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DIALYSIS – TRANSPLANTATION

Significance of minimodeling in dialysis patients with adynamic bone disease

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Significance of minimodeling in dialysis patients with adynamic bone disease.

Background. We previously concluded from histomorphometric analysis that minimodeling contributes to bone formation in adynamic bone disease in patients with primary hypoparathyroidism. Presently we investigated whether this mechanism might be peculiar to adynamic bone disease.

Methods. We histomorphometrically analyzed bone specimens obtained at biopsy or autopsy from 26 maintenance hemodialysis patients with hyperparathyroidism necessitating parathyroidectomy (group A) and from 27 dialysis patients with hypoparathyroidism (group B); respective mean ages were 60 ± 7 years vs. 64 ± 8 years; dialysis duration 14 ± 6 years vs. 11 ± 9 years; and serum intact parathyroid hormone (PTH) 1205 ± 439 pg/mL vs. 41 ± 27 pg/mL. Group B was divided further into outpatient and inpatient subgroups.

Results. By histomorphometry, group A patients were diagnosed with osteitis fibrosa, and those in group B with adynamic bone disease. Minimodeling bone volume and minimodeling bone number were significantly greater in group B than group A ($P = 0.0028$ and $P = 0.0008$, respectively). Minimodeling bone volume correlated significantly and positively correlated with total bone volume in group B ($P = 0.0016$), but not in group A. In group B, minimodeling bone volume and total bone voluem were greater in outpatients than inpatients ($P < 0.0001$ and $P = 0.025$, respectively). Minimodeling bone volume and total bone volume showed significant negative correlation with age in group B ($P < 0.001$ and $P = 0.005$, respectively).

Conclusion. Minimodeling might contribute to bone formation in dialysis patients with adynamic bone disease, in the absence of remodeling stimulated by parathyroid hormone (PTH), especially in relatively young patients with good activities of daily living.

Idiopathic adynamic bone disease associated with low serum parathyroid hormone (PTH) concentrations is a type of renal osteodystrophy occurring in dialysis patients. This bone disease has been noted particularly in elderly individuals, diabetic patients, and patients undergoing chronic ambulatory peritoneal dialysis (CAPD) [1]. Elevating serum plasma calcium levels by administering calcitriol and calcium carbonate may foster development of adynamic bone disease in these patients [2]. Several reports have suggested a close relationship between increased incidence of hip and vertebral fractures in dialysis patients and adynamic bone disease [3–5]. Reduced bone mineral density in patients with adynamic bone disease has been postulated to predispose to fracture [3]. However, several studies form no relationship between hypoparathyroidism and low bone mineral density [6, 7]. Whether adynamic bone disease itself causes fractures is controversial. London et al [8] recently found that the arterial calcification in end-stage renal disease (ESRD) patients is associated with adynamic bone disease.

To clarify the pathophysiology of adynamic bone disease, we previously investigated bone morphology and metabolism in two patients with primary hypoparathyroidism who long had shown low PTH concentrations. In both, histomorphometric analysis yielded values consistent with a diagnosis of adynamic bone disease. However, normal bone was diagnosed because bone volume was preserved and dense bone-trabecular connectivity was noted, with normal lamellar structure. We found that in these cases bone formation is supported by a mechanism called "minimodeling," which is characterized by hump-like structures [9]. We next examined whether minimodeling took place in a patient with secondary hypoparathyroidism treated with hemodialysis for 30 years. We found adynamic bone disease to be associated with bone formation by minimodeling in this patient, although trabecular connectivity was poor and bone islands were relatively prominent [9].

Presently, to determine whether minimodeling is a specific characteristic of adynamic bone disease, we compared minimodeling bone volume between dialysis patients with hyperparathyroidism requiring parathyroidectomy and patients with hypoparathyroidism. Next

Key words: idiopathic adynamic bone disease, minimodeling, remodeling, hypoparathroidism, hyperparathyroidism, activities of daily living.

