The Role of Disease Duration and Hypertension in Albumin Excretion of Type I Diabetes Mellitus

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ABSTRACT
The objective of this study was to examine the relationship between blood pressure, albumin excretion, and renal function in patients with type I diabetes mellitus. The study design was as follows: nonselected consecutive patients with type I diabetes mellitus were divided into three groups by level of albumin excretion rate (AER): <20 μg/min, 20 to 200 μg/min, and >200 μg/min. The setting for the study was an outpatient diabetic clinic in a tertiary referral center. There were 166 patients studied: 53% men, 47% women, 86% white, 17% treated for hypertension. Seventy-six percent had an AER <20 μg/min, 47% had an AER of 20 to 200 μg/min, and 6% had an AER of >200 μg/min. Glycosylated hemoglobin did not differ between groups. AER was increased with age and disease duration (P < 0.005 by analysis of variance) after 10 yr of disease. Serum creatinine (P < 0.005) and systolic (P < 0.005) and diastolic (P < 0.01) blood pressures were also increased with AER. Serum creatinine and blood pressure were found to be increased in parallel after 10 yr of disease, but both remained within the normal range overall. A comparison of individual blood pressures in patients not taking antihypertensive drugs (N = 138) with age-related blood pressures of nondiabetic subjects revealed increased systolic and diastolic blood pressures at all ages. Group comparison demonstrated a significant link between increased AER and serum creatinine (declining renal function) and increased blood pressure after a latent period of 10 yr. Blood pressure appears to be increased from the earliest age in diabetes compared with healthy populations. Precedence of either blood pressure or renal dysfunction could not be established in these cross-sectional comparisons. We suggest that "incipient hypertension" and evidence of incipient nephropathy are concurrent manifestations of a common vascular disease.

Key Words: Albuminuria, microalbuminuria, hypertension, risk factors

Diabetic nephropathy is a serious chronic complication in both insulin-dependent and noninsulin-dependent diabetes. Hypertension is common to the extent that the diagnosis of patients with diabetic renal disease almost always includes the presence of hypertension (1). Cross-sectional studies demonstrate the presence of increased blood pressure with the development of nephropathy. It remains unclear, however, whether hypertension precedes the renal dysfunction or occurs as a consequence of renal disease. Previous studies have failed to demonstrate the exact temporal relationship between the onset of early hypertension and renal disease. On the other hand, studies of family cohort and lithium-sodium transport have indicated a role for hypertension in the development of diabetic nephropathy (2,3).

Studies during an earlier phase of the disease may define the factors leading to a progression of diabetic nephropathy. The appearance of significant quantities of urinary protein (dipstick positive) and eventual renal failure are preceded by a latent phase that is characterized by increased urinary albumin excretion. This dipstick-negative, low-grade increase in albumin excretion, also called microalbuminuria, may be predictive of renal failure (4–11). The finding has been used as the basis for the concept of incipient diabetic nephropathy (5,6,12–14). Few studies have examined the specific relationship between blood pressure and albumin excretion during the earlier phases of the disease. Elevated blood pressure (>140/90 mm Hg) was only seen in patients with an albumin excretion >30 μg/min (15).

We examined the relationship between blood pressure and albumin excretion in a large outpatient population of unselected patients with insulin-dependent diabetes mellitus. We observed significant
differences in renal function, blood pressure compared with population norms, and other clinical parameters in groups with increasing albumin excretion. Elevation of blood pressure, albuminuria, and renal dysfunction were altered in parallel when comparing groups with increased disease duration. Subjects with diabetes had elevated blood pressures at all phases of the disease compared with age-related normal values.

MATERIALS AND METHODS

The patients in this study were recruited consecutively from the outpatient clinics of the Veterans Administration Medical Center and the Department of Pediatrics at the University of Kansas Medical Center. Subjects were not preselected and were asked to participate at the time of a regularly scheduled clinic visit. Entry criteria consisted of the presence of insulin-dependent (type I) diabetes mellitus and the willingness to collect urine. The 166 patients were treated with intermittent insulin; one or more antihypertensive medicines were used in 28 patients. The duration of disease was determined from clinical records. Patients with the systemic complications of amputation and blindness were excluded. We further divided the population into groups with a 24-h albumin excretion rate (AER) of <20 µg/min (group I), a low-grade increase in AER (>20 µg and <200 µg/min; group II), and overt increase in AER (>200 µg/min; group III). Clinical characteristics of the patient groups are given in Table 1.

Blood pressure was examined in the sitting position after the patient rested for 5 min. Standard sphygmomanometer recordings were used. The disappearance of all sounds was used to characterize diastolic blood pressure.

