Kidney International, Vol. 36 (1989), pp. 1112–1118

Optimal correction of acidosis changes progression of dialysis osteodystrophy

ALFRED LEFEBVRE, MARIE CHRISTINE DE VERNEJOUL, JEAN GUERIS, BERNARD GOLDFARB, ANNE MARIE GRAULET, and CAROLINE MORIEUX

INSERM U18, Service de médecine nucléaire, Hôpital Lariboisière, 6 rue Guy Patin, 75010, AURA, 5 rue du Bessin, 75015, Service de biostatistique, Hôpital Necker, 75734 Paris, France

Optimal correction of acidosis changes progression of dialysis osteodystrophy. To investigate an eventual role of acidosis on hemodialysis osteodystrophy we prospectively studied 21 patients who were dialyzed with different amounts of bicarbonate in the dialysate for 18 months. According to the level of bone formation rate (BFR) on a prestudy bone biopsy, patients were split in two subgroups. Inside these two subgroups patients were randomly allocated to two therapeutics groups: 10 patients (group A) were dialyzed with the conventional amount of bicarbonate (33 ± 2 mmol/liter) in the dialysate; the rest of the patients (group B, $N = 11$) had 7 to 15 mmol/liter sodium bicarbonate added to the dialysate to obtain 24 mEq predialysis bicarbonate plasma levels. An effective correction of acidosis was shown in group B by a higher predialysis plasma bicarbonate level (15.6 ± 1 group A vs. 24.0 ± 0.6 mEq/liter group B, $P < 0.005$), which was reached three months after start of the study. Compared to the prestudy bone biopsy, osteoid and osteoblastic surfaces increased in group A but not in group B on the bone biopsies performed at the end of the study. Parathormone plasma level (iPTH), measured with an antiserum which cross reacts with the 44-68 region of PTH molecule, increased during the study in group A but not in group B. This finding suggested progression of secondary hyperparathyroidism (HPT) only in group A patients. Osteocalcin plasma values increased in both groups during the 18 months of the study. Consequently the two subgroups of patients formed on the basis of BFR level were evaluated separately. The subgroup of patients with normal-high BFR on the prestudy bone biopsy had a high bone resorption and elevated iPTH and osteocalcin plasma levels at start of the study. In this subgroup of patients, the osteocalcin plasma level increased more in group A than in group B during the study. The subgroup of patients with normal-low BFR had lower osteocalcin levels, and seven of ten patients had aplastic bone disease at start of the study. In this subgroup, osteocalcin plasma values were unchanged during the study in group A but increased in group B. There was no significant modification of plasma or bone aluminium in any group during the time of the study. Therefore, an optimal correction of acidosis could decrease progression of HPT in patients with high bone turnover, and stimulate bone turnover in patients with low bone formation.

Renal osteodystrophy is the result of a constellation of metabolic disorders related to renal failure [1]. Phosphate retention and abnormal vitamin D metabolism are believed to trigger hypocalcemia and subsequent parathyroid hyperplasia [2, 3]. More recently it has been shown also that iatrogenic bone aluminium overload is an important determinant of renal osteodystrophy, often associated with osteomalacia and aplastic bone disease [4]. However, other metabolic abnormalities occur during renal osteodystrophy and their respective role is far from clear. Among them, acidosis has been suspected to have some role in renal failure bone lesions. Indeed, during chronic acidosis bone carbonates buffers the metabolic acid load: bone carbonate is decreased in uremic [5] patients. In patients with end-stage renal failure acidosis has been shown to be frequently associated with osteomalacia [6]. However, early studies failed to show any improvement of osteomalacia in acidotic uremic patients treated with bicarbonate [7, 8]. Acidosis is not completely corrected by dialysis therapy [9]; its eventual role in dialysis osteodystrophy has not yet been investigated. We therefore prospectively compared two groups of patients dialyzed for 18 months with different amounts of bicarbonate in the dialysate. Our results suggest that a better correction of dialysis acidosis can prevent progression of secondary hyperparathyroidism in hemodialyzed patients.

Methods

Patient selection

Twenty-one dialyzed patients completed the study. Patient selection for the study was made on the following criteria: 1) patients had to give their informed consent to participate to this study which included 2 bone biopsies; 2) patients with severe radiological osteitis fibrosa, plasma calcium above 11 mg/dl, parathyroidectomy, diabetes mellitus and treatment by corticosteroid were excluded from the study.

Patient subgroups

One to three months before the start of the study the selected patients had a bone biopsy. According to the level of bone formation rate on this bone biopsy, patients were classified in either low-normal ($N = 10$) or high-normal ($N = 11$) bone formation rate subgroups. There was no significant difference in age, sex, initial nephropathy, duration of dialysis and pre-study treatment between two subgroups (data not shown). This stratification according to prestudy bone morphometry was done to have an equivalent spectrum of bone disease in the two different treatment groups. Half of the patients in either the high-normal

Received for publication April 20, 1989
and in revised form July 6, 1989
Accepted for publication July 12, 1989

or the low-normal bone formation rate subgroups were then randomly allocated to the control group ($N = 10$), and the rest of them ($N = 11$) to the acidosis corrected group.

