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Three Dimensional Cancellous Bone Structure in Hypoparathyroidism

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Abstract

By conventional 2-dimensional histomorphometric analysis, we have shown that cancellous bone architecture is markedly altered in hypoparathyroidism. We have now extended these observations to a 3-dimensional analysis using microcomputed tomography. Percutaneous iliac crest bone biopsies were analyzed by high-resolution microcomputed tomography from the following 25 subjects with hypoparathyroidism: 5 postmenopausal women, 13 premenopausal women and 7 men. Thirteen living premenopausal healthy controls and 12 cadaver subjects without bone disease served as matched controls. Hypoparathyroid subjects had significantly greater bone surface density (BS/TV: 5.74 ± 4.7 vs. 3.73 ± 1.01 mm²/mm³ [mean $\pm$ SD]; $p=0.04$), trabecular thickness (Tb.Th: 0.25 ± 0.19 vs. 0.17 ± 0.04 mm; $p=0.04$), trabecular number (Tb.N: 2.99 ± 3.4 vs. 1.62 ± 0.39 mm⁻¹; $p=0.05$) and connectivity density (Conn.D: 16.63 ± 18.7 vs. 8.39 ± 5.8 mm³; $p=0.04$) in comparison to matched controls. When an additional 8 hypoparathyroid (total $n=33$) and 24 cadaver (total cadaver $n=36$) subjects were added to the groups for an unmatched analysis, hypoparathyroid subjects had significantly greater cancellous bone volume (BV/TV: 26.98 ± 10 vs. $15.39 \pm 4\%$; $p<0.001$), while trabecular separation (Tb.Sp: 0.642 ± 0.10 vs. 0.781 ± 0.13 mm; $p<0.001$) and estimation of the plate-rod characteristic (SMI: -0.457 ± 1.52 vs. 0.742 ± 0.51 ; $p<0.001$) were significantly lower, the latter observation implying a more plate-like trabecular structure. Variables of cancellous bone structure in the hypoparathyroid subjects, as assessed by microcomputed tomography, were highly correlated with those assessed by conventional histomorphometry. We conclude that cancellous bone in hypoparathyroidism is abnormal, suggesting that parathyroid hormone is required to maintain normal trabecular structure. The effect of these structural changes on bone strength remains to be determined.

Keywords

hypoparathyroidism; microcomputed tomography; parathyroid

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Introduction

Hypoparathyroidism, a disorder in which PTH is low or absent, is associated with unusual structural and dynamic features of bone ¹. Using conventional 2D histomorphometry, iliac crest bone biopsy samples from hypoparathyroid subjects were recently found to display significant alterations in several indices of cancellous microarchitecture, including increased cancellous bone volume and trabecular width ¹. Conventional 2-dimensional histomorphometry is a powerful research tool but it has an inherent limitation when it is used to assess skeletal microarchitecture ². Specifically, the primary morphometric data are obtained on a relatively small number of sections, which represent only a fraction of the biopsy volume. Moreover, all 3-dimensional indices are extrapolated from primary measurements made in 2 dimensions. Microcomputed tomography (microCT) of the bone biopsy specimen overcomes this limitation by allowing direct 3-dimensional analysis of the entire biopsy specimen. We have now applied this more complete analysis to our hypoparathyroid bone biopsy samples so as to provide additional and more direct data than could be achieved by a 2-dimensional approach alone.

Materials and Methods

Subjects

33 subjects with documented hypoparathyroidism underwent percutaneous iliac crest bone biopsies. The 2D histomorphometric data have been published on these subjects ¹. Patients were recruited from the Metabolic Bone Diseases Unit of Columbia University Medical Center and from the Hypoparathyroidism Association. The diagnosis of hypoparathyroidism was established by the simultaneous presence of serum calcium and PTH concentrations below the lower limits of normal on at least 2 occasions, separated by an interval of at least 30 days. Hypoparathyroidism had to have been present for at least 3 years, so as to establish a chronic state of PTH deprivation. Patients were excluded if they had adrenal insufficiency or autoimmune gastrointestinal disease. Patients were also excluded if they had been on a bisphosphonate within 5 years prior to study entry or for greater than 6 months duration at any time, if they were women within 5 years of onset of menopause, or if they used any of the following medications: estrogens, progestins, raloxifene, calcitonin, systemic corticosteroids, fluoride, bisphosphonates, lithium, statins, loop diuretics, or methotrexate. Patients with potentially confounding disorders were also excluded (Paget's disease of bone, diabetes mellitus, chronic liver or renal disease, acromegaly, Cushing's syndrome, rheumatoid arthritis, or multiple myeloma).

