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# Evidence for abnormal calcium homeostasis in patients with adynamic bone disease

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**Evidence for abnormal calcium homeostasis in patients with adynamic bone disease.** To investigate whether the derangements in calcium kinetics in patients with renal osteodystrophy are similar in the various histologic forms of this metabolic bone disease, 43 patients on chronic maintenance dialysis underwent calcium kinetic studies using the double isotope technique, iliac crest bone biopsies for mineralized bone histology and histomorphometry and determinations of serum indices of calcium and bone metabolism. Intestinal calcium absorption was not different among the three histologic groups. However, women exhibited lower calcium absorption in each histologic form ($P < 0.01$). Patients with predominant hyperparathyroid bone disease showed plasma calcium efflux, calcium accretion rate and calcium retention markedly above normal values. Patients with low turnover bone disease exhibited a normal or slightly decreased plasma calcium efflux and calcium accretion rate together with a disproportionately low calcium retention. Patients with mixed uremic osteodystrophy presented with a calcium kinetic profile intermediary to the two other forms. Good relationships existed between plasma calcium efflux, calcium accretion rate, calcium retention and histomorphometric parameters of bone turnover as well as serum levels of parathyroid hormone. However, no serum parameter could indicate with certainty the underlying bone disease. These findings demonstrate that adynamic bone disease does not merely represent an academic finding but is characterized by a very low bone capacity to buffer calcium and inability to handle an extra calcium load. This is particularly relevant for the daily care of end-stage renal failure patients presently receiving higher than ever amounts of vitamin D and calcium salts.

Control of calcium and bone homeostasis remains a major challenge to the nephrologist caring for patients on chronic dialysis. Patients on dialysis present either with low, normal or elevated serum calcium levels. Hypercalcemia may develop either spontaneously or after administration of vitamin D metabolites or calcium salts. The most frequent histologic patterns of the underlying bone disease in past years were predominant hyperparathyroid bone disease and mixed uremic osteodystrophy [1–6]. More recently, however, states of low bone turnover, particularly adynamic bone disease, also referred to as aplastic bone disease, have been reported in an increasing number of patients on chronic maintenance dialysis [7–11]. It is not known whether adynamic bone disease with its decreased bone turnover merely reflects a histologic entity or has clinical consequences such as abnormalities in calcium homeostasis.

The goals of the study were to answer whether or not derangements in calcium homeostasis are similar among the three major histologic forms of renal osteodystrophy and attempt to unravel factors associated with abnormal calcium metabolism in dialyzed patients not treated with vitamin D metabolites or calcium salts.

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## Methods

### *Patients and protocol*

From 1989 to 1991, eighty patients on chronic maintenance dialysis from the same geographic area were asked to participate in the study. Inclusion criteria were: age ranging from 18 to 80 years, willingness to undergo an iliac crest bone biopsy, and willingness to participate in calcium kinetic studies for 28 days. Exclusion criteria were: treatment with active vitamin D metabolites or calcium salts within the last six months, systemic illnesses or organ diseases other than diabetes that may affect bone metabolism (that is, gastrointestinal diseases, liver diseases, etc.), malignancies, sarcoidosis, tuberculosis, acquired immunodeficiency syndrome, chronic alcoholism, drug addiction, immobilization, parathyroidectomy, and bilateral nephrectomy. Also excluded were patients with a failed transplant within the last six months and those taking medications known to affect bone metabolism (diphenylhydantoin, steroids, cyclosporin) during the last six months.

Forty-three patients were enrolled in the study after informed consent was obtained. Twenty-seven women and 16 men qualified and agreed to participate in the study. Twenty-six patients were on chronic maintenance hemodialysis (HD) and 17 were on continuous ambulatory peritoneal dialysis (CAPD). All but two patients were anuric. Chronic hemodialysis treatment was performed at the same center three times a week, five hours each time using a hollow fiber dialyzer with a hemophane (1.3 $m^2$, $N = 18$; Gambro, Hechingen, Germany) or polysulfone (0.65 $m^2$, $N = 8$; Fresenius, Oberursel, Germany) membrane and MTS 2008 dialysis machine (Fresenius). The dialysate contained 3.5 mEq/liter calcium and 0.75 mEq/liter magnesium. All patients on CAPD underwent four two-liter exchanges per day using commercially available dialysate containing 3.5 mEq/liter of calcium and 0.75 mEq/liter of magnesium (Dianeal, Baxter, Munich, Germany).

