PARATHYROID HORMONE IN PATIENTS WITH DIABETES MELLITUS AND END-STAGE RENAL DISEASE ON CHRONIC HAEMODIALYSIS

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Summary

Serum immunoreactive parathyroid hormone in patients with juvenile-onset diabetes mellitus and end-stage renal failure on chronic haemodialysis treatment is significantly lower than the values obtained from patients with adult-onset diabetes mellitus and non-diabetic patients with end-stage renal disease being similarly dialysed. The major determinants of parathyroid hormone secretion, such as calcium and magnesium, do not seem to be the factors responsible for this difference. The histology of the parathyroid glands in juvenile-onset patients shows fibrosis and collagen infiltration which reduce the functional mass of the glands.

Introduction

Loss of trabecular and/or cortical bone mass has been documented in patients with juvenile-onset diabetes mellitus (JODM) as well as in those with adult-onset diabetes mellitus (AODM) long before renal failure sets in [1]. The osteopenia, on the one hand, is thought to be an inherent part of the disease rather than a complication of the various metabolic and/or hormonal abnormalities of diabetes [2], and on the other, that it is an acquired defect of bone formation [3]. However, studies of calcium homeostasis in adult diabetic patients without renal failure reveal normal values for serum total and ionised calcium, immunoreactive parathyroid hormone (iPTH) and metabolites of Vitamin D [4]. With an ever-increasing number of diabetic patients developing ESRD and requiring CHD, peritoneal dialysis and/or renal transplantation, we are concerned with the potential magnitude of problems related to metabolic bone disease(s) in these patients.

We initially studied the changes in serum iPTH of JODM with ESRD who were already on CHD treatments. Our preliminary findings [5] and those of Avram [6] showed that the serum iPTH in JODM on CHD was much lower
compared to non-diabetics with ESRD on CHD. The current report expands on our initial study to include patients with AODM with ESRD on CHD treatment.

Subjects

Fifteen patients with JODM, seven patients with AODM, and 17 non-diabetics on CHD were studied. The mean age of the JODM patients (34 years) and that of the non-diabetic patients (36 years) was similar; most of the non-diabetics had chronic glomerulonephritis. The AODM patients were slightly older (48 years). All the JODM and five of the AODM patients were on varying doses of insulin. The patients were either totally anuric or had creatinine clearance of 1.0ml/min or less. During the study, no patient received any calcium supplement, Vitamin D, Cimetidine, Propranolol or other drugs that could influence calcium homeostasis or PTH secretion. The patients dialysed 15–18 hours/week using plate dialysers against a bath containing 3.75mEq/L of Ca++ and 2.0mEq/L of Mg++ and the usual solutes. The time on CHD treatment was similar for the three groups of patients (3–30 months). No patient had undergone total or subtotal parathyroidectomy. Patients were included in the study at the time when they were clinically stable.

Procedures and methods

Fasting blood specimens (10–15ml) were drawn anaerobically before the start of the subsequent dialysis. The specimens were allowed to clot and the serum was then collected anaerobically. Total calcium and magnesium were determined by atomic absorption spectrophotometry, free or ionised calcium by the selective ion electrode system (Orion®), inorganic phosphate (Pi) by a colorimetric technique adapted for the autoanalyser (Technicon®), serum iPTH by radioimmunoassay using antiserum that detected the carboxyl terminal [7]. The normal values in our laboratory are as follows: serum total calcium: 9.0–10.5mg/dl, free or ionised calcium: 2.12–2.49mEq/L, magnesium: 1.4–2.4mEq/L, inorganic phosphate: 2.5–4.5mg/dl, and iPTH: ≤2.0ng/ml.

The data are presented as mean ± 1 SEM. Non-paired t-test was used to compare the groups and p value of <0.05 was considered significant.

Results

The mean serum iPTH in the JODM patients was significantly lower compared to the values obtained from AODM and non-diabetic patients. Indeed, the mean iPTH level for the JODM was only 20–25 per cent of the values for the other two groups of patients. The mean serum total calcium in JODM was, likewise, much less than the values from either AODM or non-diabetics. However, the mean serum free or ionised calcium was not significantly different from the values obtained from the other groups. The same could be said for the mean serum magnesium and the Pi values. The serum concentrations of these variables in the AODM patients were not significantly different from the non-diabetic subjects (Table I).
<table>
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<th>I JODM (n = 15)</th>
<th>II AODM (n = 7)</th>
<th>III non-DM (n = 17)</th>
<th>p Values</th>
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| Serum iPTH (ng/ml) | 5.25 ± 1.1     | 24.1 ± 6.0     | 24.9 ± 4.0          | I vs II = 0.003,  
|                 |                |                |                     | I vs III = 0.001,  
|                 |                |                |                     | II vs III = NS     |
| Serum total Calcium (mg/dl) | 6.81 ± 0.6     | 10.63 ± 0.5    | 9.81 ± 0.5          | I vs II = <0.001,  
|                 |                |                |                     | I vs III = <0.001,  
|                 |                |                |                     | II vs III = NS     |
| Serum ionised Calcium (mEq/L) | 2.41 ± 0.1     | 2.72 ± 0.1     | 2.47 ± 0.1          | I vs II = 0.03,    
|                 |                |                |                     | I vs III = NS,      
|                 |                |                |                     | II vs III = NS     |
| Serum Magnesium (mEq/L)      | 2.27 ± 0.2     | 2.61 ± 0.1     | 2.40 ± 0.1          | I vs II = NS,      
|                 |                |                |                     | I vs III = NS,      
|                 |                |                |                     | II vs III = NS     |
| Serum inorganic Phosphate (mg/dl) | 4.25 ± 0.2     | 3.60 ± 0.2     | 4.25 ± 0.4          | I vs II = 0.02,    
|                 |                |                |                     | I vs III = NS,      
|                 |                |                |                     | II vs III = NS     |

