Diabetic Control and the Renin-Angiotensin System, Catecholamines, and Blood Pressure

J. Barry Ferriss, James A. O'Hare, Cecily C. M. Kelleher, Patrick A. Sullivan, Margaret M. Cole, Hazel F. Ross, and Denis J. O'Sullivan

SUMMARY  Diabetic ketoacidosis is usually associated with marked secondary hyperaldosteronism. Plasma levels of renin, angiotensin II, and aldosterone are markedly raised before treatment in most patients, with values falling rapidly toward normal as metabolic control is restored. In a few patients, mostly those with long-term complications of diabetes, plasma levels of renin, angiotensin II, and aldosterone before treatment remain within the normal range. In moderately hyperglycemic patients who have glycosuria but not ketonuria, plasma levels of all three substances are significantly higher than when control is improved. Occasionally, moderately hyperglycemic patients have mild secondary hyperaldosteronism. Improved metabolic control in such patients causes a rise in plasma volume and a rise in total exchangeable sodium, the latter to levels significantly above normal. Plasma catecholamine levels are markedly elevated in diabetic ketoacidosis, probably as a consequence of the ketoacidotic state. In nonketotic patients with moderate hyperglycemia, basal plasma norepinephrine levels are normal; catecholamine responses to exercise may be exaggerated, however. Epidemiological and animal studies suggest a relationship between blood pressure and blood glucose levels. There are few clinical studies of the effects of altering metabolic control of diabetes on blood pressure, and this is an important area for further study. (Hypertension 7 [Suppl II]: II-58-II-63, 1985)

KEY WORDS  • angiotensin II • aldosterone • plasma renin activity • plasma volume • exchangeable sodium • norepinephrine • diabetes mellitus • hypertension

The abnormalities that occur in diabetic ketoacidosis have been investigated in detail. Less attention has been given to disturbances associated with poorly controlled nonketotic diabetes, although this metabolic state is all too common among our diabetic patients. In particular, the long-term effect of poor metabolic control on blood pressure is poorly understood.

In this review we briefly discuss abnormalities of the renin-angiotensin system and catecholamines in ketoacidosis. Disturbances that occur in nonketotic, poorly controlled diabetes mellitus are also examined; these include changes in the renin-angiotensin system, body sodium, and plasma volume with altering metabolic control. The findings emphasize the importance of assessing metabolic control when examining these variables in diabetic patients. Finally, the possible effect of poor metabolic control of diabetes on blood pressure is discussed.

The Renin-Angiotensin System in Ketoacidosis

Ten years ago Christlieb et al.1 described marked secondary hyperaldosteronism in diabetic ketoacidosis. Plasma renin activity (PRA) was grossly elevated in 13 patients in ketoacidosis, levels falling rapidly toward normal as metabolic control was restored. Plasma aldosterone concentrations, measured in four patients, were also raised.

Several groups confirmed these observations. Scott et al.2 reported raised levels of PRA and aldosterone in seven of eight patients in ketoacidosis. Waldhaeusl et al.3 also described marked elevations of renin and aldosterone in a small group of severely hyperglycemic and mostly ketoacidotic patients. We found high levels of plasma angiotensin II4 and aldosterone5 in most patients in ketoacidosis (Figure 1). Plasma angiotensin II concentrations were within the normal range in 5 of 14 patients, however, all of whom had long-term complications of diabetes such as retinopathy, neuropathy, and nephropathy. Even in these patients there was some decrease in plasma angiotensin II with improved metabolic control.