Underlying renal diseases were diabetes mellitus ($N$ = 11), interstitial nephritis ($N$ = 7), chronic glomerulonephritis ($N$ = 11), polycystic kidney disease ($N$ = 4), obstructive nephropathy ($N$ = 2), nephrosclerosis ($N$ = 1) and unknown origin ($N$ = 7).

All patients were on an unrestricted diet except for potassium, phosphate and fluid intake. None of the patients was on recombinant human erythropoeitin. Oral phosphate binders (aluminum trihydroxide) were given to patients as needed (mean dose: 1,210 ± mg/day, median 1,320 mg/day, range: 0 to 2,970 mg/day).

At the beginning of the study, all patients underwent iliac crest bone biopsies with blood drawings for determinations of blood levels of ionized calcium, phosphorus, alkaline phosphatase, parathyroid hormone, $1,25(OH)_2D$, 25(OH)D and osteocalcin. Calcium kinetic studies were performed during the following 28 days.

### *Calcium kinetic studies*

Calcium kinetic parameters were evaluated by employing a double isotope technique with radiocalcium. The morning of a nondialysis day, 0.4 MBq $^{47}Ca$ was administered intravenously as carrier-free calcium chloride (Medgenix Diagnostics, Fleurus, Belgium; specific activity 242 MBq $^{47}Ca$/mg Ca, that is, i.v. administration <100 μg Ca). At the same time, 0.2 MBq $^{45}Ca$ was given orally (Medgenix Diagnostics; specific activity 660 MBq $^{45}Ca$/mg Ca). This was dissolved in 100 ml of deionized water and adjusted to a total calcium content of 18 mg by the addition of a 20% calcium gluconate solution. Venous blood samples were drawn before, and 15, 30, 60, 120, 180 and 240 minutes after administration. Additional samples were collected after 24 hours and after seven days. $^{47}Ca$ in plasma samples was measured in a well-type NaI (Tl)-scintillation counter, and $^{45}Ca$ in plasma was measured by liquid scintillation counting after complete decay of $^{47}Ca$ [12]. Whole body measurements were carried out before the administration of the radiotracers and two hours, 1, 7, 14, 21, and 28 days thereafter [12]. From these measurements, whole body retention of intravenously given $^{47}Ca$ was evaluated as percentage of initial activity, corrected for radioactive decay [13].

From these measurements, the following parameters were derived:

(a) Fractional intestinal absorption of calcium, calculated from the ratio of activities of $^{45}Ca$ and $^{47}Ca$ in the blood sample drawn 24 hours after administration.

(b) Plasma calcium efflux, calculated as the ratio of activity concentrations of the intravenous tracer at 1 and 24 hours after injection. This empirical parameter reflects the exchange of the administered tracer with the exchangeable calcium pool and can be derived directly from the measurements.

(c) The fraction of the intravenously administered tracer retained in the whole body four weeks after administration. This parameter reflects bone calcium retention and is inversely related to the total tracer calcium excretion.

(d) The bone accretion. This parameter quantifies the movement of calcium from the exchangeable bone calcium pool to mineralized bone; it can be derived from the time course of the activity curves in plasma and the time course of the whole body retention curve. The determination of the bone accretion rate requires the use of a computer for the data fitting procedure and assumes a catenary four compartment model to describe the calcium exchange processes. In this study, the computer code SAAM-27 [14] run on a SPERRY 1191 computer, was used for this data analysis. The program determines iteratively a set of model parameters that provide a best fit to the observed values. Results were compared to values previously obtained in normal subjects using the same method [13–15].

### *Serum biochemical and hormonal determinations*

Serum phosphorus, calcium and alkaline phosphatase concentrations were determined using standard laboratory techniques (Hitachi 717 E, Boehringer Mannheim, Germany). Serum parathyroid hormone levels were determined in triplicate by the two-sites immunoradiometric assay (IRMA) for intact PTH [16, 17] using the Allegro™ Intact PTH assay kit from Nichols Institute, Bad Nauheim, Germany. The intra- and inter-assay coefficients of variation were 7.6% and 9.8%, respectively [16]. Serum levels of $1,25(OH)_2D$ were determined by a radioimmunoassay [18]. The intra- and inter-assay coefficients of variation were 12% and 16.8%, respectively. Serum levels of 25-hydroxyvitamin D [25(OH)D] were measured by competitive protein binding analysis [19]. Serum osteocalcin levels were determined with a competitive radioimmunoassay for the determination of intact human osteocalcin (OSCAtest, Henning, Berlin, Germany). The intra- and inter-assay coefficients of variation were <10% and <20%, respectively.

