

# Irreversible Bone Loss in Osteomalacia

## Comparison of Radial Photon Absorptiometry with Iliac Bone Histomorphometry during Treatment

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### Abstract

We examined the relationships between the changes in bone mineral deficit in the radius, determined by single-energy photon absorptiometry at standard proximal and distal sites, and in the ilium, determined by bone histomorphometry, during the treatment of osteomalacia of diverse etiology in 28 patients. In the ilium, relative osteoid volume decreased by 75–80% in both cortical bone (from 6.0% to 1.5%) and trabecular bone (from 30.1% to 6.6%) during a mean treatment duration of 2 yr. There was also a significant fall in iliac cortical porosity from 10.3% to 7.8%. As a result, mineralized bone volume increased by 7.5% in cortical and by 40.1% in trabecular bone; the cortical and trabecular increments were correlated ( $r = 0.69$ ,  $P < 0.001$ ). The properly weighted increase for the entire tissue sample was 18.6%. By contrast, there was no change in bone mineral at either radial site, although there was a 2% increase at both sites when allowance was made for age-related bone loss during treatment. The proximal and distal age-adjusted increments were correlated ( $r = 0.76$ ,  $P < 0.001$ ), but there was no correlation between the changes in any photon absorptiometric and any histomorphometric index. In that iliac cortical bone turnover in normal subjects was 7.2%/yr, we estimated the rate of bone turnover to be  $<2\%/yr$  at both proximal and distal radial sites, including any trabecular bone present at the distal site. Compared to appropriate control subjects, the bone mineral deficits fell during treatment from 19.2% to 17.1% at the proximal radius ( $>95\%$  cortical bone) and from 20.5% to 18.5% at the distal radius ( $>75\%$  cortical bone). In the ilium the deficits, assuming attainment of normal values for osteoid volume and cortical porosity, fell from 41.7% to 36.1% in cortical and from 31.5% to 6.3% in trabecular bone, the properly weighted combined deficit falling from 38.6% to 27.7%. The irreversible iliac cortical deficit was entirely due to cortical thinning because of increased net endosteal resorption; the resultant expansion of the marrow cavity offset the modest loss of fractional trabecular mineralized bone. We conclude: (a) in osteomalacia there is a large irreversible and a small reversible bone mineral deficit at both proximal and distal radial sites, in similar proportion to the iliac cortex but of smaller

magnitude; (b) the anatomic basis of the irreversible bone mineral deficit at all three sites that persists despite correction of the mineralization defect by appropriate treatment is thinning of cortical bone, most likely owing to prolonged secondary hyperparathyroidism; (c) there is no evidence that the proportion of trabecular bone in the distal radius at any site proximal to the radioulnar joint has any relevance to the interpretation of measurements made at that site; (d) there are at least three functional subdivisions of trabecular bone depending on proximity to hematopoietic marrow, fatty marrow, or synovium; and (e) single photon absorptiometry of the radius is an excellent method for measuring cortical bone mass in the appendicular skeleton, but is of little value for the assessment of changes in trabecular bone status.

### Introduction

Single-energy photon absorptiometry (SPA)<sup>1</sup> of the radius has been extensively used in the last 10 years for the measurement of bone mass (1, 2). Although newer techniques, such as dual photon absorptiometry (3) and quantitative computed tomography (4) have several advantages, they are less readily available and more expensive. Widespread application of SPA in clinical practice has recently been advocated, both for detecting osteopenia and for monitoring the response to treatment in metabolic bone disease (5). Several different sites in the radius have been used for SPA with the Norland–Cameron bone mineral analyzer. The most common is the midshaft or proximal site about one-third to one-half of the forearm length away from the wrist, where the bone is almost entirely ( $>95\%$ ) cortical (6). Some investigators also use a distal site in the radial metaphysis closer to the wrist joint, where there is a higher proportion of trabecular bone (6, 7). Because of the flared shape of the bone, repositioning error is greater than at the proximal site, and distal measurements have been criticized because of low precision (8).

Nevertheless, use of the distal site has persisted because of the clinical importance of studying trabecular bone (9) and the commonly held belief that relatively larger bone mineral deficits at the distal site reflect a higher rate of turnover and consequent faster rate of loss in trabecular than in cortical bone (5, 10–12). These differences certainly hold for the axial skeleton (13, 14) but have not been demonstrated for the appendicular skeleton, which is neither accessible to biopsy nor, with rare exceptions, examined at autopsy. Indeed, both proximal and distal sites differ much more from the spine in their response to various diseases than they do from each other (3, 11). In order to gain further insight into the anatomical basis of bone mineral measurements

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1. Abbreviations used in this paper: BM, bone mineral; BW, bone width; CT, computed tomography; MB(V), mineralized bone (volume); OS, osteoid; ROV, relative osteoid volume; SPA, single photon absorptiometry; ST, soft tissue; TB(V), total bone (volume); TT, total tissue.

(15), especially at the distal site, we have compared the changes found by SPA of the radius with contemporaneous changes found by iliac bone histomorphometry brought about by the treatment of osteomalacia. This condition is associated with substantial calcium retention during recovery (16) and by inference, a large deficit in total body calcium. To accomplish our aim we devised a new method of analyzing bone histologic data to derive quantities that could be validly compared with those derived from SPA. An unexpected finding, which provides an additional theme for our study, was the magnitude of irreversible bone loss revealed by both techniques in a disease usually regarded as curable.

#### *Patient selection and study design*

We considered for the study all patients with osteoid excess on bone biopsy, in whom repeat biopsy showed significant improvement after treatment and in whom SPA of the radius was carried out within 1 mo before or after each biopsy; in a few cases with biopsies > 1 yr apart, this interval was extended to 2 mo. Histologic criteria were an initial relative osteoid volume (ROV) of >7.5% with a fall of >60%, or an initial value of >10% with a fall of >40%. Of 32 patients reviewed, four did not meet these criteria. The remaining 28 patients included 17 white females, 2 black females, 7 white males, and 2 black males; the ages were 15–76 yr with a mean of 52.3 yr. Five women were premenopausal and 14 women postmenopausal.

