

Differential Effects of Endocrine Dysfunction on the Axial and the Appendicular Skeleton

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ABSTRACT In 100 patients with various types of endocrine dysfunction, we measured bone mineral density (BMD) at the midradius (>95% cortical bone) and distal radius (75% cortical and 25% trabecular bone) by single photon absorptiometry and at the lumbar spine (>66% trabecular bone) using the new technique of dual photon absorptiometry. BMD in each endocrine disorder deviated in at least one site from the sex-specific age regression of 187 normal subjects. For patients with primary hyperparathyroidism, hypercortisolism, and hyperthyroidism this deviation was negative (suggesting bone loss), whereas for patients with secondary hyperparathyroidism due to chronic renal failure, acromegaly, and postsurgical hypoparathyroidism it was positive (suggesting bone gain). When all six states of endocrine dysfunction were compared concomitantly by multivariate analysis of variance, the profile of the changes in BMD differed significantly ($P < 0.001$), indicating a nonuniform response of bone to the various hormonal alterations. When values for BMD at each of the three scanning sites were compared, the midradius and distal radius did not differ significantly; either of the radius measurements, however, differed significantly ($P < 0.001$) from the lumbar spine. Thus, the BMD of the axial skeleton cannot be reliably predicted from measurements made in the appendicular skeleton. We conclude that the effects of endocrine dysfunction on bone density are complex and are both disease and site specific.

INTRODUCTION

Parathyroid hormone, cortisol, thyroxine, and growth hormone affect bone remodeling and, thereby, can

alter skeletal mass. Alterations in bone mineral density (BMD)¹ resulting from states of hormonal dysfunction have previously been studied only in the appendicular skeleton. In a few instances, total body calcium has been measured by neutron-activation analysis; these results, in general, have agreed with those of appendicular measurements. Both appendicular and total body calcium measurements, however, are relatively insensitive to changes in trabecular bone, especially when these changes occur in the axial skeleton. The appendicular skeleton is composed predominantly of cortical bone, whereas the axial skeleton contains large amounts of trabecular bone (1). Moreover, because the whole skeleton contains 85% cortical but only 15% trabecular bone (2), changes in trabecular bone would have a relatively small effect on total body calcium measurements. If changes in density of cortical and trabecular bone and changes in circulating hormones occurred *pari passu* in all regions of the skeleton, BMD measurements of the appendicular skeleton would suffice. There are several reasons for believing, however, that BMD measurements of the axial skeleton will be required to characterize definitively the skeletal effects of states of endocrine dysfunction. First, the metabolic activity of the two bone types differs considerably: cortical bone has a turnover rate of only 3%/yr (3), whereas trabecular bone has a turnover rate of up to 30%/yr (4). Second, autopsy studies have shown good correlation for BMD among sites containing large amounts of cortical bone but a poorer correlation between BMD of these sites and that of the vertebrae (5). Third, in most metabolic bone diseases, fractures occur almost exclusively at skeletal sites that contain substantial amounts of trabecular bone.

These considerations led us to examine the possi-

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Received for publication 7 December 1981 and in revised form 16 February 1982.

¹ Abbreviations used in this paper: BMC, bone mineral content; BMD, bone mineral density; iPTH, immunoreactive parathyroid hormone.

bility that states of hormonal dysfunction have differential effects on the appendicular and axial skeleton. We tested this hypothesis by making concurrent measurements of BMD in both regions of the skeleton in patients with primary hyperparathyroidism, secondary hyperparathyroidism due to chronic renal failure, hypercortisolism, hyperthyroidism, acromegaly, and postsurgical hypoparathyroidism.

