parents in normoalbuminuric patients than observed in patients who developed microalbuminuria during 6.6 years of follow-up.* Our findings added that even when albuminuria is within its normal range, the association between AER and a family history of EH exists. How a predisposition to EH would contribute to the onset of diabetic nephropathy is not clear. Several studies have shown that nondiabetic offspring of essential hypertensive parents have abnormalities in renal hemodynamics.10,11 Moreover, hyperglycemia can induce renal hemodynamic changes similar to those seen in individuals with a predisposition to EH.12 It seems reasonable to think that these two factors together may have additive deleterious effects in the diabetic kidney. In fact, it was shown that IDDM patients who were offspring of nondiabetic essential hypertensive parents exhibited an increase in glomerular filtration rate and mean arterial pressure, whereas renal vascular resistance and sodium excretion were nonsignificantly increased and decreased, respectively.6 We speculate that in the presence of a genetic predisposition to EH, critical alterations in the renal microcirculation of IDDM patients would expose their glomeruli to increased intraglomerular pressure, contributing to the development of the diabetic nephropathy. Poor metabolic control has also been considered to be a factor mediating glomerular hyperfiltration in IDDM, and it was hypothesized that both poor metabolic control and hyperfiltration are required for the development of nephropathy, although other factors may be operative.13 In our study, urinary glucose excretion, taken as an index of metabolic control, was not different among the groups of patients. Possible influences of hyperglycemia on AER were not observed in our patients, because no correlation between AER and urinary glucose excretion was detected when the entire group of 42 patients was considered. Prospective studies are necessary to clarify whether our findings are

### Clinical Data and Frequency of Familial History of Essential Hypertension in Study Patients

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=14)</th>
<th>Group 2 (n=14)</th>
<th>Group 3 (n=14)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>12.9±2.3</td>
<td>12.2±1.9</td>
<td>13.6±1.6</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes duration, y</td>
<td>5.6±3.7</td>
<td>5.1±2.5</td>
<td>5.2±2.7</td>
<td>NS</td>
</tr>
<tr>
<td>AER, μg/min</td>
<td>1.27±0.35</td>
<td>2.43±0.49</td>
<td>6.37±3.43</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>20.05±3.02</td>
<td>19.10±2.90</td>
<td>20.11±3.12</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>103.4±10.8</td>
<td>103.9±12.3</td>
<td>103.7±16.6</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>68.4±9.3</td>
<td>66.4±4.9</td>
<td>67.8±10.2</td>
<td>NS</td>
</tr>
<tr>
<td>Insulin requirement, (U/kg)/d</td>
<td>0.87±0.19</td>
<td>0.92±0.28</td>
<td>0.98±0.30</td>
<td>NS</td>
</tr>
<tr>
<td>UGE, g/24 h</td>
<td>6.2±6.1</td>
<td>11.0±9.9</td>
<td>10.1±9.3</td>
<td>NS</td>
</tr>
<tr>
<td>EH family history, %</td>
<td>28.6</td>
<td>64.3</td>
<td>78.6</td>
<td>&lt;.03</td>
</tr>
</tbody>
</table>

AER indicates albumin excretion rate; BMI, body mass index; BP, blood pressure; UGE, urinary glucose excretion; and EH, essential hypertension. Values are mean±SD.

*Group 1 vs groups 2 and 3.
identifying a subgroup of normoalbuminuric patients at high risk for developing microalbuminuria.

References


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