PART XVI

RENAL OSTEODYSTROPHY

Chairmen:  F Kokot
            A Válek
THE EVOLUTION OF RENAL OSTEODYSTROPHY IN PATIENTS UNDERGOING CONTINUOUS AMBULATORY PERITONEAL DIALYSIS (CAPD)

V Calderaro, D G Oreopoulos, H E Meema, R Ogilvie, H Husdan, R Khanna, C Quinton, T Murray*, D Carmichael

Toronto Western Hospital, and *St Michael’s Hospital, University of Toronto, Canada

Summary

Since the introduction of continuous ambulatory peritoneal dialysis by Popovich et al [1] and the subsequent modification of the technique by Oreopoulos et al [2], an increasing number of patients with end-stage renal disease are maintained on this new treatment modality.

To date, there has not been any report of the effect of CAPD on the evolution of renal osteodystrophy which is one of the major complications of chronic renal failure. In this report we will present the results of our radiological and biochemical studies of renal osteodystrophy in 28 patients who have been on CAPD from 6 to 23 months.

Patients and methods

Twenty-eight patients (10 men and 18 women) ranging in age from 22 to 74 (average 51.3) years have been studied during their CAPD treatment. The duration of CAPD varied from 6 to 23 months. Eighteen of them had been treated with intermittent peritoneal dialysis before CAPD for a period of 3–54 months; the remaining 10 were treated exclusively by CAPD.

In addition to CAPD, the patients were treated with 50,000 units of Vitamin D₃ once a week and phosphate binders in doses required to maintain their serum phosphorus below 5mg%. Five patients received treatment with 1,25 dihydroxyvitamin D₃ in doses adjusted to maintain their serum calcium at the upper limits of normal.

Biochemical Studies

These included measurement of serum calcium, corrected for serum proteins, serum phosphorus, calculation of calcium x phosphorus product, and serum bicarbonate every month; in addition plasma 25-hydroxyvitamin D₃ and parathyroid hormone concentrations were determined every six months.
Serum calcium was measured with the Model AA/120 atomic absorption spectrophotometer (Varian-Techtron) and corrected for serum protein using the modified formula of Parfit (adjusted serum calcium (mg/dl) = measured serum calcium (mg/dl)/0.6 + T.P./19.4) [3].

The basic AutoAnalyser (Technicon) was used to determine serum phosphorus values (N-4b methodology). Serum alkaline phosphatase values were measured with the Technicon AutoAnalyser (SMA-12/60 No. SF4-0006FG5 method).

Plasma parathyroid hormone concentration was measured by radioimmunoassay [4]; the antiserum used (GP-1) has recognition sites for both the aminoterminal and carboxyterminal portions of the hormone molecule. 25(OH) Vitamin D$_3$ was measured using Hadad's competitive protein binding method [5].

Although most biochemical investigations were performed monthly, for the purposes of this paper only the values corresponding to the radiological investigations were used.

Peritoneal calcium balances were calculated in 21 samples among 7 patients who were admitted to a metabolic ward in the hospital. The effluent dialysate was acidified before calcium was measured to avoid precipitation of calcium phosphate (due to the presence of phosphate and the alkalinisation of the dialysate following six hours in the peritoneal cavity). To calculate the peritoneal calcium balance the amount of calcium in the effluent volume was subtracted from that in the original volume; the difference was an expression of peritoneal calcium balance. The peritoneal calcium balance of the above samples ($\bar{x} \pm S.D.$) was found to be negative, and equal to 50mg per day ($\pm$ 36mg).

**Radiological Studies**

All patients initially had an extensive skeletal survey including thorax, lumbar spine, pelvis, both knees, and both hands, ankles and feet; for the latter three examinations industrial (fine-grain) film was used. In order to limit radiation exposure to the patients, smaller skeletal surveys were performed subsequently at six-monthly intervals, the lumbar spine, pelvis and knees being excluded. Such examinations were considered adequate for follow-up since x8 microradioscopy of hand bones permits reasonably accurate assessment of intracortical and periosteal bone resorption [6]. The thorax and metatarsals are in our experience by far the commonest sites of development of spontaneous fractures, and arterial calcifications are usually detected earliest in areas anterior or posterior to the ankles [7].

Concurrently with each skeletal survey examination, cortical bone mineral mass (M) was measured in the proximal radius by an X-ray photodensitometric method and the combined cortical thickness (C) of the radius was measured in the same area. The ratio M/C expresses the cortical bone mineral density [6,8]. A decreasing cortical thickness is a measure of endosteal bone resorption, whereas a decrease in cortical bone density largely reflects development or progression of intracortical resorption [6].