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we examined whether ability to carry out activities of daily living and age also influenced minimodeling bone volume among the patients with hypoparathyroidism.

METHODS

Patient characteristics

Bone specimens were collected from both biopsies and autopsies from 1997 to 2003. Patients with hyperparathyroidism necessitating parathyroidectomy (group A) ($N = 26$) included 13 men and 13 women; ages ranged from 49 to 69 years (mean ± SD, 60 ± 7 years). These patients had been treated with hemodialysis from 4 to 24 years (14 ± 6 years). Six patients were diabetic, while 20 were nondiabetic. Group A patients were regularly treated in the outpatient dialysis clinic.

Patients with hypoparathyroidism (group B) ($N = 27$) included 14 men and 13 women, with ages ranging from 49 to 77 years (mean ± SD, 64 ± 8 years). Patients had undergone dialysis for 4 to 30 years (11 ± 9 years). Diabetic patients numbered 7, while 20 patients were nondiabetic. Patients who had undergone parathyroidectomy were not included. No patient had a pathologic fracture. Group B patients were divided into two subgroups: patients regularly treated in the outpatient dialysis clinic (group B1) and patients regularly treated in the inpatient dialysis facility (bed-bound institutionalized patients) (group B2). Group B2 patients were more malnutritional and more severely ill or complicated with comorbid events than group A and B1 patients. Eleven of the 14 patients in the group B1 were treated in the outpatient dialysis clinic to just before death (mainly due to cardiovascular and cerebral vascular events). Patients in group B1 numbered 14 (four diabetic patients and ten nondiabetic) and had ages from 49 to 71 years (mean ±SD, 63 ± 10 years). Patients in group B2 numbered 13 (three diabetic patients and ten nondiabetic) and had ages from 60 to 77 years (mean ±SD, 68 ± 8 years).

Parathyroid tissue was surgically removed (parathyroidectomy) in group A patients with severe hyperparathyroidism due to hypercalcemia [11.6 ± 0.7 (10.2 to 13.5)] of serum calcium (mg/dL) adjusted by the formula [serum calcium (mg/dL) − albumin (g/dL) + 4.0] and hyperphosphatemia [8.7 ± 1.1 (7.1 to 10.0) mg/dL] who were resistant to the treatments with calcium-containing phosphorus binders and vitamin D derivatives.

Group B hypoparathyroid patients were administered therapeutic agents such as calcium-containing phosphorus binders and vitamin D derivatives. The serum calcium level was 10.2 ± 0.7 (8.8 to 11.5) of the measured level of serum calcium (mg/dL) adjusted by the formula [serum calcium (mg/dL) − albumin (g/dL) + 4.0]; the serum phosphate level was 5.1 ± 1.0 (3.2 to 7.2) mg/dL. Three out of 27 patients were administered 1 to 2 g of aluminum-chelating agents per day. However, we did not inspect the aluminum deposition in bone. We made this decision in view of the very low level of serum aluminum [8.6 ± 7.2 (0 to 29) μg/L] and the absence of any clinically significant effects from aluminum intoxication in this time period.

Right iliac bone biopsy was performed after double tetracycline labeling according to the following schedule in all patients included in the A group: 03 (on medicine) and 14 (off medicine) and 03 (on medicine) and 14 (off medicine). Twenty-four of the 27 patients in group B were evaluated based on the right iliac bone specimens obtained at autopsy without previous double labeling by tetracycline. The other three patients underwent biopsy after tetracycline administration.

The blood samples from the biopsied cases were taken prior to heparinization in hemodialysis on the day before the bone biopsy. The blood samples from the autopsied cases were taken prior to heparinization in hemodialysis within 1 month before the autopsy. Plasma intact PTH concentration were determined with an immunoradiometric assay (IRMA) (Nichols Institute Diagnostics, San Clemente, CA, USA). Bone Gla protein (BGP) (osteocalcin) also was measured with IRMA.