The control group consisted of 13 living premenopausal healthy controls. In addition to the living controls samples, trabecular bone samples that were collected as part of the European BIOMED-I project *Assessment of Quality of Bone in Osteoporosis* ³ from 36 human cadaver samples were included. All samples were prepared in a standardized fashion from the anterior-superior part of the iliac crest and were fixed in phosphate buffered formaldehyde. The study was approved by the Institutional Review Boards of Columbia University Medical Center and the ethical committee of the Catholic University of Leuven, Belgium. Written, informed consent was given by all living subjects.

Micro-computed tomography

Prior to embedding for histomorphometric analysis, samples were analyzed by high-resolution microCT. The microtomographic imaging system (μ CT 40, Scanco Medical AG, Brüttisellen, Switzerland) was equipped with a 5 μ m focal spot X-ray tube as a source. A two-dimensional CCD, coupled to a thin scintillator as a detector permitted acquisition of 210 tomographic images in parallel. The long axis of the intact biopsy was oriented along the rotation axis of

the scanner. The X-ray tube was operated at 50 kVp and 160 μ A with an integration time set to 200 ms and all projection frames were recorded 6 times and then averaged. Scans were performed at an isotropic, nominal resolution of 8 μ m (high resolution mode).

The whole intact biopsy was scanned, which resulted in an average scan height of 10 mm and a measurement time of approximately 10 hours. A cylindrical volume of interest was then placed in the digital image data to select the trabecular bone compartment. The mineralized tissue was segmented from soft tissue by a global thresholding procedure ⁴, with a threshold value set to 34% of the maximum grayscale value.

Bone surface (BS) area was calculated using the marching cubes method to triangulate the surface of the mineralized bone phase 5. Bone volume was calculated using tetrahedrons corresponding to the enclosed volume of the triangulated surface 6. Total volume (TV) was the volume of the sample that was examined. To compare samples of varying size, normalized indices, BV/TV and BS/TV, were used. Trabecular thickness was determined by filling maximal spheres into the structure with distance transformation 7 and then calculating the average thickness of all bone voxels. Trabecular separation was calculated by the same procedure, except the voxels representing non-bone tissue were filled with maximal spheres. Trabecular number was calculated as the inverse of the mean distance between the mid-axes of the trabeculae.

Connectivity density, which expresses the number of connections per cubic millimeter, was derived from the Euler number ⁸ as follows: $\text{ConnD} = (1 - \text{Euler number})/\text{TV}$. The Euler number (χ) is fundamental to all determinations of connectivity. In cancellous bone, it is defined as follows ⁹: $\chi = \beta_0 - \beta_1 + \beta_2$, where β_0 is the number of bone particles (traditionally assumed to be 1); β_1 is the connectivity, that is, the maximum number of connections that must be broken to split the structure into two parts; and β_2 is the number of marrow cavities fully surrounded by bone. The higher the value the more connections are present in the structure.

The Structure Model Index (SMI) is an estimation of the plate-rod characteristic of the structure ¹⁰. SMI is calculated by a differential analysis of a triangulated surface and is defined as $\text{SMI} = 6\{[BV(dBS/dr)]/BS^2\}$, where dBS/dr is the surface area derivative with respect to a linear measure r , corresponding to the half thickness or the radius assumed constant over the entire structure. This derivative is estimated by a simulated thickening of the structure by translating the triangulated surface by a small extent in its normal direction and dividing the associated change of surface area with the length of the extent. For an ideal plate and rod structure the SMI value is 0 and 3, respectively. For a structure with both plates and rods of equal thickness, the value is between 0 and 3, depending on the volume ratio between rods to plates. Negative values are possible and denote a structure resembling a Swiss cheese structure with voids fully encapsulated by the surrounding bone.