### *Bone biopsy, mineralized bone histology and histomorphometry*

Prior to biopsies, patients were administered tetracycline hydrochloride at a dose of 500 mg b.i.d. for two days. The drug was discontinued during the following ten days and then given again at the same dose for another three days. Bone biopsies were performed four days after the last labeling day. Bone specimens were taken from the anterior iliac crest using an electric drill (Institute Straumann, Waldenburg, Switzerland) with an inner diameter of 5 mm.

Bone samples were processed as previously described [6]. Sections were stained with the modified Masson-Goldner trichrome stain [20], the aurin tricarboxylic acid stain [21] and solochrome azurine [22] for detection of aluminum and the modified Gomori stain for detection of iron [23]. Unstained sections were prepared for phase contrast and fluorescent light microscopy.

Static and dynamic parameters of bone structure, formation and resorption were measured using the Osteoplan system II (Kontron, Munich, Germany) as previously described [24, 25]. The histologic sections were analyzed after completion of the study without knowledge of the patients' names or biochemical or calcium kinetic results. All histomorphometric parameters comply with the nomenclature and were calculated according to the ASBMR histomorphometry nomenclature committee [26].

Patients were also grouped according to the histologic findings into predominant hyperparathyroid bone disease (severe or mild), mixed uremic osteodystrophy, low turnover bone disease encompassing adynamic bone disease and low turnover osteomalacia as previously described [6]. Bone biopsies were independently interpreted by two investigators. When discrepancies occurred in borderline cases (less than 1%), additional sections were cut, reviewed, discussed and assigned to one of the three categories.

### *Statistical analysis*

Results are expressed as means ± SEM. Differences in continuous variables were assessed by standard analysis of variance. When a significant F value was obtained, difference between

**Table 1.** Demographic and clinical characteristics of 43 dialyzed patients according to histologic groups of renal osteodystrophy

| | Low turnover bone disease | Mixed uremic osteodystrophy | Predominant hyperparathyroid bone disease |
|---|---|---|---|
| Number of patients | 16 | 20 | 7 |
| Men/women | 9/7 | 4/16 | 3/4 |
| Mode of dialysis | | | |
| HD/CAPD | 10/6 | 10/10 | 6/1 |
| Diabetics/ nondiabetics | 5/11 | 6/14 | 0/7 |
| Age (years) | 64.8[a] ± 3.2 (67) | 60.4[a] ± 2.6 (63) | 42.6[b] ± 5.6 (43) |
| Range | 32–78 | 31–78 | 23–59 |
| Duration of dialysis (months) | 14.2[a] ± 4.9 (8) | 18.5[a] ± 6.4 (4) | 53.4[b] ± 16.8 (71) |
| Range | 1–65 | 1–112 | 1–108 |
| Number of patients with positive SBA | 6 | 9 | 3 |
| % of trabecular surface in SBA-positive patients | 64 ± 9 (67) | 57 ± 7 (52) | 47 ± 8 (47) |
| Range | 30–94 | 31–85 | 32–61 |

Results are given as mean ± SEM (median).

Positive SBA is stainable aluminum of the bone-osteoid interface/bone surface.

[a,b] Values with different letters are statistically significant ($P < 0.01$) by one-way analysis of variance with Scheffe post hoc test

means was determined by the Scheffe post hoc test. Differences in distribution were analyzed using the Chi-square test. Regression analyses, calculations of coefficients of correlation and partial correlation coefficients were performed. All tests were two-sided. Computations were done using SPSS software V3.1 (SPSS, Inc, Chicago, Illinois, USA) on an IBM PS computer, model 60.

