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Preserved Three-dimensional Cancellous Bone Structure in Mild Primary Hyperparathyroidism

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Abstract

By conventional 2-dimensional, histomorphometric analysis, we and others have previously shown that cancellous bone architecture is preserved in mild primary hyperparathyroidism (PHPT). We have now extended these observations to a 3-dimensional analysis using microcomputed tomography (microCT). Iliac crest bone biopsies were analyzed from the following subjects with PHPT: 22 postmenopausal women; 7 premenopausal women; similar numbers of normal pre- and postmenopausal women served as controls. Fifteen men with PHPT were also studied. Postmenopausal women with PHPT demonstrated features of preserved cancellous bone as shown by smaller age-related declines in cancellous bone volume (BV/TV) and connectivity density (Conn.D) and no change in bone surface/total volume (BS/TV) as compared to normal women. In postmenopausal women with PHPT, cancellous bone volume (BV/TV), bone surface/total volume, and connectivity density (Conn.D) were all higher, and trabecular separation (Tb.Sp) was lower than in postmenopausal controls. In sharp contrast to the findings in normal women, no structural variables in PHPT women were correlated with age. Also of note, there was no difference in any 3-dimensional index between women and men with PHPT.

We conclude that three-dimensional, cancellous bone microarchitecture is preserved in patients with mild primary hyperparathyroidism.

Keywords

Primary Hyperparathyroidism; Bone Microarchitecture; Histomorphometry

INTRODUCTION

By conventional, 2-dimensional histomorphometric analysis of the bone biopsy specimen, we and others have shown previously that cancellous bone microarchitecture is preserved in patients with mild primary hyperparathyroidism (PHPT) (1–11). However, conventional 2-dimensional histomorphometry has a number of inherent limitations when used to assess

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microarchitecture (12). For example, the primary morphometric data are obtained on a small number of sections, representing only a fraction of the biopsy volume. Any 3-dimensional indices are extrapolated values from primary measurements. Microcomputed tomography of the bone biopsy specimen overcomes these limitations by allowing direct 3-dimensional analysis of the entire biopsy. Applying this more complete analysis of the bone biopsy specimen would be expected, therefore, to provide additional and more direct data in these subjects than can be achieved by our former 2-dimensional approach.

MATERIALS AND METHODS

Percutaneous iliac crest bone biopsies were obtained from patients with mild PHPT. Their clinical characteristics and histomorphometric profiles have previously been published in detail (2–5,9). The cohort that underwent biopsy was representative of the entire study group. They included 44 patients with PHPT: 7 premenopausal women, aged 26–49; 22 postmenopausal women, aged 47–74; 15 men, aged 28–68; 15 normal premenopausal women, aged 27–37; and 5 normal postmenopausal women, aged 51–66. All biopsies were fixed and dehydrated in ethanol, embedded in polymethylmethacrylate. Bone histomorphometry was performed as previously described (2–5,9). All variables were calculated and expressed according to the guidelines of the ASBMR nomenclature committee (13). The study was approved by the Institutional Review Boards of Columbia University Medical Center and Helen Hayes Hospital. Written, informed consent was given by all subjects.

The embedded samples were analyzed by microCT using a μ CT40 imaging system (Scanco Medical, Bassersdorf, Switzerland) with a nominal resolution of 10 μ m. The variables and method of analysis are described in full by Hildebrand et al (14).

Data are expressed as mean $\pm$ SEM. The significance of differences between 2 groups was assessed using two-sample *t*-tests. Linear regression analysis was performed between the microCT variables and age in normal women or women with PHPT, and between 3-dimensional microCT and 2-dimensional histomorphometric variables of bone structure. Statistical analysis was performed using the NCSS 2004 program (Kaysville, Utah, USA).

RESULTS

Bone microarchitecture in normal women

Normal postmenopausal women had reduced cancellous bone volume (BV/TV), and bone surface/total volume (BS/TV) but increased bone surface/bone volume (BS/BV), compared to normal pre-menopausal women. These changes were associated with a decrease in trabecular number (Tb.N) and connectivity density (Conn.D) and an increase in trabecular separation (Tb.Sp) with a trend towards a decrease in trabecular thickness (Tb.Th) (Figure 1, Table 1). Correlation between these structural variables and age demonstrated that increasing age is associated with a decrease in BV/TV, BS/TV, Tb.N and Conn.D but an increase in Tb.Sp in normal women (Figure 2).

