The Relationship of the Renin-Angiotensin System in Type I Diabetes to Microvascular Disease 

PAUL L. DRURY AND H. JONATHAN BODANSKY

SUMMARY There are conflicting data on the relationship between diabetes mellitus and its complications and the renin-angiotensin-aldosterone system. Much of this relates to the patient populations studied (those with types I and II diabetes) and the definitions of diabetic complications. We studied plasma renin activity and concentration, and factors involved in their control (age, blood pressure, and sodium excretion) in 40 healthy subjects (group 1), 18 patients with type I diabetes without complications (group 2), and 31 with type I diabetes with proliferative retinopathy (group 3). The groups were well matched for age, sex, and body weight, but patients in group 3 had higher supine blood pressures than those in the other two groups (133/78 mm Hg vs 118/74 group 1, p < 0.01; 120/72 group 2, p < 0.05). Median plasma renin activity, both supine and erect, was 60 to 120% higher in group 3 than in group 1 (p < 0.001) and 55 to 75% higher than in group 2 (p < 0.05). There was good evidence of a fall in both values with increasing age in all three groups. Patients in groups 1 and 2 showed evidence of inverse relationships of both blood pressure and urinary sodium with plasma renin activity/concentration ratio, but these relationships were not apparent in subjects in group 3. There is thus evidence of unpaired regulation of renin secretion in persons with type I diabetes with proliferative retinopathy, the commonest form of microvascular disease. This may contribute to the relative hypertension and progression of complications. (Hypertension 7 [Suppl II]: 11-84—11-89, 1985)

KEY WORDS • hypertension • retinopathy • nephropathy • sodium • renin activity • renin concentration

THERE are widely differing reports on the relationship between diabetes mellitus and its complications and the renin-angiotensin system. Abnormal renin activity (usually reduced) has been described by some authors especially in patients with diabetic nephropathy1-3 and autonomic neuropathy,4-7 and less obviously, in diabetic patients with hypertension and retinopathy. It has generally been thought that these are secondary effects of the complications rather than primary pathophysiological mechanisms, mediated by diabetic glomerulosclerosis in the case of nephropathy and reduced sympathetic efferent flow due to autonomic neuropathy. There are, however, reports of increased renin activity among diabetics whether or not they have hypertension or complications.8 This article briefly reviews previous studies and presents our recent findings on the regulation of renin secretion in type I diabetes.

A major relevant factor in the interpretation of these findings may be the increased exchangeable sodium widely reported in diabetic patients.9-12 This raises the possibility that reduced renin secretion is an appropriate response to sodium overload (although plasma volume is not raised) and the increased blood pressure associated with clinical nephropathy, incipient nephropathy, and retinopathy. If, as suggested by several studies in nondiabetic patients,13-15 renin falls with increasing blood pressure, reduced renin activity might be a normal physiological homeostatic response to the higher blood pressure in these patients. The issues are considered elsewhere in this journal.16

Many of the earlier studies (pre-1979) understandably did not differentiate between type I (insulin-dependent) and type II (noninsulin-dependent) diabetics.17 In addition, age matching of control subjects in some studies has been poor, making difficult the interpretation of renin levels that fall with age.18,19 The definition of nephropathy has also varied from study to study.

Perez et al.1 described lower plasma renin activity (PRA) in patients with nephropathy than in control subjects, a finding confirmed by two other groups.2,3 For patients with autonomic neuropathy, stimulation of renin secretion by posture or sodium deprivation demonstrated low PRA levels even where basal PRA was normal4-7; many of these subjects also had abnormal renal function. There appear to be no studies in
which patients were selected primarily for the presence of retinopathy, which is the commonest form of microvascular disease.

We originally wished to examine the hypothesis that increased renin, and hence angiotensin II, levels might be involved in the pathogenesis of the increased blood pressure associated with microvascular disease, and might even contribute to the vascular damage in these subjects. Our initial data showed higher PRAs in diabetic patients with proliferative retinopathy than in those without complications, and we therefore extended our studies by incorporating a nondiabetic control group and measuring plasma renin concentration (PRC). The present analysis concerns the effect of factors known to be involved in the control of renin secretion, namely, age, blood pressure, and sodium intake. We postulated that there might be abnormal regulation of renin secretion in these patients, perhaps as a result of very early diabetic nephropathy. To elucidate this we have included measurements of albumin excretion, which has been shown to be raised in early nephropathy, with high levels (> 15–30 μg/min) predictive of later clinical nephropathy.