Bone histomorphometry

After completion of microCT scans, the hypoparathyroid biopsy specimens were processed, sectioned and stained following established procedures ¹¹. Histomorphometric analysis used a digitizing image-analysis system, consisting of a high-resolution three-chip color video camera, a tablet, a computer and its display, and a morphometric program (OsteoMeasure Version 4.00C, OsteoMetrics, Inc, Atlanta, GA). All variables were expressed and calculated according to the recommendations of the American Society for Bone and Mineral Research ¹².

Conventional indices of bone structure were evaluated on Goldner-stained, 7- μ m-thick sections. The cancellous bone volume (BV/TV), trabecular width (Tb.Th), trabecular number (Tb.N), and trabecular separation (Tb.Sp) were derived from the 2-dimensional measurement

of total tissue area, cancellous bone area, and perimeter using stereological techniques, and assuming a parallel plate model¹³. The measurements of bone structure parameters were performed at x20 magnification.

Statistical analysis

Data are expressed as mean $\pm$ SD. The significance of differences between two groups was assessed using two-sample *t*-tests. The groups were compared in 2 ways: 1) 25 hypoparathyroid subjects as compared to 25 age- and sex-matched controls, and 2) 33 hypoparathyroid subjects as compared to 36 non-matched controls. A Pearson's correlation coefficient was used to assess the relationship between 3-dimensional microCT and 2-dimensional histomorphometric variables of bone structure. All statistical analyses were performed using SPSS for Windows (version 11.0; SPSS, Chicago, IL).

Results

Hypoparathyroid Subjects

The characteristics of the 33 hypoparathyroid subjects are presented in Table 1. All were Caucasian, except for one Hispanic postmenopausal woman and one Asian postmenopausal woman. All subjects were receiving calcium and vitamin D, and on this replacement therapy most had normal calcium values; a few subjects had serum calcium levels below the lower limits of normal. All patients had previously been well documented to have hypoparathyroidism by concomitant hypocalcemia and low PTH levels. TSH was measured in 14 of the 18 postsurgical subjects. The mean TSH was 5.9 ± 16 uU/ml (nl range: 0.34-4.25 uU/ml). 6 of the postsurgical patients had hyperthyroidism postoperatively and 2 had hypothyroidism postoperatively. Of the 6 hyperthyroid postsurgical subjects, TSH levels were undetectable (<0.03 uU/ml) in 3 but were measurable in the other 3 (0.21, 0.23, 0.04 uU/ml).

Controls

The living premenopausal control group consisted of 13 healthy women without bone disease, ranging in age from 27 to 38 years (mean 32 ± 4 years). The cadaver control group consisted of 13 females and 23 males, with ages ranging from 35 to 87 years (mean 71 ± 12 years) 3· 14· 15. The main causes of death were cardiovascular diseases (n= 14), respiratory diseases (n= 9), and cerebrovascular attacks (n= 6); the remaining causes of death were sepsis (n=5), dehydration (n=1) and postoperative multi-organ failure (n=1). Subjects who had a history of a vertebral, hip or forearm fracture were excluded, as were subjects who possibly had a condition that could affect the bone (organ transplantation, malignancy, liver failure or amyotrophic lateral sclerosis). For 25 of the hypoparathyroid subjects, a matched control biopsy was available, either from a living premenopausal woman (n=13) or from a postmenopausal cadaver female control (n=5) or a male cadaver control (n=7).

Bone microarchitecture in hypoparathyroidism

Visualization of the hypoparathyroid samples revealed trabecular plates that were substantially increased in both number and thickness; representative images from a subject with hypoparathyroidism and a control subject are shown in Figure 1.