Osteoid excess was the result of intestinal malabsorption of vitamin D and calcium in 14 patients (five postgastrectomy, four intestinal bypass surgery for obesity, three adult celiac disease, one granulomatous ileitis and one chronic pancreatitis), chronic renal failure in seven patients (three not yet dialyzed, four on dialysis), light chain nephropathy with Fanconi syndrome in two patients, and anticonvulsant therapy, fluoride therapy, nonfamilial hypophosphatemia, vitamin D dependency, and nutritional vitamin D deficiency in one each. All patients had osteomalacia in the colloquial sense, but according to rigorous kinetic criteria based on *in vivo* double-tetracycline labeling, four patients would be more accurately classified as preosteomalacic, because the osteoid accumulation was mainly due to increased bone formation from secondary hyperparathyroidism rather than to impaired mineralization (17).

In three dialysis patients the treatment for osteomalacia was successful renal transplantation; the healing time was taken as the time from operation to the second biopsy. These patients (but no others) received corticosteroid therapy during healing. In the remaining 25 patients, medical treatment (some form of vitamin D or metabolite in 24 patients, supplemental phosphate in 3 patients, or attempted treatment of the underlying disease in 9 patients) was begun immediately after the biopsy and healing time was taken as the time between biopsies. In two patients an intestinal bypass was reversed several years after medical treatment had begun. Mean healing time as defined was 23.7 mo (range 6–78), mean time between biopsies 25.3 mo (range 6–78), and mean time between SPA measurements 25.0 mo (range 7–77). In 15 of 19 patients with a healing time of <24 mo, additional SPA measurements were made after the second biopsy, so that, in all patients except four, we observed the response to a minimum treatment duration of 2 yr, with a mean extended healing time of 35.9 mo (range 14–77). The four excluded patients were demographically and etiologically similar but had a mean healing time of only 11 mo. Because suitable patients were infrequently encountered, the entire study extended over a period of 9 years. During this time 29 other patients with

nonrenal osteomalacia were examined; they could not be considered for inclusion because repeat biopsy was not obtained, but were clinically and histologically similar to the study group.

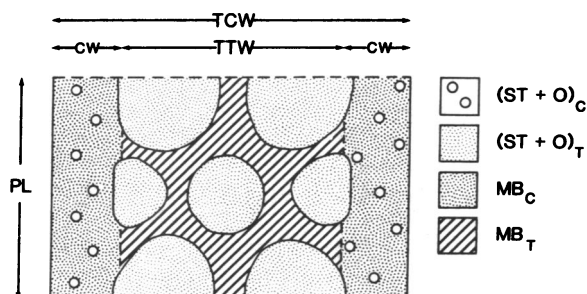
#### **Methods**

SPA of the radius on the nondominant side was performed using the Norland–Cameron bone mineral analyzer with improved forearm-positioning platform 67 cm from the floor. The forearm was held in the prone position parallel to the median plane, and particular care was taken to avoid excessive abduction or rotation of the upper arm (18). The instrument was calibrated daily using a standard provided by the manufacturer that had been recalibrated against a primary standard made available by Dr. R. Mazess (19). A new  $^{125}\text{I}$  source was installed every 4 mo, usually when the count rate fell below 1,000/s (20). The distal measurement site was located at 1.5 cm proximal to the middle of the round eminence on the volar surface of the arm at the distal end of the ulna, just proximal to the wrist, often referred to, conveniently but erroneously, as the ulnar styloid process. The proximal measurement site was located at one-third of the distance from the ulnar “styloid” to the olecranon process. The index settings for both arm positions were recorded. Means of four scans were obtained at each site, and the results expressed as bone mineral (BM) in grams per centimeter, bone width (BW) in centimeters, and bone mineral/bone width (BM/BW) in grams per square centimeter.

After the first scan in each patient the measurement sites were located by skin markers and the scanned forearm was x-rayed in the normal supine position, to detect any anatomic abnormality or pathologic process that might affect the results; in a few cases this led to repetition of the measurements on the opposite side. Measurements on the x-rays also provided a rough check on the accuracy of scanning site location. For subsequent scans the arm was repositioned longitudinally using the same index settings. If necessary, the lateral position and rotation of the forearm were adjusted until the BW was within 2% of the previous value, in that only trivial change in BW should occur if repositioning is accurate (21). All measurements were performed by one or other of two operators who both attained a precision of <1.5% at the proximal site and <2% at the distal site for all three measurements, and whose results for all six measurements in 50 metabolically stable patients measured at intervals of <1 yr were highly correlated ( $r > 0.99$ ) and did not differ significantly in mean value.

Bone biopsy specimens were obtained, embedded, and stained as previously described (22, 23). Using the Zeiss MOP-3 digitizing system, the areas of mineralized bone (MB), unmineralized bone or osteoid (OS), and soft tissue (ST) were measured separately in both cortices and in the entire medullary space; the transitional zone (24), if identifiable, was included with the latter. Mineralized bone volume (MBV), cortical or trabecular, as percent total (hard + soft) tissue (%TT) is given by  $\text{MB}/(\text{MB} + \text{OS} + \text{ST}) \cdot 100$  and total bone volume (TBV) in the same units, cortical or trabecular, is given by  $(\text{MB} + \text{OS})/(\text{MB} + \text{OS} + \text{ST}) \cdot 100$ . Relative osteoid volume (ROV) as percent total bone (%TB) is given by  $\text{OS}/(\text{MB} + \text{OS}) \cdot 100$ . Mean cortical width was determined by dividing the mean area of the two cortices by the mean of the inner and outer periosteal lengths, and trabecular tissue width similarly from the trabecular tissue area (Fig. 1). This method accurately corrects for varying obliquity of the biopsy core to the plane of the ilium, provided it has been taken from the correct zone with inner and outer borders parallel (22).

