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Clinical Research Article

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Bone Material Strength Index as Measured by Impact Microindentation is Low in Patients with Primary Hyperparathyroidism

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Abbreviations: BMD, bone mineral density; BMI, body mass index; BMSi, Bone Material Strength index; BP, bisphosphonate; DMAb, denosumab; DXA, dual-energy x-ray absorptiometry; FN, femoral neck; IMI, impact microindentation; LS, lumbar spine; PHPT, primary hyperparathyroidism; PTH, parathyroid hormone; VFA, vertebral fracture assessment.

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Abstract

Context: In primary hyperparathyroidism (PHPT) bone mineral density (BMD) is typically decreased in cortical bone and relatively preserved in trabecular bone. An increased fracture rate is observed however not only at peripheral sites but also at the spine, and fractures occur at higher BMD values than expected. We hypothesized that components of bone quality other than BMD are affected in PHPT as well.

Objective: To evaluate bone material properties using impact microindentation (IMI) in PHPT patients.

Methods: In this cross-sectional study, the Bone Material Strength index (BMSi) was measured by IMI at the midshaft of the tibia in 37 patients with PHPT (28 women), 11 of whom had prevalent fragility fractures, and 37 euparathyroid controls (28 women) matched for age, gender, and fragility fracture status.

Results: Mean age of PHPT patients and controls was 61.8 ± 13.3 and 61.0 ± 11.8 years, respectively, $P = .77$. Calcium and PTH levels were significantly higher in PHPT patients but BMD at the lumbar spine (0.92 ± 0.15 vs 0.89 ± 0.11, $P = .37$) and the femoral neck (0.70 ± 0.11 vs 0.67 ± 0.07, $P = .15$) were comparable between groups. BMSi however was significantly lower in PHPT patients than in controls (78.2 ± 5.7 vs 82.8 ± 4.5, $P < .001$). In addition, BMSi was significantly lower in 11 PHPT patients with fragility fractures than in the 26 PHPT patients without fragility fractures (74.7 ± 6.0 vs 79.6 ± 5.0, $P = .015$).

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Conclusion: Our data indicate that bone material properties are altered in PHPT patients and most affected in those with prevalent fractures. IMI might be a valuable additional tool in the evaluation of bone fragility in patients with PHPT.

Key Words: Bone Material Strength index (BMSi), bone quality, fractures, impact microindentation (IMI), primary hyperparathyroidism, osteoporosis

Primary hyperparathyroidism (PHPT) is a common endocrine disorder characterized by an inappropriate excess of parathyroid hormone (PTH) resulting in elevated serum calcium, usually caused by an adenoma of the parathyroid glands. PTH plays an important role in the maintenance of bone mass and integrity, but its continuous excess in PHPT increases bone turnover in favor of bone resorption, resulting in bone loss predominantly at cortical sites with relative preservation at trabecular sites (1-4). An increased fracture rate, however, has been found at all relevant skeletal sites including the spine, and fractures occur at higher bone mineral density (BMD) levels than expected (3). These findings suggest that in PHPT factors contributing to bone quality other than BMD are also affected. These factors include bone architecture on the macro- and microlevels, and tissue material properties. Microarchitecture of cortical and trabecular bone at the radius and the tibia have been assessed in postmenopausal women with PHPT using high-resolution peripheral quantitative computed tomography and found to be altered compared with healthy controls (5). Tissue material properties of bone, however, are the least understood and the hardest to evaluate and could until recently only be assessed ex vivo by using transiliac bone biopsy specimens. Since the introduction of the impact microindentation (IMI) technique, these properties have become measurable in humans in vivo at the midshaft of the tibia (6). The resistance of cortical bone to indentation, measured as Bone Material Strength index (BMSi), is altered in patients with fragility fractures compared with patients without fractures, independently of BMD (7-10), and is strongly associated with material properties of subperiostal mineralized bone surface (11).

