LOW INCIDENCE OF HYPERPARATHYROIDISM IN DIABETIC RENAL FAILURE

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Summary

The first study compared two groups on dialysis: 25 patients with diabetes mellitus and 25 matched non-diabetic patients, in relation to the presence of signs of hyperparathyroidism, to assess the reported low incidence of hyperparathyroidism in these patients. The diabetic group showed significantly lower values of PTH, Alk phosphatase, percentage of patients requiring vitamin D treatment, and less evidence of hyperparathyroidism on X-ray and in bone histomorphometry.

In the second study 16 patients with chronic renal failure due to diabetic nephropathy were compared to 27 patients with the same degree of renal failure of other origin, the diabetic nephropathy group showed no increase in PTH, with falling creatinine clearance. Despite this low PTH, the phosphaturia was higher in the diabetic nephropathy group (Tm PO₄/Cr: 1.94±0.43 vs 2.5±0.68).

In conclusion, patients with diabetes mellitus are less prone to develop hyperparathyroidism in progressive renal failure. This could be due to a relative increase in phosphaturia during declining function.

Introduction

The number of patients with diabetes mellitus being accepted on dialysis and transplantation programmes is growing rapidly, and therefore the characteristics of this group of patients are increasingly better known.

There is a reduced incidence of hyperparathyroidism in diabetic dialysed patients [1–3]. This study investigates why diabetic patients show this lack of hyperparathyroidism. First we compared a group of diabetic patients on dialysis with a paired group of non-diabetic patients and secondly we studied a group of diabetic patients before they reached the dialysis phase and compared them to a group of non-diabetic patients with the same degree of renal failure to determine whether the renal handling of minerals differed.
Methods

Patients

In the first study 25 patients with diabetes mellitus on dialysis for a period of time ranging from one to 49 months were compared to a group matched according to age, sex and length of time on dialysis.

In the second study 26 patients with chronic renal failure (creatinine clearance 5–40ml/min) of various origin and 17 patients with diabetic nephropathy were compared.

Total calcium, inorganic phosphate, alkaline phosphatase and creatinine were determined by autoanalyzer; C-terminal PTH by a radioimmunoassay with rabbit antibody against PTH (65–84), (Immunonuclear); plasma cAMP by a RIA of rabbit antibody; plasma calcitonin by RIA; and urinary cAMP by a third RIA of Beckton-Dickinson (201.677). The renal tubular threshold of phosphate (TmPO4/C Cr) was calculated by the method of Bijvoet [4].

The normal values in our laboratory are: C-PTH <1ng/ml, cAMP is expressed as nmol/100ml C Cr=1.62±1.1; TmPO4/C Cr=3.63±0.56mg/100ml. CT=58.27±28.1pg/ml.

Iliac crest bone biopsies were obtained in six diabetic and seven non-diabetic dialysis patients. Non-decalcified specimens stained with toluidine blue, hema-
toxylin and eosin, and Von Kossa, were processed by an image analyser (Morpho-
mat 30, Zeiss) and the following parameters were measured. Volume of trabecular bone relative to total bone (Vt), number of osteoclasts/mm of trabecular perimeter (Cr), percentage of surface covered by osteoid (Sf), percentage of trabecular volume occupied by osteoid (Vosf) and by osteoclastic resorption (Sr), and calculated mean width of osteoid seams (WOS).

The presence of bone pain, X-ray appearances, Alkaline phosphatase greater than 450mU, and cPTH >3ng/ml, are the criteria used in our centre to start dialysis patients on vitamin D treatment.

Statistical analysis of differences between groups was undertaken using Mann-Whitney’s U-test, and ‘t’ test for paired differences in the first study. Correlations were computed by the method of least squares. Only p values <0.05 were considered significant.