METHODS

Patients. We studied 100 patients with endocrine dysfunction. There were 29 patients (21 female and 8 male) with primary hyperparathyroidism. In 26 of them, the diagnosis was confirmed by surgical removal of a parathyroid adenoma; in the remaining 3, the diagnosis was based on clinical and laboratory criteria, including hypercalcemia and an elevated level of serum immunoreactive parathyroid hormone (iPTH). 21 patients presented with asymptomatic hypercalcemia, and 8 presented with nephrolithiasis; none presented because of bone disease. The mean serum calcium concentration was 11.6 mg/dl (range, 10.3–14.4) (normal range, 8.9–10.1). The mean serum iPTH level was 156 μ eq/ml (range, 39–2,200) (normal range, <75) when antiserum GP-235 was used. This antiserum has major immunologic determinants for the carboxyl-terminal portion of the PTH molecule. Five patients had elevated values for serum alkaline phosphatase. Three had vertebral compression fractures. Fine-grain hand roentgenograms were obtained in 11 of the patients; none had subperiosteal bone resorption.

There were 14 patients (seven female and seven male) with secondary hyperparathyroidism due to chronic renal failure. The renal failure was caused by chronic glomerulonephritis (seven patients), diabetes (four patients), analgesic abuse (one patient), polycystic kidney disease (one patient), and unknown causes (one patient). 10 patients were undergoing chronic hemodialysis. In these patients, the mean serum iPTH level was 1,022 μ eq/ml (range, 200–2,400). Four patients with chronic renal failure were treated with dietary protein restriction and phosphate binding gels without hemodialysis. In these latter patients, the mean glomerular filtration rate was 32 ml/min per 1.73 m² (range, 17–50) and the mean serum iPTH value was 145 μ eq/ml (range, 130–160). 3 of the 14 patients received a preparation of vitamin D. Three of seven patients who had fine-grain hand roentgenograms had subperiosteal bone resorption. None had vertebral compression fractures, and two had roentgenographically apparent osteosclerosis.

There were 17 patients (11 female and 6 male) with chronic hypercortisolism. The condition was endogenous in seven patients (due to an adrenocorticotrophic hormone-secreting pituitary tumor in six and to idiopathic bilateral adrenal hyperplasia in one). For this group, the mean value for morning plasma cortisol was 34 μ g/dl (range, 31–38) (normal range, 7–28) and mean value for urinary free cortisol was 685 μ g/24 h (range, 146–1,032) (normal range, 24–108). 10 patients had exogenous hypercortisolism due to oral administration of prednisone (mean dose 30 mg/d, range, 5–80) for a mean of 2.3 yr (range, 1–3 yr). The reasons for treatment were temporal arteritis (three patients), chronic obstructive pulmonary disease (five patients), pemphigus (one patient), and rheumatoid arthritis (one patient). 11 of the 17 patients had vertebral compression fractures.

There were 13 patients (11 female and 2 male) with hy-

perthyroidism due to diffuse toxic goiter (Graves' disease). The mean serum thyroxine level was 19.0 μ g/dl (range, 11.6–32.6) (normal range, 5.0–13.5). The estimated mean duration of hyperthyroidism was 13 mo (range, 2–30).

There were seven patients (five female and two male) with acromegaly. All had active disease by clinical and laboratory criteria, and none had clinical or laboratory evidence of other endocrine abnormalities. None had vertebral compression fractures. The mean basal value for serum growth hormone was 102 ng/ml (range, 30–200) (normal range: men <5, women <10).

20 patients (16 female and 4 male) had hypoparathyroidism occurring as a complication of a surgical procedure for localized thyroid carcinoma (15 patients) or nontoxic goiter (5 patients), conditions not expected to affect BMD. We did not include patients who became hypoparathyroid as a result of operation for primary hyperparathyroidism or hyperthyroidism because these conditions might have caused accelerated bone loss. The median age of patients at the time of study was 62 yr (range, 29–86) and 12 of them were postmenopausal women. The median duration of hypoparathyroidism was 17 yr (range, 7–36). Hypoparathyroidism was diagnosed on the basis of clinical features including paresthesias of the lips and fingers, positive Chvostek's sign, and Trousseau's sign associated with hypocalcemia; these symptoms recurred if therapy was discontinued. All were receiving supplementary calcium (1–3 g/d), vitamin D (50,000 U/d or its equivalent), and levothyroxine (150–250 μ g/d). All were euthyroid by standard clinical and laboratory criteria. None of the hypoparathyroid patients had vertebral compression fractures.