In the present study, we aimed to evaluate if bone material properties, as assessed by IMI, are altered in patients with primary hyperparathyroidism compared with euparathyroid controls. In addition, we aimed to evaluate whether BMSi differed between PHPT patients with or without fragility fractures.

Patients and Methods

Study Design

This was a cross-sectional study evaluating BMSi in men and women with PHPT and in euparathyroid controls with osteoporosis, osteopenia, or normal BMD. Patients and controls were studied at the outpatient clinics of Leiden University Medical Center (LUMC), a national expertise center for PHPT. The study was approved by the Medical Ethics Committee of the LUMC and written informed consent was obtained from all individual participants included in the study. All procedures performed were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Patients with PHPT

Patients aged 18 years or older with a diagnosis of PHPT attending the outpatient clinic of the Department of Endocrinology of LUMC between October 2018 and February 2020 were asked to participate in the study. The diagnosis of PHPT was made in the case of a repeatedly elevated calcium concentration (albumin corrected), with nonsuppressed PTH in the absence of vitamin D deficiency.

Controls

Men and women with or without fragility fractures who had normal serum calcium levels and no history of hyperparathyroidism served as controls. They were recruited from the outpatient clinics of the Center for Bone Quality or from the regional Fracture Liaison Service of LUMC and were matched for age and gender and the presence or absence of fragility fractures.

Exclusion criteria for both groups were a metabolic bone disease other than osteoporosis, any untreated endocrine disorder, severe liver insufficiency, or chronic kidney disease stage IV or V, immobilization, a contraindication for IMI measurement (12), or inability to provide informed consent. In addition, the use of any treatment affecting bone metabolism other than calcium and vitamin D was also an exclusion criterion with the exception of bisphosphonate (BP) or denosumab (DMAb) in patients with PHPT.

Methods

A full medical history, use of medication including agents affecting bone metabolism, vitamin D supplementation,

dietary calcium intake, and a detailed fracture history with documentation of sites and dates of occurrence of fractures were obtained from all subjects. A fragility fracture was defined as any low-energy fracture, excluding those of the hands, feet, and skull. Data on clinical risk factors for fracture as used in the FRAX algorithm were obtained from all subjects (FRAX) (13).

Laboratory Parameters

Serum calcium (albumin corrected), phosphate, creatinine, and alkaline phosphatase concentrations were measured using semi-automated techniques. Plasma intact PTH was measured by Immulite 2500 (Siemens Diagnostics, Breda, The Netherlands) and serum 25-hydroxyvitamin D concentrations by the 25-OH-vitamin D TOTAL assay (DiaSorin D.A./N.V., Brussels, Belgium).

Bone Mineral Density

Areal bone mineral density (BMD) was measured at the lumbar vertebrae (L1-L4) and at the left and right hip using dual-energy x-ray absorptiometry (DXA) with the Hologic QDR Discovery A (Hologic, Bedford, MA, USA). Mean BMD values of the femoral neck were used in the analysis. NHANES III reference values compatible with reference values of the Dutch population were used to calculate T-scores. Osteopenia and osteoporosis were diagnosed according to World Health Organization criteria.

Vertebral Fracture Screening

Single energy x-ray lateral vertebral fracture assessment (VFA) images of the spine (T4-L4) by DXA or conventional anteroposterior and lateral radiographs of the thoracic and lumbar spine were performed following standard protocols for the detection of vertebral deformities at time of inclusion. Images were independently evaluated by 2 experienced readers using the semiquantitative method of Genant (14).

Impact Microindentation

BMSi was measured in all patients by IMI using a handheld microindenter device (OsteoProbe® RUO, Active Life Scientific, CA, USA) on the midshaft of the tibia as described previously (15). In brief, the patient was placed in a decubitus supine position with the tibia in external rotation to orient the flat surface of the medial tibia diaphysis in a horizontal position. The measurement site was defined as the mean distance between the medial malleolus and the distal apex of the patella. Following disinfection of the area and local anesthesia of the skin and periosteum with lidocaine 1%, the test probe was gently inserted in the skin until the bone surface was reached. After at least 5 adequate measurements, 5 additional measurements were performed on a polymethylmethacrylate calibration phantom. BMSi was calculated by the computer software. The intra-observer and interobserver coefficient of variation in our center are 2.2% and 1.6%, respectively.