Discussion

We have extended our initial observation that patients with JODM and ESRD on CHD treatments have significantly lower values of iPTH, a feature not found in AODM patients. Inasmuch as the severity of the renal failure and the specifics of the dialysis treatments were similar in the three groups of patients, the much higher values of iPTH in the AODM and non-diabetic subjects could not be explained simply by accumulation of carboxyterminal fragments [8]. The much lower value of iPTH in JODM patients is due to either an enhanced peripheral metabolism of iPTH or to suppressed glandular secretion, or both. The former seems remote since the two organs involved primarily with PTH degradation — the kidney and the liver — are unlikely to have selectively developed enhanced catabolic functions. These patients had virtually no renal functional mass. Thus, the renal mechanisms for PTH uptake — glomerular filtration and tubular re-absorption — are probably non-existent.

The major factors that influence PTH secretion, i.e., calcium [9] and magnesium [10,11] were not significantly different in JODM patients. The low serum total calcium was due in part to the hypoalbuminemia. But the ionised, biologically active calcium was normal and not significantly different from the non-diabetics. Concern for magnesium was for two reasons: first, both hypoa- and hypermagnesaemia inhibit parathyroid gland activity [10–12] and second, hypomagnesaemia had been shown to enhance the development and progression of diabetic retinopathy [13]. As noted in Table I, the serum magnesium in JODM was normal and not significantly different from the other groups. Hence, it appears that neither cation was directly involved in the lower level of iPTH
Figure 1. Histologic features of the parathyroid glands in JODM with ESRD on CHD (A) and in non-diabetic ESRD patient on CHD (B). Note the presence of elongated cells (fibroblasts) and polymorphonuclear leucocytes (left and right upper corners) in (A) and the numerous clear cells in (B)
in the JODM patients. Most of the JODM patients have clinical features of autonomic dysfunction. Lack of, and deficiency in circulating catecholamines may contribute to the relatively low iPTH since it has been shown that catecholamines stimulate PTH secretion [14].

Two patients with JODM died from sepsis. On necropsy the parathyroid glands were not enlarged; they were fibrotic. On microscopic examination there was paucity of clear cells; numerous fibroblasts and collagen-like material were evident; inflammatory cells were also present (Figure 1A). These findings contrast with the typically enlarged, hyperplastic glands with abundant clear cells and chief cells in the non-diabetic subjects (Figure 1B). These histologic features suggest that the functional tissue of the parathyroid glands in JODM is much less than the non-diabetic, hence a lower iPTH secretion.

Acknowledgments

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Open Discussion

AHLMEN (Gothenburg) Thank you for a nice observation but is there perhaps a more simple explanation? I would like to know the original diseases of your control group, because it is a well known fact that diabetic nephropathy progresses to uraemia much faster than for example interstitial nephritis and most forms of glomerulonephritis. The pictures shown could just as well indicate that there is a long standing secondary hyperparathyroidism among the patients in your control group.
PABICO That may be the case. At the moment we are looking at patients with diabetic nephropathy from the first manifestation of their renal disease and we have now included in a prospective study a continuing measurement of parathyroid hormone. We could not adequately compare or match the individual patients with non-diabetics because of the different nature of the disease process.

CANNATA (Spain) As you may know serum aluminium can interfere directly with the release of parathyroid hormone. Have you measured serum aluminium concentration in the different groups?

PABICO We have not measured aluminium but we have all the specimens deep frozen so this may be possible later. However, the water used in our system is ion free as far as we can determine but two patients with diabetic end-stage renal disease who had severe bone disease presented to Dr Coburn some time ago and aluminium concentrations were measured and they were not elevated more than the rest of the dialysis patients. That is a very small number, we have not really done more.

ROTTEMBOURG (Paris) Do you know the residual renal function of your two groups of patients?

PABICO We have looked at this, as I mentioned and they all were virtually anatomically and functionally anephric.