Urine was collected in standard plastic containers without additive. Patients were asked to avoid vigorous exercise during the time of urine collections. All participants received written and verbal instructions on the collection of a timed day and night urine collection. Collection times were recorded on prepared forms. Timed urine collections were combined to yield a 24-h collection. The volume of all collections was measured with graduated cylinders, and aliquots were frozen at -20°C until analyzed.

Albumin concentration was measured in either fresh or thawed frozen urine specimens by a double antibody RIA (Diagnostic Products Corp., Los Angeles, CA). The approximate sensitivity of the assay is 1 µg/mL with intra-assay and interassay coefficients of variation of about 3% for a concentration range of 5 to 30 µg/mL. Specimens with more than 30 µg/mL were diluted to determine albumin concentrations within the preferred range. Creatinine in urine and serum specimens was determined by a standard automated analyzer technique (Technicon Instrument Corp., Tarrytown, NY). Glycosylated hemoglobin was determined in the University Clinical Laboratories (normal range, 6 to 8.5%). The AER was expressed as micrograms per minute, corrected for a body surface area of 1.73 m². Results are given as mean ± SE. Analysis of variance and paired and unpaired t tests were used for statistical comparisons of groups. Nonparametric statistics were also used. A P value of <0.05 was accepted as significant.

RESULTS

The subjects in this study (N = 166) included 53% male and 47% female patients. The distribution of race (86% white, 12% black, 2% hispanic) resembled that of the community. Clinical and laboratory characteristics are given in Table 1. The majority of patients had a normal AER (126 or 76% <20 µg/min; 30 or 16% >20 and <200 µg/min; 10 or 6% >200 µg/min). Thus, the overall prevalence of abnormal AER (24%) was similar to that reported previously (9,16).

Overall mean blood pressures were normal for the entire population when a World Health Organization standard definition of 140/90 mm Hg was used (Table 1). Twenty-eight (16.7%) patients were receiving treatment for hypertension at the time of the study. Individual blood pressures in the remaining 138 patients were examined as a function of age (Figure 1). The majority of these patients who did not take antihypertensive medicines were shown to have increased blood pressure when compared with the mean blood pressures in male subjects without diabetes in a large population study from the same geographic area of the United States (17).

Clinical parameters and blood pressure were reexamined as a function of AER in all patients (Table 2). There was no difference between AER groups (<20, 20 to 200, and >200 µg/min) with respect to random glucose and diabetes control as determined

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TABLE 1. Clinical and laboratory characteristics in patients with type I diabetes mellitus (N = 166)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>24.6 ± 14.1</td>
</tr>
<tr>
<td>Duration (yr)</td>
<td>8.98 ± 6.7</td>
</tr>
<tr>
<td>Surface (m²)</td>
<td>1.74 ± 0.27</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mm Hg)</td>
<td>119.8 ± 19.3</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mm Hg)</td>
<td>75.9 ± 11.6</td>
</tr>
<tr>
<td>Insulin (IU)</td>
<td>50.64 ± 25.2</td>
</tr>
<tr>
<td>GHBAC (%)</td>
<td>13.1 ± 6.4</td>
</tr>
<tr>
<td>No (mEq/L)</td>
<td>139.8 ± 5.5</td>
</tr>
<tr>
<td>K (mEq/L)</td>
<td>4.43 ± 0.64</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.79 ± 0.64</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>15.2 ± 8.2</td>
</tr>
</tbody>
</table>

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by glycosylated hemoglobin. An increase in the AER was associated with increased age and disease duration \((P < 0.005\) by analysis of variance). Renal function, as characterized by rising plasma creatinine concentrations, declined significantly from group I to group III \((P < 0.005\). The most significant change in serum creatinine and blood pressure was seen in patients whose AER had increased to >200 \(\mu\)g/min (group III). The progression of AER from groups I to III was also accompanied by a significant increase in both systolic \((P < 0.005\) and diastolic \((P < 0.01\) blood pressures. Creatinine excretion was not different between groups.

Linear regression analyses were also used in the entire group of patients to evaluate the relationship between albumin excretion rate \((\log)\) and clinical and laboratory parameters (Table 3). Because there was a significant effect between AER and age \((r = 0.249; P < 0.01\)), we controlled for this variable. There was no significant relationship between AER and the laboratory parameters of glucose control, namely serum glucose concentration, glycosylated hemoglobin, or insulin usage. The relationship with systolic and diastolic blood pressures was significant as was the association between AER and serum creatinine. The association with creatinine clearance was weak and insignificant. There was no significant relationship between plasma urea concentrations and AER.