Dialysis therapy

The study lasted 18 months. The patients of the control group had no change in their dialysis treatment compared to prestudy time. They were dialyzed for four hours three times weekly, with water treated by reverse osmosis and containing: K 2 to 3 mmol/liter, calcium 1.75 mmol/liter, magnesium 0.75 mmol/liter, sodium 143 ± 2 mmol/liter, and 33 ± 2 mmol/liter bicarbonate. In the acidosis corrected group the dialysate composition was the same except that a sodium bicarbonate concentrate solution was added and sodium chloride reduced so that sodium in the dialysate was 143 ± 2 mmol/liter. During the first four to six weeks of the study, a fixed amount of 7 mEq/liter of bicarbonate was added to the dialysate. During this period, predialysis plasma bicarbonate increased from one to the following dialysis in each patient. A steady predialysis plasma bicarbonate level was achieved in each patient. The amount of sodium bicarbonate added was then adjusted in each patient to obtain a predialysis bicarbonate value of approximately 24 mEq/liter. The amount of sodium bicarbonate needed in dialysate varied from 7 to 15 mEq/liter depending on the patients.

Associated treatments

Six patients in the control group and five patients in the acidosis corrected group had antihypertensive drugs. No other treatment was given to the patients except for phosphate binder, calcium carbonate and vitamin D. These three treatments were prescribed according to the biological data: phosphate binder (1 to 5 g aluminium gel) when plasma phosphate was above 6 mg/dl, calcium carbonate up to 4 g a day to obtain plasma calcium level above 9.0 mg/dl, and 1α vitamin D (up to 0.75 μg/day) was prescribed when a 9.0 mg/dl plasma calcium level could not be achieved with 4 g of calcium carbonate alone.

Biochemical measurements

Predialysis pH, pre- and postdialysis creatinine, sodium, potassium, chloride, calcium, phosphate were measured every two weeks by automated method (SMAC). Plasma alkaline phosphatase, aluminum, immunoactive parathormone (iPTH), and osteocalcin were measured every three months. Plasma iPTH was measured by radioimmunoassay using 53-84 and 44-68 antibodies raised in sheep. The characteristics of the assays are as follows: A C-terminal PTH antiserum was raised in sheep immunized with synthetis hPTH (53-84). The tracer used was S2-Tyr-hPTH 53-84 radioiodinated using the chloramine T procedure and purified by HPLC. The bioiodinated fraction of the tracer was used after dilution in order to obtain 20 pg/ml of tracer per tube. Synthetic hPTH (53-84) was used as the standard. Standards or samples were incubated with anti-PTH antibody used at 1/100,000 dilution. After 24 hours at 4°C, radioiodinated PTH was added. After an additional day at 4°C, antibody-[^{125}I]PTH complexes were precipitated and quantified. The limit of detection of the assay was 10 pg/ml and the normal range was 20 to 45 pg/ml.

PTH was also determined with a mid region assay. The antiserum was raised in sheep using synthetic hPTH-44-68. Radioiodinated synthetic ^{43}Tyr-hPTH (44-68) was used as a tracer, and hPTH (44-68) was used as the standard. The procedure used was similar as for the C-terminal PTH assay except that the antiserum was diluted at 1:25,000. The limit of detection was 50 pg/ml and the normal range was 80 to 220 pg/ml. At the end of the study 1-84 PTH was also measured using an N-terminal antibody recognizing the entire molecule (Nicols Institute). The normal range was 10 to 65 μg/ml. Osteocalcin was measured by radioimmunoassay using an antibody raised against bovine osteocalcin (ORIS CEA, France). The normal range was 4 to 9 ng/ml. Serum aluminum was measured every month by atomic absorption spectrophotometry in a graphite furnace.

Bone histomorphometry

Bone biopsies were performed one to three months before the start of the study and repeated in every patient 18 months after the start of the study. Bone histomorphometry was assessed after double tetracycline labeling according to the following schedule: two days on tetracycline, ten days off, two days on. Bone biopsy was performed two days after the last tetracycline dose on the anterior iliac crest. Measurements were performed in trabecular bone as already described [10]. Bone volume, osteoid volume, osteoid surface, osteoblast and osteoclast surfaces (%) were measured on three sections stained by toluidine blue. Osteoblast surfaces are the trabecular surfaces covered with plump osteoblasts, surfaces are the trabecular surfaces in contact with an osteoclast independently of the existence of a lacuna. Osteoid thickness was measured with an image analyzer at equidistant points on all the trabecular bone and was expressed in μm. Mineral apposition rate and the extent of single and double surfaces were assessed on two unstained, 10 μm thick sections. Mineralizing surfaces were determined from the double-labeled surfaces plus single-labeled surfaces divided by two. Bone formation rate (BFR, $\mu m^3/\mu m^2$ per day) was calculated as mineralization rate multiplied by total labeled surfaces. Normal values from our laboratory have been previously published [10]. Normal range for bone formation rate is 0.08 ± 0.03 $\mu m^3/\mu m^2$/day. Therefore the value of 0.08 $\mu m^3/\mu m^2$/day was chosen to split patients in two subgroups one the pre-study bone biopsy. Sections were stained for aluminum by the aurin tricarboxylic acid method. The percentage of trabecular surfaces stained with aluminum, whether or not they were covered by osteoid, was also measured. Two bone samples obtained at the end of the study were uninterpretable and one patient refused his bone biopsy.