The absolute volumes of mineralized cortical and trabecular bone beneath the external bone surface, in cubic centimeters per square centimeter of periosteal area, are given by multiplying the combined cortical and the trabecular tissue widths, respectively, by the corresponding fractional MBV values. The absolute volumes when divided by total core width (combined cortical + trabecular tissue) give the relative volumes of mineralized cortical and trabecular bone in cubic centimeters per cubic centimeter of bone organ volume, equivalent to fractional MBV for the entire biopsy core. Both absolute and relative volumes of MB, when multiplied by appropriate values for BM density in grams per



**Figure 1.** Diagram of section through iliac bone biopsy. TCW, total core width (cm); PL, periosteal length (cm). Total section area = mean PL  $\times$  TLW. (ST + O) = area of soft tissue + osteoid (cm<sup>2</sup>). MB = area of mineralized bone (cm<sup>2</sup>), in both cases identified by subscript as cortical (C) or trabecular (T). CW, cortical width (cm), either outer (O) or inner (I). Combined cortical width (CCW) = CW<sub>O</sub> + CW<sub>I</sub> = ((ST + O)<sub>C</sub> + MB<sub>C</sub>)/mean PL. TTW, trabecular tissue width = ((ST + O)<sub>T</sub> + MB<sub>T</sub>)/mean PL. The different expressions of MBV are calculated as follows:

$$\text{Cortical MBV (\%)} = \text{MB}_C \times 100 / (\text{CCW} \times \text{mean PL});$$

$$\text{Cortical MBV (cm}^3/\text{cm}^2) = \text{MBV (\%)} \times \text{CCW}/100 = \text{MB}_C/\text{mean PL};$$

$$\text{Cortical MBV (cm}^3/\text{cm}^3) = \text{MB}_C/(\text{mean PL} \times \text{TCW}).$$

Note that in this context three-dimensional and two-dimensional units are interchangeable according to the DeLesse theorem (25). Similar calculations apply for trabecular MBV.

$$\text{Combined MBV (cm}^3/\text{cm}^2) = (\text{MB}_C + \text{MB}_T)/\text{mean PL};$$

$$\text{Combined MBV (cm}^3/\text{cm}^3) = (\text{MB}_C + \text{MB}_T)/(\text{mean PL} \times \text{TCW}).$$

cubic centimeter (15, 26, 27), give corresponding amounts of BM in grams per square centimeter periosteal area and grams per cubic centimeter bone organ volume. Allowing for differences in geometry, these quantities, with the cortical and trabecular components summed, are equivalent to radial BM in grams per centimeter and BM/BW in grams

per square centimeter, respectively. The missing dimension in the latter corresponds to the unmeasured vertical path length of the photon beam through the radius, and if this length is  $4/\pi$  (1.273) cm, which is not far from anatomic reality (28, 29), the individual iliac and radial values are exactly comparable. The derivation of total MBV with its different referents is further explained in the legend to Fig. 1.

The change in magnitude of mineral deficit at both ilium and radius as a result of treatment was determined by comparison with reference values. For iliac bone histomorphometry these values were obtained from 20 white women aged 36–72 yr (mean 55.2), who were either normal volunteers or patients with a mistaken radiologic report of osteoporosis later found to be free of metabolic bone disease. For radial SPA reference values were obtained in two ways: First, the decade-specific values obtained for white subjects in Wisconsin (30) were converted by interpolation to age-specific values, because age-related bone loss is a continuous rather than a stepwise process. The validity of using values from another state and of this interpolation were tested by comparing predicted with observed values in 293 white female patients aged 18–89 yr attending a general medical clinic, who on record review were found to be free of any disease or medication exposure known to affect bone. For proximal BM/BW the mean predicted and observed values were 0.678 and 0.674, respectively, and for distal BM/BW the corresponding values were 0.495 and 0.496. Reference values for blacks were obtained by applying the mean black/white ratio of 1.06 found for Michigan (31) to the age-specific Wisconsin values. The computations were carried out using the University of Michigan MIDAS system on a database established on the Wayne State University MTS system. Second, 28 persons from the same pool of medical clinic patients were individually and simultaneously matched for age (within 2 yr), sex, and race with the study group, with rematching in the same manner for the posttreatment measurements.

## Results

There was a small but significant fall in height and a 7% increase in mean body weight, the latter accounted for largely by the three transplant patients given corticosteroids and the two patients who underwent intestinal shunt revision. There was no significant change in mean BM, BW, or BM/BW at either the proximal or distal site (Table I); the 99% confidence limits for

