Plasma renin activity in diabetes mellitus

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Summary

1. The plasma renin activity (PRA) was measured in 76 diabetic patients who were attending an outpatients clinic. Of these patients 16 had untreated hypertension and 28 had diabetic complications, which ranged from microaneurysms to renal failure and blindness.

2. Compared with age- and sex-matched normotensive control subjects, both normotensive and hypertensive diabetic patients had significantly higher PRA ($P < 0.001$).

3. Hypertensive diabetic patients also showed a higher PRA than matched hypertensive control subjects ($P < 0.005$). There were no significant differences between diabetic patients with hypertension or complications compared with those without these features.

4. Although this elevation of PRA could be due to a change in another component of the renin–angiotensin system, hypersecretion of renin is the most likely explanation.

Key words: diabetes mellitus, hypertension, plasma renin activity.

Abbreviation: PRA, plasma renin activity.

Introduction

Cardiovascular and renal complications are now the major cause of death in patients with diabetes mellitus. It is not surprising, therefore, that hypertension is common in the diabetic population (Freedman, Moulton & Spencer, 1958; Stamler, Berkson & Lindberg, 1972), but, despite this, malignant hypertension rarely occurs. This may result from the suggestion that the PRA is low in diabetic patients who have complications or hypertension, and that this low PRA prevents the development of malignant phase hypertension (Christlieb, 1974a). However, normal and high PRA values have been found in hypertensive diabetic patients (Gossain, Werle, Sholiton, Srivastava & Knowles 1975), and in addition the malignant phase can occur in essential hypertensive patients with low or normal PRA values (Brown, Davis, Lever & Robertson, 1966). We have therefore measured the PRA in patients with diabetes mellitus, including patients with and without complications or hypertension, and compared the results with measurements in age- and sex-matched normotensive and hypertensive subjects.

Patients and methods

Diabetic subjects

The 76 patients studied were selected from a diabetic clinic, each fulfilling the diagnostic criteria of the British Diabetic Association (Fitzgerald & Keen, 1964). None had evidence of ketoacidosis or fluid depletion at the time of the PRA estimation, and none was taking drugs known to interfere with the renin–angiotensin system. The blood pressure was measured on at least two occasions, and the patients were examined for the presence of overt diabetic complications.

In 16 patients the mean outpatient blood pressure was greater than the 90th percentile for age and sex on two or more occasions (Acheson, 1973), and were accepted as hypertensive. Complications of their diabetes were seen in 28 patients,
four of whom had microaneurysms only; 17 had proliferative retinopathy. Diabetic nephropathy, defined as proteinuria $>1.5$ g/24 h and a serum creatinine $>200 \mu$mol/l, was present in seven (mean protein excretion 2.2 g/24 h, mean serum creatinine 279 $\mu$mol/l). Symmetrical peripheral sensory neuropathy in all limbs, or diabetic amyotrophy, was present in seven patients. Several patients had more than one such complication.

**Normal subjects**

In 83 volunteer subjects, hospital workers or their relatives, in whom the mean blood pressure lay between the 10th and 90th percentiles (Acheson, 1973), blood was taken for PRA estimation under the same conditions as in the patients, along with a 24 h urine collection for sodium excretion. From these subjects 45 were matched for age and sex with the 45 diabetic normotensive subjects who had no complications of their diabetes.

**Hypertensive patients**

Sixteen hypertensive subjects were matched for age and sex with the 16 hypertensive diabetic patients, all being either untreated or had all drugs discontinued for at least 3 weeks before PRA measurement. In each the mean outpatient blood pressure was greater than the 90th percentile for age and sex on two or more occasions (Acheson, 1973). None showed clinical or biochemical evidence of diabetes or of a primary cause of their hypertension. Patients with papilloedema, retinal haemorrhages or exudates were excluded. None of the subjects was taking oral contraceptives before or at the time of study.

**Assay methods**

Venous blood (10 ml) was taken from ambulant (upright posture for at least 3 h) subjects (control subjects and patients) by using Vacutainers, into a precoded tube containing 150 mg of dipotassium ethylenediamine tetra-acetate (EDTA) and the tubes were kept in ice until the plasma was separated in a cold centrifuge. A 24 h urine collection from each subject was obtained to determine daily sodium excretion. Samples were stored at $-20^\circ$C until assay of PRA, which was carried out within 6 weeks. PRA was measured by the radioimmunoassay of generated angiotensin I, two incubation times being used to establish linear generation, as described by Sealey, Laragh, Gerten-Baines & Aceto (1974), except that phenylmethylsulphonyl fluoride was used as an angiotensinase inhibitor.

Statistical comparisons were made by an unpaired $t$-test. Values are given as means $\pm$ SEM.