Statistical methods

Comparison between control and acidosis corrected groups were performed by unpaired Student's t-test for which usual assumptions (Gaussian repartition, homoscedasticity) were satisfied. When smaller groups (determined by high or low level of bone formation rate) were formed, we used a non-parametric two-way analysis of variance on ranks (Friedman's test). Analysis of the differences between initial and final values inside each of the two groups of patients was done by Student's paired t-test and/or analysis of variance. The evolution all along the period of treatment was analyzed by mean of linear regression; heterogeneity of slopes was assessed by testing interaction between time and group of treatment inside a linear model of variance analysis. Calculus calculations were performed using

Table 1. Biochemical and bone histomorphometric parameters in the two subgroups defined on bone histomorphometry basis before start of the study

	Normal-low bone formation rate $N = 10$	Normal-high bone formation rate $N = 11$	Normal values
Plasma 53-84 PTH *pg/ml*	266.5 ± 38.8	545.9 ± 80.6[b]	20–45
Plasma 44-68 PTH *pg/ml*	1261 ± 395	2937 ± 719	80–220
Plasma osteocalcin *ng/ml*	11.2 ± 2.6	26.2 ± 2.6[b]	3–8
Extent of stainable aluminum surfaces on bone biopsy %	67.5 ± 10.9	40.9 ± 9.8	
Bone formation rate $\mu m^3/\mu m^2/day$	0.009 ± 0.005	0.128 ± 0.038[a]	0.08 ± 0.03
Osteoblastic surfaces %	0.6 ± 0.3	7.1 ± 2.3[a]	3.6 ± 1.2
Resorption surface %	0.5 ± 0.2	2.8 ± 0.5[b]	0.5 ± 0.2

Values are expressed by mean ± SEM.
Different from patients with normal low bone formation rate: [a] $P < 0.05$, [b] $P < 0.01$

the SAS package (ANOVA, GLM, REG, NPAR and T TEST procedures). Significant differences correspond to P values less than 0.05.

Results

Among the 21 patients of the study, eleven had a bone formation rate superior to the normal value (0.08 $\mu m^3/\mu m^2$/day) and ten had a bone formation rate below this normal value. These two groups of patients, defined according to bone formation rate levels, had different biochemical and histological results (Table 1). Before the start of the study, plasma 53-84 iPTH and osteocalcin plasma levels were higher in the normal-high formation group. Bone formation rate, osteoblastic and osteoclastic resorption surfaces were also higher and increased above control values in the normal-high bone formation subgroup. Among the 10 patients with normal-low bone formation rate, seven had a value below 0.031 $\mu m^3/\mu m^2$/day, the lowest value of our control group, and a mean osteoid thickness below 15 μm. They could be classified as aplastic bone disease patients. None of the patients met the histological criteria for osteomalacia. The two treatment groups were randomly formed among these two subgroups (**Methods**). The clinical spectrum of the control and acidosis corrected groups were the same: there were five females and five males in the control group, and six females and five males in acidosis corrected group. Ages were 49.9 ± 14.1 in controls and 51.2 ± 9.1 in the acidosis corrected group. Duration of dialysis was 6.2 ± 3.0 years in controls and 6.6 ± 3.3 in the acidosis corrected group. Initial nephropathy was not different between both groups. Biochemical (ionogram, calcium phosphate metabolism) and bone histomorphometric values at start of the study were also the same in the two treatment groups (Tables 2, 3 and 4).

The addition of bicarbonates in dialysate induced an effective increase in predialysis bicarbonate and pH in the eleven patients of the acidosis corrected group (Table 2). As displayed in Figure 1, this effect was significant from three months after the start of the study and remained steady all along the course of the study. In both groups there were no changes in plasma proteins, creatinine, hematocrit and potassium between the start and the end of the study (Table 2). However, in the acidosis corrected group, there was a decrease in postdialysis

Table 2. Ionogram at start and at the end of the study in controls (group A, $N = 10$) and acidosis corrected (group B, N = 11) patients

	Group	Start of the study	End of the study
Predialysis bicarbonate *mEq/liter*	A	16.80 ± 0.92	16.50 ± 0.88
	B	15.64 ± 1.06	24.00 ± 0.61[a]
Postdialysis bicarbonate *mEq/liter*	A	20.80 ± 1.07	19.40 ± 0.92
	B	21.00 ± 0.88	29.00 ± 0.57[a]
Predialysis pH	A	7.35 ± 0.02	7.35 ± 0.02
	B	7.35 ± 0.02	7.39 ± 0.01[a]
pO_2	A	96.50 ± 4.70	88.50 ± 4.24
	B	93.80 ± 6.18	76.70 ± 2.03
pCO_2	A	34.70 ± 1.26	35.60 ± 2.04
	B	35.30 ± 2.17	37.70 ± 0.89
Creatinine *mg/dl*	A	12.09 ± 0.60	11.73 ± 0.57
	B	11.52 ± 0.83	10.40 ± 0.60
Protein *g/dl*	A	7.2 ± 0.1	7.3 ± 0.1
	B	7.1 ± 0.1	7.1 ± 0.1
Hematocrit %	A	29.10 ± 2.08	31.00 ± 2.65
	B	30.40 ± 1.81	31.50 ± 1.77
Predialysis potassium *mEq/liter*	A	5.38 ± 0.22	5.56 ± 0.14
	B	5.47 ± 0.15	5.15 ± 0.24
Postdialysis potassium *mEq/liter*	A	3.62 ± 0.12	3.50 ± 0.13
	B	3.78 ± 0.13	3.55 ± 0.08

Values are expressed by mean ± SEM. If not mentioned, predialysis samples were analyzed.
[a] Significantly different ($P < 0.05$) from the value at start of the study

Table 3. Calcium and phosphate metabolism plasma values in control (group A, $N = 10$) and acidosis corrected (group B, $N = 11$) patients