## Results

### *Characteristics of patients enrolled in the study*

The patients enrolled in the study exhibited the typical patterns of renal osteodystrophy (Table 1). In addition to the known histomorphometric differences between the three histologic groups—predominant hyperparathyroid bone disease (PHBD), mixed uremic osteodystrophy (MUO) and low turnover bone disease (LTBD) [6]—bone volume/tissue volume was significantly higher in patients with PHBD (35.5 ± 5.6%) than in the other patients (MUO = 21.9 ± 1.3%, LTBD = 18.1 ± 1.2, $P < 0.001$).

No difference in demographic or clinical characteristics was found when patients were grouped according to their mode of dialysis, gender or underlying kidney disease. Also, no differences in prevalence and extent of bone aluminum deposition were observed between the histologic groups (Table 1) or between men and women, various modes of dialysis or presence or absence of diabetes.

Biochemical results in the three histological groups are shown in Table 2. Hypercalcemia was found in patients with LTBD ($N$ = 3) and MUO ($N$ = 2) and in only one patient with PHBD. Parathyroid hormone concentrations were statistically different among the three histologic groups, (Table 2). All patients with MUO and PHBD had serum parathyroid hormone values above the normal range and patients with LTBD had either normal ($N$ = 6) or elevated ($N$ = 10) levels. When serum biochemical and hormonal results were analyzed according to gender, diabetes or bone aluminum accumulation, no differences were found either overall or within each histologic group.

The known relationships between serum levels of parathyroid hormone, alkaline phosphatase and osteocalcin in patients with end-stage renal disease [6] were also observed in the population studied ($r$ ranging from 0.73 to 0.88, $P < 0.001$). Similarly, serum parathyroid hormone and alkaline phosphatase levels showed the previously reported [27, 28] good relationship with histomorphometric parameters of bone formation, resorption and turnover ($r$ ranging from 0.61 to 0.74, $P < 0.01$). Osteocalcin levels displayed a positive relationship with parameters of bone formation ($r$ ranging from 0.75 to 0.85, $P < 0.001$) [29].

### *Calcium kinetic studies*

All but one patient had intestinal calcium absorption below the normal range. There was no difference in calcium absorption among the three histologic groups and calcium absorption was significantly lower in women than in men regardless of the histologic group (Fig. 1). The only patient exhibiting normal intestinal calcium absorption had LTBD and was hypercalcemic. No difference in intestinal calcium absorption was observed between diabetic and nondiabetic patients, patients undergoing HD or CAPD and patients with or without bone aluminum accumulation.

Plasma calcium efflux and calcium accretion rate were significantly higher in the patients with PHBD than in the two other groups, and did not differ between LTBD and MUO (Figs. 2 and 3). There was no difference in plasma calcium efflux and calcium accretion rate between men and women, diabetic and nondiabetic patients, presence or absence of aluminum deposition in bone overall or within each histologic group. Calcium retention was statistically different among the three groups; however, considerable overlap did not allow to differentiate the three histologic groups (Fig. 4). One patient with PHBD exhibited calcium retention below normal; he also had the highest aluminum deposition at the bone osteoid interface (61%) and the lowest bone volume (18%) in this group. No difference in calcium retention was observed when results were analyzed according to gender, mode of dialysis, kidney diseases or degree of aluminum accumulation.

### *Correlations between calcium kinetics, serum biochemistry and bone morphometry*

There were positive correlations between plasma calcium efflux, calcium accretion rate and calcium retention (Table 3) but no correlation with intestinal calcium absorption. Plasma calcium efflux, calcium accretion rate and calcium retention correlated positively with serum levels of alkaline phosphatase and parathyroid hormone (Table 3). Similarly, with a lower number of patients ($N$ = 20), there were positive correlations between osteocalcin and plasma calcium efflux, calcium accretion rate and calcium retention (Table 3). No relationships were found between the three parameters of calcium kinetics and serum concentrations of ionized calcium, phosphorus, $1,25(OH)_2D$ and 25(OH)D.