Statistical Analysis

Results are presented as mean ± SD unless stated otherwise. Descriptive statistics were used to describe clinical and laboratory parameters. Normality assumptions were checked by inspection of histograms and tested by a Kolmogorov–Smirnov test. Differences in baseline characteristics between patients and controls were assessed using a paired t-test or Wilcoxon signed ranks test and McNemar's test for normally and not normally distributed continuous and for categorical variables, respectively. Conditional logistic regression was used to assess BMSi and BMD values adjusted for body mass index (BMI) to compare BMSi and BMD values between patients and controls. Correlations between BMSi values and patients' or disease characteristics were examined by Pearson's and Spearman's tests for normally and not normally distributed variables, respectively. Based on pilot data from our center, the sample size to detect a significant difference in BMSi between groups with a power of 0.8 at a significance level of .05 is 33. $P < .05$ was considered to be statistically significant. All analyses were performed using SPSS software for Windows (version 25.0; SPSS Inc., Chicago, IL, USA) and graphs were constructed with Graphpad Prism (version 8.0; Graphpad Software Inc., La Jolla, CA, USA).

Results

Thirty-seven of 41 eligible patients with PHPT agreed to take part and were included in the study (Fig. 1). Median time since diagnosis was 8.0 months (interquartile range [IQR] 2.0-54.5 months) and mean age at diagnosis was 59.3 ± 14.1 years. At time of inclusion, 12 patients (32.4%) were using antiresorptives (n = 9; 4 oral BP, 4 iv BP, 1 DMAb) for a median duration of 29 months (IQR 9.5-61.0 months) and/or cinacalcet (n = 7), a calcimimetic drug. Reasons for treatment with antiresorptives in 9 of these 12 patients were severe hypercalcemia in 4 patients and a DXA diagnosis of osteoporosis in a patient with a contraindication for surgery. In 4 patients the antiresorptive treatment had been initiated due to osteoporosis or osteopenia with and without fractures before the diagnosis of PHPT.

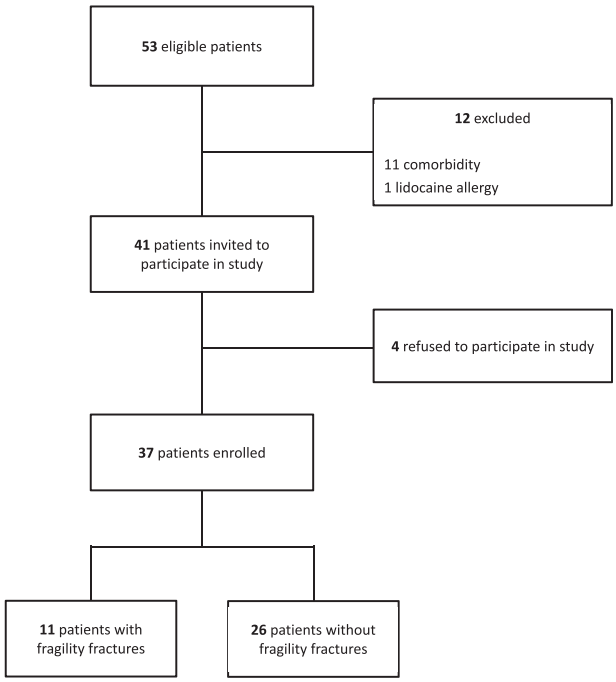

Figure 1. Patient flowchart.