High renin levels in ketoacidosis have been attributed to fluid volume depletion,1 although other factors
may also be important. Among our patients, pretreatment plasma angiotensin II concentrations were not related to indirect indexes of dehydration but were inversely related to pH \( (r = -0.65, p < 0.01) \). It is probable that hydrogen ions do not directly stimulate renin secretion, but pH may reflect the metabolic disturbance that stimulates renin more accurately than indexes of dehydration. Activation of the renin-angiotensin system in ketoacidosis may be clinically important. Circulating angiotensin II may be important in maintaining blood pressure in sodium-depleted subjects, while secondary hyperaldosteronism, which increases renal potassium wasting, may also protect patients from even more marked hyperkalemia than actually occurs. In some circumstances, high angiotensin II concentrations may cause multifocal myocardial necrosis and cardiac arrest; it is not known if the grossly raised concentrations sometimes seen in ketoacidosis can cause myocardial damage.

**Plasma Catecholamines in Ketoacidosis**

Circulating catecholamine levels are also elevated in established ketoacidosis. Christensen described consistently raised plasma norepinephrine values in untreated patients, levels being positively related to the severity of the metabolic disturbance. Plasma epinephrine concentrations were elevated in only some patients. Once metabolic control was restored, both norepinephrine and epinephrine values were similar to those of healthy controls. Waldhausl et al. reported a 10-fold increase in mean plasma norepinephrine and a 20-fold increase in mean plasma epinephrine levels in poorly controlled diabetic patients, mostly in ketoacidosis. Plasma concentrations again fell rapidly toward normal as metabolic control was restored.

The lipolytic and ketogenic action of catecholamines may further aggravate established ketoacidosis. A rise in plasma norepinephrine and epinephrine does not precede the development of ketoacidosis when insulin is withdrawn, however. This suggests that elevated levels are sequelae of ketoacidosis rather than an initiating cause.

**The Renin-Angiotensin System in Poorly Controlled Nonketotic Diabetes**

Abnormalities of the renin-angiotensin system in poorly controlled nonketotic diabetes are less marked than in ketoacidosis. Christlieb et al. were unable to demonstrate a significant change in PRA with improved metabolic control in nonketotic patients, while in the alloxan-diabetic rat, PRA was suppressed in proportion to the severity of diabetes.
As illustrated in Figure 2, we found a significant fall in PRA, plasma angiotensin II, and plasma aldosterone with improved metabolic control of diabetes.⁵ ¹² ¹³ All patients were free of ketonuria, but most had glycosuria when metabolic control was poor. The changes were observed in types I and II diabetes and in patients with and without complications of diabetes. On the other hand, patients studied on two occasions without alteration of metabolic control failed to show a change in any of these variables (see Figure 2). During poor metabolic control, plasma concentrations of angiotensin II were more than two standard deviations above the mean of healthy controls in 7 (22%) of 32 patients, while plasma aldosterone concentrations were similarly elevated in 6 (20%) of 30 patients. This indicates that some patients with poorly controlled diabetes have mild secondary hyperaldosteronism, even in the absence of ketosis.⁵

These findings illustrate the need to define the degree of metabolic control when studying the renin-angiotensin system in diabetic patients. Plasma levels of angiotensin II close to or within the normal range may exert a pressor effect¹⁴ and the higher plasma angiotensin II concentrations during poor metabolic control may contribute to higher blood pressure levels.

Plasma Catecholamines in Poorly Controlled Nonketotic Diabetes

Altered metabolic control of diabetes does not cause marked changes in basal circulating catecholamine concentrations in the absence of ketosis. Improvement of metabolic control by continuous subcutaneous insulin infusion did not alter basal concentrations of epinephrine or norepinephrine.¹⁵ ¹⁶ Catecholamine responses to exercise were exaggerated during conventional control, however, returning to normal during insulin infusion.¹⁵

We measured plasma norepinephrine in 11 nonketotic diabetic patients free of long-term complications, both when metabolic control of diabetes was poor and again when control improved. Plasma norepinephrine was determined using the solvent extraction system of Smedes et al.¹⁷ and analysis by high-performance liquid chromatography (Waters Associates, Milford, MA, USA), with electrochemical detection (Bio-Analytical Systems, West Lafayette, IN, USA) (detection limit < 75 pg/ml; intraassay and interassay coefficients of variation < 10%). Samples were taken when patients were supine after overnight rest and again when upright for 10 minutes.