**Table I.** Changes in Body Size and in SPA of the Radius during Treatment of Osteomalacia

Quantity	Pretreatment	Posttreatment	% Difference	P
Age (yr)	52.4 $\pm$ 2.9	54.4 $\pm$ 2.9	—	—
Height (cm)	165.5 $\pm$ 1.7	165.0 $\pm$ 1.6	−0.3	<0.05
Weight (kg)	62.7 $\pm$ 2.9	67.2 $\pm$ 3.8	+7.2	<0.05
Proximal				
BM (g/cm)	0.730 $\pm$ 0.048	0.731 $\pm$ 0.047	+0.13	NS
BW (cm)	1.292 $\pm$ 0.034	1.289 $\pm$ 0.034	−0.3	NS
BM/BW (g/cm <sup>2</sup> )	0.567 $\pm$ 0.033	0.570 $\pm$ 0.032	+0.5	NS
Adjusted for expected loss		0.578 $\pm$ 0.032	+1.91	<0.01
BM/BW (g/cm <sup>2</sup> ) (extended*)	0.578 $\pm$ 0.032	0.582 $\pm$ 0.030	+0.6	NS
Adjusted for expected loss		0.594 $\pm$ 0.029	+2.72	<0.01
Distal				
BM (g/cm)	0.703 $\pm$ 0.050	0.708 $\pm$ 0.050	+0.74	NS
BW (cm)	1.778 $\pm$ 0.050	1.777 $\pm$ 0.050	−0.01	NS
BM/BW (g/cm <sup>2</sup> )	0.402 $\pm$ 0.026	0.405 $\pm$ 0.029	+0.82	NS
Adjusted for expected loss		0.412 $\pm$ 0.025	+2.28	<0.02
BM/BW (g/cm <sup>2</sup> ) (extended*)	0.406 $\pm$ 0.027	0.409 $\pm$ 0.025	+0.6	NS
Adjusted for expected loss		0.417 $\pm$ 0.024	+2.75	<0.05

Data expressed as means $\pm$ SE ( $n$  = 28). Posttreatment values adjusted for expected loss owing to age by adding the individual differences in age predicted values. \* Changes during extended mean treatment period of 35.9 mo;  $n$  = 27, because the youngest subject experienced catch-up growth after the second biopsy.

the change in mean BM/BW were  $\pm 2.0\%$  at the proximal site and  $\pm 2.5\%$  at the distal site. Excluding the three patients treated with corticosteroids made no difference to the magnitude or lack of significance of the changes. Individual changes outside the 99% confidence limits occurred in four cases (three up, one down) at the proximal site (change  $> 5\%$ ), and in three cases (two up, one down) at the distal site (change  $> 6.5\%$ ). When adjustment was made for the fall expected with increase in age, there were significant increases in mean BM/BW of 1.9% at the proximal site and 2.3% at the distal site. Continued changes after the second biopsy were observed in several patients, and the number of significant deviations from base-line values rose to seven at the proximal site (five up, two down), and four at the distal site (three up, one down). But excluding the youngest patient, who experienced a catch-up growth spurt, results for the comparison of mean values were essentially unchanged by extending the duration of observation (Tables I and II). There was no significant difference between the changes at the proximal and distal sites, whether or not adjusted for expected loss owing to aging (Table II), but there was a highly significant correlation between the changes at the two sites, however expressed. Neither absolute nor age-adjusted values changed in the four excluded cases.

There was no significant change in total biopsy core width or in either of its components, combined cortical width or trabecular tissue width (Table III). There was a significant increase in cortical bone volume, representing a 25% reduction in mean intracortical porosity, but no change in trabecular bone volume. In both cortical and trabecular bone the relative osteoid volume fell by  $> 75\%$ , with corresponding increases in MBV. With normal values for cortical ROV of 0.4% and for trabecular ROV of 1.9%,  $> 80\%$  of the excess osteoid had mineralized (Table III). The properly weighted mean increase in MB for the entire biopsy core was  $\sim 18\%$ , whether the referent was periosteal surface area or total bone tissue volume (Table IV). Too few reference values were available to adjust the results for age in the same manner as with SPA. Both absolute and relative increases in total MBV were substantially higher in trabecular than in cortical bone, although the absolute gains in fractional MBV were similar (Ta-

Table II. Comparison of Proximal and Distal Increments in BM/BW during Treatment of Osteomalacia

Quantity	Proximal	Distal	P (difference)	r
Absolute increment (mg/cm <sup>2</sup> *)				
(nonage-adjusted)	2.9 $\pm$ 4.2	3.1 $\pm$ 3.4	NS	0.76§
Absolute increment (mg/cm <sup>2</sup> )				
(age-adjusted)	10.9 $\pm$ 3.8	9.0 $\pm$ 3.5	NS	0.75§
(extended‡)	15.9 $\pm$ 5.5	18.1 $\pm$ 5.2	NS	0.78§
Relative increment (%)				
(age-adjusted)	2.7 $\pm$ 0.9	3.4 $\pm$ 1.6	NS	0.82§
(extended‡)	3.9 $\pm$ 1.2	4.6 $\pm$ 2.0	NS	0.78§

Data expressed as means $\pm$ SE ( $n = 28$ ). Note that means of percent differences are not the same as percent differences in means.

\* Note use of smaller unit for more convenient location of decimal point.

‡ During extended mean treatment period of 35.9 mo ( $n = 27$ ).

§  $< 0.001$ .

Table III. Changes in Standard Histomorphometry of Ilium during Treatment of Osteomalacia

Quantity	Pre-treatment	Post-treatment	% Difference	P
Total biopsy core width (mm)	8.20 $\pm$ 0.51	8.28 $\pm$ 0.46	+1.0	NS
Combined cortical width (mm)	1.78 $\pm$ 0.14	1.78 $\pm$ 0.11	-0.3	NS
Trabecular tissue width (mm)	6.42 $\pm$ 0.39	6.50 $\pm$ 0.35	+1.2	NS
Cortical bone volume (%)	89.7 $\pm$ 1.1	92.2 $\pm$ 0.9	+2.8	$< 0.005$
Intracortical porosity (%)	10.3 $\pm$ 1.1	7.8 $\pm$ 0.9	-24.6	$< 0.005$
Cortical ROV (%)	6.05 $\pm$ 1.23	1.50 $\pm$ 0.32	-75.3	$< 0.001$
Cortical MBV (%)	84.5 $\pm$ 1.9	90.8 $\pm$ 1.1	+7.5	$< 0.001$
Trabecular bone volume (%)	18.2 $\pm$ 1.4	18.5 $\pm$ 1.3	+1.4	NS
Trabecular ROV (%)	30.1 $\pm$ 3.3	6.6 $\pm$ 1.1	-78.5	$< 0.001$
Trabecular MBV (%)	12.3 $\pm$ 0.9	17.2 $\pm$ 1.2	+40.3	$< 0.001$
Trabecular MBV <sub>c</sub> * (%)	12.4 $\pm$ 0.9	17.1 $\pm$ 1.1	+37.5	$< 0.001$

Data expressed as means $\pm$ SE.

