Changes in blood pressure, body fluids, circulating angiotensin II and aldosterone, with improved diabetic control

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Summary

1. We studied 12 normotensive non-ketotic diabetic patients during poor metabolic control, with sustained hyperglycaemia, and again, after an interval of 3 weeks, when metabolic control was improved. On each occasion we measured blood pressure, total exchangeable sodium, plasma volume, transcapillary escape rate of albumin, and plasma concentrations of angiotensin II and aldosterone.

2. With improved diabetic control there was a small but significant fall in arterial pressure. Total exchangeable sodium was normal when control was poor but rose significantly to above normal with improved control.

3. Plasma volume also rose significantly with improved control, and the transcapillary escape rate of albumin fell and the intravascular mass of albumin rose.

4. Plasma angiotensin II and aldosterone concentrations were significantly above normal during poor metabolic control, but fell to normal with improved control.

5. These findings indicate a resetting of the relationship between blood pressure and exchangeable sodium when diabetic control improves. The association between exchangeable sodium and concentrations of angiotensin II and aldosterone also appears altered in diabetic patients. These changes associated with varying metabolic control must be considered when studying cardiovascular disease in diabetic patients.

Key words: albumin, aldosterone, angiotensin II, diabetes, plasma volume, sodium.

Introduction

Epidemiological studies [1] suggest that newly diagnosed diabetic patients have higher blood pressures than established treated diabetic patients, and an independent positive relationship has been observed between blood pressure and blood glucose, both in adults [1] and in children [2]. However, there is little available information on the effects of changing diabetic control on blood pressure and body fluid volumes in non-ketotic diabetic patients. There have been conflicting clinical [3, 4] and experimental [5, 6] reports on the influence of varying diabetic control on the renin–angiotensin–aldosterone system. We investigated the simultaneous effects of improved diabetic control on blood pressure, total exchangeable sodium, plasma volume, transcapillary escape rate of albumin, plasma angiotensin II and aldosterone, in non-ketotic diabetes mellitus.

Methods

We studied 12 diabetic patients (nine male), whose mean age was 54 years (range 27–73 years). The three women were postmenopausal. Six were newly diagnosed and six were known diabetic patients whose mean duration of diabetes was 6.7 years (range 1–19 years). Nine patients had maturity-onset (type II) diabetes and three had juvenile-onset (type I) diabetes. Eight patients were treated by diet and oral hypoglycaemic agents, and four were treated by diet and insulin. Three patients had diabetic polyneuropathy and two of these had background retinopathy. None had significant proteinuria and all had normal plasma urea and creatinine. None had cardiac or liver disease and none was on treatment other than that for diabetes.
Patients were first studied while in poor diabetic control. All had recent thirst and polyuria, but none had ketonuria. Diabetic control was improved by dietary measures, together with oral hypoglycaemic agents \((n = 8)\) or insulin therapy \((n = 4)\). The patients were then discharged from hospital and readmitted for repeat studies an average of 3 weeks \((\text{range} \ 2-6 \text{ weeks})\) later. All patients were admitted to a metabolic ward and intake sodium and potassium was unrestricted during each study period.

Blood pressure was measured supine, after overnight rest, between 09-00 and 10-00 hours on the second hospital day, with a London School of Hygiene sphygmomanometer. Blood pressure values reported are the means of five measurements taken over a 20 min period \((\text{diastolic phase} \ 5)\), before venepuncture. Mean arterial pressure was calculated from the diastolic plus one-third of the pulse pressure. Diabetic control was assessed from 

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\text{Hb A}_1
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measurements and a 24 h \((\text{five sample})\) blood glucose profile. A fall in both 

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\text{Hb A}_1, \text{fasting and mean} \ 24 \text{ h blood glucose was required for an improvement in diabetic control. Total exchangeable sodium was measured by the} 24\text{Na dilution technique with correction for urinary loss, and results were expressed both in absolute terms and as the} \% \text{predicted by the leanness index} \ [7], \text{derived from a control population of} \ 33 \text{non-diabetic patients. Plasma volume, transcapi}

\text{illary escape rate of albumin and intravascular mass of albumin were measured as previously described} \ [8]. \text{Blood volume was calculated from a corrected packed cell volume. Plasma angiotensin II} \ [9] \text{and aldosterone} \ [10] \text{were measured by radioimmunoassay. Statistical analyses were performed by paired and unpaired Student’s} \ t\text{-test as appropriate.}

Results

The changes that occurred with improved diabetic control are summarized in Table 1. There was a highly significant fall in 

