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CLINICAL INVESTIGATION

Continuous ambulatory peritoneal dialysis and bone

JAMES A. DELMEZ, MICHAEL D. FALLON, MICHELE A. BERGFELD, BARBARA K. GEARING, C. SUE DOUGAN, and STEVEN L. TEITELBAUM

Department of Medicine, Renal Division, Chromalloy American Kidney Center, Washington University School of Medicine, and Department of Pathology, Jewish Hospital at Washington University Medical Center, St. Louis, Missouri, USA

Continuous ambulatory peritoneal dialysis and bone. We studied the effects of continuous ambulatory peritoneal dialysis (CAPD) on the histological manifestations of uremic bone disease. Twelve patients underwent bone biopsy immediately prior to and after one year of such treatment. Those with larger quantities of non-mineralized bone matrix (osteoid) experienced a reduction in relative osteoid volume, mean osteoid seam width, and total osteoid surface. Moreover, the use of time–spaced kinetic markers of mineralization (tetracycline) enabled us to demonstrate that CAPD usually decreased the amount of non-mineralized bone matrix by shortening mineralization lag time (that is, the interval from organic matrix deposition to its mineralization). The changes in the histomorphology appeared to occur independently of bone aluminum. These data indicate that CAPD generally enhances the mineralizing capacity of individual osteoblasts and suggests that such therapy is beneficial to the uremic skeleton.

The pathogenesis of renal osteodystrophy is among the best understood of any generalized disorder of the skeleton. Fortunately, this insight has been translated into successful therapeutic programs resulting in a progressive reduction in the proportion of hemodialysis patients who develop clinically significant bone disease [1].

Continuous ambulatory peritoneal dialysis (CAPD) is a new alternative to hemodialysis but has relatively unique metabolic consequences which potentially influence the skeleton. In contrast to hemodialysis, for example, CAPD leads to removal of immunoreactive parathyroid hormone (iPTH) [2]. Both normal [2] and low [3, 4] levels of 25-hydroxyvitamin D have been noted in patients undergoing treatment with CAPD. Because CAPD may impact on bone and has been reported to lead to progressive renal osteodystrophy [5], we evaluated the effects of twelve months of such treatment on the histology of the uremic skeleton and found it beneficial.

Methods

Twelve patients were studied immediately prior to, and after one year of CAPD. Their clinical characteristics are detailed in Table 1. Four patients were maintained on hemodialysis for between three and nine years, respectively, and the remaining eight were treated medically before CAPD. Of these eight, three patients were nephrotic. All had creatinine clearances less than 5 ml/min/1.73 m^2 at the start of CAPD and become oliguric within three to four months of treatment. The dialysis regimen was as previously described [2]. Each patient usually exchanged three, 1.5% and one 4.25% dextrose dialysate solutions (Dianeal, Baxter–Travenol Laboratories, Deerfield, Illinois, USA) per day.

Table 1. Clinical characteristics of the twelve study patients

Patient	Sex	Age	Prior hemodialysis	Renal disease	Nephrotic	Al $(OH)_3$ g/day
1	M	58	No	Interstitial nephritis	No	0.75
2	M	63	No	Diabetes (type II)	Yes	4.3
3	F	50	No	Diabetes (type II)	Yes	1.5
4	F	53	No	Diabetes (type II)	Yes	4.2
5	F	56	Yes	Interstitial nephritis	No	2.0
6	F	50	Yes	Glomerulonephritis	No	4.0
7	M	48	No	Unknown	No	1.5
8	F	62	Yes	Polycystic kidney disease	No	4.0
9	F	36	No	Interstitial nephritis	No	3.0
10	M	68	No	Hypertension	No	1.4
11	M	52	Yes	Crescentic glomerulonephritis	No	9.0
12	F	52	No	Unknown	No	1.0

All subjects received oral calcium supplements in an attempt to maintain circulating ionized calcium levels at, or slightly above, the upper limits of normal (5.0 mg/dl). In most patients, the amount of ingested elemental calcium was between 500 and 2,000 mg per day. Serum phosphorus concentrations were controlled by aluminum hydroxide administration. No patient was taking anticonvulsant drugs, vitamin D, or corticosteroids, nor was there evidence of liver disease in any subjects.