\* Recalculated using means of pre- and posttreatment TBV to minimize effect of sampling variation on individual results.

ble V). The individual changes in the two types of tissue were significantly correlated. There was no correlation between the changes in any histologic index (cortical, trabecular, or combined), and the changes in any SPA index (proximal or distal), whether the changes were expressed in absolute or relative terms.

The values for SPA after treatment for two years are compared with reference values in Table VI. In subjects who did not differ in height, weight, or BW, as well as being matched for age, race, sex, and menopausal status, a substantial mineral deficit of 15–20% remained. The deficit was of similar relative magnitude at both proximal and distal sites, with or without division by BW, and whichever source of reference values was used. The posttreatment values for histomorphometry are compared with reference values in Table VII. Again, whether the referent was periosteal area or bone organ volume, a substantial deficit remained, which is underestimated because reference values for males and for blacks would be higher than for white females. The combined deficit was almost entirely accounted for by cortical thinning owing to increased net endosteal resorption. The resultant expansion of the marrow cavity offset the reduction in fractional trabecular MBV, so that total trabecular mineral, allowing for complete healing of the osteomalacia, was not significantly reduced.

Pre- and posttreatment mineral deficits at both sites of SPA in the radius and for both types of bone in the ilium are compared in Table VIII and Fig. 2. Both absolute and relative deficits were substantially greater in the ilium, representative of the axial skeleton, than in the radius, representative of the appendicular skeleton. The iliac deficits are likely underestimated, because in partially treated osteomalacia some of the histologically mineralized bone would not yet have attained normal mineral density.  $> 80\%$  of the initial mineral deficit in trabecular bone was reversible, but most of the deficit in cortical bone was irreversible and of substantial magnitude, amounting to more than one-third of the reference value (Fig. 3). At both proximal and distal radius sites, the SPA response to the disease process and to its treatment resembled that of pure cortical bone, the deficits being  $\sim 90\%$  irreversible. Both absolute and relative deficits were of

Table IV. Mineral Accumulation in the Ilium during Treatment of Osteomalacia

Quantity	Pretreatment	Posttreatment	% Difference	P
Cortical MBV ( $\text{cm}^3/\text{cm}^2$ )*	0.149±0.008	0.160±0.009	+7.5	<0.001
Cortical MBV ( $\text{cm}^3/\text{cm}^3$ )‡	0.189±0.012	0.203±0.012	+7.2	<0.001
Trabecular MBV <sub>C</sub> ( $\text{cm}^3/\text{cm}^2$ )*	0.077±0.006	0.109±0.009	+40.1	<0.001
Trabecular MBV <sub>C</sub> ( $\text{cm}^3/\text{cm}^3$ )‡	0.096±0.007	0.132±0.009	+39.2	<0.001
Combined MBV§ ( $\text{cm}^3/\text{cm}^2$ )*	0.226±0.010	0.269±0.013	+18.6	<0.001
Combined MBV <sup>  </sup> ( $\text{cm}^3/\text{cm}^3$ )‡	0.285±0.014	0.335±0.015	+17.5	<0.001

Data expressed as means±SE. \* Referent is periosteal surface area. ‡ Referent is total bone tissue volume. § If multiplied by bone mineral density in  $\text{g}/\text{cm}^3$ , comparable to BM in  $\text{g}/\text{cm}$ . <sup>||</sup> If multiplied by bone mineral density in  $\text{g}/\text{cm}^3$ , comparable to BM/BW in  $\text{g}/\text{cm}^2$ .

similar magnitude at the two sites, the latter about one-half of the corresponding deficit in the iliac cortex (Table VIII).

None of the analyses or conclusions were affected by subdividing the patients on the basis of age (16 > 50, 12 < 50), sex, race, or disease (14 with and 14 without intestinal malabsorption).

## Discussion

Designation of a BM deficit as irreversible is based on the response to correcting the primary pathologic process, and leaves open the possibility of restitution by some other treatment yet to be discovered. With this proviso, it is useful to classify a deficit as reversible or irreversible, because the anatomic basis and pathophysiology are different. Reversible deficits include an increase in temporarily missing bone, or remodeling space, owing to increased bone turnover (15) and accumulation of unmineralized osteoid tissue owing both to increased turnover and to impaired mineralization (17). Our histologic studies demonstrated both these components of the reversible deficit in the ilium; demonstration of the third component—incompletely mineralized bone—would require chemical analysis of bone tissue (32). The concept of remodeling space applies to trabecular as well as to cortical bone, but is more difficult to demonstrate because of different geometry and greater sampling variation. Irreversible deficits result from incomplete replacement of re-

sorbed bone at the completion of a remodeling cycle, or terminal remodeling imbalance (33). This is manifested in trabecular bone as reduced number and thickness of structural elements (34), and in cortical bone as incomplete radial closure leading to a permanent increase in porosity (27, 35). Most importantly, sub-endosteal cavitation is increased with eventual complete removal of the inner one-third to one-half of the cortex (34). The resultant cortical thinning was the major component of irreversible bone loss in the ilium in our study.