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\text{Hb A}_1, \text{fasting blood glucose and in mean} \ 24 \text{ h blood glucose, with improved control. There was also a small but significant fall in both systolic and diastolic arterial pressures. Total exchangeable sodium was normal during poor control, but rose to levels significantly above normal with improved control. Plasma volume rose and packed cell volume fell significantly with improved control. Transcapillary escape rate of albumin fell, whereas plasma albumin concentration and intravascular mass of albumin rose significantly with improved control.}

**Table 1. Mean values of variables measured when diabetic control was poor and when metabolic control improved, together with values for normal subjects studied under the same conditions.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Poor control</th>
<th>Improved control</th>
<th>(n)</th>
<th>(P)</th>
<th>Normal subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting blood glucose ((\text{mmol/l}))</td>
<td>13.9 ± 1.1</td>
<td>7.2 ± 0.7</td>
<td>12</td>
<td>&lt;0.001</td>
<td>---</td>
</tr>
<tr>
<td>Mean 24 h blood glucose ((\text{mmol/l}))</td>
<td>16.5 ± 0.9</td>
<td>8.0 ± 0.5</td>
<td>12</td>
<td>&lt;0.001</td>
<td>---</td>
</tr>
<tr>
<td>(\text{Hb A}_1)</td>
<td>12.4 ± 0.5</td>
<td>9.3 ± 0.3</td>
<td>12</td>
<td>&lt;0.001</td>
<td>---</td>
</tr>
<tr>
<td>Blood pressure ((\text{mmol/l}))</td>
<td>124.8 ± 5.4</td>
<td>121.8 ± 4.7</td>
<td>12</td>
<td>&lt;0.02</td>
<td>120.3 ± 1.7</td>
</tr>
<tr>
<td>Systolic</td>
<td>77.6 ± 2.3</td>
<td>71.8 ± 2.3</td>
<td>12</td>
<td>&lt;0.05</td>
<td>72.4 ± 1.4</td>
</tr>
<tr>
<td>Mean</td>
<td>92.6 ± 3.1</td>
<td>88.4 ± 2.6</td>
<td>12</td>
<td>&lt;0.02</td>
<td>88.9 ± 1.3</td>
</tr>
<tr>
<td>Plasma angiotensin II ((\text{supine}))</td>
<td>36.3 ± 9.0*</td>
<td>15.7 ± 3.2</td>
<td>12</td>
<td>&lt;0.02</td>
<td>14.9 ± 5.0</td>
</tr>
<tr>
<td>Plasma aldosterone ((\text{supine}))</td>
<td>812.2 ± 56.6***</td>
<td>525.2 ± 72.0</td>
<td>10</td>
<td>&lt;0.02</td>
<td>422.4 ± 29.5</td>
</tr>
<tr>
<td>Total exchangeable sodium ((\text{mmol}))</td>
<td>3103.0 ± 111.7</td>
<td>3196.0 ± 105.0</td>
<td>9</td>
<td>&lt;0.01</td>
<td>2967.1 ± 93.0</td>
</tr>
<tr>
<td>Total exchangeable sodium ((% \text{predicted}))</td>
<td>102.6 ± 1.2</td>
<td>106.0 ± 1.3***</td>
<td>9</td>
<td>&lt;0.01</td>
<td>100.0 ± 1.8</td>
</tr>
<tr>
<td>Serum sodium ((\text{mmol/l}))</td>
<td>133.8 ± 0.6**</td>
<td>138.2 ± 0.7</td>
<td>12</td>
<td>&lt;0.001</td>
<td>139.2 ± 0.4</td>
</tr>
<tr>
<td>Serum potassium ((\text{mmol/l}))</td>
<td>4.1 ± 0.1</td>
<td>3.9 ± 0.1</td>
<td>12</td>
<td>&lt;0.05</td>
<td>4.0 ± 0.1</td>
</tr>
<tr>
<td>Plasma volume ((\text{ml} /1.73 \text{m}^2))</td>
<td>2860.0 ± 122.4</td>
<td>3102.0 ± 145.3</td>
<td>11</td>
<td>&lt;0.05</td>
<td>2887.0 ± 141.0</td>
</tr>
<tr>
<td>Packed cell volume ((%))</td>
<td>41.3 ± 1.2</td>
<td>38.4 ± 1.1</td>
<td>12</td>
<td>&lt;0.005</td>
<td>40.0 ± 0.6</td>
</tr>
<tr>
<td>Blood volume ((\text{ml} /1.73 \text{m}^2))</td>
<td>4616.0 ± 207.0</td>
<td>4814.0 ± 221.0</td>
<td>11</td>
<td>N.S.</td>
<td>4684.0 ± 232.0</td>
</tr>
<tr>
<td>Transcapillary escape rate of albumin ((%))</td>
<td>9.2 ± 1.1**</td>
<td>6.8 ± 0.9</td>
<td>8</td>
<td>&lt;0.01</td>
<td>5.7 ± 0.7</td>
</tr>
<tr>
<td>Plasma albumin ((\text{g/l}))</td>
<td>35.8 ± 0.9</td>
<td>37.8 ± 1.2</td>
<td>12</td>
<td>&lt;0.02</td>
<td>36.2 ± 1.0</td>
</tr>
<tr>
<td>Intravascular mass of albumin ((\text{g} /1.73 \text{m}^2))</td>
<td>102.9 ± 8.5</td>
<td>118.3 ± 10.6</td>
<td>11</td>
<td>&lt;0.01</td>
<td>104.3 ± 5.5</td>
</tr>
<tr>
<td>Body wt. ((\text{kg}))</td>
<td>70.5 ± 3.1</td>
<td>71.0 ± 3.1</td>
<td>12</td>
<td>N.S.</td>
<td>69.4 ± 2.6</td>
</tr>
<tr>
<td>24 h urine sodium excretion ((\text{mmol}))</td>
<td>109.0 ± 14.6</td>
<td>131.0 ± 14.6</td>
<td>10</td>
<td>N.S.</td>
<td>119.8 ± 10.7</td>
</tr>
<tr>
<td>24 h urine potassium excretion ((\text{mmol}))</td>
<td>52.0 ± 0.2</td>
<td>50.0 ± 0.3</td>
<td>10</td>
<td>N.S.</td>
<td>42.1 ± 3.6</td>
</tr>
</tbody>
</table>
Mean concentrations of plasma angiotensin II and aldosterone were significantly higher than normal during poor control, but fell to normal levels with improved control. Serum sodium rose and serum potassium fell with improved control. Body weight and urinary 24 h sodium and potassium excretion did not change significantly.