	Group	Start of the study	End of the study
Predialysis calcium *mg/dl*	A	9.3 ± 0.1	9.3 ± 0.1
	B	9.5 ± 0.1	9.2 ± 0.2
Postdialysis calcium *mg/dl*	A	11.9 ± 0.3	12.0 ± 0.4
	B	11.2 ± 0.2	11.2 ± 0.3
Predialysis phosphate *mg/dl*	A	5.1 ± 0.2	5.5 ± 0.3
	B	5.1 ± 0.3	4.6 ± 0.6
Postdialysis phosphate *mg/dl*	A	3.6 ± 0.2	2.9 ± 0.2
	B	3.0 ± 0.2	2.7 ± 0.2
Alkaline phosphatase *IU/liter*	A	99.5 ± 13.3	132.9 ± 35.3
	B	74.9 ± 9.0	80.9 ± 14.8
53-84 PTH *pg/ml* ($N = 20$–45)	A	429.0 ± 95.9	374.4 ± 82.9
	B	398.2 ± 62.7	335.7 ± 70.3
44-68 PTH *pg/ml* ($N = 80$–220)	A	1904 ± 649	5277 ± 1528
	B	2354 ± 652	3405 ± 1033
1-84 PTH *pg/ml* ($N = 10$–65)	A	ND	234 ± 88
	B	ND	126 ± 35
Osteocalcin *ng/ml* ($N = 4$–9)	A	19.5 ± 3.9	60.0 ± 24.0
	B	18.7 ± 3.2	34.8 ± 11.3
Aluminum *μg/ml*	A	33.2 ± 19.4	32.1 ± 18.1
	B	34.6 ± 17.5	42.1 ± 17.8

Values are expressed by mean ± SEM in controls (A) and acidosis corrected (B) patients. None of the values are significantly different. If not mentioned, predialysis samples were analyzed. ND, not determined.

Table 4. Bone histomorphometry at start and at the end of the study in control (A) and acidosis corrected (B) patients

	Group	Start of the study	*N*	End of study	*N*
Bone volume %	A	22.88 ± 3.06	10	20.22 ± 2.53	9
	B	23.01 ± 1.95	11	21.77 ± 2.86	9
Osteoid volume %	A	5.32 ± 0.98	10	15.06 ± 2.51[b]	9
	B	6.03 ± 1.44	11	12.49 ± 2.29[a]	9
Osteoid surfaces %	A	39.03 ± 7.21	10	60.35 ± 5.57[b]	9
	B	41.30 ± 8.59	11	57.57 ± 4.97	9
Osteoblast surfaces %	A	3.53 ± 1.14	10	9.87 ± 2.37[b]	9
	B	4.38 ± 2.49	11	5.32 ± 1.33	9
Osteoclast surfaces %	A	1.75 ± 0.53	10	1.67 ± 0.61	9
	B	1.67 ± 0.51	11	0.98 ± 0.24	9
Osteoclasts/mm^2	A	0.84 ± 0.24	10	1.33 ± 0.59	9
	B	1.06 ± 0.35	11	0.82 ± 0.22	9
Bone formation rate	A	0.077 ± 0.025	10	0.135 ± 0.053	9
$\mu m^3/\mu m^2/day$	B	0.085 ± 0.045	10	0.041 ± 0.020	9
Osteoid thickness μm	A	9.3 ± 0.7	10	9.5 ± 0.8	9
	B	10.6 ± 1.2	11	11.1 ± 1.1	9
Stainable aluminum %	A	48.8 ± 10.0	10	39.8 ± 11.0	9
	B	58.6 ± 11.9	11	53.1 ± 11.1	10
Biochemical aluminum	A	1.74 ± 0.39	7	1.19 ± 0.22	7
μg/g dry bone	B	2.50 ± 0.68	10	1.68 ± 0.47	9

Results are expressed by mean ± SEM.
[a] Significantly different at $P < 0.05$ from the value at start of the study
[b] Significantly different at $P < 0.005$ from the value at start of the study

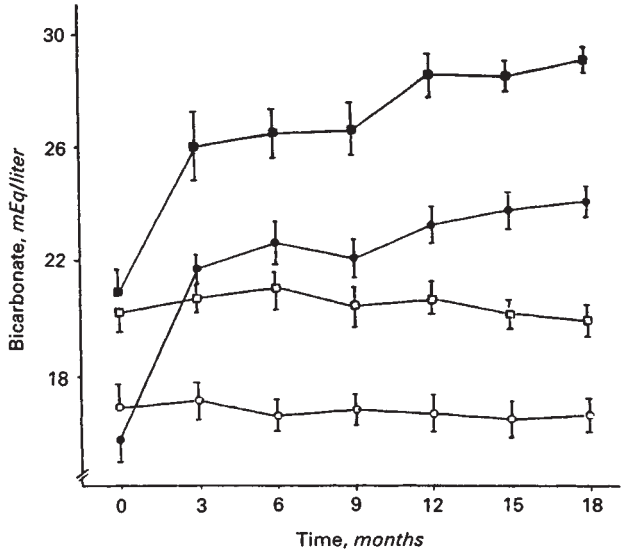

Fig. 1. *Evolution with time of pre- and postdialysis plasma bicarbonate in controls and acidosis corrected patients during the 18 months of the study.* Symbols are: pre- (○——○) and postdialysis (□——□) values in control group; pre- (●——●) and postdialysis (■——■) values in acidosis corrected group. From the third month, values were significantly ($P < 0.05$) higher in acidosis corrected patients than in controls. Points and bars are mean ± SEM.