**Results**

The frequency histogram of PRA in the 76 diabetic subjects (males : females 52:24) showed a unimodal skewed curve, which was transformed into a continuous normal distribution by expressing PRA as the square root, as in the normal subjects (Fig. 1). Parametric statistical analysis has therefore been on the square root of PRA values. The mean PRA of the diabetic population was 3.0 pmol h$^{-1}$ ml$^{-1}$, which was significantly higher than in the normal population (1.5 pmol h$^{-1}$ ml$^{-1}$; $P < 0.01$). The weak correlation of PRA with age seen in the normal population ($PRA = -0.013$ age + 2.136, $r = 0.22, P = 0.05$) was similar to that in the diabetic population ($PRA = -0.037$ age + 4.814, $r = 0.32, P = 0.007$).
Plasma renin activity in diabetes

TABLE 1. Plasma renin activity (PRA) with differing treatment regimens
Square root PRA values are mean ± SEM. M/F: male/female.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No.</th>
<th>Mean PRA (pmol h⁻¹ ml⁻¹)</th>
<th>√PRA (pmol h⁻¹ ml⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary restriction only</td>
<td>23</td>
<td>2.81 ± 1.6</td>
<td>1.6 ± 0.13</td>
</tr>
<tr>
<td>(M/F 15:8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet + sulphonylurea</td>
<td>14</td>
<td>2.61 ± 1.5</td>
<td>1.5 ± 0.13*</td>
</tr>
<tr>
<td>(M/F 9:5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet + insulin</td>
<td>35</td>
<td>3.38 ± 1.7</td>
<td>1.7 ± 0.10*</td>
</tr>
<tr>
<td>(M/F 27:8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet + metformin</td>
<td>4</td>
<td>3.16 ± 1.7</td>
<td>1.78 ± 0.58*</td>
</tr>
<tr>
<td>(M/F 2:2)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Not significant, compared with dietary restriction alone.

TABLE 2. Effect of hypertension or complications on plasma renin activity (PRA) in diabetic patients
For details see Table 1.

<table>
<thead>
<tr>
<th>Clinical subgroup</th>
<th>No.</th>
<th>Mean PRA (pmol h⁻¹ ml⁻¹)</th>
<th>√PRA (pmol h⁻¹ ml⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive without</td>
<td>45</td>
<td>3.0 ± 0.09</td>
<td>1.6 ± 0.09</td>
</tr>
<tr>
<td>complications</td>
<td>(M/F 30:15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive with</td>
<td>28</td>
<td>3.28 ± 1.7</td>
<td>1.7 ± 0.10*</td>
</tr>
<tr>
<td>complications</td>
<td>(M/F 20:8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With hypertension</td>
<td>16</td>
<td>3.13 ± 1.7</td>
<td>1.7 ± 0.15*</td>
</tr>
<tr>
<td>(M/F 11:5)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Not significant compared with normotensive diabetes without complications.

\[ r = 0.26, P < 0.05 \] There was no significant correlation between PRA and blood sugar concentration or duration of diabetes.

The treatment used to control the diabetes might influence PRA, so that PRA values were compared in patients receiving four different regimens (Table 1). There was no significant difference in PRA between patients on these treatment regimens.

The PRA values in 45 normotensive patients who had no complications of diabetes were compared with those in two further groups: the 16 hypertensive patients and the 28 patients with diabetic complications. There was no significant difference in PRA values between these groups (Table 2). When the patients with complications were further subdivided there was no difference between any of the subgroups: in those with nephropathy the mean PRA was 2.9 pmol h⁻¹ ml⁻¹, with neuropathy 3.0 pmol h⁻¹ ml⁻¹, with proliferative retinopathy 2.9 pmol h⁻¹ ml⁻¹ and with microaneurysms alone 3.1 pmol h⁻¹ ml⁻¹.

The PRA of normotensive diabetic patients who lacked any complications of their diabetes was then compared with that of normotensive age- and sex-matched control subjects (Table 3). There was a significantly higher PRA in the diabetic patients \((P < 0.01)\) despite a significantly higher sodium excretion \((P < 0.05)\). Hypertensive diabetic patients were then compared with hypertensive age- and sex-matched control subjects, but again the PRA in the diabetic patients was significantly higher \((P < 0.05)\), despite the sodium excretion being similar (Table 3).

**Discussion**

Our results suggest that PRA is elevated in most patients with diabetes mellitus, whereas Christlieb (1974b) showed that PRA was reduced in diabetic rats. However, normal values have been reported in patients with uncomplicated diabetes mellitus (Campbell, Ewing, Anderton, Thompson, Horin & Clarke, 1976; Christlieb, Kaldany & D'Elia, 1976). Gossain et al. (1975) also found the mean PRA to be higher in a diabetic population, but their results were not significant, possibly as they did not study enough patients.
These discrepancies may be explained in part by differences in PRA assay methods. Thus Christlieb et al. (1976) employed a bioassay for control subjects but measured PRA in diabetic patients by immunoassay. However, the absence of a normal distribution for raw values of PRA may provide a more tenable explanation. Thus, in our study, the distribution of PRA was skewed in both the control and diabetic populations, and transformation into a normal distribution by the use of the square root of values was needed before applying parametric statistical tests.