Biochemical determinations

Eleven of the twelve patients had at least two determinations of ionized calcium, phosphorus, immunoreactive parathyroid hormone (iPTH), and alkaline phosphatase within two months prior to initiation of CAPD. Thereafter, these parameters were measured every four to six weeks and the mean values for the twelve month period, calculated. Circulating ionized calcium was measured using a flow–through membrane, electrode (Orion Research, Cambridge, Massachusetts, USA) and phosphorus by routine laboratory methods adjusted for the Technicon Auto Analyzer (Technicon Instruments Corpora-

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Table 2. Biochemical determinants*

Patient	Ionized calcium, *mg/dl*		Phosphorus, *mg/dl*		Alkaline phosphatase IU/liter		iPTH *μl Eq/ml*	
	Pre-CAPD	1 yr. CAPD	Pre-CAPD	1 yr. CAPD	Pre-CAPD	1 yr. CAPD	Pre-CAPD	1 yr. CAPD
1	3.95 (1)	5.06 ± 0.13 (13)	6.55 ± 0.59 (4)	4.38 ± 0.35 (19)	144 ± 17 (7)	67 ± 8 (6)	225 ± 14 (6)	82 ± 6 (19)
2	4.34 ± 0.1 (3)	4.85 ± 0.2 (11)	3.71 ± 0.82 (4)	5.02 ± 0.24 (12)	180 ± 12 (3)	71 ± 12 (4)	61 ± 5 (5)	28 ± 5 (11)
3	4.61 ± 0.06 (2)	5.39 ± 0.15 (11)	5.37 ± 0.31 (9)	3.77 ± 0.22 (13)	91 ± 5 (7)	72 ± 3 (6)	63 ± 1 (3)	22 ± 2 (18)
4	4.44 ± 0.07 (3)	4.63 ± 0.21 (6)	3.89 ± 0.51 (4)	4.70 ± 0.69 (8)	262 ± 10 (5)	134 ± 5 (5)	111 ± 14 (3)	59 ± 11 (9)
5	5.0 ± 0.11 (6)	5.11 ± 0.10 (11)	5.06 ± 0.36 (4)	5.22 ± 0.37 (10)	49 ± 2 (8)	67 ± 5 (6)	114 ± 14 (5)	127 ± 8 (21)
6	5.24 ± 0.21 (3)	4.95 ± 0.15 (11)	4.82 ± 0.6 (4)	4.96 ± 0.15 (11)	170 ± 30 (2)	173 ± 20 (5)	320 ± 24 (4)	520 ± 88 (11)
7	4.54 ± 0.3 (2)	4.80 ± 0.12 (13)	5.8 ± 1 (2)	5.56 ± 0.34 (16)	192 ± 23 (3)	128 ± 16 (7)	182 ± 13 (5)	178 ± 30 (14)
8	5.42 ± 0.09 (5)	5.20 ± 0.25 (7)	5.39 ± 0.26 (5)	4.58 ± 0.29 (7)	79 ± 9 (6)	118 ± 11 (3)	279 ± 78 (5)	394 ± 72 (9)
9	4.55 ± 0.14 (2)	4.46 ± 0.08 (10)	6.18 ± 1.75 (4)	5.52 ± 0.35 (11)	270 ± 14 (3)	211 ± 16 (4)	246 ± 81 (2)	644 ± 50 (9)
10	4.83 ± 0.29 (4)	5.11 ± 0.12 (11)	4.85 ± 1.63 (4)	4.96 ± 0.40 (13)	76 ± 5 (4)	54 ± 3 (4)	97 ± 61 (3)	39 ± 6 (9)
11	4.24 ± 0.12 (3)	4.59 ± 0.06 (10)	7.18 ± 1.70 (3)	7.50 ± 0.50 (12)	111 ± 19 (4)	124 ± 16 (7)	515 ± 38 (3)	835 ± 84 (12)
12	5.14 ± 0.63 (2)	4.74 ± 0.13 (8)	5.24 ± 0.90 (5)	5.05 ± 0.47 (8)	64 ± 5 (4)	55 ± 6 (6)	65 ± 10 (3)	40 ± 7 (9)
Normal Range	4.5–5.0		2.5–4.5		35–100		<10	

* Parentheses include number of determinations.

tion, Tarrytown, New York, USA). Parathyroid hormone levels were determined by a radioimmunoassay which recognizes the intact molecule and its carboxy-terminal portions [6]. The majority of iPTH detected in the serum of patients on CAPD is composed of the biologically inactive fragments of the terminal part of the molecule [2].

