PART XXI

NEPHROLOGY I  801

Chairmen:  G Bianchi
           G Cinotti

PART XXII

NEPHROLOGY: EXPERIMENTAL  837

Chairmen:  E Bartoli
           A Dal Canton

PART XXIII

NEPHROLOGY II  866

Chairmen:  F Goodwin
           G Mecca
PLASMA RENIN ACTIVITY, PLASMA ALDOSTERONE AND DISTAL URINARY ACIDIFICATION IN DIABETICS WITH CHRONIC RENAL FAILURE

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Summary

The renin-angiotensin-aldosterone system and the acidification capacity of the renal tubule were studied in 13 diabetic patients with chronic renal failure. As a whole, the group showed hyporeninaemic hypoaldosteronism (HH). Studied alone, 12 of the 13 patients presented the requirements for HH. This group showed hypercholaemic hyperkalaemic metabolic acidosis with a disturbance in renal acidification which may be classified as Type IV renal tubular acidosis.

The results of this group were compared to those of another two groups; one of diabetic patients without chronic renal failure and the other with chronic renal failure (C Cr <40ml/min); both were seen to show different behaviour to that of the group affected by the two processes.

Introduction

The clinical characteristics of hypoaldosteronism were first described by Hudson in 1957 [1] and since then only a few sporadic cases have been reported; by 1980 50 cases had appeared in the literature, most of them secondary to hypo-reninism. All these showed a defect in renal acidification, leading to hyper-cholaemic hyperkalaemic metabolic acidosis. An increased incidence of cases of hyporeninaemic hypoaldosteronism (HH) has been described in Type I diabetic patients with a marked reduction in glomerular filtration (GF) and in patients with interstitial nephropathy [2,3].

The incidence of case reports of HH in diabetics is increasing steadily; however, the incidence of this process and its pathogenesis in diabetic patients remain unknown. The present work studied a randomly chosen group of Type I diabetics with a glomerular filtration of <40ml/min to determine the incidence of this defect. The influence of chronic renal failure and diabetes on the defect in renal acidification was also studied.
<table>
<thead>
<tr>
<th></th>
<th>Plasma Aldosterone (pg/ml)</th>
<th>PRA (ng/mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Upright</td>
<td>Supine</td>
</tr>
<tr>
<td>Control</td>
<td>1.12±0.43</td>
<td>2.42±0.66</td>
</tr>
<tr>
<td>Diabetics</td>
<td>0.43±0.24</td>
<td>0.62±0.39</td>
</tr>
<tr>
<td>CRF + Diabetics</td>
<td>2.83±1.9b</td>
<td>3.93±2.11bc</td>
</tr>
<tr>
<td></td>
<td>0.71±0.24</td>
<td>1.38±0.35(^a)</td>
</tr>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Notes:
- \(^a\) p<0.05 compared to control.
- \(^b\) p<0.001 compared to control.
- \(^c\) p<0.001 compared to CRF + Diabetics.
- \(^d\) p<0.05 compared to CRF + Diabetics.
- \(^e\) p<0.01 compared to CRF + Diabetics.

### Comparison:
- The post-furosemide values show a significant increase compared to the supine values for all groups.
- The PRA values are significantly lower in the supine position compared to the upright position for all groups.

### Discussion:
- The increase in plasma aldosterone levels post-furosemide suggests a decrease in sodium reabsorption.
- The lower PRA in the supine position could indicate a decrease in renin activity.
<table>
<thead>
<tr>
<th></th>
<th>Plasma</th>
<th></th>
<th>NH₄Cl Overload</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C&lt;sub&gt;cr&lt;/sub&gt; ml/min</td>
<td>Na&lt;sup&gt;+&lt;/sup&gt; mEq/L</td>
<td>Cl&lt;sup&gt;-&lt;/sup&gt; mEq/L</td>
<td>K&lt;sup&gt;+&lt;/sup&gt; mEq/L</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>116.65</td>
<td>± 10.67</td>
<td>140.8</td>
<td>± 1.5</td>
</tr>
<tr>
<td>Diabetics CRF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>24.11</td>
<td>± 6.74&lt;sup&gt;a&lt;/sup&gt;</td>
<td>140.1</td>
<td>± 2.61</td>
</tr>
<tr>
<td>CRF</td>
<td>24.23</td>
<td>± 9.32&lt;sup&gt;a&lt;/sup&gt;</td>
<td>137</td>
<td>± 3.2&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diabetics</td>
<td>102.06</td>
<td>± 24.51&lt;sup&gt;d&lt;/sup&gt;</td>
<td>138.4</td>
<td>± 3.8</td>
</tr>
</tbody>
</table>

a) p<0.001 control  
b) p<0.01 control  
c) p<0.05 control  
d) p<0.001 diabetic + CRF  
e) p<0.01 diabetic + CRF  
f) p<0.05 diabetic + CRF  
g) p<0.05 CRF