Applying these concepts to the radius, increased remodeling space and osteoid accumulation together amounted to only ~2% of the bone mineral at both proximal and distal measurement sites before treatment (Table I), about one-quarter as much as in the iliac cortex. Because there was the same relative increase in osteoid volume (~15-fold) in both cortical and trabecular bone in the ilium, it is likely that the magnitude of the reversible deficit is proportional to the previous rate of bone turnover. Mean iliac cortical bone turnover in our 20 normal subjects was 7.2%/yr, which suggests that normal bone turnover in the radius is about one-quarter as great, or ~2%/yr at both measurement sites, and including whatever trabecular bone is present at the distal site. This figure agrees closely with previous estimates of

Table V. Comparison of Cortical and Trabecular Increments in MBV during Treatment of Osteomalacia

	Cortical	Trabecular	P (difference)	r
Total MBV*				
( $\text{mm}^3/\text{cm}^2$ )‡				
Absolute increment	11.2±2.9	31.1±7.0	<0.001	0.69 <sup>  </sup>
Relative increment (%)	8.6±2.0	51.7±15.8	<0.01	0.55 <sup>††</sup>
Fractional MBV§ (%)				
Absolute increment	4.7±0.9	6.3±1.4	NS	0.60 <sup>  </sup>
Relative increment (%)	6.9±2.4	52.0±1.7	<0.01	0.47 <sup>**</sup>

Data expressed as means±SE.

\* Referent is periosteal surface area.

‡ Note use of smaller unit for more convenient location of decimal point.

§ Referent is tissue volume. Note difference between % as a unit of measurement and as an index of relative change.

<sup>||</sup>  $P < 0.001$ .

<sup>††</sup>  $P < 0.005$ .

<sup>\*\*</sup>  $P < 0.01$ .

Table VI. Comparison of Radial SPA between Treated Osteomalacia (n = 27) and Matched Normal Controls (n = 27)

	Post-treatment	Normal control	% Difference	P
Age (yr)	55.8±2.6	55.9±2.6	-0.2	—
Height (cm)	165.1±1.7	165.2±2.1	-0.1	NS
Weight (kg)	68.3±3.8	70.3±3.7	-2.8	NS
Proximal				
BM (g/cm)	0.746±0.046	0.924±0.044	-19.3	<0.001
BW (cm)	1.294±0.035	1.317±0.028	-1.7	NS
BM/BW ( $\text{g}/\text{cm}^2$ )	0.581±0.032	0.696±0.023	-16.5	<0.001
BM/BW ( $\text{g}/\text{cm}^2$ )	0.581±0.032	0.701±0.019*	-17.1	<0.001
Distal				
BM (g/cm)	0.715±0.051	0.932±0.046	-23.3	<0.001
BW (cm)	1.781±0.051	1.800±0.050	-1.1	NS
BM/BW ( $\text{g}/\text{cm}^2$ )	0.409±0.026	0.514±0.016	-20.4	<0.001
BM/BW ( $\text{g}/\text{cm}^2$ )	0.409±0.026	0.502±0.011*	-18.5	<0.001

Patient who subsequently experienced catch-up growth excluded.

\* Predicted from age-specific values in whites with adjustment for race as explained in text.

Table VII. Comparison of Iliac MBV between Treated Osteomalacia ( $n = 28$ ) and Normal White Female Controls ( $n = 20$ )

	Posttreatment	Normal control	% Difference	P
Age (yr)	54.4±2.9	55.5±2.0	-1.1	NS
Height (cm)	165.0±1.6	164.2±1.3	+0.5	NS
Weight (kg)	67.2±3.8	69.2±2.1	-2.9	NS
Total biopsy core width (mm)	8.24±0.44*	8.11±0.55	+1.6	NS
Combined cortical width (mm)	1.78±0.11	2.68±0.16	-33.6	<0.001
Cortical MBV ( $\text{cm}^3/\text{cm}^2$ )‡	0.160±0.009	0.251±0.016	-36.2	<0.001
( $\text{cm}^3/\text{cm}^3$ )§	0.203±0.012	0.327±0.021	-37.9	<0.001
	0.210±0.012 <sup>  </sup>	0.327±0.021	-35.8	<0.001
Trabecular MBV (%)	17.1±1.1	22.0±1.4	-22.3	<0.01
Trabecular MBV ( $\text{cm}^3/\text{cm}^2$ )‡	0.109±0.009	0.120±0.014	-9.2	NS
( $\text{cm}^3/\text{cm}^3$ )§	0.132±0.009	0.144±0.011	-8.3	NS
	0.138±0.009 <sup>  </sup>	0.144±0.011	-4.2	NS
Combined MBV ( $\text{cm}^3/\text{cm}^2$ )‡	0.269±0.013	0.372±0.025	-27.5	<0.001
	0.281±0.014 <sup>  </sup>	0.372±0.025	-26.0	<0.001
Combined MBV ( $\text{cm}^3/\text{cm}^3$ )§	0.335±0.018	0.471±0.019	-28.8	<0.001
	0.348±0.015 <sup>  </sup>	0.471±0.019	-26.1	<0.001

Data expressed as means±SE.

\* Mean of pre- and posttreatment.

‡ Referent is periosteal surface area.

§ Referent is total bone tissue volume.

<sup>||</sup> Recalculated with mean normal ROV and cortical porosity.

cortical bone turnover in the appendicular skeleton by a variety of methods (36). Although much higher values than 2%/yr have been frequently assumed for trabecular bone in the distal radius, bone turnover has never been measured at this site. A very low rate is consistent with the virtual absence of bone remodeling in trabecular bone adjacent to fatty rather than to hematopoietic marrow in dogs (37), and with the complete disappearance of hematopoietic marrow from the appendicular skeleton by age 25 in humans (38).

Clearly, this conclusion applies with certainty only to the measurement site we have chosen. The method of locating the distal site for a patient's first measurement is crude. The anatomic

landmark, in addition to being incorrectly named, varies considerably in ease of recognition and precise localization between subjects and in some papers is not even mentioned. Nevertheless, it seems unlikely that any user of the Norland-Cameron instrument could be exempt from our conclusion. No one locates the distal scanning site at a shorter distance from the external landmark, and measurements on forearm x-rays indicated a value for this distance in our study of  $1.42 \pm 0.22$  cm (mean±SD), not significantly different from the target value of 1.5 cm. Furthermore, malfunction of the instrument becomes increasingly common as the radioulnar joint is approached. A recent procedural modification dispenses with the external landmark and locates the distal site at a radius-ulna separation of 0.5 cm (39). In our study this separation measured on radiographs was  $0.77 \pm 0.18$  cm, and would have been less in the prone position used for SPA (40).