Bone histomorphometry

Patients underwent a bone biopsy at the start of CAPD and following one year of treatment. Each 5 mm transileal bone specimen, obtained two days after two, three-day courses of tetracycline (oxytetracycline, 1 g/day) separated by two weeks, was fixed, embedded, and cut into non-decalcified sections as previously described [7, 8]. The following histomorphometric parameters were quantitated by use of an Osteoplan Image Analyzer (Zeiss, Inc., New York, New York, USA) and the parameters determined by tetracycline were quantitated by use of an ocular grid:

(a) Total bone volume—fraction of marrow space occupied by bone matrix;

(b) Relative osteoid volume (decimal fraction)—fraction of trabecular bone matrix composed of osteoid (non-mineralized bone matrix);

(c) Mean osteoid seam width (μm)

(d) Total osteoid surface (decimal fraction)–fraction of trabecular bone surface lined by osteoid seams;

(e) Osteoclast number/mm^2—number of osteoclasts per mm^2 of space containing trabecular bone and marrow;

(f) Fibrotic surface (decimal fraction)—fraction of trabecular bone surface in apposition to fibrous tissue;

(g) Linear extent of mineralization—the decimal fraction of trabecular bone surface capable of assuming a tetracycline lab el.

(h) Cellular rate of mineralization (μm/day)—mean distance between the midpoints of double tetracycline labels divided by 17 (number of days between the midpoint of the two courses of tetracycline);

(i) Decimal fraction of osteoid seams exhibiting a tetracycline label;

(j) Mineralization lag time (days)—this is a calculated value derived by dividing the product of the decimal fraction of tetracycline labeled seams and the mean osteoid seam width by the cellular rate of mineralization [8].

The "static" (non-tetracycline based) parameters were compared to iliac crest bone processed in our laboratory from twelve, similarly aged white females (mean age 48.8 ± 18.5 (SD) years who died suddenly and the dynamic measurements (tetracycline based), compared to those of normal women, published by Melsen and Mosekilde [9, 10].

The histological stain for aluminum deposition in bone was performed according to the method of Maloney et al [11].

Statistics

Statistical analyses were performed using the Student's *t*-test and linear regression by least squares. All results are reported as the mean ± SEM.

Table 3. Static analysis of bone histology

Patient	Total bone volume (TBV)		Relative osteoid volume (decimal fraction)		Mean osteoid seam width (μm)	
	Pre-CAPD	1 yr. CAPD	Pre-CAPD	1 yr. CAPD	Pre-CAPD	1 yr. CAPD
1	20.39	19.89	0.20	0.08	15.9	10.4
2	24.36	23.13	0.22	0.10	14.9	8.5
3	18.39	28.12	0.06	0.04	8.7	6.3
4	13.72	19.15	0.35	0.07	18.8	12.0
5	10.75	12.49	0.25	0.06	9.9	9.1
6	12.65	12.64	0.11	0.10	15.4	11.5
7	10.46	10.51	0.17	0.25	14.3	13.8
8	16.07	20.74	0.13	0.06	8.5	10.5
9	40.08	45.58	0.33	0.08	24.6	13.9
10	16.66	20.40	0.03	0.04	6.9	7.1
11	16.78	14.70	0.07	0.09	7.3	8.7
12	17.77	22.57	0.13	0.17	11.0	13.2
$\bar{X}$ ± SEM	18.7 ± 7.96	20.82 ± 9.31	0.17 ± 0.03	0.09 ± 0.02	13.0 ± 1.5	10.4 ± 0.9
Normal Range	5.1–38.7		0–0.06		0–23	