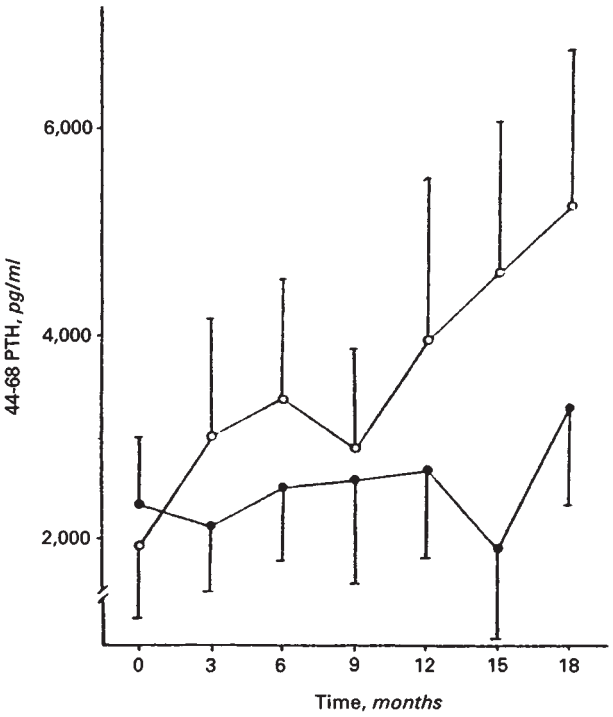

Fig. 2. *Evolution with time of 44-68 PTH plasma level in control (○——○) and acidosis corrected (●——●) patients.* There is a significant increase of the values with time in the control group (slope 489.12 ± 230.47, $P < 0.05$) but not in the acidosis corrected group. Data are mean ± SEM.

plasma potassium value with time during 18 months of the study (slope: 0.005 ± 0.002, $P < 0.05$), whereas in the control group plasma potassium values did not change during the study.

Table 3 shows that pre- and postdialysis plasma calcium and phosphate values at the start and at end of the study were unchanged. Accordingly, predialysis plasma PTH, alkaline phosphatase, osteocalcin and aluminum values at the start and at end of the study were not different between groups. Eventual changes with time of iPTH and osteocalcin in both groups were studied. Plasma 53-84 iPTH did not change with time in any group (data not shown); by contrast, plasma 44-68 iPTH increased with time in the control group but not in the acidosis corrected group (Fig. 2). Plasma osteocalcin increased with time in both groups (Fig. 3).

Considering the bone histomorphometry data (Table 4), relative osteoid volume increased in both groups during the study. Osteoid surfaces and osteoblastic surfaces increased in the control group but not in the acidosis corrected group. There were no significant changes between groups or with time in bone formation rate, mean osteoid thicknesses, resorption parameters and biochemical or stainable bone aluminum.

The relationship of two histomorphometric parameters (osteoblastic and osteoclastic surfaces) with osteocalcin and iPTH measured with different antibodies at start and at the end of the study were studied (Table 5). Resorption and formation parameters correlated with all these biochemical values were significant. On the second bone biopsy the correlation coefficient of morphometric parameters with 53-84 PTH was lower than the one observed with 44-68 PTH, 1-84 PTH and osteocalcin.

To discover if the effect of acidosis correction was different according to the type of bone disease, we studied the plasma osteocalcin levels in the two subgroups, defined on a histomorphometric basis at start of the study. In the subgroup of patients with normal-high bone formation at start of the study, osteocalcin increased significantly less with time in the acidosis

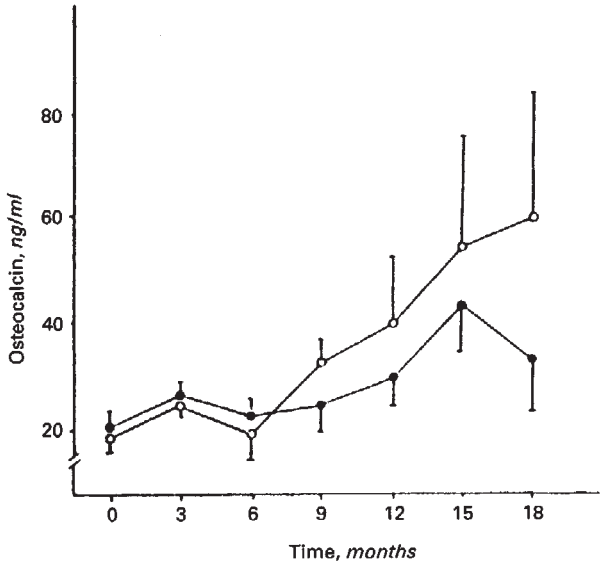

Fig. 3. *Evolution with time of osteocalcin plasma level in control (○—○) and acidosis corrected (●—●) patients.* Values increased with time in acidosis corrected group (slope 3.29 ± 1.22, $P < 0.01$) and in the control group (slope 7.30 ± 2.52, $P < 0.005$). Data are mean ± SEM.

Table 5. Correlation between two histomorphometric parameters (osteoblastic and resorption surfaces) and plasma osteocalcin or PTH value measured with different antibodies at start and at the end of the study

	Osteoblastic surfaces		Resorption surfaces	
Plasma	First bone biopsy	Second bone biopsy	First bone biopsy	Second bone biopsy
Osteocalcin	0.69[c]	0.84[b]	0.71[c]	0.85[c]
53-84 PTH	0.68[c]	0.49[a]	0.72[c]	0.63[b]
44-68 PTH	0.52[a]	0.83[c]	0.67[c]	0.86[c]
1-84 PTH	ND	0.87[c]	ND	0.74[c]

[a] $P < 0.05$
[b] $P < 0.01$
[c] $P < 0.001$

corrected than in the control group (Fig. 4A). By contrast in the subgroup of patients with low bone formation rate plasma osteocalcin did not change with time in control patients but increased significantly in acidosis corrected patients (Fig. 4B). There was no significant change with time in iPTH level when considering the two subgroups independently.