A somewhat more specific assessment of intracortical resorption was made from fine detail radiographs of hands by x8 microradioscopy of metacarpals II, III and IV. A grading method was used [6] by which grades 0 and 1+ represent
normal variations and grades 2+ and 3+ indicate distinctly increased net intracortical resorption. Subperiosteal resorption was also studied by microradioscopy, but in the middle phalanges of digits II, III and IV, and was graded similarly [6].

Results

Biochemical investigations

Table I shows the mean (± S.D.) values of serum calcium, phosphorus, CO₂ content, alkaline phosphatase and Ca × P product before and at 6, 12 and 12–24 months on CAPD. The only significant (p<0.05) changes that were observed were those of serum phosphorus which decreased from 5.7 ± 2.1 to 4.9 ± 1.3 at 6 months and of alkaline phosphatase which increased from 131 ± 90IU to 187 ± 92IU at 12 months. The Ca × P product decreased to normal but the change was not statistically significant.

TABLE I. Changes in serum Ca, P, Alk. phosph., CO₂ content and Ca × P product with time on CAPD

<table>
<thead>
<tr>
<th></th>
<th>Duration of CAPD (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Serum Ca (mg/dl)</td>
<td>9.6±1.0</td>
</tr>
<tr>
<td>Serum P (mg/dl)</td>
<td>5.7±2.1</td>
</tr>
<tr>
<td>Serum alk. phosph.</td>
<td>131±90</td>
</tr>
<tr>
<td>(I.U./ml)</td>
<td></td>
</tr>
<tr>
<td>Serum CO₂ content</td>
<td>20.9±3.9</td>
</tr>
<tr>
<td>(mEq/L)</td>
<td></td>
</tr>
<tr>
<td>Ca × P product</td>
<td>53.6±20</td>
</tr>
<tr>
<td>25(OH)D₃ (ng/ml)</td>
<td>–</td>
</tr>
<tr>
<td>iPTH (ng/ml)</td>
<td>–</td>
</tr>
</tbody>
</table>

(Normal range for 25(OH)D₃ = 10ng/ml and for iPTH = 0–0.25ng/ml)

Plasma levels of 25-hydroxyvitamin D₃ remained within the normal range whereas plasma immunoreactive parathyroid hormone was increased at 6 months (0.38 ± 0.2ng/ml) and remained elevated throughout the study (Figure 1).

Radiological investigations

Photodensitometric measurements: the mean values of bone mineral mass showed a trend towards decreasing values, but these changes were not statistically significant, neither was there any significant change in the bone mineral density. However,
Figure 1. Changes in serum 25(OH)D₃ and plasma iPTH with time on CAPD (normal levels for 25(OH)D₃ > 10ng/ml and for iPTH 0–0.25ng/ml)

TABLE II. Changes in bone mineral mass, density, and cortical thickness with time on CAPD

<table>
<thead>
<tr>
<th></th>
<th>Duration of CAPD (months)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Bone mineral mass (mg/cm²)</td>
<td>531 ± 135</td>
<td>515 ± 114</td>
<td>537 ± 127</td>
<td>497 ± 107</td>
</tr>
<tr>
<td>Bone mineral density (mg/cm³)</td>
<td>940 ± 100</td>
<td>900 ± 160</td>
<td>960 ± 160</td>
<td>930 ± 160</td>
</tr>
<tr>
<td>Cortical thickness (mm)</td>
<td>5.59 ± 0.9</td>
<td>5.58 ± 0.8</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

*p < 0.05
the combined thickness decreased significantly (p < 0.05) with time on CAPD (Table II).

Subperiosteal resorption progressed in 28% of the patients. In addition 10 patients (36%) in whom subperiosteal resorption was abnormal to start with, remained abnormal throughout the study (Figure 2). Only in three patients (10.7%) did subperiosteal resorption improve (Table III and Figure 3). Intracortical resorption remained undetectable in 6 patients, progressed in 13 and improved

---

**Figure 2.** Course of subperiosteal resorption among those patients in whom the disease progressed (n = 7) or remained abnormal (n = 11) throughout the study

**Table III.** Changes in subperiosteal resorption among 28 patients on CAPD

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>During</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>Absent</td>
<td>12</td>
<td>8</td>
</tr>
</tbody>
</table>

Changes during CAPD

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased</td>
<td>7</td>
</tr>
<tr>
<td>Decreased</td>
<td>3</td>
</tr>
<tr>
<td>Unchanged:</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>11</td>
</tr>
<tr>
<td>Absent</td>
<td>7</td>
</tr>
</tbody>
</table>
only in two. In 7 patients it was abnormal at the beginning of CAPD and remained abnormal during the study (Table IV and Figures 4 and 5).