Table 3. Continued

Patient	Total osteoid surface (decimal fraction)		Osteoclasts/mm^2		Fibrotic surface (decimal fraction)	
	Pre-CAPD	1 yr. CAPD	Pre-CAPD	1 yr. CAPD	pre-CAPD	1 yr. CAPD
1	0.55	0.29	3.38	0.80	0.342	0.004
2	0.62	0.55	0.97	0.12	0.093	0
3	0.27	0.26	0.03	0.00	0.006	0
4	0.83	0.36	0.00	0.60	0.008	0.012
5	0.62	0.21	0.31	0.37	0.029	0.020
6	0.37	0.41	1.16	1.24	0.341	0.440
7	0.36	0.65	1.65	0.78	0.232	0.280
8	0.69	0.37	0.79	1.18	0.026	0.015
9	0.72	0.48	4.31	2.16	0.352	0.352
10	0.23	0.38	0.00	0.00	0.003	0.000
11	0.56	0.77	0.15	0.19	0.284	0.131
12	0.81	0.76	0.11	0.49	0.003	0.032
$\bar{X}$ ± SEM	0.55 ± 0.66	.46 ± 0.05	1.07 ± 0.41	0.66 ± 0.18	0.143 ± 0.044	0.107 ± 0.046
Normal Range	0–0.40		0–0.35		0	

Results

Biochemical parameters

The levels of ionized calcium, phosphorus, alkaline phosphatase, and iPTH prior to and during the twelve-month treatment period on CAPD are shown on Table 2. There was no overall change in the ionized calcium (pre 4.69 ± 0.13 mg/dl, during 4.91 ± 0.08 mg/dl) or phosphorus (pre 5.34 ± 0.29 mg/dl, during 5.10 ± 0.26 mg/dl) levels during the study periods. However, there was a significant fall in the alkaline phosphatase concentration while on CAPD (pre 140 ± 21, during 106 ± 15, $P < 0.05$). As previously reported [2], the effects of CAPD on iPTH levels are variable. In five patients there was an approximate fifty percent or more drop in iPTH concentrations while on CAPD, whereas there was a greater than fifty percent rise in three. The remaining four patients did not demonstrate such marked changes.

Bone histology

The initial biopsies of all twelve patients had some features of renal osteodystrophy (Table 3). Ten had an abundance of osteoid if expressed as a proportion of bone matrix (relative osteoid volume) or eight if defined in terms of percentage of bone surface covered by unmineralized matrix (total osteoid surface). The number of osteoclasts was increased in six and all had peritrabecular marrow fibrosis, a distinctly abnormal finding which in renal failure reflects enhanced PTH effect on bone. Four had histological evidence of bone aluminum accumulation (Table 4), two of whom (No. 5 and No. 6) had been maintained on hemodialysis. Analysis of the kinetic histomorphometric parameters indicate that nine of twelve patients had a decreased fraction of osteoid seams capable of assuming a tetracycline label (Table 5). The general failure of uremic osteoblasts to mineralize bone is more globally expressed in terms of the mineralization lag time which was markedly prolonged in eight of twelve patients.

Table 4. Aluminum stains of the bone biopsies

Patient	% Total surface picking up aluminum (decimal fraction)		% Aluminum surface/ %TOS (decimal fraction)	
	Pre-CAPD	1 yr. CAPD	Pre-CAPD	1 yr. CAPD
1	0.00	0.00	0.00	0.00
2	0.00	0.00	0.00	0.00
3	0.00	0.00	0.00	0.00
4	0.19	0.32	0.23	0.89
5	0.35	0.24	0.57	1.15
6	0.39	0.11	1.07	0.26
7	0.00	0.00	0.00	0.00
8	0.29	0.00	0.41	0.00
9	0.00	0.00	0.00	0.00
10	0.00	0.15	0.00	0.40
11	0.00	0.00	0.00	0.00
12	0.00	0.00	0.00	0.00
$\bar{X}$ ± SEM	0.10 ± 0.05	0.07 ± 0.03	0.19 ± 0.10	0.23 ± 0.11