Bone specimen processing and examination

Undecalcified thin sections 5 μm in thickness were prepared from bone specimens and stained by the Villanueva method. Sections were observed with an epifluorescence microscope using ultraviolet excitation. In a portion of bone trabecula magnified at ×160, parameters were measured directly with an image analysis system linked to a microcomputer.

Quantitative histomorphometric analysis of trabecular bone remodeling was carried out using the following calculations:

$$\text{Total bone volume(BV/TV)} = [\text{bone volume(BV)/tissue volume(TV)}] \times 100(\%)$$

$$\text{Osteoid volume(OV/BV)} = [\text{osteoid volume(OV)/bone volume(BV)}] \times 100(\%)$$

$$\text{Eroded surface(ES/BS)} = [\text{eroded surface(ES)/bone surface(BS)}] \times 100(\%)$$

$$\text{Osteoclast number(N Oc/BS)} = [\text{osteoclast number(N Oc)/bone surface(BS)}] \times 100(\text{N/mm})$$

The osteoclast number was calculated by one layer. The osteoclast diameter ranged from 35 to 55 μm in group A and 20 to 30 μm in group B.

$$\text{Fibrous tissue volume(Fb V/TV)} = [\text{fibrous tissue volume(Fb V)/tissue volume(TV)}] \times 100(\%)$$

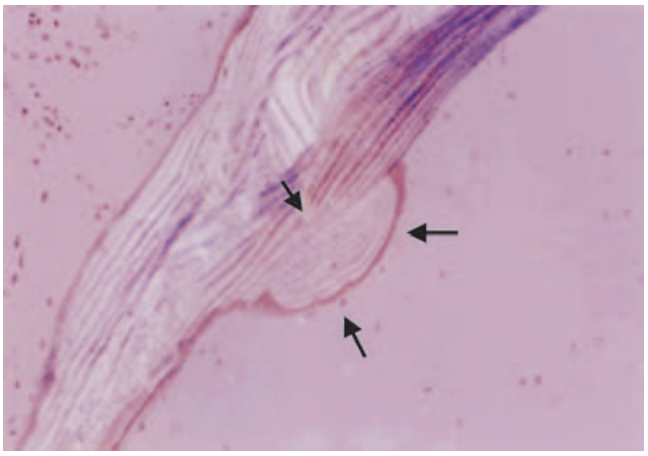

Fig. 1. Minimodeling characterized by hump-like structure (arrows). Polarizing microscopy ×200.

Sites of cancellous bone formation were classified as showing either remodeling or minimodeling. A remodeling site was defined as a scalloped cement line with interrupted collagen fibers in the adjacent bone underlying the bone formation site, thus indicating previous bone resorption. Minimodeling sites were defined as bone formation sites with smooth cement lines without interruption of surrounding collagen fibers, showing no evidence of previous bone resorption [10] (Fig. 1). Lamellar bone and woven bone were observed in a mixed pattern on the biopsied bone specimens of the patients with secondary hyperparathyroidism. Minimodeling was observed on the surface of the lamellar bone, but not the woven bone. Accordingly, minimodeling was measured as a part of lamellar bone. Bone histomorphometry concerning minimodeling used the following calculations:

Minimodeling bone volume (Mi Mo BV/BV)
= [absolute minimodeling bone volume (Mi Mo BV)/ bone volume (BV)] × 100(%)

Minimodeling bone number(N Mi Mo/BV)
= [absolute minimodeling bone number(N Mi Mo)/ bone volume(BV)](N/mm^2)

Statistical analysis

Results are expressed as mean ± SD. Statistical analysis was performed using StatView version 5.0 for Macintosh (Apple Computers Japan, Inc., Shinjuku, Tokyo, Japan). Differences between groups were compared using the Mann-Whitney *U* test for nonnormally distributed variables, while normally distributed variables were compared using unpaired *t* tests. To evaluate the relationship between variables, Pearson's correlation coefficient was used for normally distributed variables, while Spearman's ranked correlation coefficient was used when variables were nonnormally distributed. A *P* value less than 0.05 was considered to indicate significance.