**Table 2.** Biochemical parameters in 43 dialyzed patients according to histologic groups of renal osteodystrophy

| | Low turnover bone disease | Mixed uremic osteodystrophy | Predominant hyperparathyroid bone disease | Normal values |
|---|---|---|---|---|
| Ionized calcium *mmol/liter* | 1.1 ± 0.06[a] (1.1) | 1.0[a] ± 0.05 (1.0) | 1.2[a] ± 0.08 (1.1) | 1.05–1.3 |
| Range | 0.6–1.5 | 0.6–1.3 | 1.1–1.6 | |
| Phosphorus *mg/dl* | 5.7[a] ± 0.25 (5.3) | 5.2[a] ± 0.35 (5.3) | 5.4[a] ± 0.46 (5.3) | 2.5–4.8 |
| Range | 4.3–7.8 | 1.9–8.3 | 3.4–7.5 | |
| Alkaline phosphatase *U/liter* | 111[a] ± 8.0 (106) | 191[a] ± 18.6 (162) | 700[b] ± 145 (823) | <190 |
| Range | 55–162 | 100–405 | 86–1214 | |
| Parathyroid hormone *pg/ml* | 116[a] ± 30 (61) | 575[b] ± 99 (543) | 1275[c] ± 130 (1276) | 10–55 |
| Range | 28–390 | 66–2067 | 924–1962 | |
| Osteocalcin *μg/liter* | 10.6[a] ± 2.64 (10) | 26.5[a] ± 8.61 (15) | 95.0[b] ± 7.00 (95) | 1.8–6.6 |
| Range | 2.7–22.0 | 6.0–99.9 | 88–102 | |
| 1,25 Vitamin D *ng/liter* | 24.5[a] ± 2.56 (24) | 25.8[a] ± 3.68 (21) | 23.4[a] ± 3.45 (19) | 35–90 |
| Range | 10–43 | 13–79 | 16–39 | |
| 25 Vitamin D *μmol/liter* | 55.5[a] ± 15.6 (26) | 41.2[a] ± 6.6 (38) | 76.5[a] ± 19.7 (76) | 50–300 |
| Range | 10–201 | 10–106 | 27–130 | |

Results are given as mean ± SEM (median).
[a,b,c] Values with different letters are statistically significantly different ($P < 0.01$) by one-way analysis of variance with Scheffe post hoc test
[d] Osteocalcin measurements were obtained in a subset of 20 patients

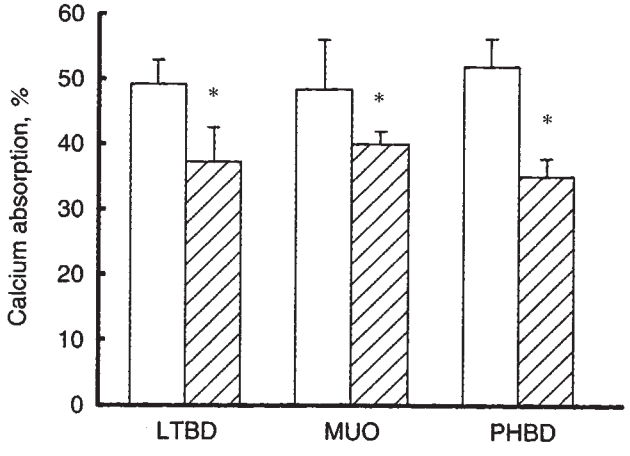


**Fig. 1.** *Intestinal calcium absorption in 43 dialyzed patients with low turnover bone disease (LTBD), mixed uremic osteodystrophy (MUO) and predominant hyperparathyroid bone disease (PHBD).* Bars indicate mean values of intestinal calcium absorption. Error bars represent SEM. Asterisks indicate a significant difference between the values for men and women ($P < 0.01$, Student *t*-test).