Results

Study 1

As shown in Table 1 the diabetes mellitus dialysis group, in spite of close matching with the control group, had lower values of iPTH: 1.44±0.79ng/ml in diabetic group and 3.76±2.03ng/ml in non-diabetic group; alkaline phosphatase 293±143 and 473±443U/ml respectively; percentage of patients having X-ray signs of phalangeal subperiosteal reabsorption: 4 per cent in the diabetic group and 24 per cent in the control group; histomorphometric values of osteoclastia in bone biopsy; percentage of patients that required vitamin D treatment: 12 per cent and 36 per cent respectively.
TABLE I

<table>
<thead>
<tr>
<th></th>
<th>Diabetes mellitus group on haemodialysis</th>
<th>Non-diabetic group on haemodialysis</th>
<th>Stat</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time on dialysis (months)</td>
<td>14.7</td>
<td>14.86</td>
<td>td = -0.36</td>
<td>NS</td>
</tr>
<tr>
<td>iPTH (ng/ml)</td>
<td>1.44±0.79</td>
<td>3.76±2.03</td>
<td>td = -4.8</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Alk phosphatase (U/L)</td>
<td>293±143</td>
<td>473±343</td>
<td>td = -2.07</td>
<td>&lt;0.05</td>
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<tr>
<td>Calcitonin (pg/ml)</td>
<td>252±150</td>
<td>203±70</td>
<td>td = -1.04</td>
<td>NS</td>
</tr>
<tr>
<td>% with abnormal X-rays</td>
<td>4</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% vitamin D requirement</td>
<td>12</td>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone morphometry:</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Vt (mm²/mm³)</td>
<td>0.162±0.04</td>
<td>0.215±0.148</td>
<td>U = 19</td>
<td>NS</td>
</tr>
<tr>
<td>Sr (mm²/mm³)</td>
<td>0.003±0.002</td>
<td>0.014±0.09</td>
<td>U = 7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Cr (n/mm)</td>
<td>0.23±0.21</td>
<td>1.56±0.7</td>
<td>U = 6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Sf (mm²/mm³)</td>
<td>7.6±6.7</td>
<td>45.8±37.6</td>
<td>U = 7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Wf (µm)</td>
<td>17.05±9.01</td>
<td>17.2±10.2</td>
<td>U = 30</td>
<td>NS</td>
</tr>
<tr>
<td>Vosf (%)</td>
<td>0.38±0.31</td>
<td>3.36±2.17</td>
<td>U = 8</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

TABLE II

<table>
<thead>
<tr>
<th></th>
<th>Diabetic mellitus group (D-group) (n=16)</th>
<th>Non-diabetic group Controls (n=27)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>18.8±9.1</td>
<td>18.1±9.4</td>
<td>NS</td>
</tr>
<tr>
<td>iPTH (ng/ml)</td>
<td>1.26±0.58</td>
<td>2.01±1.17</td>
<td>&lt;0.05</td>
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<tr>
<td>cAMP (nmol/100ml C Cr)</td>
<td>6.12±2.64</td>
<td>10.1±3.95</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Calcitonin (pg/ml)</td>
<td>121±45</td>
<td>116±33</td>
<td>NS</td>
</tr>
<tr>
<td>Tm PO₄/C Cr (mg/100ml)</td>
<td>1.94±0.43</td>
<td>2.5±0.68</td>
<td>&lt;0.05</td>
</tr>
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</table>

Study 2

The values of creatinine clearance, urinary cyclic AMP, TmPO₄/C Cr, and iPTH in both groups are shown in Table II.

The iPTH of the diabetic group was less than the non-diabetic group: 1.26±0.58ng/ml vs 2.01±1.17ng/ml, the difference being significant. The cAMP values
Figure 1. Creatinine clearance and iPTH in diabetic (upper) and non-diabetic (lower) groups. A significant inverse correlation was found in the non-diabetic group but failed in the others.
were above normal in both groups, but the increases in the diabetic group were lower (6.16±2.64nmol/100ml C Cr in comparison to 10.1±3.95nmol/100ml C Cr). The phosphate renal threshold was significantly lower in the diabetic group when compared to the group with renal failure of other origin (1.94±0.43mg/100ml and 2.54±0.68mg/100ml). When the figures of cAMP and iPTH of each group were plotted against creatinine clearance, the correlations shown in Figure 1 were obtained. A significant inverse linear correlation was obtained in the non-diabetic group between the decreasing values of creatinine clearance and the increasing values of iPTH (r=0.651), but in the diabetic group this correlation failed.