RESULTS

Table 1 compares between patients with hyperparathyroisism (group A) and with hypopararhyroidism (group B). In group A, plasma intact PTH and BGP were significantly higher than in group B. The osteoid volume (OV/TV), eroded surface (ES/BS), osteoclast number (N Oc/BS) and fibrous tissue volume (Fb V/TV) were significantly greater in hyperparathyroid patients (group A) than in hypoparathyroid patients (group B), reflecting a difference in histologic diagnosis of bone. All of the hyperparathyroid patients (group A) were diagnosed with osteitis fibrosa, while 3 of 27 hypoparathyroid patients (group B) were diagnosed with adynamic bone disease according to the previously reported criteria [11]. The following factors led us to conclude that the other 24 patients were compatible with adynamic bone without measurement of the bone formation rate by technetium labeling. The total osteoid volume was small (<15%), the fibrous tissue was very scant (<0.5%), the eroded surface was decreased, and the numbers of osteoblasts and osteoclasts were both decreased.

Minimodeling bone volume and minimodeling bone number were significantly greater in hypoparathyroid patients (group B) than in the hyperparathyroid patients (group A) ($P = 0.0028$ and $P = 0.0008$, z score $= -2.85$ and z score $= -3.75$, respectively). The distribution of minmodeling bone volume on patients of both groups is shown in Figure 2.

To investigate whether bone volume apparently formed by minimodeling is associated with total bone volume, the correlation between minimodeling bone volume and total bone volume in patients with hypoparathyrodism (group B) was analyzed. Minimodeling bone volume showed a significant positive correlation with total bone volume ($r^2 = 0.304$, $P = 0.0016$) (Fig. 3). On patients with hyperparathyrodism (group A), no correlation was found between minimodeling bone volume and total bone volume ($P = 0.66$) (Fig. 4). These results suggest that minimodeling contributes to preseration of bone volume in patients with hypoparathyroidism, but not in those with hyperparathyroidism.

We considered the contribution of activities of daily living status to minimodeling in patients with hypoparathyroidism. Minimodeling bone volume and total bone volume were compared between outpatient dialysis and inpatient dialysis patient populations (Figs. 5 and 6). Minimodeling bone volume and total bone volume in outpatients (group B1) were significantly greater than in inpatients (group B2) with hypoparathyroidism ($P < 0.0001$ and $P = 0{,}025$, z score $= -3.43$ and z score $= -2.29$, respectively). Thus, good activities of daily

Table 1. Comparison between hyperparathyroidism (group A) and hypoparathyroidism (group B)

	Hyperparathyroidism (group A)	Hypoparathyroidism (group B)	*P* value	z score
Number	26	27		
Age *years*	60 ± 7	64 ± 8	0.13	−1.52
Hemodialysis duration *years*	14 ± 6	11 ± 9	0.07	−1.83
Intact parathyroid hormone *pg/mL*	1205 ± 439	41 ± 27	<0.0001	−6.42
Bone Gla protein (BGP) *ng/mL*	334 ± 208	26 ± 40	<0.0001	−5.82
Tissue volume (TV) mm^2	14.3 ± 4.6	20.4 ± 6.9	0.0054	−2.78
Bone volume (BV) mm^2	3.5 ± 1.7	2.9 ± 1.5	0.1574	−1.05
Bone volume (BV/BV)%	24.7 ± 8.2	14.3 ± 6.3	0.0019	−3.96
Osteoid volume (OV/BV)%	7.9 ± 5.6	2.66 ± 3.08	0.0003	−3.98
Eroded surface (ES/BS)%	27.6 ± 10.3	10.4 ± 7.9	<0.0001	−4.63
Osteoclast number (N Oc/BS) *N/mm*	1.1 ± 1.3	0.19 ± 0.23	<0.0001	−4.70
Fibrous tissue volume (Fb V/TV)%	6.1 ± 7.9	0.15 ± 0.24	<0.0001	−6.25
Minimodeling bone volume (Mi Mo BV/BV%	1.44 ± 1.08	3.65 ± 2.96	0.0028	−2.85
Minimodeling bone number (N mi Mo/BV) N/mm^2	1.63 ± 1.17	5.34 ± 4.54	0.0008	−3.75
Mi Mo BV/N Mo mi BV μm^2	11,748 ± 8199	8351 ± 4276	0.23	−1.38