All patients were unselected except for meeting the diagnostic criteria defined above. Patients with primary hyperparathyroidism, secondary hyperparathyroidism due to chronic renal failure, hypercortisolism, hyperthyroidism, and acromegaly were recruited and studied during their medical evaluation at the Mayo Clinic. Patients with postsurgical hypoparathyroidism were residents of southern Minnesota who had had medical consultation at the Mayo Clinic within the preceding 5 yr. The patients were identified through the medical records and invited to participate in the study.

Results for BMD in patients with endocrine dysfunction were compared with previously published (6) normative data from 187 normal subjects (105 women and 82 men; age range, 20–89 yr). The percentile distribution for normals was determined nonparametrically.

Bone densitometry. BMD was determined at the midradius and at the distal radius, 2 cm above the styloid process, by using single photon absorptiometry as described by Cameron and Sorenson (7). In our laboratory, the technique has a coefficient of variation of 3% for the midradius and 3–5% for the distal radius (8). Bone mineral content (BMC) of the lumbar spine was determined by dual photon absorptiometry, with use of our modification (6, 9) of the method of Mazess et al. (10). Radiation transmission scanning of the L₁–L₄ region of the lumbar spine was done by using two separate photon energies (44 and 100 keV) from a ¹⁵³Gd source. The use of a dual energy source permits calculation of BMC by elimination of the soft tissue contribution to radiation transmission. BMD, expressed in grams per square centimeter, was computed by dividing BMC by the projected area of the spine. Edge-detection, point-by-point BMD measurements, and data acquisition were computer-assisted. The technique has a coefficient of variation of 2.3%.

The approximate composition of bone at the three scanning sites is as follows (8, 11): midradius (>95% cortical

TABLE I
Mean BMD for Each Scanning Site, Expressed as Positive or Negative Standard Deviations from the Age- and Sex-specific Normal Mean

Group	No.	Lumbar spine	Midradius	Distal radius
Normal subjects	187	0.00	0.00	0.00
Primary hyperparathyroidism	29	-1.15*	-0.45	-0.92†
Secondary hyperparathyroidism (chronic renal failure)	14	0.11	1.15§	0.02
Hypercortisolism	17	-1.94*	0.29	-0.33
Hyperthyroidism	13	-0.82*	-0.70	-0.67
Acromegaly	7	0.68†	0.83	0.41
Postsurgical hypoparathyroidism	20	1.50*	0.70†	0.68§

* $P \leq 0.001$.

† $P \leq 0.01$.

§ $P \leq 0.05$.

bone), distal radius (75% cortical and 25% trabecular bone), and lumbar spine (>66% trabecular bone).

Statistical methods. To investigate the changes of BMD at each scanning site and at two or three sites concomitantly, we used linear regression, two-sample univariate and multivariate t tests, and paired t tests. These comparisons were made within and across states of endocrine dysfunction. All P values reported were two-tailed.

In order to compare men and women of varying ages, individual BMD values were expressed as standard deviation from the predicted mean for normal subjects obtained from regression equations that predicted the bone density as a function of age. The SD corresponds to "standardized departures from normal," "standardized deviations," or z -scores. Separate regression equations were used for men and for women. The BMD difference (observed minus predicted mean) divided by $S_{y,x}$ (the estimate of the variability about the fitted regression line) is the SD. By definition, the mean SD from the sex-specific age regression for normal subjects

is zero. The methods described in the Statistical Analysis System (12) were used to carry out all statistical computations.