Supine and upright plasma norepinephrine concent-

**Figure 2.** Mean values (±SEM) of plasma renin activity (PRA), plasma angiotensin II, and aldosterone in diabetic patients free of ketonuria studied when fasting and supine overnight. Values during poor metabolic control (open circles) and when control improved (closed circles) are shown on the left; the mean of five to six blood glucose measurements over 24 hours were 15.9 ± 0.5 and 7.9 ± 0.4 mmol/L respectively (p < 0.001); mean urinary volumes were 1589 ± 118 and 1436 ± 112 ml respectively (NS) on the two study occasions. The mean interval between studies was 6 weeks. Values when metabolic control was unchanged on two occasions (closed triangles) are shown on the right. Means of five to six blood glucose measurements over 24 hours were 12.9 ± 1.4 and 12.6 ± 1.7 mmol/L respectively (n = 10, ns). The mean interval between studies was 6 weeks.

**TABLE 1.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Improved</th>
<th>Control Unchanged</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRA (ng/ml/h)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.6</td>
<td>0.3</td>
</tr>
<tr>
<td>SEM</td>
<td>± 0.1</td>
<td>± 0.1</td>
</tr>
<tr>
<td>n</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>p Value</td>
<td>&lt;0.01</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Plasma Angiotensin II (pg/ml)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>SEM</td>
<td>± 5</td>
<td>± 3</td>
</tr>
<tr>
<td>n</td>
<td>32</td>
<td>10</td>
</tr>
<tr>
<td>p Value</td>
<td>&lt;0.02</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Plasma Aldosterone (ng/100ml)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>SEM</td>
<td>± 4</td>
<td>± 2</td>
</tr>
<tr>
<td>n</td>
<td>30</td>
<td>6</td>
</tr>
<tr>
<td>p Value</td>
<td>&lt;0.01</td>
<td>NS</td>
</tr>
</tbody>
</table>
trations were similar and the postural response was unchanged when metabolic control improved (Figure 3). Values were similar in patients receiving and not receiving insulin on each occasion. The findings were in keeping with observations that basal plasma catecholamines are unchanged by poorly controlled nonketotic diabetes.

**Plasma Volume and Exchangeable Sodium in Poorly Controlled Nonketotic Diabetes**

It has been suggested that osmotic volume expansion associated with hyperglycemia may contribute to the increased prevalence of hypertension in younger diabetic patients. Blood volume was increased in both alloxan-diabetic and streptozotocin-diabetic rats. In humans, plasma volume was higher in normotensive diabetic patients than in matched controls in one study, but others found a similar plasma volume in normotensive diabetics and controls. Christlieb et al. did not note a change in blood volume when metabolic control improved in nonketotic patients.

We studied 12 patients with nonketotic diabetes when metabolic control was poor and again when control improved. On each occasion, blood pressure was measured under standardized conditions after overnight rest, using a London School of Hygiene Sphygmomanometer (Cinetronics Ltd., Mildenhall, England), and the average of five readings taken over 20 minutes was calculated. Plasma volume was measured in 11 of these patients and exchangeable sodium in 9. The mean interval between studies was 3 weeks. With improved metabolic control of diabetes, there was a significant fall in both systolic and diastolic blood pressures, while plasma volume and exchangeable sodium each rose significantly (Figure 4). Exchangeable sodium was similar to that of healthy control subjects when metabolic control was poor, but rose to levels significantly above normal when metabolic control improved. In this small series there was an inverse relationship between the change in exchangeable sodium and the change in both systolic (r = −0.78, p < 0.01) and diastolic (r = −0.66, p < 0.05) blood pressures.