Creatinine clearance and Na<sup>+</sup>, Cl<sup>-</sup>, HCO<sub>3</sub><sup>-</sup> levels and urinary acidification after short NH₄Cl overload in all four groups.
Materials and Methods

This study was carried out on three groups of patients and on one control group as follows: Group A 23 healthy individuals as controls; Group B 13 type I diabetic patients with an age range of 21–67 and a C Cr <40 ml/min (problem group); Group C nine non-diabetic patients with chronic renal failure, C Cr <40 ml/min; Group D eight diabetic patients without renal impairment.

The age ranges of all the groups were similar. Plasma urea, Cr, Cl⁻, Na⁺, K⁺, pH and arterial gases and C Cr and proteinuria was determined in all. Also studied in the urine of all patients and in 17 of the controls, having ascertained the absence of infection, were: pH, ammonium, titratable acidity (TA) and net acid excretion (NAE), both basal and after a short load of NH₄Cl (100 mg/kg over two hours).

In all the groups erect and supine plasma renin activity and plasma aldosterone were measured and also after i.m. administration of 20 mg of frusemide. All patients received a diet of about 100 mEq of Na⁺ daily. NH₄ was determined by titration [4]. PRA and plasma aldosterone by radioimmunoassay [5,6].

Statistical Studies One-way analysis of variance was carried out; the discrepancy between the mean values of the different groups was verified according to Newman-Keuls Multiple Range Test.

Results Results are included in Tables I and II.

Discussion

The results of the patients with diabetes mellitus and chronic renal failure show that as a group the patients had hypoaldosteronism, as shown by the absolute values of plasma aldosterone compared to the control group (Table I) and by the plasma aldosterone (ng/dl)/plasma potassium ratio of 1.45 ± 0.7, compared with 4.07 ± 0.8 (p<0.001) for the control group. Values lower than three considered as indicative of hypoaldosteronism [7]. Studied individually, 12 of the patients presented data sufficient to be classed as presenting hypoaldosteronism, thereby underlining the high occurrence of this process in this kind of patient. The cause of the hypoaldosteronism must be related to the decreased PRA in these patients. It is feasible that the suprarenal cortex, has normal function but that renin stimulation is not sufficient. Different studies have shown the function of the suprarenal cortex to be normal [8]. In support of this is the positive linear correlation found between plasma renin and aldosterone (r = 0.47) (p<0.005). The fact that this correlation is not as close as that shown by the control group (r = 0.757, p <0.001) could be due to the stimulating effect of the high plasma potassium. The biochemical profile of the problem group (Table II) was hyperchoreaemic hyperkalaemic metabolic acidosis, coinciding with what has been described previously for hyporeninaemic hypoaldosteronism.

This disturbance in acid-base balance is due to a defect in renal acidification shown by these patients, known as renal tubular acidosis (Type IV) or distal
hyperchloaemic hyperkalaemic renal tubular acidosis [9], and is characterised by an acid urinary pH, though with a low NAE which does not correspond to the urinary pH. The basal urinary findings in this group was pH 5.36 ± 0.63; NH₄: 21.89 ± 11.62μEq/min; TA: 13.94 ± 5.33μEq/min, NAE: 31.07 ± 13.85μEq/min. These data show that with a relatively acid pH, the NH₄ and TA values are low. After a NH₄Cl load (Table II), the urinary pH was seen to decrease to 4.72 ± 0.41 (p<0.001), a similar value to that shown by normal individuals, though without a significant increase in NAE, fundamentally due to a failure in NH₄ excretion. The elimination of TA was also less than normal. The behaviour of the problem group compared to that of the controls is very characteristic, since the urinary pH fell in both groups similarly, though NH₄ and TA were much greater for the controls (p<0.001).