Discussion

In the evolution of renal failure, a progressive increment in PTH secretion ending in hyperparathyroidism, is a common and well known event. The pathogenesis of this process is probably multifactorial and based on the stimulus of hypocalcaemia upon PTH secretion, phosphorus retention, skeletal resistance to PTH, the lack of vitamin D, and the progressive retention of C-terminal fragments of poorly metabolised PTH.

Slatopolsky et al were the first to show that prevention of phosphorus retention, maintaining the plasma values within the normal range, could avoid the appearance of overt hyperparathyroidism in late renal failure [5]. Since then phosphorus retention has been recognised as a fundamental factor in the pathogenesis of hyperparathyroidism, in spite of the fact that the phosphaturia of the remaining nephrons is greater in renal failure and that the insufficient kidney is able to adapt to phosphorus intake variations [6].

In our studies we have shown that the kidneys of diabetic patients with renal failure can excrete more phosphorus than similar non-diabetic patients. This finding could explain why diabetic patients are less prone to develop hyperparathyroidism when they reach the terminal phase of renal failure [1,7,8]. In renal failure from other causes, when the creatinine clearance falls there is an increase of PTH. In diabetic patients these increases are only minor.

Our results suggest that the increased phosphaturia of diabetic patients is not a secondary event to PTH stimulus, but the primary one, and possibly the reason for the lack of increased PTH in these patients. Furthermore, the lower cAMP generation argues against the possibility of tubular hypersensitivity to PTH [9].

The finding of a relative hyperphosphaturia is not an unexpected event. The phosphaturic effect of glucosuria is well known [10]. More recently a direct action of the insulin on the phosphorus tubular handling has been proved. The effect of insulin pumps to normalise phosphorus renal threshold in diabetic patients without renal failure has also been reported. A role for the insulin in the antiphosphaturic effect of somatostatin has been suggested recently. Certainly, all these facts do not argue against the well known fact of the normal plasma concentration of phosphorus, and PTH in diabetic patients without renal failure.

Our studies seem to prove that diabetic patients on dialysis have fewer signs of hyperparathyroidism than matched patients with the same time on dialysis.
It also seems probable that the hyperphosphaturia caused by insulinopenia and glucosuria persists through the course of progressive renal failure, and this possibly is the reason for the lack of hyperparathyroidism in such patients when they require dialysis.

References

1. Rivero AJ, McKenna BA, Pabico RC et al. *ASAIO 1980; 9: 60*
5. Slatopolsky E, Bricker NS. *Kidney Int 1973; 4: 141*

Open Discussion

DE PAEPE (Belgium) I may have missed the point, but did you compare bone biopsies of diabetic patients without renal insufficiency and normal control patients? Is it possible that there are differences to explain the different response to PTH?

AUBIA We have compared two groups of dialysis patients, one with diabetes and the other non-diabetic. The difference in the number of osteoclasts and the number of surfaces with active reabsorption was lower in the diabetic group.

DE PAEPE In your opinion is this due to lower plasma PTH or could it be that the target organ is less sensitive to PTH?

AUBIA We do not have any answer to that question.

CANNATA (Oviedo) You may know that aluminium can depress PTH secretion. Have you studied in any way the aluminium exposure in both groups. In addition have you considered the osmotic effect of the glucosuria?

AUBIA The aluminium levels of both groups are similar and both are in the safe level, between 50–70ng/ml. The second question is probably the most interesting. We have only results in the last seven patients and all have glucosuria but we have not been able yet to establish any relationship between the degree of glucosuria and phosphaturia.

KERR (London) That is a very impressive piece of evidence that diabetic nephropathy is different from other forms of chronic renal failure, but I cannot think of a physiological explanation for this unless it is vascular damage to the
parathyroids. It would be nice to exclude other possible explanations, such as that diabetic patients eat less phosphate which might explain why you get less hyperparathyroidism in your dialysis population. Is there any difference in the diet of your diabetic patients or the rest of your dialysis population?

AUBIA There is apparently no difference in the diets.

BANKS (Bristol) Have you studied any non-insulin dependent diabetics?

AUBIA No, we have not.