Fractures: three patients developed new fractures (two pathological and one traumatic); the traumatic and one of the pathological fractures healed during the treatment. In addition, two patients who had pathological fractures (and histologically proven osteomalacia) at the start of CAPD showed healing with callus formation while on CAPD.

Arterial calcifications remained unchanged. No new calcifications developed while on CAPD.

**TABLE IV. Changes in intracortical resorption among 28 patients on CAPD**

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>During</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>Absent</td>
<td>18</td>
<td>11</td>
</tr>
</tbody>
</table>

Changes during CAPD

- Increased: 13
- Decreased: 2
- Unchanged:
  - Present: 7
  - Absent: 6
Figure 4. Course of intracortical resorption among those patients (n = 11) in whom the diseases remained undetectable or improved.

Figure 5. Course of intracortical resorption among those patients in whom the disease progressed (n = 10) or remained abnormal (n = 7) throughout the study.

Discussion
Despite the negative peritoneal calcium balance, serum calcium remained unchanged indicating the effectiveness of compensatory mechanisms either by increasing calcium absorption from the gut or by increasing bone resorption or both. Increased bone resorption obviously continues in most of these patients as indicated by the increased parathyroid hormone levels as well as by the maintenance or even pro-
gression of bone resorption in a significant number of them. These findings of ours are in contrast to previous reports that parathyroid hormone levels decrease in patients on CAPD [9]. Previous reports have shown that some parathyroid hormone fractions are removed by CAPD, but this did not lead to suppression of plasma parathyroid hormone which decreased only when its secretory rate could be controlled by successful control of serum calcium [10].

Continuous ambulatory peritoneal dialysis is superior to intermittent peritoneal dialysis in controlling serum phosphorus, and thus a normal serum Ca x P product was maintained in most of these patients[11].

The increase in serum alkaline phosphatase probably reflects the persistence of hyperparathyroid bone disease. Although we did not perform fractionation studies, the liver function tests were normal (unpublished data) supporting the contention that the increased alkaline phosphatase is produced by bone cell activity.

Our recent observations (unpublished) on non-dialysed, haemodialysed and intermittently peritoneally dialysed patients indicate that subperiosteal resorption, once established progresses at a somewhat higher rate in dialysed than in non-dialysed patients. Our present data agree with this observation. Radiologically diagnosed subperiosteal resorption improved only in a few patients, whereas in the majority of them it did not, and actually progressed in some in whom it was not present before CAPD. These changes occurred despite treatment with vitamin D3 in most or 1,25-dihydroxyvitamin D3 in some.

Intracortical resorption also increased or remained abnormal in most of the patients indicating the prevalence of a high bone turnover. The decreasing cortical thickness indicates progression of endosteal resorption which probably also reflects the increased levels of parathyroid hormone.

In contrast to osteitis fibrosa, osteomalacia seems to respond to treatment with CAPD. In two of the patients who had osteomalacia and multiple pseudo-fractures, these did not respond to treatment with 1,25(OH)2 Vitamin D3 or DHT and intermittent peritoneal dialysis. However, these pseudo-fractures healed after 4 months on CAPD. Although this may reflect the effects of prolonged treatment with 1,25(OH)2 Vitamin D3, this is doubtful because the fractures persisted despite 2 years and 8 months treatment with Vitamin D analogues before CAPD was started. Similarly a third patient, not included in this report, who had pseudo-fractures while on intermittent peritoneal dialysis healed his fractures after 6 months of combined treatment with CAPD and Vitamin D3. Three additional patients who formed new fractures while on CAPD (2 pathological and 1 traumatic) eventually formed callus and their fractures healed. It seems that CAPD has some beneficial effect on the healing of osteomalacic fractures by enhancing calcification of bone collagen in the presence of Vitamin D. A calcifying defect in these cases has been ascribed to either an immaturity of the bone collagen [12] or to the presence of circulating inhibitors of calcification [13]. In the past, intermittent peritoneal dialysis was shown to be very effective in removing these inhibitors [14] and it is possible that CAPD may be superior to intermittent peritoneal dialysis in this respect. Similarly, it is possible that CAPD may be contributing to the maturation of collagen and thus facilitating its calcification by removing unidentified toxins (middle molecules [15]) which may be responsible
for the immaturity of the collagen. Based on this study one would consider as an indication for CAPD those patients on haemodialysis or intermittent peritoneal dialysis who have osteomalacia and pseudofractures not responding to prolonged treatment with \(1,25(\text{OH})_2\text{D}_3\).