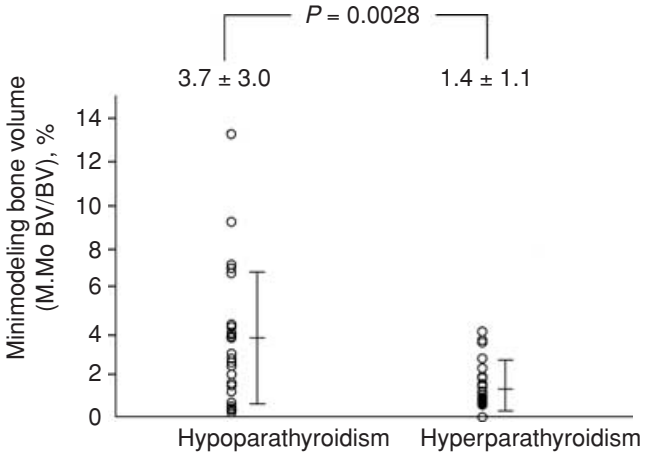

Fig. 2. Comparative study of minimodeling bone volume (Mi Mo BV/BV) between patients with hyperparathyroidism necessitating parathyroidectomy and patients with hypoparathyroidism. Results are expressed as means ± SD. Minimodeling bone volume in the hypoparathyroidism group was significantly greater than in the hyperparathyroidism group ($P = 0.0028$, z score = −2.85).

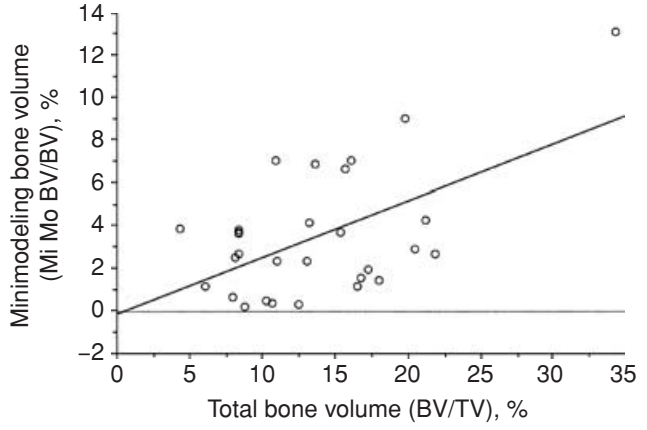

Fig. 3. Correlation between minimodeling bone volume (Mi Mo BV/BV) and total bone volume (BV/TV) in patients with hypoparathyroidism. Minimodeling bone volume showed a significant positive correlation with total bone volume ($r^2 = 0.304$, $P = 0.0016$).

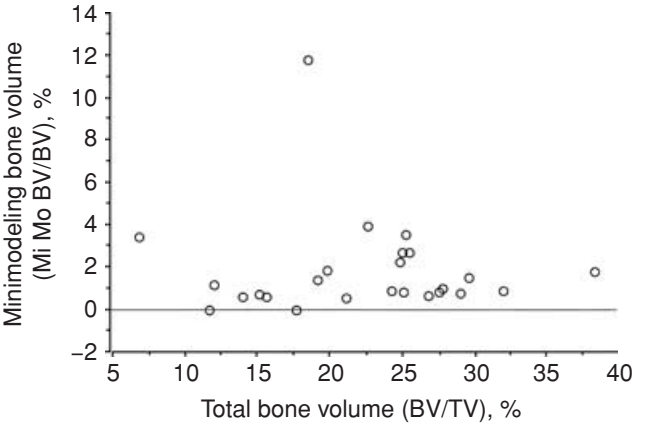

Fig. 4. Correlation between minimodeling bone volume (Mi Mo BV/BV) and total bone volume (BV/TV) in patients with hyperparathyroidism. No significant correlation was found between these two variables ($P = 0.66$).