Finally, the treatment prescribed to the patients during the three months preceding the start of the study and during the 18 months study was recorded (Table 6). There was no therapeutic difference between control and acidosis corrected groups except for 1α vitamin D treatment. The prescription of 1α vitamin D, which depended on plasma calcium value, was lower in acidosis corrected group during the study than during the three months preceding the study.

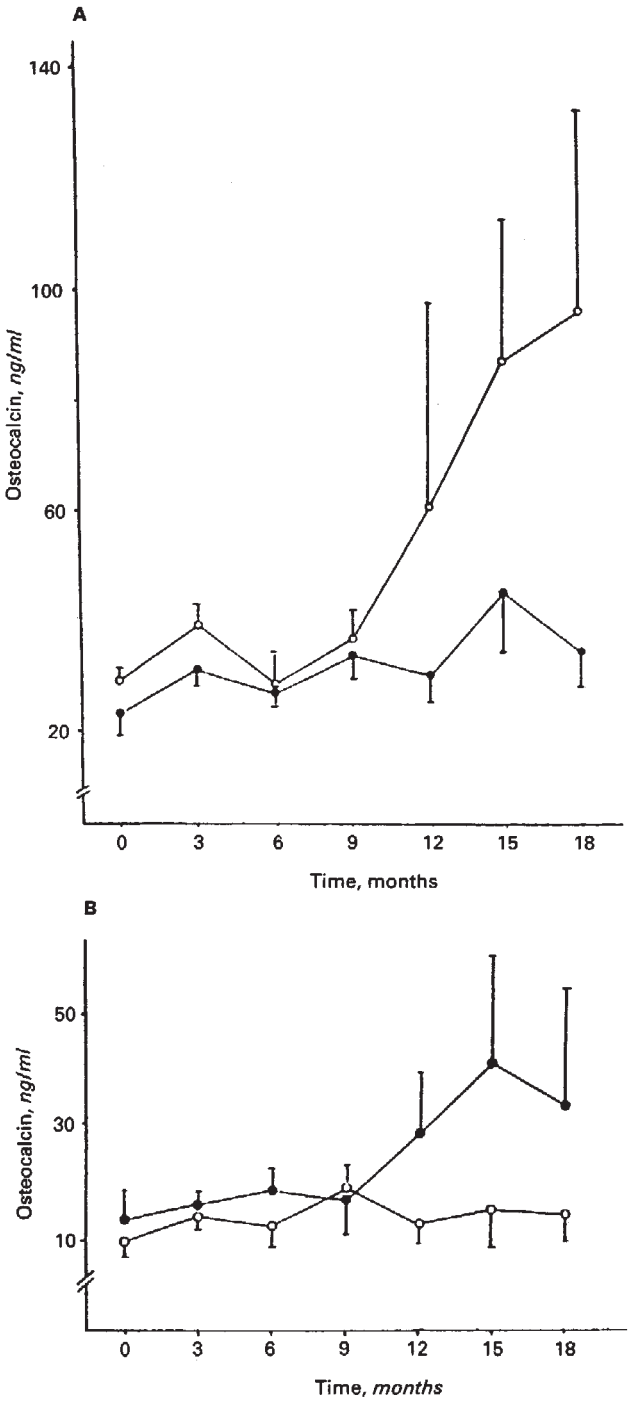

Fig. 4. A. *Evolution with time of plasma osteocalcin levels in the subgroup of patients with normal-high bone formation.* Symbols are: control (○—○) and acidosis corrected (●—●) patients. Results are expressed by mean ± SEM. The slope is 12.1 ± 4.04, ($P < 0.05$) in control group and 2.27 ± 0.99 ($P < 0.03$) in acidosis corrected group. The 2 slopes are different at $P < 0.05$. **B.** Evolution with time of plasma osteocalcin level in the subgroup of patients with normal-low bone formation. Results are expressed by mean ± SEM. There is a significant increase of the values with time in acidosis corrected group (slope 4.63 ± 2.35, $P < 0.05$) but not in the control group.

Discussion

Our data show that in patients dialyzed with a conventional amount of bicarbonate in the dialysate, there is a progression of secondary hyperparathyroidism and bone turnover during an 18 month period. This assumption is sustained by an increase, during the study, of 44-68 iPTH and plasma osteocalcin levels. In parallel there was an increase with time of osteoformation

Table 6. Average drug prescription in the 3 months preceeding start and during the 18 months of the study

	$CaCO_3$ *g/day*		(1 α) Vitamin D $\mu g/day$		Aluminum gel *g/day*	
	Start	End	Start	End	Start	End
Controls (A)	4.80 ± 2.30	5.0 ± 2.23	0.40 ± 0.63	0.41 ± 0.61	3.8 ± 1.7	3.0 ± 1.5
Acidosis corrected (B)	3.82 ± 3.38	3.55 ± 2.21	0.37 ± 0.26	0.14 ± 0.77[a]	2.9 ± 1.5	2.45 ± 1.4