Primary indices

In the matched analysis (n=25 per group), bone surface density (BS/TV) was significantly higher in comparison to controls (Table 2). In the unmatched analysis (n= 33 hypoparathyroid subjects and n= 36 cadaver controls), bone volume fraction (BV/TV) and bone surface-volume-ratio (BS/BV) were also significantly higher in comparison to controls (Table 3).

Directly assessed indices

In the matched analysis, trabecular thickness (Tb.Th) and trabecular number (Tb.N) were both significantly higher in comparison to controls (Table 2). In the unmatched analysis, trabecular separation (Tb.Sp), was additionally significantly lower in the hypoparathyroid subjects (Table 3).

Directly assessed nonmetric indices

In the matched analysis, Connectivity density (Conn D), a parameter that estimates the number of trabecular connections per mm³, was markedly elevated (Table 2). In the unmatched analysis, the Structure Model Index (SMI), a parameter that assesses the plate-rod characteristic in trabecular bone, was additionally abnormally low. This parameter typically ranges from 0 (most plate-like) to 3 (most rod-like). In the hypoparathyroid subjects, the SMI was negative, consistent with a higher proportion of plate-like structures and even the occurrence of encapsulated void spaces (Table 3).

Relationship of microcomputed tomography and histomorphometric variables of bone structure

Variables of cancellous bone structure as in the hypoparathyroid subjects assessed by microCT were significantly correlated with those assessed by conventional histomorphometry (Figure 2).

Discussion

Hypoparathyroidism is characterized by unusual structural and dynamic properties of bone, accompanied by an increase in bone mineral density¹. By conventional 2-D histomorphometric assessment, we have previously observed that subjects with hypoparathyroidism have greater cancellous bone volume (BV/TV) and trabecular width (Tb.Wi) in comparison to matched controls. Using 3-dimensional microcomputed analysis, we now confirm and extend our previous findings, demonstrating that cancellous bone is markedly abnormal in hypoparathyroidism.

Over the past 3 decades, conventional 2D quantitative histomorphometry of transiliac crest bone biopsies has provided a wealth of information about bone microarchitecture in a number of important metabolic bone diseases, such as postmenopausal osteoporosis¹⁶, osteoporosis in men¹⁷, primary hyperparathyroidism¹⁸, renal bone disease¹⁹ and idiopathic osteoporosis in premenopausal women²⁰. Using 2D histomorphometry, indices such as cancellous bone volume (BV/TV) and surface density (BS/BV) are directly obtained from 2D images. However, indices such as trabecular thickness (Tb.Th), trabecular separation (Tb.Sp), and trabecular number (Tb.N) are indirectly derived measurements, with the assumption of a fixed structural model¹⁴. Because trabecular bone might have a variable structure within a single biopsy sample, extrapolation of 2D analyses to 3-dimensional quantities might be inferential or even misleading². Microcomputed tomography of the bone biopsy specimen overcomes these limitations because the analysis is truly volumetric (3-dimensional), direct and encompasses the entire biopsy specimen.

In this study, examination of each structural parameter by 3-dimensional microCT revealed marked changes in cancellous microarchitecture. In comparison to controls, hypoparathyroid subjects had significantly greater cancellous bone volume (BV/TV), with markedly increased trabecular number (Tb.N) and trabecular thickness (Tb.Th) and lower trabecular separation (Tb.Sp). Connectivity density (Conn D), a parameter that estimates the number of trabecular connections per mm³, was markedly elevated. Even more dramatic was the low value for the estimation of the plate-rod characteristic (Structure Model Index; SMI). This parameter reflects

the relative proportions of plate-and rod-like structures in trabecular bone, ranging from 0 (most plate-like) to 3 (most rod-like). In hypoparathyroid subjects, the negative value for SMI was consistent with an unusually dominant plate-like structure. A transition from a rod-like to a plate-like structure typically enhances bone strength^{21, 22}, leading to the expectation that bone strength on this basis, should be augmented with the plate-like bone of hypoparathyroidism. . The markedly increased connectivity density might also be associated with increased bone strength. In addition, the increased mass of bone might confer higher stiffness and compressive strength.