Bone microarchitecture in women and men with PHPT

Postmenopausal women with PHPT demonstrated features of preserved cancellous bone structure, as evidenced by smaller age-related declines in BV/TV and Conn.D, and no change in BS/TV, as compared to normal women. In postmenopausal women with PHPT, BV/TV, BS/TV, and Conn.D were all higher, and Tb.Sp was lower than in postmenopausal controls. There were no differences in any of the measured variables between premenopausal women with PHPT and normal premenopausal women (Figure 1, Table 1). In sharp contrast to the findings in normal women, structural variables in women with PHPT were not significantly

correlated with age (Figure 2). Also of note, there was no difference in any 3-dimensional index between women and men with PHPT (Table 1).

Relationship of microCT and histomorphometric variables of bone structure

Variables of cancellous bone structure as assessed by microCT were highly correlated with those assessed by conventional histomorphometry. Although there were small systematic differences in some of the indices when the same parameters assessed by 2-dimensional or 3-dimensional approaches were compared to each other (BV/TV, Tb.Th, Tb.Sp), the correlations were consistently high (Figure 3).

DISCUSSION

Over the past 25 years, bone histomorphometry has played an important role in elucidating the skeletal effects of mild, asymptomatic PHPT with regard to structure and cellular activity. One unexpected finding by others and us is that, despite a significant increase in bone turnover in mild PHPT, cancellous bone microstructure is conserved, compared to that in age-matched controls (1–11). These findings are consistent with relative preservation of bone mineral density in cancellous bone, a site that illustrates the proclivity of PTH to be anabolic. This observation contrasts with cortical skeletal sites in which PHPT is classically associated with bone loss. (2,15,16). However, conventional 2-dimensional bone histomorphometry has a number of acknowledged limitations when used to assess microarchitecture (12). Chief among these limitations is that the data are obtained from a few sections, representing only a small fraction of the biopsy volume. Extrapolations to 3-dimensional indices can only be inferential. Microcomputed tomography of the bone biopsy specimen overcomes these limitations because the analysis is direct and includes the entire sample. Using this technique, we have confirmed and extended our previous observations, as well as those from other laboratories (1–11), suggesting that cancellous bone microstructure is truly conserved in mild PHPT. Specifically, we found that 3-dimensional indices of cancellous bone structure, such as cancellous bone volume and trabecular connectivity do not decline and trabecular separation does not increase as a function of age and menopause in women with mild PHPT.

These results further emphasize the idea that all high turnover states are not necessarily detrimental to bone structure. If bone balance is negative at the level of the bone remodeling unit (BRU), it follows that the higher the turnover, the greater the expected loss of structural integrity. This is typically the case in the postmenopausal, estrogen-deficient woman. On the other hand, if bone balance at the BRU level is not negative, or even positive, then high turnover will be associated with maintenance or improvement of structural features. When PTH is used as a therapy for osteoporosis, increased turnover is associated with improved bone balance. The only formal studies of bone balance that have been conducted in PHPT help to confirm that it is normal or increased. Eriksen et al (1) reported a 20% lower final resorption depth in 19 patients with PHPT (6 men and 13 women of mean age 47 yr). This was accompanied by a smaller, 8.8% reduction in wall width as compared to normal subjects. Bone balance was calculated to be zero or slightly positive. In a study of 23 women, aged 50 yr or greater, Christiansen et al. (6) reported normal values for resorption depth, wall width and bone balance in PHPT. Two other studies have, in fact, reported increased wall width in postmenopausal women with PHPT (8,9), suggesting that the effects of continuously elevated PTH may not be too different in this respect from that observed with daily injections of low-dose PTH, when used as a treatment for osteoporosis (17–19).

This study is limited by the relatively small sample size of both patient and control groups. Despite these limitations, agreement between identical variables measured in 2-dimensional histomorphometry or 3-dimensional microcomputed tomography was excellent.

In conclusion, cancellous bone microarchitecture is relatively well preserved in mild PHPT, a finding now confirmed by 3-dimensional microcomputed analysis of bone biopsy specimens.