Two groups of patients with type I diabetes and a population of age- and sex-matched healthy controls were studied. One group of patients was selected for the presence of proliferative retinopathy, the most easily characterized form of microvascular disease; the other, with equal duration of diabetes, was free of complications detectable by sensitive techniques.

Patients and Methods

Patients

Forty healthy subjects and 49 patients with type I diabetes were studied; all gave informed consent to the study, which was approved by the hospital ethics committee. The healthy subjects were free of known cardiovascular, renal, and endocrine disease, and all had blood pressures of less than 160/95 mm Hg. All had postprandial blood glucose levels of less than 6.7 mmol/L.

Thirty-one of the diabetic patients were selected for the presence of proliferative retinopathy; the diagnosis was made by ophthalmologists experienced in diabetic eye disease and confirmed by fluorescein angiography. Two had serum creatinine levels greater than 0.11 mmol/L and two more had persistent proteinuria above 0.5 g/day.

Eighteen of the diabetics were free of symptoms or signs of microvascular or macrovascular diabetic complications. All had normal renal function as judged by serum creatinine (< 0.11 mmol/L), creatinine clearance (> 75 ml/min), and urinary albumin excretions (< 30 μg/min by radioimmunoassay). None had symptoms of autonomic neuropathy and all had normal responses of the RR interval to deep breathing using the criteria of Weiling et al. and normal postural blood pressure responses (drop in systolic pressure of < 10 mm Hg at two min) after standing. All had normal fundi as evaluated through dilated pupils by experienced physicians. None had signs of large vessel disease and none was hypertensive. Details of the three groups are given in Table 1.

Protocol

All subjects continued free sodium intake and were taking no drugs except insulin for diabetics; the dose was unchanged for at least 2 weeks before the study. No diabetic was ketoacidotic at the time of study. A 24-hour urine collection for sodium, potassium, creatinine, and albumin excretion (after December 1978) was performed in the 24 hours before the study.

### Table 1. Clinical and Biochemical Details of the Subjects Studied

<table>
<thead>
<tr>
<th>Variable</th>
<th>Diabetic patients with retinopathy</th>
<th>Diabetic patients without complications</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>31</td>
<td>18</td>
<td>40</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>20:11</td>
<td>12:6</td>
<td>26:14</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>37±9</td>
<td>39±11</td>
<td>39±14</td>
</tr>
<tr>
<td>Percentage of desirable body weight</td>
<td>108±14</td>
<td>106±10</td>
<td>107±12</td>
</tr>
<tr>
<td>Supine systolic/diastolic blood pressure (mm Hg)</td>
<td>133±20†±78±16</td>
<td>120±11/72±11</td>
<td>118±12/74±8</td>
</tr>
<tr>
<td>Duration of diabetes (yr)</td>
<td>24±8</td>
<td>20±8</td>
<td>—</td>
</tr>
<tr>
<td>Insulin dose (U·kg⁻¹·24 hr⁻¹)</td>
<td>0.85±0.20</td>
<td>0.80±0.26</td>
<td>—</td>
</tr>
<tr>
<td>Plasma sodium (mmol/L)</td>
<td>138±3†</td>
<td>138±3†</td>
<td>141±2</td>
</tr>
<tr>
<td>Plasma potassium (mmol/L)</td>
<td>4.4±0.5*</td>
<td>4.4±0.4*</td>
<td>4.1±0.3</td>
</tr>
<tr>
<td>Serum creatinine (mmol/L)</td>
<td>0.08±0.01</td>
<td>0.08±0.01</td>
<td>0.10±0.04</td>
</tr>
<tr>
<td>Glycosylated hemoglobin (%)</td>
<td>12.1±1.7†</td>
<td>10.5±1.5</td>
<td>—</td>
</tr>
<tr>
<td>Urinary sodium (mmol/24 hr)</td>
<td>128±40*</td>
<td>143±46</td>
<td>162±62</td>
</tr>
<tr>
<td>Urinary potassium (mmol/24 hr)</td>
<td>62±20*</td>
<td>69±22</td>
<td>79±28</td>
</tr>
</tbody>
</table>

Data are presented as mean ± sd.
* \( p < 0.05 \)
† \( p < 0.01 \) vs controls.
‡ † \( p < 0.05 \) vs diabetics without complications.
Initial blood samples for PRA and PRC, electrolytes, creatinine, and glycosylated hemoglobin were taken between 0800 and 0900 hours after an overnight fast. The diabetic patients then received their usual morning insulin and all subjects received breakfast, after which they remained upright for 4 hours, being allowed to sit for 5 minutes each hour. Samples for erect PRA and PRC were taken between 1200 and 1300 hours.