[a] Significantly lower at $P < 0.05$ than the value recorded at start of the study

histomorphometric parameters in this group of patients. The value of the biochemical parameters we used to evaluate bone turnover and PTH secretion deserves some comment. The two different antibodies used to evaluate PTH during the study were significantly correlated with morphometric parameters of bone resorption and formation. The relationship between morphometric parameters and 53-84 PTH on the second bone biopsy was the lower one observed, and this loose correlation might explain the lack of modification with time of 53-84 PTH during the study whereas 44-68 PTH and osteocalcin increased during the same period. In this study 1-84 PTH, measured only at the time of the second bone biopsy, was not more closely correlated to morphometric parameters than 44-68 PTH; amino terminal antibodies have been reported to be better predictors of renal osteodystrophy than other mid-region antibodies [11], but we could not confirm this findings with the antibodies we used. Finally osteocalcin, as has already been observed in dialyzed patients [12, 13], was closely correlated to both formation and resorption histomorphometric parameters.

All patients had recommended treatment to decrease secondary hyperparathyroidism progression: calcium in dialysate was 1.75 mmol/liter; they received oral calcium carbonate and 1α vitamin D was prescribed when calcium carbonate was insufficient to maintain plasma calcium above 9 mg/dl. The partial inefficacy of such a treatment to prevent progression of secondary hyperparathyroidism in some patients has already been observed [14]. In contrast in patients whose acidosis was optimally corrected by addition of bicarbonate in the dialysate, 44-68 PTH plasma level did not increase during the study. Therefore, worsening of secondary hyperparathyroidism in the course of maintenance hemodialysis was prevented by a better correction of acidosis.

Contrasting with the PTH finding, osteocalcin increased in both treatment groups. This result can be explained by different evolution of osteocalcin values according to the subgroup of patients. The group of dialyzed patients involved in this study included patients with different levels of bone turnover and PTH. They were part of a group of patients whose characteristics related to aluminum overload have already been reported [10]. Only half of the patients had a bone formation rate above normal value at start of the study. This subgroup of patients had histological signs of mild to severe secondary hyperparathyroidism (HPT) and elevated plasma iPTH. In these patients plasma osteocalcin increased more in the control group than in the acidosis corrected group. Therefore, the prevention of HPT-induced bone turnover progression by acidosis correction appeared when only patients with secondary hyperparathyroidism were considered.

The effect of acidosis on calcium phosphate metabolism has been extensively studied in rats in vivo and in vitro. Metabolic acidosis triggers an increase in bone resorption and a decrease in bone formation in parathyroidectomized rats [15]. This finding suggests that the effect of acidosis on bone is independent of PTH. Indeed, acidosis enhances in vitro bone resorption; in organ culture, calcium release from bone is increased by metabolic acidosis [16] and this effect is mediated through cell activity [17]. This might be related to the increase in isolated osteoclast resorption activity observed when the medium pH is decreased [18]. Clinical study also suggests that acidosis affects bone independently of PTH. When acidosis is induced by oral ammonium chloride administration in normal subjects, PTH is reported unchanged in most of the studies (19–21). End organ responsiveness to PTH is not affected since basal nephrogenic cyclic AMP [20] or calcemic response to PTH injection [22] is not different from control.

In light of such experimental data we suggest the following interpretation of our observations: in dialyzed patients acidosis might contribute to increase bone resorption and therefore plasma phosphate released from bone; plasma phosphate was slightly higher in patients whose acidosis was less corrected. Hypocalcemia, one of the parathormone secretion enhancers, is partly dependent on hyperphosphatemia during dialysis [1, 2]. The increase in plasma phosphate would induce progression of secondary hyperparathyroidism and therefore the bone turnover rate. Such speculative interpretation cannot be proved, but is highly suspect when considering the lack of increased parathyroid secretion [20–22] along with increased bone resorption [20] observed in normal subjects in whom acidosis was experimentally created. This interpretation is also in agreement with the fact that the doses of 1α(OH)D required to maintain calcemia above 9 mg/dl during the course of the study could be decreased in patients whose acidosis was better corrected.

Among the patients with normal-low bone remodelling, seven out of ten had aplastic bone disease. Surprisingly, the evolution of osteocalcin value in this subgroup was inverse to the one observed in the subgroup of patients with secondary hyperparathyroidism. Because most of these patients had a pathologically low bone turnover at start of the study, the increase in osteocalcin plasma value could be considered as a positive result. This subgroup of patients had an important amount of aluminum on their bone biopsies. As an average, in the whole group of patients bone and serum aluminum were not changed according to correction of acidosis. Dialysate alkalosis has been reported to increase aluminum dializability [23], but we did not observe any change in the aluminum burden after 18 months. There was no increase in iPTH level to trigger this increase in osteocalcin. Therefore, we cannot exclude that a correction of acidosis per se stimulated the low bone turnover of these patients. Indeed, in acidotic rats bone formation rate was markedly decreased [15].

In conclusion, an optimal correction of acidosis has a beneficial effect on dialyzed patient's renal osteodystrophy. We showed that it could prevent progression of secondary hyper-

parathyroidism. Furthermore, it might increase bone formation in the subgroup of dialyzed patients with low bone turnover.

Acknowledgments

We are indebted to Dr. Moynot and Dr. Masselot for referring patients, and to Mrs. Gouin for preparation of this manuscript.

Reprint requests to Dr. M.C. de Vernejoul, INSERM U18, Hôpital Lariboisière, 6 rue Guy Patin, 75010, Paris, France.