It is likely that data in other studies of Campbell et al. (1976) and Christlieb et al. (1976) were similarly distributed, as in both 2 SD from the mean value falls below zero. This failure to transform data suitably may obscure substantial differences between control and diabetic subjects. It is likely therefore that previous work does not contradict our findings that PRA is raised in diabetes mellitus. This appears to be independent of the type of diabetes, whether insulin dependent or independent. Since there is no significant difference between PRA values in diabetic patients receiving different treatment, this does not appear to influence PRA values. Simultaneous estimation of blood sugar, as an index of diabetic control, showed no correlation with PRA values, so that the raised PRA was unlikely to be due to hyperglycaemia.

It was thought previously that the coincident hypertension in patients with diabetes produces the low PRA (Christlieb et al., 1976), but analysis of their data shows that the mean PRA appeared to be higher than in a comparable hypertensive population, although this difference was not statistically significant. Therefore this again does not contradict our findings that the PRA was higher in diabetic hypertensive patients than in hypertensive subjects matched for age and sex.

Previous studies have examined PRA in complicated diabetes, PRA being low in nephropathy (Roginsky, Abasamis & Asad, 1973) and in some cases of neuropathy, particularly severe autonomic neuropathy (Campbell et al., 1976). We did not find such a relationship between low PRA and diabetic complications, but our patients were less severely affected than those in other series. For example, in one such study (Christlieb et al., 1976) patients with nephropathy and low PRA had a mean urinary protein loss of 5.8 g/24 h, markedly reduced plasma albumin and packed cell volume, and a high blood urea. Such patients would presumably be volume expanded and this, in combination with an advanced degree of renal damage, would readily produce the hypo-reninaemia. Our results therefore suggest that PRA is raised despite diabetic complications, until advanced renal failure ensues. A raised PRA in diabetes mellitus may arise through several different mechanisms. PRA can be increased by a rise in renin substrate, but this has not been measured in diabetic patients. Decreased clearance of renin would appear unlikely, as none of our patients had clinical evidence of liver disease.

Hypersecretion of renin may arise from extracellular volume depletion, reduced renal perfusion pressure, β-adrenoreceptor stimulation, hypopreninaemia or potassium depletion (Davis, 1973). None of these was present in the patients we studied as the diabetes was under good control. Renin secretion is partly under feedback control by angiotensin II and renal perfusion pressure, and therefore the raised PRA may result from an altered sensitivity of the juxtaglomerular baroreceptor.

This defect may involve baroreceptor sensitivity, simulating a reduced renal perfusion pressure, so raising PRA; such a change may result from basement membrane thickening, which has been demonstrated even in recent-onset diabetes (Österby, 1974).

Our findings are clinically important since the

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### TABLE 3. Comparisons with age- and sex-matched non-diabetic populations

<table>
<thead>
<tr>
<th>Clinical subgroup</th>
<th>No.</th>
<th>Age (years)</th>
<th>Mean PRA (pmol h⁻¹ ml⁻¹)</th>
<th>√PRA (pmol h⁻¹ ml⁻¹)</th>
<th>Urinary Na⁺ (mmol/24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive control subjects</td>
<td>45</td>
<td>44.3 ± 2.28</td>
<td>1.40</td>
<td>1.29 ± 0.06</td>
<td>143.8 ± 4.9</td>
</tr>
<tr>
<td>Normotensive diabetic patients without complications</td>
<td>45</td>
<td>45.0 ± 2.38</td>
<td>1.80</td>
<td>1.85 ± 0.11</td>
<td>171.3 ± 8.4</td>
</tr>
<tr>
<td>Hypertensive control subjects</td>
<td>16</td>
<td>53.3 ± 3.10</td>
<td>1.31</td>
<td>1.23 ± 0.11</td>
<td>161 ± 14.6</td>
</tr>
<tr>
<td>Hypertensive diabetic patients</td>
<td>16</td>
<td>54.4 ± 3.23</td>
<td>1.33</td>
<td>1.87 ± 0.17</td>
<td>162.4 ± 19.5</td>
</tr>
</tbody>
</table>

Mean values ± SEM are shown for age, √PRA and urinary Na⁺. N.S., Not significant.
previous studies reporting low PRA in hypertensive diabetic patients have been used to explain the relatively low incidence of malignant hypertension in diabetes (Christlieb, 1974a) and to validate the preferential use of thiazide diuretics to counter the postulated hypervolaemia. However, our results suggest that treatment of the hypertensive diabetic patient should follow the conventional approach used for 'essential' hypertension, although care should be exerted in the use of β-adrenoreceptor-blocking agents since they mask hypoglycaemic symptoms (Abramson, Arky & Woeber, 1966).

References