The PRA was measured by a modification of the method of Haber et al. at pH 7.4, and PRC using nephrectomized sheep substrate and calibrated with MRC standard renin (National Institute of Medical Research, Mill Hill, UK). Intraassay and interassay variations were 5.0 and 7.9% for PRA and 13.2 and 14.1% for PRC.

Blood pressure (phases 1 and 5) was recorded as the mean of five readings taken at 1-minute intervals with 5 minutes initial recumbency, using a standard mercury sphygmomanometer.

Statistics
As in other studies, PRA and PRC were not normally distributed. Logarithmic transformation yielded an apparently normal distribution (normal scores test) with similar standard deviations in all groups. These transformed values were used throughout for statistical analysis. Otherwise, standard linear regression techniques were applied. A p value of less than 0.05 was regarded as significant.

As several studies have shown an inverse relationship between PRA and blood pressure, an empirical renin-blood pressure index was calculated as the product of supine PRA and supine blood pressure, therefore being expressed as mm Hg x nmol of angiotensin I (ANG I) per hour per liter. This was intended to test whether there was any abnormality of the normal inverse relationship.

Results
Details of the groups, together with basal biochemical values, are shown in Table 1; subjects were well matched for age, sex, and body weight. Urinary sodium excretion per 24 hours was slightly greater in the healthy subjects (162 mmol) than in the diabetics with retinopathy (128 mmol, p < 0.05) but not significantly different from the patients without complications (143 mmol). In both diabetic groups, plasma sodium levels were significantly lower and plasma potassium slightly higher than in the healthy subjects.

Albumin excretion rates in the group with proliferative retinopathy (available for 21 of 31 patients) are shown in Figure 1. In approximately 70% of such patients the rates were elevated.

Median values for PRA and PRC while supine and erect are shown in Table 2. Levels of both PRA and PRC were similar in healthy subjects and diabetic patients without complications, while PRA in diabetics with retinopathy was significantly higher than in the

<table>
<thead>
<tr>
<th>Group</th>
<th>Plasma renin activity (nmol ANG 1·h⁻¹·L⁻¹)</th>
<th>Plasma renin concentration (mU/L of MRC renin)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Supine</td>
<td>Erect</td>
</tr>
<tr>
<td>Diabetic patients with retinopathy (n = 31)</td>
<td>0.62*†</td>
<td>1.80*†</td>
</tr>
<tr>
<td>Diabetic patients without complications (n = 18)</td>
<td>0.40</td>
<td>1.06</td>
</tr>
<tr>
<td>Controls (n = 40)</td>
<td>0.28</td>
<td>1.19</td>
</tr>
</tbody>
</table>

Results are medians.
* p < 0.001 vs controls.
† p < 0.05 vs diabetic patients without complications.
healthy individuals ($p < 0.001$ supine and erect), and both PRA and PRC were higher than in the diabetic patients without complications ($p < 0.05$ in all circumstances).

**Age**

Among controls, both supine and erect PRA and PRC showed significant and similar falls with increasing age ($r = -0.49$ to $-0.61$, $p < 0.01$). All regressions were similarly negative in the diabetic patients without complications ($r = -0.06$ to $-0.47$), but only significant for PRC in the erect position. The diabetics with retinopathy also showed negative regression equations ($r = -0.21$ to $-0.41$, significant for supine and erect PRA; Figure 2).

**Sodium**

Controls showed significant negative correlations between 24-hour urinary sodium excretion and erect PRA and PRC ($r = -0.34$ and $-0.32$, $p < 0.05$), other regression equations being negative ($-0.15$ to $-0.25$, $p$ NS). Diabetic patients without complications showed negative regressions ($r = -0.21$ to $-0.53$, $p < 0.05$ only for supine PRA), while those with retinopathy showed generally positive but not significant regressions ($r = +0.19$ to $-0.08$).

**Blood Pressure**

Among control subjects, PRA and PRC showed negative regressions with systolic, diastolic, and mean blood pressures, only reaching significance for erect PRC and mean blood pressure ($r = -0.31$, $p < 0.05$). The relationships were apparently stronger for diabetic patients without complications ($r = -0.32$ to $-0.57$, $p < 0.05$ for 3 of 12 comparisons; Figure 3), but totally absent for those with retinopathy ($r = -0.04$ to $+0.27$; all NS). Ten of the 12 latter regression equations were of positive slope.