The deficit in aldosterone is thought to be the main factor in the pathogenesis of the defect in renal acidification [3,8]. The most feasible hypothesis is that which relates the rise in potassium, as a consequence of hypoaldosteronism and hyperglycaemia, to an inhibitory effect of NH₄ synthesis and elimination. Sebastian [10] found an inverse linear correlation between serum K⁺ and the urinary excretion of NH₄ in three patients with HH receiving fludrocortisone. He also found a positive linear correlation between urinary NH₄ excretion and urinary pH and concluded that the absence of NH₄ excretion was the cause of the fall in urinary pH.

These latter data were not borne out in our patients in whom we observed a negative correlation between the NH₄ and the PH (r = 0.588, p<0.05), both in basal conditions and after a NH₄Cl overload. This behaviour is similar to that described in other disturbances in renal acidification in which reduced NH₄ secretion leads to an alkaline urine. Ditella [10] has reported similar behaviour to that of our patients in adrenalectomised rats subjected to a NH₄Cl overload. The explanation of why the urinary pH falls with low levels of NH₄ and TA is elusive. One possibility is that small amounts of hydrogen ions could be free in the urine, considerably reducing the pH.

The interpretation of the results in the problem group poses the question of whether the endocrine-metabolic disturbance is due to diabetes or to chronic renal failure, or to both processes. Our results point to the notion that diabetics without chronic renal failure are hyporeninaemic compared with the control group, with a poor response to the upright position and the administration of frusemide. However, the PRA values are higher than those found in diabetics with chronic renal failure although only significantly after frusemide (p<0.05). This group also showed no differences in aldosterone values compared to the control group although there is a clear elevation compared with the group of diabetics with chronic renal failure in the upright position and after frusemide (p<0.05 and p<0.001 respectively).

The group of patients with chronic renal failure also showed a significant increase in PRA compared with the controls and even higher compared to the problem group (Table I). Plasma aldosterone is higher compared with that of the diabetics with chronic renal failure but shows no differences compared with the control group.

The renal acidification of the diabetics with chronic renal failure is also
different to that of the other groups of patients (Table II). The group of patients with chronic renal failure, as would be expected after a NH₄Cl overload, show less of a decrease in urinary pH with a lower excretion of NH₄ and TA compared with the control group (Table II). However compared with the problem group, the urinary pH decreases less, though NH₄ secretion is greater. The group of diabetics show a similar increase in urinary pH after a NH₄Cl overload compared with the problem group, although with a higher NAE (p<0.05) due to greater NH₄ secretion (p<0.05).

These data indicate that hyporeninaemic hypoaldosteronism is very common in patients with diabetes mellitus and chronic renal failure. It may also be seen that the endocrine-metabolic picture of this group is clearly different from that of patients with either diabetes or chronic renal failure separately. The most probable hypothesis is that diabetes is the main cause of the process, leading to chronic renal failure and hyporeninaemic hypoaldosteronism. The influence of both processes on distal tubular function induces the defect in renal acidification which is characteristic of this group of patients.

References

2. Caroll HJ, Farber SJ. Metabol Clin Experim 1964; 13: 808

Open Discussion

FEEST (Exeter) I question your interpretation of your data on urine acidification, ammonium excretion and titratable acid excretion in your study group. You have shown results similar to those found in any group with depressed renal function. Unless you have a very carefully matched control group of non-diabetic patients with identical age and renal function, I suspect your results are only demonstrating that your patients have a diminished number of functioning nephrons.

TABERNERO Our patients with chronic renal failure behaved differently from those patients who have chronic renal failure and diabetes.

FEEST I am not sure that this is valid unless your control group of chronic renal failure patients have identical creatinine values.

TABERNERO The creatinine clearances were similar in both groups.
ZOCALI (Reggio Calabria) I am not surprised by your results because it is well established that some degree of renal impairment is necessary in diabetic patients to unmask type IV renal acidosis. I think however that your data could have been more convincing if you had also compared diabetic patients with chronic renal failure with a subset of chronic renal failure patients closely matched for PRA and aldosterone values.

TABERNERO I agree with you.

BIANCHI (Chairman) Do you think that the age of the patients may influence the plasma renin activity? We know that with ageing there is a slow decline in the response of arterioles to stimulation.

TABERNERO The age range of the groups we studied were comparable.