The static (non-tetracycline–based) features of the biopsies improved in most patients after one year of CAPD. In those eight patients with an initial increase in total osteoid surface, seven experienced a decline ($P < 0.05$) (Fig. 1). Although not statistically significant, there was also an overall decrease in the relative osteoid volume (pre 0.17 ± 0.03, 1 year 0.09 ± 0.02) and mean osteoid seam width (pre 13.0 ± 1.5 μm, 1 year 10.4 ± 0.9 μm). The improvement was most evident in those patients demonstrating the greatest accumulation of osteoid on the initial biopsy. The number of osteoclasts per mm^2 decreased from 1.07 ± 0.41 to 0.66 ± 0.66, and the fibrotic surface fell from 0.143 ± 0.044 to 0.107 ± 0.046. While changes in these indices of osteitis fibrosa (OF) did not reach significance, this may reflect the variable effects of CAPD on iPTH levels. In most patients the changes of OF mirrored those changes in serum iPTH levels. Overall, there was a close correlation with iPTH levels and fibrotic surface ($r = 0.585$, $P = 0.003$).

Eight patients had no histological evidence of aluminum accumulation at the start of CAPD, whereas in four, the cation was present on initial biopsy. Despite the continued ingestion of aluminum–containing gels, only one of the eight patients without aluminum on the initial biopsy developed subsequent evidence of its accumulation in bone. Of the four who initially had aluminum, two developed increased and two decreased amounts of aluminum after one year of CAPD (Table 4).

CAPD had dramatic effects on tetracycline–based measurements (Table 5). Following one year of therapy all but one biopsy contained double tetracycline labels, and the mean cellular rate of mineralization became almost twice the normal, a phenomenon we have previously noted in hemodialyzed patients [12]. Most strikingly, the mineralization lag time diminished in seven of eight patients in whom it was initially prolonged ($P < 0.025$) (Fig. 2).

These data suggest that one year of CAPD had, in most patients, a beneficial effect but offers no information regarding the specificity of this treatment. We, therefore, retrospectively studied the bone biopsies of nine patients who had been maintained on hemodialysis for 12.6 ± 6.1 (SD) months. While these biopsies were essentially no different than those obtained from the pre-CAPD group, they generally contained more osteoid than encountered following one year of peritoneal

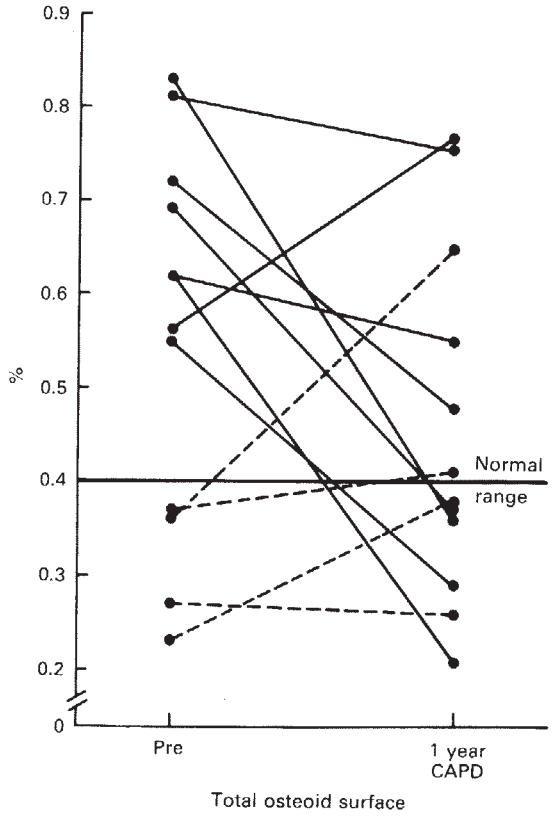

Fig. 1. *The effect of CAPD on total osteoid surface.* Of the eight patients with large amounts of ostoid, seven demonstrated improvement after 12 months on CAPD ($P < 0.05$).

dialysis. This difference in the effects of the two forms of dialysis is most dramatically illustrated by the approximate 50% greater extent of total osteoid surface in the hemodialysis relative to CAPD patients ($P < 0.005$).