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References

1. Eriksen EF, Mosekilde L, Melsen F. Trabecular bone remodeling and balance in primary hyperparathyroidism. *Bone* 1986;7:213–21. [PubMed: 3768200]
2. Silverberg SJ, Shane E, De La Cruz L, Dempster DW, Feldman F, Seldin D, Jacobs TP, Siris ES, Cafferty M, Parisien MV, Lindsay R, Clemens T, Bilezikian JP. Skeletal disease in primary hyperparathyroidism. *J Bone and Mineral Res* 1989;4:283–291.
3. Parisien M, Silverberg SJ, Shane E, De La Cruz L, Lindsay R, Bilezikian J, Dempster DW. The histomorphometry of bone in primary hyperparathyroidism: Preservation of cancellous bone structure. *J Clin Endocrinol Metab* 1990;70:930–938. [PubMed: 2318948]
4. Parisien MV, Mellish RWE, Silverberg SJ, Shane E, Lindsay R, Bilezikian JP, Dempster DW. Maintenance of cancellous bone connectivity in primary hyperparathyroidism: trabecular strut analysis. *J Bone Miner Res* 1992;7:913–919. [PubMed: 1442205]
5. Parisien M, Cosman F, Mellish RWE, Schnitzer M, Nieves J, Silverberg SJ, Shane E, Kimmel D, Recker RR, Bilezikian JP, Dempster DW. Bone structure in postmenopausal hyperparathyroid, osteoporotic and normal women. *J Bone Min Res* 1995;10:1393–1399.
6. Christiansen P, Steiniche T, Vesterby A, Mosekilde L, Hesse I, Melsen F. Primary hyperparathyroidism: iliac crest trabecular bone volume, structure, remodeling, and balance evaluated by histomorphometric methods. *Bone* 1992;13:41–9. [PubMed: 1581108]
7. van Doorn L, Lips P, Netelenbos JC, Hackeng WH. Bone histomorphometry and serum concentrations of intact parathyroid hormone (PTH(1–84)) in patients with primary hyperparathyroidism. *Bone Miner* 1993;23:233–42. [PubMed: 8148668]
8. Vogel M, Hahn M, Delling G. Trabecular bone structure in patients with primary hyperparathyroidism. *Virchows Arch* 1995;426:127–34. [PubMed: 7757282]
9. Dempster DW, Parisien M, Silverberg SJ, Liang X-G, Schnitzer M, Shen V, Shane E, Kimmel DB, Recker R, Lindsay R, Bilezikian JP. On the mechanism of cancellous bone preservation in postmenopausal women with mild primary hyperparathyroidism. *J Clin Endocrinol Metab* 1999;84:1562–1566. [PubMed: 10323380]
10. Uchiyama T, Tanizawa T, Ito A, Endo N, Takahashi HE. Microstructure of the trabecula and cortex of iliac bone in primary hyperparathyroidism patients determined using histomorphometry and node-strut analysis. *J Bone Miner Metab* 1999;17:283–8. [PubMed: 10575593]
11. Steiniche T, Christiansen P, Vesterby A, Ullerup R, Hesse I, Mosekilde LE, Melsen F. Primary hyperparathyroidism: bone structure, balance, and remodeling before and 3 years after surgical treatment. *Bone* 2000;26:535–43. [PubMed: 10773596]
12. Muller R, Van Campenhout H, Van Damme B, Van Der Perre G, Dequeker J, Hildebrand T, Rueggsegger P. Morphometric analysis of human bone biopsies: a quantitative structural comparison of histological sections and micro-computed tomography. *Bone* 1998;23:59–66. [PubMed: 9662131]
13. Parfitt A, Drezner M, Glorieux F, Kanis J, Malluche H, Meunier P, Ott S, Recker R. Bone histomorphometry: standardization of nomenclature, symbols, and units. Report of the ASBMR Histomorphometry Nomenclature Committee. *J Bone Miner Res* 1987;2:595–610. [PubMed: 3455637]
14. Hildebrand T, Laib A, Muller R, Dequeker J, Rueggsegger P. Direct three-dimensional morphometric analysis of human cancellous bone: microstructural data from spine, femur, iliac crest, and calcaneus. *J Bone Miner Res* 1999 Jul;14(7):1167–74. [PubMed: 10404017]