RESULTS

Comparison of patients with endocrine dysfunction and normal subjects. Table I gives mean values for SD at three scanning sites for each of the six states of endocrine dysfunction. Individual values are displayed graphically in Fig. 1A and B. For patients with primary hyperparathyroidism, the mean SD was negative at all three scanning sites and was significantly less than zero at the distal radius and the lumbar spine. For patients with secondary hyperparathyroidism, the mean SD was positive at all three scanning sites but

TABLE II
Comparison of BMD Values among the Three Scanning Sites for Each Endocrine Disorder*

Group	Midradius minus lumbar spine†		Distal radius minus lumbar spine†		Midradius minus distal radius†	
Primary hyperparathyroidism	(+)	0.03	(+)	NS	(+)	NS
Secondary hyperparathyroidism	(+)	0.05	(+)	NS	(+)	NS
Hypercortisolism	(+)	<0.001	(+)	<0.001	(+)	NS
Hyperthyroidism	(+)	NS	(+)	NS	(+)	NS
Acromegaly	(+)	NS	(-)	NS	(+)	NS
Postsurgical hypoparathyroidism	(-)	0.001	(-)	0.002	(+)	NS

* The variables of interest are the standard deviation from normal (observed - predicted/ $S_{y,x}$ in normals).

† Two-tail P value associated with the paired t test for significance of the mean difference between the two scanning sites. The sign of the mean difference for the positive or negative deviation (in SD) from normal is given in parentheses. Thus, a parenthetical plus sign indicates that the algebraic differences of the first minus the second term for a given column is positive.

significantly so only for the midradius. For patients with hypercortisolism, there was a striking disparity between results obtained at appendicular and axial scanning sites. The mean SD was slightly positive at the midradius but slightly negative at the distal radius. Neither value was significantly different from zero. By contrast, the lumbar spine had a large and highly significant negative value for the mean SD. In fact, this was the largest mean deviation, positive or negative, seen among any of the six endocrine disorders. In patients with hyperthyroidism, the mean SD was negative at all three scanning sites but significantly so only for the lumbar spine. For patients with acromegaly, the mean SD was positive at all three scanning sites but significantly so only at the lumbar spine. Finally, for patients with postsurgical hypoparathyroidism, the mean SD was positive and significantly greater than zero at all three scanning sites. For the lumbar spine, all patients but one male had BMD values >50th percentile, and half of them, including two octogenarian women, had values >95th percentile for age- and sex-comparable normal persons.

When the three scanning sites were analyzed separately, each endocrine disorder had at least one site at which mean SD was significantly different from zero; this was the lumbar spine in five of the six endocrine disorders, the midradius in two of the six, and the distal radius in two of the six.

Comparison of changes in BMD values among the three measurement sites. Table II evaluates how well the individual scanning sites agree with each other in assessing deviations of BMD (in SD) from normal. The midradius and distal radius agreed well and did not differ significantly from each other. The midradius and lumbar spine agreed poorly and differed significantly from each other in four of the six endocrine disorders. Agreement between the distal radius and lumbar spine was intermediate; two of the six endocrine disorders had significant differences. Over all of the six states, when all three scanning sites were analyzed concomitantly by multivariate analysis of variance, the profile of changes in BMD differed significantly ($P < 0.001$).

Global pattern of BMD changes among states of endocrine dysfunction. We next assessed whether the profile of BMD changes from normal for the three measurement sites considered concomitantly was comparable among states of endocrine dysfunction. By profile, we mean the relationship of these changes (in SD) among the three sites. Comparability of profile implies that the relationship of the changes in SD among the three sites remains constant across the states of endocrine dysfunction regardless of the level of the SD or whether the deviation in SD is positive or negative. Differences in profile induced by various states