Additional entry into logistic regression of disease

**TABLE 3. Correlations between 24-h AER and clinical and laboratory parameters, controlled for age**

<table>
<thead>
<tr>
<th>Variable</th>
<th>(r)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic Blood Pressure</td>
<td>0.318</td>
<td>0.001</td>
</tr>
<tr>
<td>Diastolic Blood Pressure</td>
<td>0.449</td>
<td>0.001</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.344</td>
<td>0.001</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>0.115</td>
<td>NS*</td>
</tr>
</tbody>
</table>

* NS, not significant.

**TABLE 2. Clinical and laboratory characteristics (mean ± SE) in patients with type I diabetes mellitus with different levels of AER**

<table>
<thead>
<tr>
<th>AER ((\mu)g/min)</th>
<th>Group</th>
<th>ANOVA (P) Value Between Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I (&lt;20)</td>
<td>II (&gt;20)</td>
</tr>
<tr>
<td>(N)</td>
<td>126</td>
<td>30</td>
</tr>
<tr>
<td>Surface ((m^2))</td>
<td>1.72 ± 0.03</td>
<td>1.84 ± 0.05</td>
</tr>
<tr>
<td>(GHb_Ac) (%)</td>
<td>13.1 ± 0.6</td>
<td>12.9 ± 0.6</td>
</tr>
<tr>
<td>Duration (yr)</td>
<td>8.0 ± 0.5</td>
<td>11.5 ± 1.4b</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>22.3 ± 1.1</td>
<td>30.7 ± 3.1a</td>
</tr>
<tr>
<td>BUN ((mg/dL))</td>
<td>13.9 ± 0.5</td>
<td>18.6 ± 0.9b</td>
</tr>
<tr>
<td>Creatinine ((mg/dL))</td>
<td>0.67 ± 0.03</td>
<td>0.82 ± 0.09c</td>
</tr>
<tr>
<td>(UXV_{cre} ) ((g/day/1.73 m^2))</td>
<td>1.15 ± 0.05</td>
<td>1.47 ± 0.08</td>
</tr>
<tr>
<td>Systolic Blood Pressure ((mm Hg))</td>
<td>117.7 ± 1.6</td>
<td>122.4 ± 3.1</td>
</tr>
<tr>
<td>Diastolic Blood Pressure ((mm Hg))</td>
<td>74.9 ± 0.9</td>
<td>77.3 ± 2.3</td>
</tr>
</tbody>
</table>

* ANOVA, analysis of variance; NS, not significant; \(GHb_Ac\), glycosylated hemoglobin; \(UXV_{cre}\), total creatinine excretion/day.

b \(P < 0.005\) compared with group I by \(t\) test.

c \(P < 0.05\), compared with group I by \(t\) test.
duration, race, and sex created minor changes in correlation but uncovered no new significant relationships.

We also examined the effect of disease duration on renal function, AER, and blood pressure in all patients. The subjects were segregated by disease duration in 5-yr intervals. A significant increase in serum creatinine concentration was found in the group of patients with 10 or more yr of disease. Plasma creatinine was 0.79 ± 0.05 mg/dL in patients with a disease duration of less than 10 yr and was significantly higher at 0.87 ± 0.07 and 1.14 ± 0.17 in patients with more than 10 and more than 20 yr of disease, respectively. Overall, this increase remained within the range of normal for the first 20 disease yr. A significant change in creatinine clearance could not be demonstrated. The AER was not increased in the group with 5 to 10 yr of disease. The AER was less than 10 μg/min and was increased significantly to 25 μg/min in patients with 10 yr or more of diabetes. Additional increases with increased disease duration (log AER) were not found to be significant. Blood pressures were significantly increased after 10 yr of disease (P < 0.001; Figure 1). Systolic blood pressures were increased stepwise in subsequent groups with more disease duration, whereas diastolic blood pressures were not increased further. Overall blood pressures remained within the range of normal blood pressures as defined by a standard definition of <140/90 mm Hg.

**DISCUSSION**

The 24% prevalence of an abnormal AER (>20 μg/min) observed in this study is similar to that reported previously (9,16). Different threshold levels have been advocated, and it is yet to be decided which level is most predictive of diabetic nephropathy (18–20). The AER in normal controls is always <10 μg/min. Albumin excretion in excess of 200 μg/min denotes an additional group with dipstick-positive “overt” proteinuria (>250 mg/P24h). The subgroups of patients with AER of less and more than 20 μg/min did not differ with respect to body size and glucose control (Table 2). There were no significant correlations of these parameters for the entire group (Table 3). This extends our previous observations in patients with type I or type II diabetes mellitus (21). In contrast, the subgroups differed significantly with respect to disease duration, age, serum creatinine concentration, and both systolic and diastolic blood pressures. The correlations were consistent with the suggestion that albuminuria is a marker of nephropathy progression. The detection of increased blood pressure in the groups with increased AER was noteworthy because the subtle increases were within the range of normal blood pressure (<140/90 mm Hg). Although clinical hypertension was not present, the increased blood pressure readings underscore the role of blood pressure elevation as a risk factor for the development of abnormal renal function (3,20,22).