15. Chen Q, Kaji H, Iu MF, Nomura R, Sowa H, Yamauchi M, Tsukamoto T, Sugimoto T, Chihara K. Effects of an excess and a deficiency of endogenous parathyroid hormone on volumetric bone mineral density and bone geometry determined by peripheral quantitative computed tomography in female subjects. *J Clin Endocrinol Metab* 2003;88:4655–8. [PubMed: 14557436]
16. Charopoulos I, Tournis S, Trovas G, Raptou P, Kaldrymides P, Skarandavos G, Katsalira K, Lyrilis GP. Effect of primary hyperparathyroidism on volumetric bone mineral density and bone geometry assessed by peripheral quantitative computed tomography in postmenopausal women. *J Clin Endocrinol Metab* 2006;91:1748–53. [PubMed: 16492695]
17. Hodsman AB, Kiesel M, Adachi JD, Fraher LJ, Watson PH. Histomorphometric evidence for increased bone turnover without change in cortical thickness or porosity after 2 years of cyclical hPTH(1–34) therapy in women with severe osteoporosis. *Bone* 2000;27:311–8. [PubMed: 10913928]
18. Dempster DW, Cosman F, Kurland ES, Zhou H, Nieves J, Woelfert L, Shane E, Plavetic K, Müller R, Bilezikian JP, Lindsay R. Effects of daily treatment with parathyroid hormone on bone microarchitecture and turnover in patients with osteoporosis: a paired biopsy study. *J Bone Miner Res* 2001;16:1846–1853. [PubMed: 11585349]
19. Ma YL, Zeng Q, Donley DW, Ste-Marie LG, Gallagher JC, Dalsky GP, Marcus R, Eriksen EF. Teriparatide increases bone formation in modeling and remodeling osteons and enhances IGF-II immunoreactivity in postmenopausal women with osteoporosis. *J Bone Miner Res* 2006;21:855–64. [PubMed: 16753016]

A. Premenopausal Normal
BV/TV = 30.3%

B. Postmenopausal Normal
BV/TV = 21.1%

C. Premenopausal PHPT
BV/TV = 30.5%

D. Postmenopausal PHPT
BV/TV = 25.3%

Figure 1.

Three-dimensional reconstructions of cancellous bone from premenopausal (A) and postmenopausal (B) normal women, and premenopausal (C) and postmenopausal (D) women with PHPT. Note the loss of microarchitectural integrity in the postmenopausal normal woman and its preservation in the postmenopausal woman with PHPT.

Figure 2.
Correlation between variables of cancellous bone microarchitecture and age in normal women (left) and women with PHPT (right).

Figure 3.
Correlation between 2-dimensional and 3-dimensional variables of cancellous bone structure.

Table 1
Cancellous Bone Micro-architecture in Normal Subjects and Patients with PHPT

MicroCT Variables	Pre-M Women		Post-M Women		Men
	Normal n=15	PHPT n=7	Normal n=5	PHPT n=22	PHPT n=15
BV/TV%	32.39 ± 2.21	34.28 ± 5.05	17.02 ± 3.34 ^a	25.66 ± 2.16 ^{a,c}	24.61 ± 1.77
BS/TV mm ² /mm ³	4.33 ± 0.13	4.69 ± 0.32	2.83 ± 0.48 ^{aa}	4.14 ± 0.16 ^{bb}	4.05 ± 0.24
BS/BV mm ² /mm ³	13.98 ± 0.73	14.74 ± 1.29	17.44 ± 1.50 ^a	17.15 ± 0.70 ^a	16.92 ± 0.69
Tb.Th mm	0.20 ± 0.01	0.20 ± 0.02	0.16 ± 0.02	0.17 ± 0.01	0.18 ± 0.01
Tb.Sp mm	0.50 ± 0.02	0.56 ± 0.04	0.84 ± 0.10 ^{aa}	0.66 ± 0.03 ^{aa,b}	0.69 ± 0.04
Tb.Nl/mm	1.80 ± 0.07	1.76 ± 0.14	1.34 ± 0.15 ^{aa}	1.51 ± 0.09 ^a	1.44 ± 0.07
Conn.DI/mm ³	10.97 ± 1.56	16.29 ± 4.70	4.28 ± 1.06 ^{aa}	10.24 ± 1.63 ^b	10.92 ± 2.32

Significant differences,
^a : p < 0.05 and
^{aa} : p < 0.01 when compared to normal premenopausal women;
^b : p < 0.05,
^{bb} : p < 0.01 and
^c : p=0.06, when compared to normal postmenopausal women.