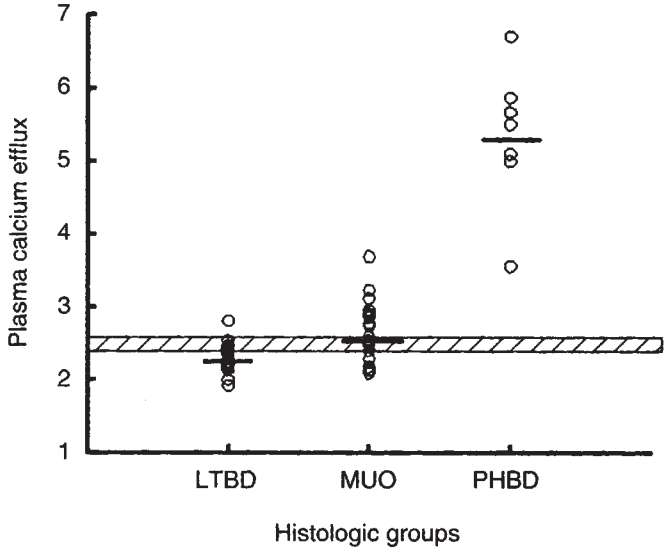


**Fig. 2.** *Plasma calcium efflux values in 43 dialyzed patients with low turnover bone disease (LTBD), mixed uremic osteodystrophy (MUO) and predominant hyperparathyroid bone disease (PHBD).* Horizontal lines indicate mean values of plasma calcium efflux for each group. Mean value of patients with PHBD was statistically different from the two other groups ($P < 0.001$, ANOVA). Shaded area indicates normal range.

There were positive relationships between calcium accretion rate, calcium retention and normal and pathologic parameters of bone formation, resorption and turnover (Table 4). The observed positive relationships between calcium accretion rate, calcium retention and bone volume were not significantly changed when partial correlation analysis controlling for bone volume was performed (Table 4). Calcium absorption did not show significant correlations with any histomorphometric parameters of bone, and none of the four indices of calcium kinetics demonstrated any relationship with the extent of stainable aluminum deposition. Regression analysis showed that only serum levels of parathyroid hormone (PTH) had a significant relationship with plasma calcium efflux ($r^2 = 0.46$, plasma calcium efflux = 2.12 + 0.012 PTH, $P < 0.001$). For calcium accretion rate, bone volume/tissue volume (BV/TV) and plasma calcium efflux (PCa-eff) entered the equation (calcium accretion rate = 99 BV/TV + 690 PCa-eff − 3298, $P < 0.001$). Calcium retention was predicted by serum levels of 1,25D and PTH and calcium accretion rate (Ca-accr) (calcium retention = 0.60 1,25D + 0.13 PTH + 0.006 Ca-accr, $P < 0.001$).

## Discussion

The results of the present study show that the various histologic forms of renal osteodystrophy are accompanied by different alterations in their calcium kinetic profiles and their abilities to handle calcium exchanges between the various compartments.

The only common aspect observed among the three histologic

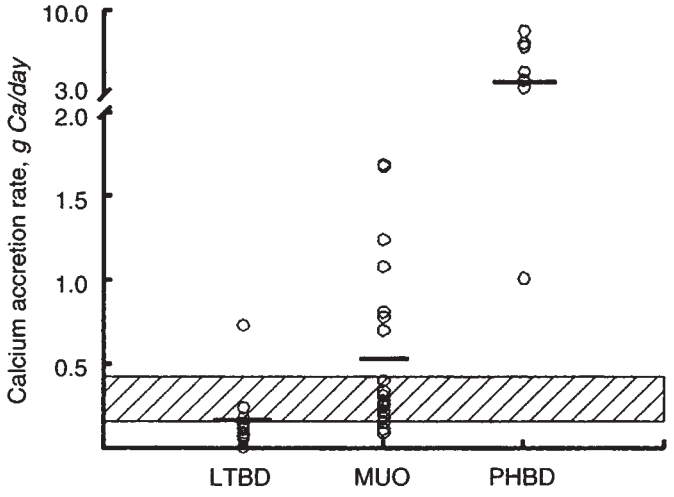


**Fig. 3.** *Calcium accretion rate values in 43 dialyzed patients with low turnover bone disease (LTBD), mixed uremic osteodystrophy (MUO) and predominant hyperparathyroid bone disease (PHBD).* The horizontal lines indicate mean values of plasma calcium efflux for each group. Mean value of patients with PHBD was statistically different from the two other groups ($P < 0.001$, ANOVA). Shaded area indicates normal range.