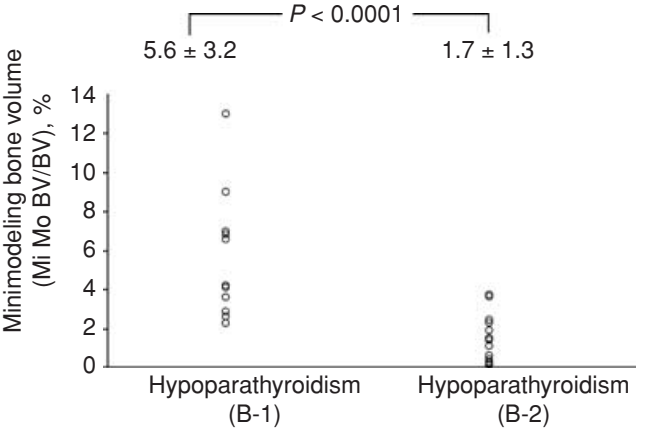

Fig. 5. Comparison of minimodeling bone volume (Mi Mo BV/BV) between patients with hypoparathyroidism treated with dialysis as outpatients (group B1) and those treated with dialysis as long-term inpatients (group B2). Results are expressed as mean ± SD. Minimodeling bone volume was significantly higher than in the latter group ($P < 0.0001$, z score = −3.43).

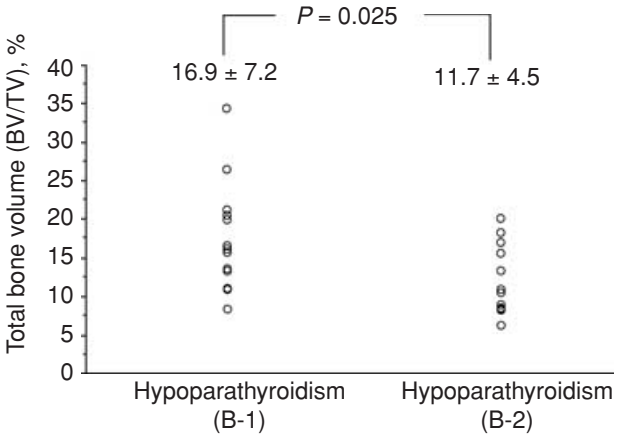

Fig. 6. Comparison of total bone volume (BV/TV) between patients with hypoparathyroidism treated with dialysis as outpatients (group B1) and those treated with dialysis as long-term inpatients (group B2). Results are expressed as means ± SD. Total bone volume in the former group was significantly higher than in the latter group ($P = 0.025$, z score = –2.29).

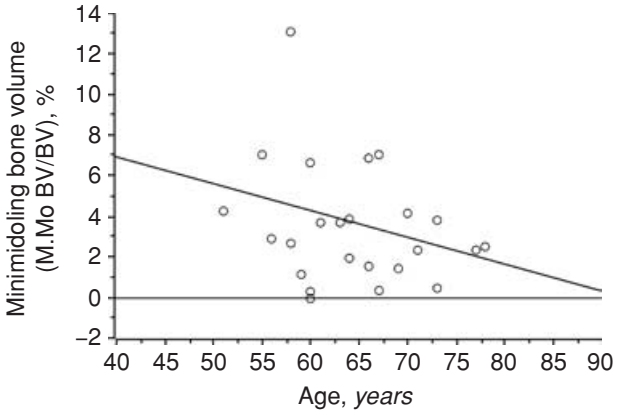

Fig. 7. Correlation between minimodeling bone volume (Mi Mo BV/BV) and age in patients with hypoparathyroidism, Minimodeling bone volume showed significant (negative) correlation with age ($r^2 = 0.208$, $P < 0.001$).

living status may contribute to formation of bone via minimodeling.