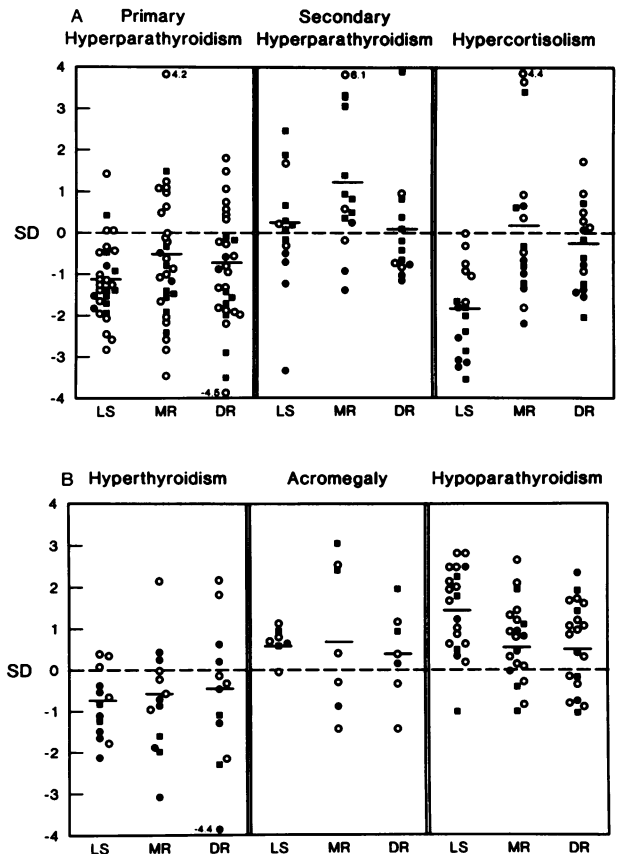


FIGURE 1 Individual values for bone mineral density, in six types of endocrine dysfunction, given for lumbar spine (LS), midradius (MR), and distal radius (DR) scanning sites for males (■) and premenopausal (●) and postmenopausal (○) females. Units are standard deviations from predicted mean for normal subjects obtained from sex-specific regression equations that predicted the bone density as a function of age. A, Primary hyperparathyroidism, secondary hyperparathyroidism, and hypercortisolism. B, Hyperthyroidism, acromegaly, and postsurgical hypoparathyroidism. The means are indicated by the short horizontal lines.

of endocrine dysfunction, therefore, cannot be explained by quantitative differences in the level of bone turnover among the different states, but rather imply that different regions of the skeleton respond differently to the various hormonal alterations. Using multivariate analysis of variance, we found significant differences among disease states ($P < 0.001$) in the profile of the mean SD. Thus, changes in BMD at the three measurement sites were not comparable, i.e., these did not occur in parallel across the six states of endocrine dysfunction.

Comparison of states of endocrine dysfunction with each other. Finally, we assessed whether each state of endocrine dysfunction could be separate from

TABLE III
Multivariate Comparisons of Means among All Possible Pairs of the Six Disease States*

	P values†				
	Secondary hyperparathyroidism	Hypercortisolism	Hyperthyroidism	Acromegaly	Postsurgical hypoparathyroidism
Primary hyperparathyroidism	0.002	0.011	(NS)	<0.001	<0.001
Secondary hyperparathyroidism	—	<0.001	0.022	(NS)	0.003
Hypercortisolism	—	—	0.022	<0.001	<0.001
Hyperthyroidism	—	—	—	0.001	<0.001
Acromegaly	—	—	—	—	<0.001

* The variables of interest are the standard deviation from normal (observed – predicted/ $S_{y \cdot x}$ in normals) for BMD of the lumbar spine and the midradius.

† Two-tail *P* value associated with multivariate two-sample *t* test for the significance of the difference between all possible pairs of the six states of endocrine dysfunction. Significant differences between a given pair of disease states means that the profile of changes in BMD among the three scanning sites did not change in parallel.

the others by considering simultaneously the mean values of SD for the midradius (predominantly cortical bone) and the lumbar spine (predominantly trabecular bone). These results are given in Table III and Fig. 2. Of the 15 pairs of comparisons, 12 were significantly different and, therefore, were distinguishable from each other. There was, however, considerable overlap for individual values.

DISCUSSION

Although many investigators have measured BMD in states of endocrine dysfunction, these measurements have not included the predominantly trabecular bone of the axial skeleton. In the present study, we compared values for BMD of the lumbar spine obtained using the new method of dual photon absorptiometry to values for the mid- and distal radius obtained concomitantly using single photon absorptiometry. With use of multivariate analysis of variance, we found significant differences in the response of bone among the scanning sites. This variability may explain some of the divergent findings reported in the medical literature for studies in which BMD was measured in endocrine and metabolic diseases at different sites in the skeleton.