Patients' characteristics and laboratory measurements of the 37 patients with PHPT (28 women) and 37 matched euparathyroid controls (28 women) are shown in Table 1. By design, the 2 groups were comparable in age and gender, and also comparable regarding the number of subjects with prevalent fragility fractures, 11 (29.7%) in PHPT patients and 11 (29.7%) in controls ($P = 1.00$). BMI was significantly higher in PHPT patients, who also—by definition—had higher serum calcium and PTH levels than controls (Table 1).

Lumbar spine (LS) and femoral neck (FN) BMD were comparable between the 2 groups (Fig. 2A), also after adjusting for BMI (LS $P = .871$, FN $P = .488$).

Bone Material Strength index

BMSi was significantly lower in patients with PHPT than in controls, 78.2 ± 5.7 versus 82.8 ± 4.5, $P < .001$ (Fig. 2B), also after adjusting for BMI ($P = .001$), and when excluding the 9 patients who were using antiresorptives ($P < .001$).

In PHPT patients, BMSi did not differ between men and women (79.6 ± 4.4 versus 77.7 ± 6.1, $P = .404$), and there

Table 1. Characteristics of patients with primary hyperparathyroidism and controls

	PHPT (n = 37)	Controls (n = 37)	*P* value
Age, years	61.8 ± 13.3 (range 37-84)	61.0 ± 11.8 (range 40-83)	.768
Male/female	9/28	9/28	1.00
BMI, kg/m^2	27.2 ± 0.9	24.7 ± 0.5	**.031**
Smoking, n (%)	0 (0.0)*	0 (0.0)*	NA
Alcohol use ≥3 U/d, n (%)	2 (5.4)*	2 (5.4)*	1.00
Time since diagnosis, months	8 (IQR 2-55)	NA	NA
Urolithiasis, n (%)	6 (16.2)	NA	NA
Fragility fracture any, n (%)	11 (29.7)	11 (29.7)	1.00
History of hip fracture, n (%)	1 (2.7)	2 (5.4)	1.00
Prevalent vertebral fracture (radiological), n (%)	5 (13.5)	5 (13.5)	1.00
History of NHNV fracture, n (%)	7 (18.9)	8 (21.6)	.772
Calcium[a], mmol/L	2.7 ± 0.2	2.3 ± 0.1	**<.001**
Phosphate[b], mmol/L	0.9 ± 0.2	1.1 ± 0.1	**<.001**
PTH[c], pmol/L	10.2 ± 1.6	3.3 ± 0.2	**<.001**
Creatinine[d], µmol/L	72.0 ± 3.2	72.0 ± 3.3	.559
25-OH Vit D[e], nmol/L	78.1 ± 27.5	79.4 ± 31.1	.847
LS BMD, g/cm^2	0.92 ± 0.15	0.88 ± 0.11	.329
T-score LS	–1.1 ± 1.3	–1.6 ± 1.1	.154
FN BMD, g/cm^2	0.70 ± 0.11	0.67 ± 0.07	.148
T-score FN	–1.5 ± 1.0	–1.7 ± 0.7	.298
BMSi	78.2 ± 5.7	82.8 ± 4.5	**<.001**

Values are expressed as mean ± SD. BMI, PTH, and creatinine are expressed as median ± SEM. *P* values in bold are significant.

Abbreviations: BMD, bone mineral density; BMI, body mass index; BMSi, Bone Material Strength index; FN, femoral neck; LS, lumbar spine; NHNV, nonhip nonvertebral; PTH, parathyroid hormone.

*Information about smoking status and alcohol consumption was missing in 1 patient and in 1 control.

[a]Calcium (albumin-corrected) reference range, 2.15-2.55 mmol/L.

[b]Phosphate reference range, 0.9-1.5 mmol/L.

[c]PTH reference range, 0.7-8.0 pmol/L.

[d]Creatinine reference range, 64-104 µmol/L for males; 49-90 µmol/L for females.

[e]25-OH Vit D reference range, 50-250 nmol/L.