Discussion

Our data indicate that one year of CAPD is not detrimental, and in fact, appears to be beneficial, to bone. The abundant quantity of non-mineralized matrix, a hallmark of renal osteodystrophy [1] is particularly effected. This change is most dramatically expressed in terms of the total osteoid surface which declined in these patients in whom it was initially increased.

The quantity of osteoid is a reflection of the relative rates of its synthesis and mineralization, and a fall in the amount of unmineralized matrix reflects either: 1) enhancement of its mineralization, or 2) a decreased rate of osteoid production [6]. Distinction between these two possibilities can only be achieved by the use of time–spaced courses of tetracycline as morphological markers of the rates of mineralization [6]. Using this approach, we measured two basic parameters of bone mineralization; namely: 1) the cellular rate of mineralization which reflects the rate of calcification by the average osteoblasts, and 2) the percentage of tetracycline–labeled osteoid, which is a measurement of the proportion of osteoblasts which have been recruited into the mineralization process. Taken with the mean osteoid seam width, these tetracycline–based param-

Table 5. Kinetic parameters of bone biopsies

Patient	Linear extent of mineralization (decimal fraction)		Cellular rate of mineralization (μm/day)		Tetracycline labeled osteoid seams (decimal fraction)		Mineralization lag time (days)	
	Pre-CAPD	1 yr. CAPD	Pre-CAPD	1 yr. CAPD	Pre-CAPD	1 yr. CAPD	Pre-CAPD	1 yr. CAPD
1	0.36	0.08	0.89	0.85	0.66	0.29	27.1	42.4
2	0.05	0	0.74	0	0.08	0	251.7	337.8
3	0	0.10	0	0.92	0	0.39	345.8	17.6
4	38	0.14	1.03	1.00	0.45	0.40	40.5	30.1
5	0.02	0.03	1.04	1.82	0.03	0.13	318.3	38.6
6	0	0.35	0	1.40	0	0.87	612.0	9.4
7	0.04	0.22	1.17	1.41	0.11	0.33	110.9	29.7
8	0.07	0.16	1.30	1.18	0.10	0.44	65.5	20.2
9	0.64	0.48	1.26	1.40	0.88	1.00	22.2	9.9
10	0.04	0.07	0	0.95	0.15	0.18	62.2	41.5
11	0.12	0.20	1.02	0.88	0.21	0.27	34.2	36.4
12	0.06	0.06	0	0.98	0.07	0.08	212.4	168.0
$\bar{X}$ ± SEM	0.15 ± 0.06	0.16 ± 0.04	0.70 ± 0.16	1.07 ± 0.13	0.23 ± 0.08	0.37 ± 0.09	175.2 ± 52.0	65.0 ± 27.6
Normal Range	0.01–0.26		0.41–0.89		0.42–1.00		8–52	

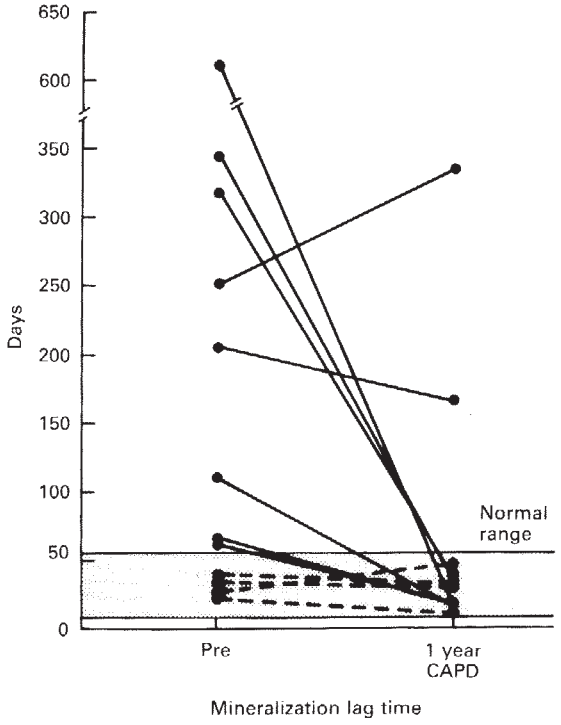

Fig. 2. *The effect of CAPD on mineralization lag time.* Of the eight patients with an initial prolonged lag time, seven improved after 12 months on CAPD ($P < 0.025$).