Finally, vascular calcifications did not progress, probably due to the maintenance of normal calcium x phosphorus product. This is in contrast with progression of arterial calcifications in patients treated with intermittent peritoneal dialysis [7] who usually have an increased Ca x P product [11].

In conclusion, whereas the osteitis fibrosa element of renal osteodystrophy progresses in patients maintained on CAPD, the osteomalacia component seems to improve. The negative peritoneal calcium balance with a dialysate calcium of 6mg% may be responsible for continued hyperparathyroidism.

Acknowledgments

We would like to thank Mrs F Razack and M Silva for their secretarial assistance in the preparation of this manuscript.

This work was supported by the U.S. National Institutes of Health, Chronic Renal Disease Programme (Contract N01 AM8 2213), and the Medical Research Council of Canada (Grant MA-3889).

References

3 Husdan H, Rapoport A, Locke S. Metabolism 1973; 22: 787
4 Murray TM, Kentmann HT. J. Endocrin 1973; 56: 493
5 Hadad JG, Chyu KJ. J Clin Endocrinol 1971; 33: 992
6 Meema HE, Meema S. Invest Radiol 1972; 7: 88
7 Meema HE, Oreopoulos DG, deVeber GA. Radiology 1976; 121: 315
8 Meema HE, Harris CK, Porrett RE. Radiology 1964; 82: 986
11 Reynolds JW, Chalmers A, Oreopoulos DG, Meema HE, Meindok H, deVeber GA. The arthropathy of chronic intermittent peritoneal dialysis. Submitted for publication
12 Russell JE, Termine JD, Aviolo LV. J Clin Invest 1973; 52: 2848
13 Yendt ER, Connor TB, Howard JE. Bull Johns Hopkins Hosp 1955; 96: 1
Open Discussion

DIEGO BRANCACCIO (Milan) I would like to know what is your impression of the clinical meaning of the increase during CAPD of the plasma level of 25(OH)D3?

CALDERARO The plasma levels of 25 hydroxy are the consequence of Vitamin D treatment. My opinion is that renal osteodystrophy is progressing not only during CAPD but also during haemodialysis and intermittent peritoneal dialysis. I would like to stress that there are some differences between CAPD and intermittent peritoneal dialysis. We found, at Toronto Western Hospital, a large difference in the development of periosteal neostosis between patients on intermittent peritoneal dialysis and those on CAPD; patients on intermittent peritoneal dialysis develop periosteal neostosis and osteosclerosis. Osteosclerosis is an unusual feature in patients on CAPD.

ROTTEMBOURG (Paris) What is the calcium intake of your patients and what is the level of calcium in the dialysate you propose?

CALDERARO We did not measure the calcium absorption in our patients. We presented the peritoneal calcium balance, not the overall calcium balance of the patients. In any case peritoneal calcium balance, in our hands, was negative. We found a mean calcium concentration of about 6mg% in our bags by atomic absorption spectrophotometry.

FOURNIER (Amiens) I just wanted to say that I quite agree with your last conclusion since in our experience with 7mg% of calcium in the dialysate we achieved a positive calcium balance and no increase in PTH levels after 6 months.

DRUEKE (Paris) You said in your abstract that you treated 5 patients with 1.25 dihydroxy calciferol. Were you able to reverse the increased bone resorption by 1.25?

CALDERARO We treated only 5 patients with 1.25 dihydroxy vitamin D for more than 1 year. Two of them with osteomalacia, developed fractures when they were on IPD. Despite 2 years of IPD plus Vitamin D₃ treatment, the fractures did not heal. When they were switched to CAPD the fractures healed after just 4 months. We think there is a combined effect of 1.25 plus CAPD; maybe because of removal of inhibitors of calcification. In this case, CAPD can act by removing some toxin(s) able to inhibit the maturation of the bone collagen.

FROEHLING (GDR) In my opinion the deterioration of bone disease in your patients in spite of normal plasma values of 25 OH Vitamin D stems from the fact that the Vitamin D requirement in CRF patients is higher compared with normal subjects.

The 25(OH)D₃ level in plasma should be three times higher, on conservative treatment, than in healthy subjects, to prevent bone disease. I believe this is also true for patients on CAPD.

CALDERARO Our last slide shows that we think that use of larger doses of Vitamin D would be better and maybe one of the means to arrest the progression of osteodystrophy; we agree with you that the requirement of Vitamin D in these patients may be higher. A combined treatment of Vitamin D plus a higher dialysate calcium concentration may constitute one of the means to treat osteitis fibrosa.