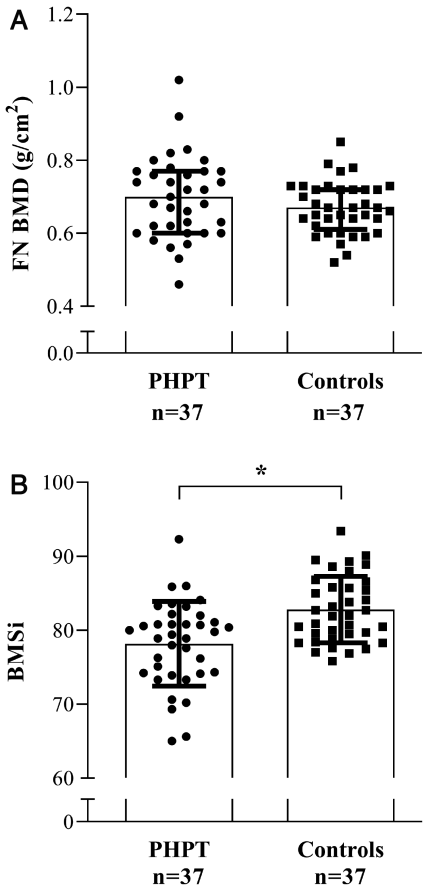

Figure 2. (A) Mean femoral neck bone mineral density (FN BMD) and (B) Bone Material Strength index (BMSi) in patients with PHPT and controls. Data are shown in box-whisker plots and statistical differences are displayed for BMSi. Boxes indicate median and inter-quantile range. Bars indicate minimum and maximum values. *$P < .001$.

was no correlation between BMSi and age (r = -0.131, $P = .440$) or BMI (r = –0.074, $P = .663$).

In contrast, there was a significant relationship between BMSi and time since diagnosis (r = –0.382, $P = .020$), with lower BMSi the longer the disease duration. There was also a significant negative relationship between BMSi and plasma PTH levels (r = –0.358, $P = .030$), and between BMSi and serum calcium concentrations (r = –0.406, $P = .013$).

There was no relationship between BMSi and BMD neither at the LS (r = –0.222, $P = .194$) nor at the FN (r = –0.041, $P = .813$). Although BMSi tended to be higher in the 9 patients treated with antiresorptives than in the 28 patients without (80.7 ± 7.4 versus 77.4 ± 5.0, $P = .133$), this was not statistically significant. All findings of this study did not change when excluding the 12 patients using antiresorptives and/or cinacalcet (Tables 1 and 2 (16)).

BMSi and Fractures

Baseline characteristics and laboratory measurements of PHPT patients with and without fragility fractures are shown in Table 2. BMSi was significantly lower in the 11 PHPT patients with prevalent fragility fractures than in the 26 PHPT patients without, BMSi 74.7 ± 6.0 versus 79.6 ± 5.0, $P = .015$ (Fig. 3), also after adjusting for BMD ($P = .017$). Patients with fractures tended to use cinacalcet more frequently and also appeared to have a lower FN BMD (Table 2). A DXA diagnosis of osteoporosis was established in 6 of them, while 4 had osteopenia and 1 normal BMD,.

BMSi of the 11 PHPT patients with fragility fractures was also significantly lower than the BMSi of the 11 controls with fragility fractures, 74.7 ± 6.0 versus 80.3 ± 4.9 ($P = .010$), while BMD was comparable between the 2 groups at both the LS (0.86 ± 0.16 versus 0.91 ± 0.12, $P = .369$) and the FN (0.62 ± 0.08 versus 0.66 ± 0.08, $P = .329$).

Discussion

We show here that BMSi values, measured by in vivo IMI, are significantly lower in patients with PHPT than in euparathyroid matched controls, independently of BMD values. Moreover, BMSi values were significantly lower in patients with PHPT with prevalent fragility fractures than in patients with PHPT without fragility fractures, and inversely related to disease severity.