The reasons for the differential response of appendicular and axial regions of the skeleton to changes in endocrine function presently are unclear. We believe, however, that regional differences in the proportional content of cortical and trabecular bone are part of the explanation. The agreement in values for deviations of BMD from normal in the various endocrine disorders was best for the midradius and distal radius, was intermediate for the distal radius and lumbar spine,

and was poorest for the midradius and lumbar spine. This rank order parallels the rank order for their proportional content of cortical and trabecular bone.

Previous measurements of BMD in primary hyperparathyroidism have been mainly restricted to appendicular bone. Pak et al. (13) found significant decreases in BMD of the distal radius in postmenopausal women with primary hyperparathyroidism, and 22 of the 29 patients in the present study had BMD values <50th percentile. Hahn et al. (14) and Parfitt et al. (15) also reported that hyperparathyroid patients had larger decreases in BMD in the distal portion than in the diaphyseal portion of the radius. Dalén and Hjern (16), using x-ray spectrophotometry to study hyperparathyroid patients, found that bones with a large trabecular component had significant decreases, whereas sites composed predominantly of cortical bone generally did not show significant changes. Loss of metacarpal cortical bone in hyperparathyroid patients has been found by using radiogrammetry (17, 18). In the present study, we found that BMD was substantially decreased at the lumbar spine, moderately decreased at the distal radius, and nonsignificantly decreased from the midradius. Thus, available data suggest that PTH excess has a greater effect in regions of predominantly trabecular bone. This is consistent with the clinical studies of Dauphine et al. (19), who showed that hyperparathyroidism increased the occurrence of vertebral fractures, particularly in postmenopausal women.

In contrast to findings in primary hyperparathyroidism, BMD was not decreased in patients with secondary hyperparathyroidism complicating chronic renal failure; indeed BMD at the midradius was significantly elevated. Although spinal osteosclerosis is rare in primary hyperparathyroidism (20), it occurs

in up to 20% of patients with secondary hyperparathyroidism resulting from renal failure (20, 21). Appendicular BMD values in secondary hyperparathyroidism have been found to be normal (21), increased (22), or decreased (18). Thus, the presence of normal or increased BMD despite marked elevations of serum iPTH suggests the presence of factors in chronic renal failure that oppose the catabolic effect of PTH excess.

The greatest disparity between values for BMD in the axial and in the appendicular skeleton was found in patients with hypercortisolism. All of them had axial BMD values that were ≤ 50 th percentile of normal, and 8 of the 17 had values that were < 5 th percentile. Hahn et al. (14) found that patients with exogenous hypercortisolism had lost proportionally more bone from the metaphysis than from the diaphysis of the radius (and, thus, presumably had lost more trabecular than cortical bone). Doyle (23) found minimal appendicular bone loss in patients with hypercortisolism despite vertebral fractures. These previously reported observations and the results that we obtained by directly measuring appendicular and axial BMD suggest that hypercortisolism causes severe and disproportionate loss of trabecular bone.

Hyperthyroidism is a recognized cause of osteoporosis and vertebral compression fractures (24). It is, therefore, somewhat surprising that studies of BMD in the appendicular skeleton have shown only marginal decreases (25). Our data suggest that part of the explanation for this discrepancy is that an excess of thyroid hormone causes greater bone loss from the axial than from the appendicular skeleton.

Albright and Reifstein (26) listed acromegaly as a cause of osteoporosis, as have contributors in many subsequent textbooks of medicine and endocrinology. More recent studies assessing BMD of the appendicular skeleton by photon absorptiometry (27) and total body calcium by neutron-activation analyses (28), however, have reported increased values. Nonetheless, the possibility remained that acromegaly increased cortical bone but decreased trabecular bone. The small number of patients with active acromegaly studied by us, however, had significant increases in BMD of the predominantly trabecular bone of the lumbar spine. Thus, osteopenia in acromegaly must be rare and, when it occurs, most probably can be explained by the presence of concurrent hypogonadism or by other complicating factors.