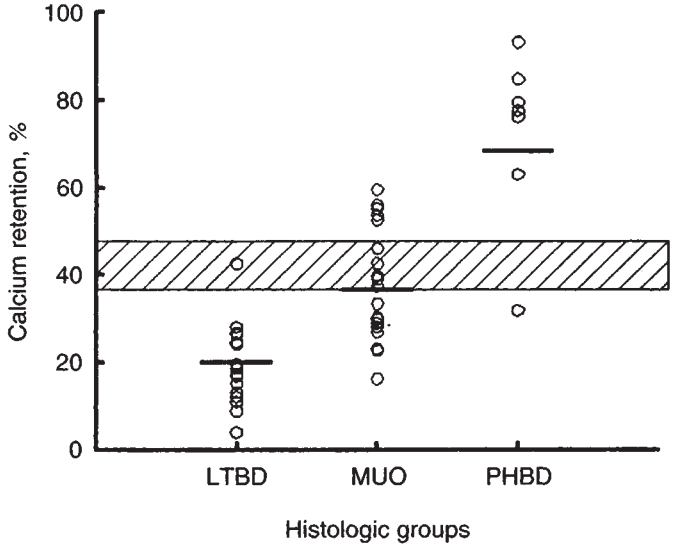


**Fig. 4.** *Calcium retention values in 43 dialyzed patients with low turnover bone disease (LTBD), mixed uremic osteodystrophy (MUO) and predominant hyperparathyroid bone disease (PHBD).* The horizontal lines indicate mean values of plasma calcium efflux for each group. All means were statistically different from each other group ($P < 0.001$, ANOVA). Shaded area indicates normal range.

forms is an intestinal calcium absorption below the normal range in patients with end-stage renal failure which confirms well-established previous observations [13, 30–33]. We found intestinal calcium absorption equally low among patients exhibiting the different histologic forms of renal osteodystrophy in the absence of administration of calcium salts or $1,25(OH)_2D_3$. This finding differs from a previously observed trend towards higher values of calcium absorption in patients with severe "osteitis fibrosa" [33].

The present study provides the novel information that female

**Table 3.** Coefficients of correlation between various parameters of calcium kinetics in 43 patients with end-stage renal failure

| | Calcium absorption | Plasma calcium efflux | Calcium accretion rate | Calcium retention |
|---|---|---|---|---|
| Alkaline phosphatase | −0.08 | 0.85[a] | 0.86[a] | 0.76[a] |
| Parathyroid hormone | −0.08 | 0.70[a] | 0.66[a] | 0.77[a] |
| Osteocalcin[c] | −0.02 | 0.70[b] | 0.72[a] | 0.73[a] |
| Calcium absorption | | −0.04 | −0.03 | 0.01 |
| Plasma calcium efflux | | | 0.86[a] | 0.76[a] |
| Calcium accretion rate | | | | 0.86[a] |

[a] $P < 0.001$
[b] $P < 0.01$
[c] Osteocalcin levels were available in a subset of 20 patients

**Table 4.** Coefficients of correlation (r) and partial correlation coefficients controlling for bone volume (Partial r) between histomorphometric parameters of bone and calcium kinetic results in 43 patients with end-stage renal failure

| Parameters of bone | Calcium accretion rate | | Calcium retention | | Plasma calcium efflux | |
|---|---|---|---|---|---|---|
| | *r* | Partial *r* | *r* | Partial *r* | *r* | Partial *r* |
| Bone volume/ tissue volume | 0.60[ac] | — | 0.68[a] | — | 0.61[a] | — |
| Osteoid volume/ bone volume | 0.76[a] | 0.54[b] | 0.74[a] | 0.42 | 0.65[a] | 0.38 |
| Woven osteoid surface/ bone surface | 0.81[a] | 0.68[b] | 0.66[a] | 0.37 | 0.66[a] | 0.44 |
| Osteoblast number | 0.76[a] | 0.63[b] | 0.76[a] | 0.51[c] | 0.69[a] | 0.41 |
| Fibrosis surface/ bone surface | 0.93[a] | 0.81[a] | 0.70[a] | 0.23 | 0.86[a] | 0.76[c] |
| Osteoclast number/ bone length | 0.80[a] | 0.57[b] | 0.79[a] | 0.50[c] | 0.79[a] | 0.42 |
| Mineralization lag time | −0.29 | −0.42 | −0.46 | −0.31 | −0.15 | −0.29 |
| Bone formation rate/ bone surface | 0.76[a] | 0.57[b] | 0.73[a] | 0.52[c] | 0.52 | 0.12 |
| Activation frequency | 0.73[a] | 0.57[b] | 0.74[a] | 0.53[c] | 0.38 | 0.01 |

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

patients with end-stage renal failure have lower intestinal calcium absorption than male patients regardless of the histologic groups of renal osteodystrophy and despite no difference in serum levels of $1,25(OH)_2D$ and parathyroid hormone between men and women. A previous study comparing intestinal calcium absorption between normal men and women did not show this difference [12]. However, in this study by Werner, Roth and Malluche [12] the male and female normal volunteers were much younger than the patients enrolled in our study which included 23 women of peri- or postmenopausal ages and no women with menstrual cycles. This may ascribe a role to estrogen deficiency in the impaired intestinal calcium absorption, in addition to the decrease in production of 1,25(OH)D in women with end-stage renal failure. It is tempting to hypothesize a vitamin D-independent action of estrogen on

intestinal calcium absorption in women with renal failure as it was shown in oophorectomized women with normal renal function [34].