Osteoporosis and fragility fractures are a known complication of PHPT and both are an indication for surgical treatment of the disease (1-3). The reported prevalence of fragility fractures in PHPT is high, 21% for vertebral fractures in a recent paper (17) as also seen in our data: Almost 30% of PHPT patients had sustained a fragility fracture, of whom 15% had a prevalent vertebral fracture. Of note, DXA T-scores of PHPT patients were in the osteopenic range, and only FN BMD, but not LS BMD, differed between fracture and nonfracture PHPT patients. This is consistent with findings from other studies, showing that bone mineral density typically is affected at sites rich for cortical bone as the FN, and relatively normal at sites rich for trabecular bone such as the spine (3). The increased fracture rate in the presence of only mildly decreased FN BMD and relatively normal lumbar spine BMD suggests that in PHPT components of bone quality other than bone mass may be altered, such as bone microarchitecture or bone material properties.

Our results indeed show a lower BMSi in patients with PHPT than in euparathyroid controls, independently of BMD values, indicating that next to BMD bone material properties are affected in PHPT. This is in agreement with a preliminary report by Starr et al. published only in abstract form in which BMSi was measured in 13 subjects with PHPT and shown to be significantly lower than that of 22 euparathyroid matched controls, 67.8 ± 9 vs 77.2 ± 8,

Table 2. Characteristics of patients with primary hyperparathyroidism with and without fragility fractures

	Fracture (n = 11)	No fracture (n = 26)	*P* value
Age, years	65.3 ± 11.3 (range 47-79)	60.4 ± 14.0 (range 37-84)	.319
Male/female	3/8	6/20	.786
BMI, kg/m^2	25.6 ± 2.1	26.0 ± 0.9	.832
Time since diagnosis, months	10 (IQR 2-69)	7 (IQR 2-51)	.682
Urolithiasis, n (%)	1 (9.0)	5 (19.2)	
Current medication use			
Antiresorptives, n (%)	3 (27.3)	6 (23.1)	.786
Calcimimetics, n (%)	0 (0.0)	7 (26.9)	.080
Calcium[a], mmol/L	2.7 ± 0.1	2.7 ± 0.2	.600
PTH[b], pmol/L	11.0 ± 0.8	10.0 ± 2.3	.544
Diagnosis by DXA			.057
Normal BMD, n (%)	1 (9.1)	5 (19.2)	
Osteopenia, n (%)	4 (36.4)	17 (65.4)	
Osteoporosis, n (%)	6 (54.5)	4 (15.4)	
LS BMD, g/cm^2	0.86 ± 0.16	0.94 ± 0.14	.115
T-Score LS	–1.6 ± 1.3	–0.9 ± 1.3	.170
FN BMD, g/cm^2	0.62 ± 0.08	0.73 ± 0.11	**.007**
T-Score FN	–2.2 ± 0.7	–1.2 ± 1.0	**.009**
BMSi	**74.7 ± 6.0**	**79.6 ± 5.0**	**.015**

Values are expressed as mean ± SD. BMI and PTH are expressed as median ± SEM. *P* values in bold are significant.
Abbreviations: BMD, bone mineral density; BMSi, Bone Material Strength index; DXA, dual x-ray absorptiometry; FN, femoral neck; LS, lumbar spine; NHNV, nonhip nonvertebral; PTH, parathyroid hormone.
[a]Calcium (albumin-corrected) reference range, 2.15-2.55 mmol/L.
[b]PTH reference range, 0.7-8.0 pmol/L.

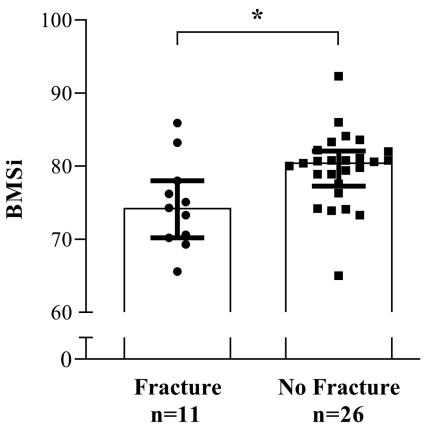

Figure 3. Bone Material Strength index (BMSi) in patients with PHPT with and without fragility fractures. Data are shown in box and whisker plots and statistical differences are displayed for BMSi. Boxes indicate median and interquartile range. Bars indicate minimum and maximum values. **P* = .015.