In patients with postsurgical hypoparathyroidism, we found a greater increase of BMD in the axial than in the appendicular skeleton. Investigators who have made metacarpal cortical area measurements by radiogrammetry have reported that bone mass was similar to that of normal subjects (17), but was higher than

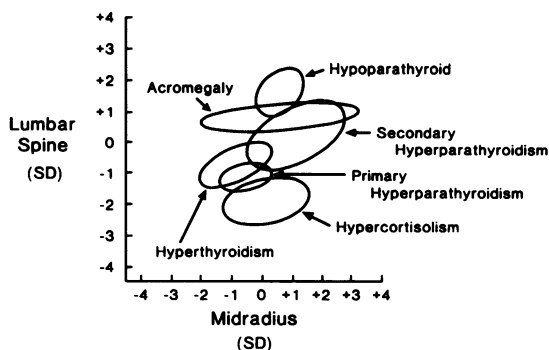


FIGURE 2 Relationship between BMD of midradius (appendicular cortical bone) and lumbar spine (axial, predominantly trabecular bone) for each of the six disease categories. Ellipses represent 95% confidence limits for the means. Units are standard deviations from predicted mean for normal subjects obtained from sex-specific regression equations that predicted the bone density as a function of age.

values obtained in patients with primary hyperparathyroidism (18). We believe that the failure of these studies to demonstrate unequivocally increased bone mass in hypoparathyroidism was due to measuring BMD only at appendicular sites composed mainly of cortical bone. Our study also differs from theirs by our exclusion of patients in whom hypoparathyroidism developed as a result of a surgical procedure for hyperthyroidism or hyperparathyroidism, conditions that may decrease BMD.

The hypoparathyroid patients in our study differed from the normal control subjects in several ways: they were deficient in PTH, they were presumably deficient in calcitonin, and they were receiving treatment with vitamin D, calcium, and thyroid hormone. We believe, nonetheless, that the observed increase in BMD was mainly, if not entirely, due to the effect of PTH deficiency. Calcitonin deficiency, if it has any effect on the skeleton, would be expected to increase bone loss. Vitamin D therapy alone has been shown to increase bone loss when administered to patients with spinal osteoporosis, whereas calcium therapy slowed the rate of bone loss but failed to increase bone mass (29). Also, untreated hypothyroidism has been found to be associated with increased appendicular BMD in some (30, 31), but not other studies (25). There is evidence that patients treated with physiologic replacement doses of thyroid hormone do not have increased bone mass (30). Only three of our patients were hypothyroid at any stage of their medical supervision.

With the exception of one male patient, our patients with hypoparathyroidism had higher BMD in the axial skeleton at any age than the predicted mean for normal control subjects. This was also true for those hypo-

parathyroid subjects who were postmenopausal women, including two octogenarians. This observation suggests that PTH deficiency protects against age-related bone loss. This protective effect could result from a permanent cessation or near cessation of bone loss, or it could reflect an early gain of bone during the immediate years after onset of hypoparathyroidism followed by continued loss but from a higher level of BMD. Because our study was cross-sectional, we could not distinguish between these alternatives.

In conclusion, our data show that bone density of the appendicular and axial skeleton changes differentially in response to endocrine dysfunction and that the induced alterations in BMD are both site and disease specific. These changes reflect regional differences in the profile of skeletal response rather than merely differences in the level of bone turnover. Thus, the mechanisms by which endocrine dysfunction affects bone are complex and BMD measurements in the appendicular skeleton do not reliably predict BMD measurements of the lumbar spine. Definitive characterization of BMD changes induced by an endocrine or metabolic disorder, therefore, mandates assessment of both the appendicular and the axial skeleton.

ACKNOWLEDGMENT

We thank Dr. Hunter Heath III for his assistance and many helpful suggestions.

This work was supported in part by research grants AM-27065, AM-25409, AM-26808, U. S. Public Health Service, National Institute of Arthritis, Metabolism and Digestive Diseases.

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