eters permitted us to calculate the mineralization lag time [10]. This value reflects both individual osteoblast activity (cellular rate of mineralization) and the capacity to recruit osteoblasts into the mineralization process (tetracycline–labeled osteoid seams). A decline in the mineralization lag time in seven of eight patients in whom it was initially prolonged, indicates that in general, CAPD has a beneficial effect upon calcification of uremic bone. In contrast, however, patient No. 2 who experienced a dramatic reduction of all osteoid–based measurements, demonstrated a worsening of the kinetics of bone calcification. This combination of diminution of both osteoid volume and mineralization rate is best explained by an attendant and profound decline in organic matrix synthesis. Despite the fact that the quantity of unmineralized bone matrix diminished under these circumstances, it is unclear if the effect was beneficial. For example, we [13] and others [14, Donald J. Sherrard, personal communication] have encountered patients with a variety of potentially osteomalacic disorders, such as renal failure and liver dysfunction, who, in association with severely disabling bone disease, have a paucity of osteoid due to reduced organic matrix synthesis.

Our contention that CAPD may be beneficial to the uremic skeleton is supported by the recent observations of Gokal et al from Newcastle–upon–Tyne [3], but there are important differences between the two studies. For example, 60% of the English patients on CAPD longer than nine months developed subnormal circulating levels of 25-hydroxyvitamin D, whereas we have previously shown normal concentrations [2]. This distinction may relate to the well established differences in the manifestations of renal osteodystrophy in England and the United States [15, 16]. Moreover, four of the seven of Gokal's sequentially biopsied patients, who had been maintained on CAPD for at least one year, received supplemental 1-alpha-hydroxyvitamin D_3. Because this drug is beneficial to the uremic skeleton [17], it is impossible to distinguish its effect from that of CAPD per se. Finally, and most importantly, the use of time–spaced markers of mineralization in the present study has permitted us to ferret out the kinetic changes leading to reduction of osteoid under the influence of this form of dialysis. More recently, Zucchelli et al [18] compared the histological changes of 17 patients treated with CAPD to 19 receiving maintenance hemodialysis. No changes in the % osteoid volume or % osteoid surface was noted in the group treated with CAPD. However, as opposed to the hemodialysis group, a significant decline in the percent absolute cancellous bone volume was noted, an observation we have been unable to confirm.

The precise factors responsible for the reduction of osteoid by CAPD are, however, enigmatic. For example, there is little

evidence that PTH per se is directly involved in the mineralization process [12]. This hormone does, however, lead to humoral events, such as altered alkaline phosphatase activity, which are more closely aligned with calcification [19]. In any event, CAPD treatment for one year appears to be associated with a general reduction in the thickness of osteoid seams, which in most patients is due to healing osteomalacia. These beneficial effects are not due to changes in bone aluminum.

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Reprint requests to James A. Delmez, M. D., Chromalloy American Kidney Center, Washington University School of Medicine, 4949 Barnes Hospital Plaza, St. Louis, Missouri 63110, U.S.A.