P = .01 (18). Interestingly, BMSi values of their younger controls were similar to the BMSi values of our PHPT patients, 11 of whom had fractures. Fracture data or relation with disease severity, however, were not reported.

In addition, we found that BMSi was lower in patients with PHPT with several types of fragility fractures than in patients with PHPT without fragility fractures, also independently of BMD values. This has not been reported before in patients with PHPT but is in keeping with the results of most studies in patients with primary osteoporosis in which BMSi was found to be lower in patients with fragility fractures than in patients without fragility fractures, independently of BMD values (7-10). Of note, although BMSi is measured at the tibia, a site rich in cortical bone, earlier studies from our group and others in patients with primary osteoporosis and fragility fractures suggest that low BMSi is associated with increased bone fragility at all relevant skeletal sites, and vertebral, nonvertebral, and hip sites (8, 9, 19).

Moreover, BMSi of PHPT patients was also lower in patients with known longer duration of the disease, and in patients with higher PTH and calcium values, suggesting that material properties of bone are more severely altered the longer the exposure to elevated PTH levels and more severely uncontrolled disease. The relation between PTH and BMSi has never been studied in hyperparathyroidism but it has been reported in a recent study by Starr et al. in 17 patients with hypoparathyroidism and 17 matched euparathyroid controls (20). It was observed that euparathyroid controls with higher PTH levels had higher BMSi values, suggesting that PTH levels might be associated with BMSi as in our study, although reversed, r = 0.58, *P* = .02. Numbers of our study and their study, however, are small.

Our study has strengths as well as limitations. One of the strengths is the consecutive inclusion of men and women with PHPT with and without fragility fractures at a tertiary referral center, giving a representative image of the whole PHPT patient population in clinical practice, and the possibility for proper matching. An additional interesting BMD measurement site would have been the distal 1/3 radius, a location known to be affected by PHPT. Unfortunately due to logistic reasons this was not possible. Nevertheless, BMD data were available from all PHPT and controls at the FN and LS, and no correlation between BMSi and BMD was found. Another limitation is the inclusion of patients with PHPT also treated with antiresorptives and/or cinacalcet. Another study performed by our group demonstrated that treatment with bisphosphonates and denosumab, given for a mean period of 2 years, increases BMSi values in patients with low bone mass and increased risk of fracture (15). While that study was performed in patients with low bone mass and increased risk of fracture in whom treatment with antiresorptives has been shown to be associated with a decrease in fracture risk (21-23), this has not been shown in patients with PHPT (1). Also, when assuming an increase in BMSi in patients with PHPT treated with bone agents the difference in BMSi between patients and controls who were treatment naive is even more remarkable. Moreover, we found no significant difference in BMSi between patients with PHPT treated with antiresorptives for a median duration of 2.5 years and treatment-naive patients. In addition, repeated analysis in only treatment-naive patients with PHPT did not change results, and sample size calculation was based on pilot data also including treated patients.

In conclusion, we show that BMSi is lower in patients with PHPT than in matched euparathyroid controls, independently of BMD, and that BMSi is the lowest in patients with PHPT and a fragility fracture. These findings indicate that tissue-level properties of bone are impaired in patients with PHPT. Our results might thus help explain the higher fracture risk than expected from measurements of BMD in PHPT probably at both at cortical and at trabecular sites. Therefore, and since the IMI technique enables physicians to evaluate in vivo tissue level material properties of bone in a minimally invasive, simple, and safe manner (6), it has the potential to be used as an additional tool to DXA BMD measurements in the evaluation of bone fragility in patients with PHPT in the clinic, although larger prospective studies are warranted.

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Additional Information

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Data Availability: The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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