An elevated exchangeable sodium has been described in metabolically controlled diabetic patients, and the increased values when metabolic control was improved are in keeping with these observations. The rise in exchangeable sodium with improved control is in keeping with short-term balance studies that showed sodium retention. It may reflect the reversal of sodium loss associated with even a mild osmotic diuresis during poor control and the direct sodium-retaining effect of insulin on the kidneys. In view of the negative association between changes in blood pressure and in exchangeable sodium, sodium retention could also result from an antinatriuresis associated with a fall in blood pressure. The rise in plasma volume with improved control in humans contrasts with findings in diabetic rats. Our findings do not support the hypothesis that plasma volume is osmotically expanded in humans when metabolic control of diabetes is poor.

**The Effect on Blood Pressure of Altering Metabolic Control**

Epidemiological studies indicate an independent association between blood pressure and blood glucose. A positive relationship has been shown between both systolic and diastolic pressures and blood glucose after a glucose load in middle-aged populations. This persisted when controlled for age, body weight, and heart rate. An independent relationship between blood
pressure and postprandial glucose was also noted in schoolchildren. The association in these populations raises the possibility of a similar relationship in diabetic subjects.

The metabolic control of diabetes may influence blood pressure levels in the rat. In streptozotocin-diabetic rats there was a dose-related blood pressure rise in normotensive animals at least, and hypertension may be reduced by insulin injections.

There are few clinical studies of the effects of altering metabolic control of diabetes on blood pressure. As mentioned, we found a small but significant fall in systolic and diastolic pressures with improved metabolic control (see Figure 4). Blood pressure often falls on repeated measurement, however, and despite efforts to standardize measurements, familiarization may have contributed to the reductions observed. We would have liked to study patients in reverse, when control was good and subsequently when control deteriorated, but had ethical reservations about allowing deliberate worsening of metabolic control for a prolonged period.

Gunderson studied acute changes in young patients with insulin-dependent diabetes with altering metabolic control. Some were newly diagnosed as having diabetes, but in most, insulin was withdrawn under supervision. Mean arterial pressure was significantly higher when metabolic control was poor, compared with values when control was optimal. Blood pressure changes with altering control were not related to changes in blood glucose but were significantly related to changes in standard bicarbonate and free fatty acids. Some patients developed mild ketoacidosis, however.

The influence of metabolic control of diabetes on blood pressure is an important area for further investigation. Because of blood pressure variation even under standardized conditions, it is difficult to demonstrate small changes. This may explain why alteration of metabolic control in small groups may not be associated with significant alterations in blood pressure, even if the degree of metabolic control does influence blood pressure levels. Because of blood pressure variability, we calculate that to detect an independent, unidirectional 4-mm change in systolic pressure between two study occasions, it would be necessary to investigate approximately 45 patients for a change at the 5% significance level and approximately 100 patients for a change at the 1% level.

Hypertension is an important prognostic indicator for the diabetic patient. Even small changes in blood
pressure may have long-term importance, and the effect of long-term poor metabolic control of diabetes on blood pressure needs fuller evaluation. If poor metabolic control causes even a small increase in blood pressure, this may be an additional explanation for the association between hypertension and diabetes. Hypertension is a quantitative disorder and any definition is arbitrary.\textsuperscript{35} In a diabetic population, poor metabolic control may move some patients from just below to just above an arbitrary upper limit of normal blood pressure for the particular age and sex. This change would cause an increased prevalence of hypertension in a diabetic population at any given time unless all are in good metabolic control, an unlikely event in current diabetic practice.

Acknowledgment
We are grateful for the financial support of the Medical Research Council of Ireland.

References
Diabetic control and the renin-angiotensin system, catecholamines, and blood pressure.
J B Ferriss, J A O'Hare, C C Kelleher, P A Sullivan, M M Cole, H F Ross and D J O'Sullivan

Hypertension. 1985;7:II58
doi: 10.1161/01.HYP.7.6_Pt_2.II58

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/7/6_Pt_2/II58