References

1. Avioli LV, Teitelbaum SL: The renal osteodystrophies, in *The Kidney*, edited by Brenner BM, Rector FC, Philadelphia, W. B. Saunders Co., 1976, pp. 1542–1591
2. Delmez JA, Slatopolsky E, Martin KJ, Gearing BN, Harter H: Minerals, vitamin D, and parathyroid hormone in continuous ambulatory peritoneal dialysis. Kidney Int 21:862–867, 1983
3. Gokal R, Ramos JM, Ellis HA, Parkinson I, Sweetman V, Dewar J, Ward MK, Keers DNS: Histological renal osteodystrophy, and 25-hydroxycholecalciferol and aluminum levels in patients on continuous ambulatory peritoneal dialysis. *Kidney Int* 23:15–21, 1983
4. Aloni Y, Shan Y, Chaimovitz C: Losses of 25-hydroxyvitamin D in peritoneal fluid: Possible mechanism for bone disease in uremic patients treated with chronic ambulatory peritoneal dialysis. *Miner Electrolyte Metab* 9:82–86, 1983
5. Calderaro V, Oreopoulos DG, Mesma HE, Ogilvie R, Husdan H, Khanna R, Quinton C, Murray T, Carmichael DL: The evolution of renal osteodystrophy in patients undergoing continuous ambulatory peritoneal dialysis (CAPD). *Proc Eur Dial Transplant Assoc* 17:533–542, 1980
6. Hruska KA, Teitelbaum SL, Kopelman R, Richardson CA, Miller P, Debnam J, Martin K, Slatopolsky E: The predictability of the histological features of uremic bone disease by non-invasive techniques. *Metab Bone Dis Relat Res* 1:39–44, 1978
7. Frost HM, Griffith DL, Jee WSS, Kimmel DB, McCandlis RP, Teitelbaum SL: Histomorphometric changes in trabecular bone of renal failure patients treated with calcifediol. *Metab Bone Dis Relat Res* 2:285–295, 1981
8. Fallon MD, Teitelbaum SL: The interpretation of fluorescent tetracycline markers in the diagnosis of metabolic bone diseases. *Human Pathol* 13:416–418, 1982
9. Melsen F, Mosekilde L: Tetracycline double-labeling of iliac trabecular bone in 41 normal adults. *Calcif Tissue Res* 26:99–102, 1978
10. Melsen F, Mosekilde L: Trabecular bone mineralization lag time determined by tetracycline double-labeling in normal and certain pathological conditions. *Acta Path Microbiol Scand* 88:83–88, 1980
11. Maloney NA, Ott SM, Alfrey AC, Miller NL, Coburn JW, Sherrard DJ: Histological quantification of aluminum in iliac bone from patients with renal failure. *J Lab Clin Med* 99:206–216, 1982
12. Teitelbaum SL, Berfeld MA, Freitag J, Hruska KA, Slatopolsky E: Do parathyroid hormone and 1,25-dihydroxyvitamin D modulate bone formation in uremia? *J Clin Endocrinol Metab* 51:247–251, 1980
13. Klahr S, Harter H, Slatopolsky E, Teitelbaum SL: Prevention of renal osteodystrophy in a patient treated by hemodialysis following abrupt transition from normal to absent renal function. *ASAIO J* 2:133–136, 1979
14. Long RG, Meinhard E, Skinner FR, Varghese Z, Wills MR, Sherlock S: Clinical, biochemical and histological studies of osteomalacia, osteoporosis and parathyroid function in chronic liver disease. *Gut* 19:85–90, 1978
15. Lumb GA, Mawer EB, Stanbury SW: The apparent vitamin D resistance of chronic renal failure. *Am J Med* 50:421–441, 1971
16. Cochra M, Platts MM, Moorhead PJ, Buxton A: Spontaneous hypercalcemia in maintenance dialysis patients: An association with atypical osteomalacia and fractures. *Miner Electrolyte Metab* 5:280–286, 1981
17. Pierides AM, Skillen AW, Ellis HA: Serum alkaline phosphatase in azotemic and hemodialysis osteodystrophy: A study of isoenzyme patterns, their correlation with bone histology, and their changes in response to treatment with 1-alpha-OHD_3 and $1,25(OH)_2D_3$. *J Lab Clin Med* 93:899–909, 1979
18. Zuccelli P, Catizone L, Casanova S, Fusaroli L, Fabbri L, Ferrari G: Renal osteodystrophy in CAPD patients. *Miner Electrolyte Metab* 10:326–332, 1984
19. Fallon MD, Whyte MP, Teitelbaum SL: Stereospecific inhibition of alkaline phosphatase by L-tetramisole prevents *in vitro* cartilage calcification. *Lab Invest* 43:489–494, 1980