The close relationship between albuminuria, age, and blood pressure led us to examine the effect of disease duration. Disease duration was closely linked to age (r > 0.850; P < 0.001). The AER was evaluated after logarithmic transformation to diminish the effects of nonlinear increases in protein excretion with progressive disease. The AER was significantly increased after 10 yr of diabetes. Once present, further increases with disease duration were not found to be significant. Creatinine was increased after 10 yr of disease duration with additional increases in the groups with longer disease duration. This change was consistent with a proportionate decrease in renal function over time, although overall increases in creatinine were in the range of normal for the first 20 yr of diabetes. Patients in this study were already beyond the phase of juvenile or early adolescent growth. Therefore, we do not believe that these changes were related to growth or changing muscle mass. Moreover, measured creatinine excretion, indexed to body surface area, did not differ among groups with different AER and ages. Corresponding creatinine clearance was not sensitive enough to denote significant differences in renal function between groups. Creatinine clearance, which reflects filtration and secretion, is subject to large extraneous variations, for example, with variable dietary protein intake, and may, therefore, be a relatively insensitive marker of early changes in glomerular function (23).

Blood pressure did not differ with disease duration between 5 and 10 yr (118/73 ± 1.5/0.8 mm Hg). Thereafter, systolic pressure was increased in groups with increased duration of disease. Diastolic pressure was also increased after 10 yr of disease, but further increases were not noted. These changes occurred in parallel with those changes noted in albumin excretion and renal function. Notably, measurements remained within the range of normal (<140/90 mm Hg). The role of blood pressure was also evident from the significant association between albuminuria and both diastolic and systolic blood pressures. This association was not merely an age-related phenomenon, as was revealed by controlling for the effects of age in the analysis. Similar results were found when we examined these associations controlled for disease duration.

The relationship of age and blood pressure is further illustrated by comparing our study population with another diabetes-free population in an adjacent geographic area of the United States. Turner et al. examined 800 normotensive nondiabetic patients in Minnesota and derived a distribution of blood pressure as a function of age in healthy individuals (17).
The early use of blood pressure-lowering agents under these circumstances manifested by abnormal glomerular barrier function (proteinuria), should occur independent of disease in small resistance vessels manifested by abnormal relaxation or contraction (hypertension). The early use of blood pressure-lowering agents under these circumstances may be warranted as a way to treat a common vascular abnormality.

ACKNOWLEDGMENTS

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Figure 2. Individual systolic (crosses) and diastolic (triangles) blood pressures in 138 patients with type I diabetes who were not taking antihypertensive medications. The lines represent mean systolic (solid) and diastolic (dashed) blood pressures as functions of age in the form of a polynomial in nondiabetic men derived from Turner et al. (17).

When we plotted individual systolic and diastolic blood pressure measurements against mean systolic and diastolic blood pressure (polynomial curves in Figure 2), we found that most of our patients had a higher blood pressure at any age. It would therefore appear that increased blood pressure exists in the patient with type I diabetes mellitus from an early age.

The study presented here examined prospectively a large, unselected, homogeneous population of patients with type I diabetes mellitus and found significant corresponding changes in increasing albumin excretion, decreasing renal function, and increasing blood pressure in patients with 10 yr of disease or more. It is evident from these cross-sectional studies that changes in blood pressure and renal function begin at an early stage and that these changes progress initially within a range of normal values. Such an increase in pressure, even when below the standard definition for hypertension, may be characterized as "incipient hypertension" (24). To the extent that diabetes mellitus is a vascular disease, it would be expected to affect all components of the vascular system simultaneously. There is little reason to believe that glomerular capillary damage, signaled by abnormal glomerular barrier function (proteinuria), should occur independent of disease in small resistance vessels manifested by abnormal relaxation or contraction (hypertension). The early use of blood pressure-lowering agents under these circumstances...

"My Dear Starling,

I have now completed the task which you allotted me in your capacity as editor of this series and which I have found more burdensome than I expected. The growth in the literature on the kidney has been extraordinary since the time when you and I began to work on it, and this increase in bulk has not gone along with an improvement in quality, but rather the reverse. No other organ of the body has suffered so much from poor work as the kidney, and in no other region of physiology does so much base coin pass as legal tender . . . . I do not flatter myself that this treatise attains finality in regard to the secretion of the urine; that is impossible at the present time. If it serves as an advanced post from which others may issue against the remaining ramparts of vitalism, its purpose will be attained."