Other aspects of this analysis suggest that bone strength might actually be compromised in this disorder. For example, thickening of trabecular bone could compromise bone strength by reducing resilience²³. In normal bone, the elastic properties of trabecular bone allow the skeleton to absorb energy by deforming reversibly when loaded²⁴⁻²⁵. Although the greater mineral content in the hypoparathyroid bone might produce greater material stiffness, it may do so at the expense of the ability of the bone to deform and thus absorb and dissipate energy²³. Without elastic deformation, it is possible that hypoparathyroid bone could be vulnerable to structural failure. While increased connectivity density might be a positive feature (see above), it could also theoretically exacerbate this problem, predisposing the bone to develop microcracks or fracture when it is loaded.

The data thus present two contrasting biomechanical elements that could lead to weaker or stronger bone in hypoparathyroidism. Since prospective data on fracture incidence is not available in this disorder, we cannot be sure. The technique of finite element analysis which has been regarded as a surrogate marker of bone strength²⁶⁻²⁸ might offer insight into this important question. It is also possible that abnormalities in thyroid status might have contributed to the bone abnormalities that were detected. Hyperthyroidism, which was present in 6 out of 14 postsurgical subjects, can contribute to bone loss^{32, 33}. However, the hypoparathyroid bone abnormalities that we found were consistent with gains in bone mass, making it less likely that hyperthyroidism played a role.

We recognize that the study is limited, in part, because of the cadaver controls. MicroCT analysis from healthy men and postmenopausal women would provide even stronger confirmation of these data but, at this time, unsectioned biopsy specimens from such control subjects are unavailable. However, the current findings are consistent with those of our previous study using 2D histomorphometry, in which age and sex matched controls from living subjects were employed.

An additional limitation is the relatively small sample size. However, given the rarity of hypoparathyroidism (it is officially recognized as an orphan disease), the number of biopsies studied here is in fact quite significant. Furthermore, despite the sample size limitation, agreement between identical variables measured by 2-dimensional histomorphometry or 3-dimensional microcomputed tomography was excellent. The strong correlations we observed between traditional 2D histomorphometry and 3D microCT of iliac crest biopsies are consistent with previous studies in our laboratories and those of other investigators conducted in populations across a wide range of ages and diverse clinical diagnoses^{2, 29-31}. Recker et al. found strong correlations between microarchitectural variables measured by both techniques in 88 postmenopausal women, with correlations ranging from 0.60 for trabecular thickness to 0.83 for bone volume³¹. We also observed strong relationships between 2D and 3D histomorphometry in transiliac crest biopsies from 44 men and women with mild primary hyperparathyroidism, ranging from 0.65 to 0.79³⁰, similar to the range we observed in this study (r values ranging from 0.52-0.89). In fact, in the current study, the direct comparisons between the 2D and 3D measurements suggest that the 3D methodology provides even greater sensitivity in assessment of BV/TV, Tb.Th, Tb.N and Tb.Sp. The positive Y-intercept indicates

that the 3D measurement is able to detect parameters that are underestimated by the 2D measurement.

We conclude that cancellous bone microarchitecture is markedly abnormal in hypoparathyroidism. It is possible that parathyroid hormone is required to maintain the normal structure of trabecular bone. How these changes in trabecular microarchitecture affect bone strength remains to be seen.

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Figure 1.

3-D μ CT images of iliac crest biopsies in a representative hypoparathyroid subject (52 year old male) on the left, and a control subject (59 year old male) on the right. The hypoparathyroid sample shown has the median BV/TV value of the overall hypoparathyroid cohort (26.3%), while a lower BV/TV value was observed in the matched control (13.0%).

Figure 2. Correlation between 2-dimensional and 3-dimensional variables of cancellous bone structure in 33 subjects with hypoparathyroidism.