We also examined correlations of minimodeling bone volume and total bone volume with age in patients with hypoparathyrodism (Figs. 7 and 8). Both minimodeling bone volume and total bone volume showed a significant negative correlation with age ($P < 0.001$ and $P = 0.005$, respectively). Minimodeling bone volume and total bone volume were compared between male and female hypoparathyroid patients. No significant correlation was found between men and women in the minimodeling bone volume or total bone volume ($P = 0.69$ and $P = 0.37$, respectively).

Thus, relatively young age may contribute to bone formation via minimodeling.

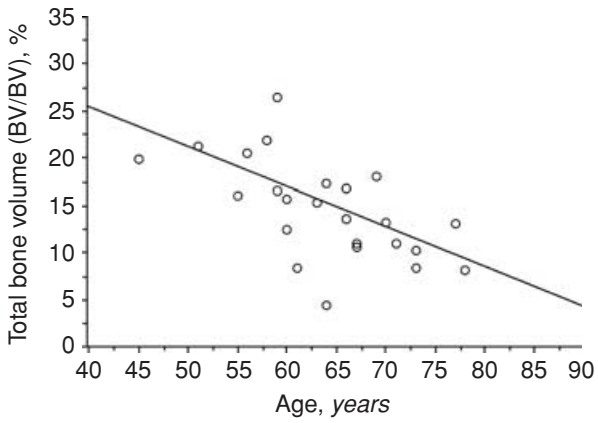

Fig. 8. Correlation between total bone volume (BV/TV) and age in patients with hypoparathyroidism. Total bone volume showed significant (negative) correlation with age ($r^2 = 0.35$, $P = 0.005$).

DISCUSSION

Various bone lesions occurring in patients with chronic renal failure share the general name of renal osteodystrophy. Adynamic bone disease represents an additional type of low-turnover bone disease, characterized clinically by a low serum PTH concentration, and histologically by low bone turnover, absence of fibrous tissue, a small amount of osteoid, and a decrease in osteoclast numbers.Adynamic bone disease is distinguished from osteomalacia by a lack of an increase in osteoid volume associated with a delay in its mineralization. Adynamic bone disease is distinct from the mild type of renal osteodystrophy because of the decreased bone formation rate in adynamic bone disease. Initially, adynamic bone disease was reported to be associated with aluminum deposition; after aluminum-containing phosphate-binding preparations were replaced by calcium carbonate and a reverse osmotic apparatus was adopted for processing water for dialysate, exposure to aluminum has been minimized [12–14], and the existence of idiopathic adynamic bone disease has become evident. Although the etiology of idiopathic adynamic bone disease is uncertain, this disease has been reported to be more prevalent in patients undergoing CAPD, elderly persons, and diabetic patients [1]. Adynamic bone disease in CAPD is believed to reflect maintenance of higher plasma calcium concentration. Excessive administration by calcitriol and calcium carbonate may contribute directly to adynamic bone disease [2].

To better understand adynamic bone disease, we previously performed histomorphometric bone analysis in two patients with primary hypoparathyroidism who had shown low circulating PTH level for many years. Cancellous trabecular bone showed findings of adynamic bone disease, including paucity of tetracycline labeling (decreased bone formation rate), a decrease in both osteoblasts and osteoclasts, scant osteoid, and absence

of fibrous tissue; Mineralized bone volume, however, was abundant [9, 11]. Since evidence of the minimodeling phenomenon was present in these two cases and tetracycline labeling occurred in an area with minimodeling, bone formation by this mechanism may have been responsible for preserving bone volume despite hypoparathyroidism and very slow bone formation rate [9].