Discussion

There was a small but significant fall in blood pressure with improved diabetic control in these patients. The present study cannot exclude influences on blood pressure other than those produced by changes in diabetic control. Should the fall in blood pressure with improved control be confirmed, however, this would have important implications. Higher blood pressures, associated with poor control, may not only accelerate atheroma formation [11] but also hasten the development of specific microvascular complications of diabetes [12, 13]. Blood pressure decreased with improved control despite a rise in plasma volume and in total exchangeable sodium. However, plasma angiotensin II concentrations fell, and changes in sympathetic activity and other unidentified factors may have contributed to the blood pressure fall.

Total exchangeable sodium rose with improved control, an observation in keeping with a previous balance study showing sodium retention after insulin treatment [14]. The increase in exchangeable sodium when control improved is in keeping with previous observations in metabolically stable diabetic patients [15, 16]. This rise in exchangeable sodium may be mediated by an increase in circulating insulin, which has a direct sodium-retaining effect on the diabetic kidney [17, 18].

The rise in plasma volume with improved metabolic control is in keeping with a previous report, which takes account of varying capillary permeability [19] but contrasts with earlier reports [2, 20]. The fall in the transcapillary escape rate of albumin with improved control is also in keeping with a previous study [19] which showed an increased transcapillary escape rate with short-term deterioration of diabetic control. This fall in transcapillary escape rate, together with the rise in the intravascular mass and concentration of albumin, is likely to favour the increase in plasma volume. This and the rise in exchangeable sodium may contribute to suppression of the renin–angiotensin system with improved control.

The elevated levels of plasma angiotensin II and aldosterone in poorly controlled diabetes are in keeping with our previous findings [4, 21]. It seems unlikely that these were the result of sodium depletion, as exchangeable sodium was normal in poorly controlled diabetic patients. Plasma and blood volume were not decreased in this study, although other stimuli to renin secretion, such as increased sympathetic nervous activity [22] or total body potassium depletion [23] may have been active during poor diabetic control. When metabolic control improved and exchangeable sodium rose above normal, angiotensin II and aldosterone concentrations fell to normal, but not below. These findings indicate an altered relationship between exchangeable sodium and both angiotensin II and aldosterone in diabetic patients. The reported changes with varying diabetic control must be borne in mind when studying cardiovascular abnormalities in diabetic patients.

Acknowledgments

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References