Table 1

Characteristics of the Hypoparathyroid Population

	N=33	Range (median)	Normal Range
Age (yrs)	48.2 ± 12	25-68	
Sex	Male: 9 Female: 24 (Premenopausal: 14 Postmenopausal: 10)		
Etiology	Postoperative: 18 Autoimmune: 13 DiGeorge: 2		
Duration of hypoparathyroidism (yrs)	17 ± 13	3-45 (11)	
Calcium supplement dose (mg)	3024 ± 2227	0-9000 (2400)	
Calcitriol supplement dose (mcg)	0.75 ± 0.6	0-3 (0.50)	
Daily vitamin D dose (IU) n=15	12,026 ± 26,299	400-100,000 (400)	
Thiazide dose (mg) n=10	25 ± 11	6.25-50 (25)	
Serum calcium (mg/dl)	8.4 ± 0.9	6.2 -10.1 ^a	8.5-10.4
PTH (pg/ml)	6.2 ± 5	<1-22	10-65
Phosphate (mg/dl)	4.4 ± 0.7	2.6-5.8	2.5-4.5
Total alkaline phosphatase activity (U/L)	68 ± 18	40-116	33-96
Urinary calcium excretion (mg/d)	250 ± 121	37-499	
25-hydroxyvitamin D (ng/ml)	56 ± 63	9-323	9-52
1,25-dihydroxyvitamin D (pg/ml)	37 ± 19	14-100	15-60

Mean±SD

^a Serum calcium extended into the normal range in certain patients as a result of their supplementation

Table 2

Variables of Bone Structure in 25 Hypoparathyroid Subjects and 25 Matched Controls (13 Living Controls and 12 Cadaver Controls)

Index	Hypoparathyroid Subjects (n=25)	Controls (n=25; 13 living and 12 cadaveric)	p-value
BV/TV (%)	24.73 ± 11.5	25.05 ± 11.3	0.9
BS/TV (mm²/mm³)	5.74 ± 4.7	3.73 ± 1.01	0.04
BS/BV (mm²/mm³)	13.83 ± 6.2	16.2 ± 3.5	0.1
Tb.Th (mm)	0.25 ± 0.19	0.17 ± 0.04	0.04
Tb.Sp (mm)	0.70 ± 0.23	0.62 ± 0.20	0.3
Tb.N (mm⁻¹)	2.99 ± 3.4	1.62 ± 0.39	0.05
SMI (1)	-0.30 ± 1.3	0.24 ± 0.7	0.09
Conn.D /mm³	16.63 ± 18.7	8.39 ± 5.8	0.04

Mean±SD

BV/TV is bone volume fraction; BS/TV is bone surface density; BS/BV is bone surface to volume ratio; Tb.Th is trabecular thickness; Tb.Sp is trabecular separation; Tb.N is trabecular number; SMI is Structure Model Index; ConnD is connectivity density.

Table 3

Variables of Bone Structure in 33 Hypoparathyroid Subjects and 36 Unmatched Cadaver Controls

Index	Hypoparathyroid Subjects (n=33)	Cadaver Controls (n=36)	p-value
BV/TV (%)	26.98 ± 9.85	15.39 ± 4.30	<0.0001
BS/TV (mm²/mm³)	3.84 ± 0.65	2.89 ± 0.77	<0.0001
BS/BV (mm²/mm³)	15.45 ± 3.93	19.10 ± 2.43	<0.0001
Tb.Th (mm)	0.193 ± 0.045	0.15 ± 0.10	<0.0001
Tb.Sp (mm)	0.642 ± 0.100	0.78 ± 0.13	<0.0001
Tb.N (mm⁻¹)	1.831 ± 0.494	1.36 ± 0.33	<0.0001
SMI (1)	-0.457 ± 1.522	0.74 ± 0.51	<0.0001
Conn.D /mm³	15.899 ± 18.402	4.96 ± 2.02	.001

Mean±SD

BV/TV is bone volume fraction; BS/TV is bone surface density; BS/BV is bone surface to volume ratio; Tb.Th is trabecular thickness; Tb.Sp is trabecular separation; Tb.N is trabecular number; SMI is Structure Model Index; ConnD is connectivity density.