Patients with severe hyperparathyroid bone disease have markedly elevated plasma calcium efflux, calcium accretion rate and calcium retention. This indicates that when calcium balance is normal or positive, these patients have the ability to increase mineralized bone volume utilizing their higher bone formation rates. Calcium retention was found to be influenced by the quantity of exchangeable calcium present in bone (calcium accretion rate) and serum levels of parathyroid hormone and 1,25(OH)D. This finding agrees with previous studies which showed that both hormones are needed to obtain efficient bone formation [35–37] because parathyroid hormone controls bone turnover, therefore the numbers of bone cells, and 1,25(OH)D stimulates the activity of individual osteoblasts in forming and mineralizing bone [37]. Conversely, a marked decrease in calcium retention was reported several months after parathyroidectomy [38]. However, the capacity of bone to absorb extra calcium may be overcome in these states of high turnover when osteoblastic activity is impaired by profound deficiency in 1,25(OH)D or toxic effects such as aluminum and possibly other factors. This results in an imbalance between bone formation and resorption leading to a diminished capacity of bone to buffer extra calcium. Also, long-term administration of calcium salts and/or treatment with vitamin D metabolites will decrease bone turnover, and the calcium kinetic profile might shift toward the ones observed in the other histologic groups, that is, lower calcium retention without a change in intestinal calcium absorption.

Patients with low turnover bone disease exhibited normal to low plasma calcium efflux and calcium accretion rate—indices of the rapidly exchangeable calcium pool. This contrasts with the marked reduction in bone calcium retention. Therefore, when subjected to calcium loads, patients with LTBD are unable to incorporate the extra calcium into the mineralized matrix of bone, and the total exchangeable calcium pool will increase which may result in hypercalcemia and/or extraosseous calcifications. In analogy, Meric, Yap and Bia [39] found that dialyzed patients treated with calcium carbonate are at higher risk for developing hypercalcemia when serum indices of bone turnover such as parathyroid hormone, osteocalcin and alkaline phosphatase were low. Consequently, administration of calcium salts for phosphate binding through increased passive intestinal calcium absorption [40] or therapy with metabolites of vitamin D by stimulation of active intestinal absorption of calcium [41] carries the potential risk of overloading the total exchangeable extracellular calcium pool with its risk of inducing hypercalcemia and/or soft tissue calcifications.

Analogous to bone histology, calcium kinetic profiles in patients with MUO lie between those of patients with PHBD and LTBD. Patients with MUO have a greater bone capacity to retain calcium than patients with LTBD; however, when challenged with a calcium load the underlying bone turnover and osteoblastic vigor will determine their ability to react.

The different calcium kinetic profiles among the three histologic groups and their good relationships with bone histology confirm the importance of the distinction among histologic groups in managing patients with renal osteodystrophy. In particular, adynamic bone disease does not merely represent an academic finding. In fact, it is characterized by a very low bone capacity to buffer calcium and an inability to handle an extra calcium load. This finding is of particular relevance since higher amounts of vitamin D and higher doses of calcium salts are presently used in the daily care of patients with end-stage renal failure. Identifying states of low bone turnover and poor calcium retention is of great clinical value in the decision to institute or discontinue therapy with calcium salts or vitamin D. Although in our study serum parathyroid hormone levels correlated well with histomorphometric parameters of bone turnover and calcium kinetics, it is of note that in the present study, patients with LTBD presented with serum concentrations of parathyroid hormone up to 390 pg/ml. This level represents more than seven times the upper normal range. Further studies are needed to clarify whether other measurable systemic substances control bone turnover or whether local factors of the microenvironment in bone such as cytokines or growth factors are primary regulators of bone turnover.

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