Rectilinear scanning of the distal forearm permits retrospective selection of the site of measurement depending on the desired radius-ulnar separation (41). Recent instrument changes by one manufacturer allow scanning to begin at 0.8-cm separation between radius and ulna and to proceed proximally in 0.4-cm steps (42). It is evident from a detailed study of the local anatomy that either none or at most one of the scanning paths is distal to our measurement site. Newer software, not yet generally available, permits scanning to proceed also in the reverse direction and measure closer to and possibly just beyond the radioulnar joint (42). The proportion of trabecular bone is higher at this site, 65% of the total, but even so trabecular bone accounts for only 42% of the variance in bone mineral (29). Furthermore, the correlation with spinal bone density determined by dual-energy photon absorptiometry is no better at this site than at the standard proximal site (43).

An even more distal site, closer to the radiocarpal joint, is accessible to computed tomography (CT), using one of several instruments designed specifically for this purpose (44-46). The results of such studies of the far distal radius, together with histologic measurements in patients with inflammatory arthritis (47), and the frequency with which bone scans are positive at the distal ends of long bones (48) all suggest that trabecular bone closely adjacent to synovial joints has a higher rate of turnover despite the absence of hematopoietic marrow, presumably reflecting a higher local blood flow. But measurements even at this far distal site correlate no better with vertebral CT than measurements at the radial midshaft (49). It is evident that treat-

Table VIII. Comparison of Mineral Deficits in Osteomalacia ( $n = 27$ ) between Radius and Ilium Sites, Adjusted for Bone Size

	Radius BM/BW		Ilium BM/BW*		
	Proximal	Distal	Cortical	Trabecular	Combined
	$\text{g}/\text{cm}^2$	$\text{g}/\text{cm}^2$	$\text{g}/\text{cm}^3$	$\text{g}/\text{cm}^3$	$\text{g}/\text{cm}^3$
Total deficit	0.135	0.103	0.163	0.055	0.219
Reversible deficit	0.015	0.010	0.022	0.044	0.066
% Total	11.1	9.7	13.2	80.4	30.2
Irreversible deficit	0.120	0.093	0.141	0.011	0.153
% Reference	17.1	18.5	36.1	6.3	27.0

Patient who experienced subsequent catch-up growth excluded. \* Assuming bone mineral density of  $1.2 \text{ g}/\text{cm}^3$  MB matrix volume (25). Deficits calculated for radius using interpolated values and assuming expected age-related change, and for ilium assuming restitution of normal ROV and cortical porosity.

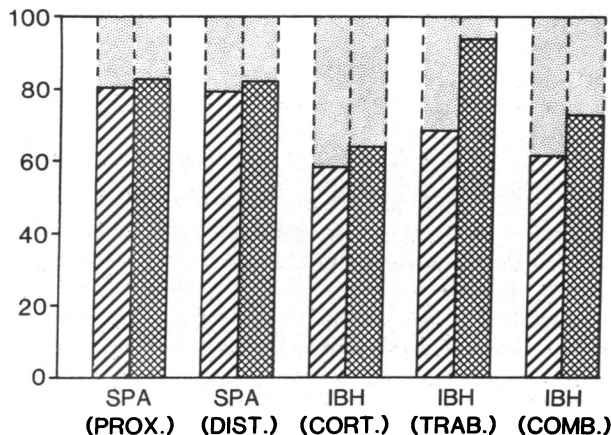


Figure 2. Effects of treatment of osteomalacia on mineral deficits. Data shown as percentage of expected value (as defined in text) before (first bar) and after (second bar) treatment. Lightly shaded areas indicate corresponding magnitudes of the deficits. SPA, single photon absorptiometry at proximal (prox.) and distal (dist.) sites. IBH, iliac bone histomorphometry of cortical bone (cort.), trabecular bone (trab.) and combined (comb.).

ing trabecular bone throughout the body as a single compartment, although an improvement on ignoring the distinction between trabecular and cortical bone altogether, is still a considerable oversimplification (9). There appear to be at least three functional subdivisions of trabecular bone with different rates of turnover, depending on proximity to red marrow, yellow marrow, or synovium, and probably an even larger number of structural subdivisions (50). Also, in view of the correlations within both ilium and radius, and lack of correlation between ilium and radius, for some purposes distinction between the axial and the appendicular skeleton may be as important as between trabecular and cortical bone.

In several earlier studies of serial SPA of the radius during treatment of disordered vitamin D metabolism, larger increases were reported than we have observed. Using the Norland instrument, the mean values in patients with rheumatoid arthritis receiving corticosteroids increased by ~2% at the proximal site and by 10–15% at the distal site after calcitriol 40–100 µg daily for 6 mo (51). Bone biopsies were performed in most patients and showed changes consistent with increased parathyroid hormone effect with only modest osteoid accumulation. Detailed histologic analysis of mineral replacement during treatment was not performed. No serial BW measurements were reported nor were any special precautions taken to exclude repositioning error

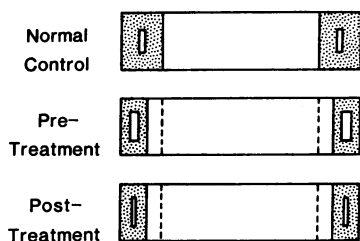


Figure 3. Reversible and irreversible mineral deficits in iliac cortical bone. Each panel represents a section through an iliac biopsy core, with the total width of the core and the width of cortical bone (shading) drawn to scale. Soft tissue and osteoid are shown as unshaded rectangles with relative areas drawn to scale. Vertical dashed lines show normal location of the cortical endosteal border.

as an explanation for the findings. For example, an apparent increase of 10% in distal BM/BW could be produced by making the second measurement only 0.15 cm more proximal than the first, assuming a 30° angle between the edge of the bone and its longitudinal axis. Trabecular bone turnover may have been increased by rheumatoid inflammation of the wrist joint, but this effect extends no >0.5 cm from the articular surface (47), far too small a distance to influence the distal measurement site. A similar study using the same measurement technique but with calcitriol instead of calcitriol showed no significant increase at either site (52).