**Renin-blood Pressure Index**

The product of supine PRA and supine blood pressure was considerably higher in diabetics with retinopathy than in controls (medians 68.1 and 32.9 systolic; 41.1 and 21.0 mm Hg·nmol Ang I·hr$^{-1}$·L$^{-1}$ diastolic, both $p < 0.0001$) (Figure 4). They were intermediate in the diabetic patients without complications (medians 55.9 systolic and 29.7 diastolic; $p < 0.05$ vs diabetics with retinopathy, $p$ NS vs controls).

**Discussion**

The present study suggested that patients with type I diabetes and microvascular disease, as defined by the presence of proliferative retinopathy, show impaired regulation of renin secretion with increasing blood pressure and with increasing sodium intake, if the latter is judged by a single 24-hour urine collection. These abnormal relationships were not seen in diabetics without complications or in healthy subjects.$^{11-13}$ The fall in PRA and PRC with age was preserved, however, as seen in many studies of both nondiabetic$^{15, 16}$ and diabetic subjects.$^9$ This implies that renin secretion in patients with microvascular disease is inappropriate for their blood pressure and possibly for their sodium status; thus angiotensin II may maintain blood pressure to a greater degree than in controls or diabetics without complications.

The basal findings of similar PRA and PRC in uncomplicated type I diabetes and 50 to 100% increased PRA in those with retinopathy differ from some previous reports.$^3, 5, 8, 26-29$ This may well be a result of patient selection, ours being confined to classic insulin-dependent disease.$^{17}$ Although our groups were
very closely matched for age, sex, and body weight, there was a slight but significant difference in 24-hour urinary sodium excretion with a free diet (extremes of 162 and 128 mmol/24 hr); over this range it is unlikely to explain our marked differences in PRA. There was also a significant difference in medium-term diabetic control as assessed by HbA1c; on the basis of the work from O'Hare et al., this could produce higher levels of angiotensin II and aldosterone. Neither of these factors could explain the abnormal relationships between PRA and PRC and blood pressure or sodium we describe, however.

We clearly cannot completely exclude the possibility of early microvascular disease in our "uncomplicated" diabetic group, although the tests used were the most sensitive currently available for nephropathy (albumin excretion at micromole level) and autonomic neuropathy (RR interval during deep breathing). Blood pressures in this group were very close to those of the controls. While very early retinopathy might not have been detected, this group was obviously grossly different in this respect from those with proved proliferative retinopathy.

It therefore appears that some of the normal homeostatic mechanisms for control of renin secretion, namely, inverse relationships with blood pressure and sodium intake, are intact in patients with type I diabetes who have no complications but are impaired in the presence of microvascular disease. It is thus likely that the renin-angiotensin system, by way of angiotensin II, contributes to maintenance of the relatively increased blood pressures seen in these subjects. Whether this relates to very early diabetic nephropathy is as yet not known, though it is of interest that about 50% of this group had increased albumin excretion; basal blood pressures in this group were also similar to those recently reported in the stage of microalbuminuria. Numbers with and without increased albumin excretion were too small to permit adequate statistical analysis.

**Figure 3.** The correlation between supine plasma renin activity and blood pressure in 40 healthy controls (closed circles), 18 diabetic patients without complications (open circles), and 31 diabetic patients with retinopathy (solid triangles). Solid lines denote significant correlations (p < 0.05); interrupted lines denote regression lines (p > 0.05). AI = angiotensin I.

**Figure 4.** Comparison of the renin-blood pressure product (systolic and diastolic) in the three groups. See text for details of calculation; units are mm Hg · mmol AI · h⁻¹ · L⁻¹.
The findings suggest that blockade of the renin-angiotensin system and sodium deprivation or depletion might be of special benefit in hypertension associated with diabetic microvascular disease. Whether the hypertension alone and/or the relatively high levels of renin contribute to the pathogenesis or progression of microvascular disease remains uncertain. Such studies might be of great importance in preventing or ameliorating diabetic microvascular disease.

Acknowledgments

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References

23. Welch SG, Boucher BJ. A rapid microscale method for the measurement of haemoglobin A1C. Diabetologia 1978;14:209-211
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P L Drury and H J Bodansky

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