Next, to elucidate whether this minimodeling mechanism was limited to primary hypoparathyroidism or also would be applicable to patients with true adynamic bone disease developing following initiation of dialysis, we performed bone histomorphometry in an autopsy case where the patient had undergone hemodialysis for 30 years, while maintaining low serum PTH concentrations over a long period. This case differed morphologically from the first two in that bone trabecular connectivity was poor, island bone was prominent and woven bone was apparent only in small areas. An adynamic state of bone could be diagnosed according to reported criteria [11]. Bone volume was preserved according to both histomorphologic analysis and bone mineral density measurement using dual-energy x-ray absorptiometry (DEXA). Hump-like bone formations indicating minimodeling were evident [9].

Formation of cancellous bone may occur according to both remodeling and minimodeling mechanisms. In remodeling, bone formation by osteoblasts occurs only where bone resorption by osteoclasts has occurred previously [15].Remodeling is regulated systemically by PTH, 1,25-dihydroxyvitamin D, and by other hormones. In minimodeling, however, bone formation resulting from osteoid deposition and successive mineralization apparently occurs at a quiescent bone surface without prior bone resorption by osteoclasts; newly formed bone therefore protrudes from older bone. In this process, activities of osteoblasts and osteoclasts are dissociated. Linear dividing lines between newly formed bone and old bone can be observed as "lamellar separation." This demarcation is clear in early stages, but soon becomes obscure as the minimodeling site is integrated with the preexisting bone. Minimodeling is reported to be regulated by dynamic external stress according to Wolff's law [16–19].

While we proposed the occurrence of minimodeling in our previous studies of only a few hypoparathyroid patients [9], whether minimodeling was specific to hypoparathyroidism remained at issue. In the present investigation we therefore compared minimodeling bone volume between dialysis patients with very high and with low PTH. Minimodeling bone volume was greater in patients in a low-PTH state than in those with high PTH, suggesting that minimodeling gives way to active remodeling in a high PTH state. However, once remodeling diminishes because of paucity of PTH, the minimodeling mechanism may be activated. We further noted that in hypoparathyroid dialysis patients, both minimodeling bone volume and total bone volume were greater in patients with relatively unimpaired activities of daily living(outpatients) than in those with more impaired activities of daily living(long-term inpatients). Minimodeling bone volume and total bone volume also were smaller in the elderly. Accordingly, among patients with adynamic bone disease reflecting low PTH, bone volume would be lost in immobilized individuals with extremely limited exercise because minimodeling would not be stimulated. On the other hand, bone volume could be preserved in the presence of adynamic bone disease when exercise was sufficient to stimulate minimodeling.

The significance of minimodeling initially attracted little discussion after the phenomenon was proposed by Frost [16–19]. More recently minimodeling gradually has come to receive greater attention. Erben [20] reported that growth of cancellous bone depended upon minimodeling while rats were growing, but maintenance of cancellous bone depended upon remodeling when rats were aging. Kobayashi et al [10] studied minimodeling in iliac bone biopsy specimens obtained from 27 postmenopausal women who underwent total hip arthroplasty. Because these patients had no apparent metabolic disorders such as renal function abnormalities, they did not have renal osteodystrophy. Minimodeling was present in 17 of 27, being absent in ten. Minimodeling bone volume, however, was very small ($0.71 \pm 1.2\%$). Patients with minimodeling had higher mineral apposition rate (MAR) and BFR/BV values than those without minimodeling. This suggests that when PTH is presumably normal, minimodeling will be minimal, but may contribute slightly to preservation of bone volume by a minor increase in bone formation rate.

CONCLUSION

Remodeling, regulated directly by PTH, has been considered a main mechanism of bone formation in renal osteodystrophy. More complete understanding of the minimodeling mechanism regulated by dynamic external stress obtained from future studies may yield clues to bone formation mechanisms in various forms of renal osteodystrophy, including adynamic bone disease.

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