Using an early form of rectilinear scanning, the mean value in epileptic patients receiving anticonvulsants increased by 4% after vitamin D<sub>2</sub> 2,000 U daily for 3 mo (53). Scanning began at a radius-ulnar separation of 0.25 cm (54) and precision was 2–4% (53). Bone biopsies were not performed, but histologic studies in other anticonvulsant-treated patients have shown increased bone remodeling probably due to secondary hyperparathyroidism rather than osteomalacia (55). Using a more recent instrument with improved precision of 1–2% and scanning more proximally (56), a smaller increase of 2% was found in anticonvulsant-treated patients given a higher dose of vitamin D<sub>2</sub> (4,000 U/d) for a longer period of time (24 wk), a rate of increase only one-quarter of that in the earlier study (57). The same relative increase was found in total body calcium, which supports our interpretation that the increase in radial BM resulted from a fall in cortical porosity rather than from mineralization of osteoid.

We demonstrated significant irreversible bone loss in our patients. The mean posttreatment value at both sites of photon absorptiometry was close to the expected value for white women at age 70, indicating acceleration of bone loss equivalent to ~15 yr of normal aging (Fig. 2), and even more if sex and race are considered. The mean posttreatment iliac-combined cortical thickness was slightly but not significantly lower than in 51 hip fracture patients with mean age 74 yr (1.78 vs. 1.82 mm, unpublished data), an acceleration of loss equivalent to at least 20 yr of normal aging (Fig. 3). Losses of such magnitude must inevitably increase fracture risk. The bone at the proximal radial measurement site is almost entirely cortical, and in both the humeral (27) and femoral (35) shafts age-related bone loss in females is due almost entirely to cortical thinning with only a small contribution from increased porosity (33). Furthermore, the rate of fall with age at the proximal site is very similar to the rate of fall of metacarpal cortical thickness (58). Consequently, increased loss at the proximal site in the present study could only have been due, as in the ilium, to cortical thinning resulting from increased net endosteal resorption.

The similarity of the changes at the distal measurement site to those at the proximal site with respect to extent and proportion of reversible loss, and absolute and relative extent of irreversible loss, together with our inference of a very low rate of turnover in trabecular bone at this site, suggest that the anatomic basis for irreversible bone loss is the same at the distal as at the proximal site. Further evidence is provided by the close similarity of posttreatment deficits in distal radial BM (10.2%) and total body calcium (9.2%) in anticonvulsant-treated patients given vitamin D (57). This conclusion is consistent with our demonstration that the magnitude of irreversible bone loss in the ilium was much greater in cortical than in trabecular bone, even though the rate of turnover was lower. The explanation for this apparent paradox is that cortical bone loss is the result of events on the cortical–endosteal surface, which behaves differently both in

health and in disease from either the trabecular or the intracortical surfaces (13, 59).

Our conclusion is at variance with the claim by several investigators that in some disease states relatively greater deficits at the distal measurement site result from its higher proportion of trabecular bone (5, 10–12, 51, 60). The same criticism can be made as for the related claims of unusually large increases in response to treatment—in none of the studies has equivalence of BW at the site of measurement between patients and controls been demonstrated. Even if a relatively greater deficit at the distal site could be convincingly established by more rigorous methods, it need not have anything to do with trabecular bone. Because cortical bone is thinner at the distal than at the proximal site, the same absolute reduction in cortical thickness would represent a greater proportional change at the distal than at the proximal site. There is in fact no evidence that the proportion of trabecular bone at the distal site has any relevance to the interpretation of measurements made at that site, or to how such measurements change in response to age, disease, or treatment, despite the repeated assertion of this assumption. Until such evidence is forthcoming, the utility of measurements on the distal radius but proximal to the radioulnar joint, whether for diagnosis or for clinical investigation, will remain unestablished (61).

By contrast, the utility of proximal radius measurements is strengthened by our data. Although recent enthusiasm for measurements on the axial skeleton is appropriate, it must not be forgotten that appendicular cortical bone constitutes at least 50% of skeletal mass (58), that age-related loss of this bone is a major determinant of the age-related increase in long bone fractures (62), and that SPA of the proximal radius still represents the best trade-off between precision and availability for the assessment of appendicular cortical bone status (63), and is an excellent predictor of total body bone mass (64). The cortical bone deficits that we found are indicative of substantially increased fracture risk, so that their pathogenesis is of some importance. Several lines of evidence suggest that these deficits most likely result from prolonged secondary hyperparathyroidism, which was either demonstrated or could be inferred with reasonable certainty in 26 of the 28 patients. Substantial bone loss and secondary hyperparathyroidism can both be found in patients with intestinal malabsorption of vitamin D and calcium long before they develop osteomalacia (65) and the same pattern of bone loss as was found in the present study is characteristic of primary hyperparathyroidism (66). Furthermore, accelerated cortical bone loss has been found in every form of secondary hyperparathyroidism in which appropriate studies have been made (67). Because secondary hyperparathyroidism is easy to correct, its early recognition in asymptomatic patients at risk in conjunction with proximal radial SPA offers the best hope of preventing irreversible damage to the skeleton of the kind we have demonstrated.

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