References

1. LEE DBN, GOODMAN WG, COBURN JW: Renal osteodystrophy: Some new questions on an old disorder. *Am J Kidney Dis* 11: 365–376, 1988
2. SLATOPOLSKY E, BRICKER NS: The role of phosphorus restriction in the prevention of secondary hyperparathyroidism in chronic renal disease. *Kidney Int* 4:141–145, 1973
3. MASSRY SG, STREIN R, GARTY J: Skeletal resistance to the calcemic action of parathyroid hormone in uremia: Role of $1,25(OH)_2D$. *Kidney Int* 9:467–474, 1976
4. OTT SM, MALONEY NA, COBURN JW: The prevalence of bone aluminum deposition in renal osteodystrophy and its relation to the response of calcitriol therapy. N Engl J Med 307:709–713, 1982
5. PELLEGRINO ED, BILTZ RM: The composition of human bone in uremia. *Medicine* 44 (5):397–416, 1965
6. MORA PLAMA FJ, ELLIS HA, COOK DB, DEWAR JH, WARD MK, WILKINSON R, KERR DNS: Osteomalacia in patients with chronic renal failure before dialysis or transplantation. *Quart J Med* 207: 332–348, 1983
7. FLETCHER RF, JONES JH, MORGAN DB: Bone disease in chronic renal failure. *Quart J Med* 128:321–339, 1963
8. STANBURY SW, LUMB GA: Metabolic studies of renal osteodystrophy. 1. Calcium, phosphorus and nitrogen metabolism in rickets, osteomalacia and hyperparathyroidism complicating chronic uremia and in the osteomalacia of the adult Fanconi syndrome. *Medicine* 41:1–31, 1962
9. BLAGG CR: Acute complications associated with hemodialysis, in *Replacement of Renal Function by Dialysis*, edited by W DRUKKER, FM PARSONS, JF MAHER, New York, M. Nijhoff Publishers, 1983
10. LEFEBVRE A, HORLAIT S, CHAPUIS P, MOYNOT A, MASSELOT JP, GUERIS J, DE VERNEJOUL MC: Cortical vs. trabecular bone aluminum in dialyzed patients. *Am J Kidney Dis* 12:220–226, 1988
11. ANDRESS DL, ENDRES DB, MALONEY NA, KOPP JB, COBURN JW, SHERRARD DJ: Comparison of parathyroid hormone assays with bone histomorphometry in renal osteodystrophy. *J Clin Endocrinol Metab* 63:1163–1169, 1986
12. CHARHON SA, DELMAS PD, MALAVAL L, CHAVASSIEUX PM, ARLOT M, CHAPUY MC, MEUNIER PJ: Serum bone gla-protein in renal osteodystrophy: Comparison with bone histomorphometry. *J Clin Endocrinol Metab* 63:892–897, 1986
13. MALLUCHE HH, FAUGERE MC, FANTI P, PRICE PA: Plasma levels of bone gla-protein reflect bone formation in patients on chronic maintenance dialysis. *Kidney Int* 26:869–874, 1984
14. MEMMOS DE, EASTWOOD JB, TALNER LB, GOWER PE, CURTIS JR, PHILLIPS ME, CARTER GD, ALAGHBAND-ZADEH J, ROBERTS AP, DE WARDENER HE: Double-blind trial of oral 1,25-dihydroxy vitamin D_3 versus placebo in asymptomatic hyperparathyroidism in patients receiving maintenance haemodialysis. *Br Med J* 282: 1919–1924, 1981
15. KRAUT JA, MISHLER DR, SINGER FR, GOODMAN WG: The effects of metabolic acidosis on bone formation and bone resorption in the rat. *Kidney Int* 30:694–700, 1986
16. BUSHINSKY DA, KREIGER NS, GEISSER I, GROSSMAN EB, COE FL: Effect of pH on bone calcium and proton fluxes in vitro. *Am J Physiol* 245:F204–F209, 1983
17. BUSHINSKY DA, GOLDRING JM, COE FL: Cellular contribution to pH mediated calcium flux in neonatal mouse calvaria. *Am J Physiol* 248:F785–F789, 1985
18. ARNETT TR, DEMPSTER DW: Effect of pH on bone resorption by rat osteoclasts in vitro. *Endocrinology* 119 (1):119–124, 1986
19. COE FL, FIRPO JJ, HOLLANDSWORTH DL, SEGIL L, CANTERBURY JM, REISS E: Effect of acute and chronic metabolic acidosis on serum immunoreactive parathyroid hormone in man. *Kidney Int* 8:262–273, 1975
20. ADAMS ND, GRAY RW, LEMANN J: The calciuria of increased fixed acid production in humans: Evidence against a role for parathyroid hormone and $1,25(OH)_2$-vitamin D. *Calcif Tiss Int* 28:233–238, 1979
21. LEMANN J, LENNON EJ: The effects of chronic acid loads in normal man: Further evidence for the participation of bone mineral in the defense against chronic metabolic acidosis. *J Clin Invest* 45:1608, 1966
22. KRAUT JA, GORDON EM, RANSOM JC, COBURN JW, KUROKAWA K: The effect of chronic metabolic acidosis on the end organ responsiveness to parathyroid hormone in man. *J Clin Endocrinol Metab* 56:619–621, 1983
23. GACEK EM, BABB AL, UVELLI DA, FRY DL, SCRIBNER BH: Dialysis dementia: The role of dialysate pH in altering the dialyzability of aluminum. *Trans Am Soc Artif Intern Organs* 25:409–415, 1979