

Clinical Research Article

Vertebral Fracture Assessment in Postmenopausal Women With Postsurgical Hypoparathyroidism

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Abstract

Context: Hypoparathyroidism is a rare endocrine disorder whose skeletal features include suppression of bone turnover and greater volume and width of the trabecular compartment. Few and inconsistent data are available on the prevalence of vertebral fractures (VF).

Objective: To evaluate the prevalence of VF assessed by vertebral fracture assessment (VFA) in postmenopausal women with chronic postsurgical hypoparathyroidism.

Design: Cross-sectional study

Setting: Ambulatory referral center.

Patients or Other Participants: Fifty postmenopausal women (mean age 65.4 ± 9 years) with chronic postsurgical hypoparathyroidism and 40 age-matched healthy postmenopausal women (mean age 64.2 ± 8.6).

Main outcome measures: Lumbar spine, femoral neck, and total hip bone mineral density were measured by dual X-ray absorptiometry (Hologic Inc., USA) in all subjects. Site-matched spine trabecular bone score was calculated by TBS iNsight (Medimaps, Switzerland). Assessment of VF was made by VFA (iDXA, Lunar GE, USA) using the semiquantitative method and the algorithm-based qualitative assessment.

Results: All-site BMD values were higher in the hypoparathyroid vs the control group. By VFA, we observed a 16% prevalence of VF in hypoparathyroid women vs 7.5% in control subjects. Among those with hypoparathyroidism who fractured, 5 (62.5%) had

grade 1 wedge, 2 (25%) had grade 2 wedge, and 1 (12.5%) had grade 2 wedge and grade 2 biconcave VF. In the hypoparathyroid group, 57% with VFs and 32% without VFs had symptoms of hypoparathyroidism.

Conclusion: We demonstrate for the first time that in postmenopausal women with chronic postsurgical hypoparathyroidism, VFs are demonstrable by VFA despite normal BMD.

Key Words: VFA, fracture, postmenopausal women, hypoparathyroidism

Hypoparathyroidism is a rare disorder of mineral metabolism characterized by low serum calcium levels and low or undetectable parathyroid hormone (PTH). The most common form occurs as a complication of anterior neck surgery. It is defined as chronic when insufficient parathyroid function persists for more than 6 months after surgery (1). A prevalence of postsurgical hypoparathyroidism ranging from 1.3 to 30/100 000 persons per year is reported by epidemiological studies from several different geographical areas (2-4). Reported incidences range from 0.8% to 13.4% after anterior neck surgery (4-6).

Most of the clinical manifestations and complications of hypoparathyroidism are related to its biochemical profile, namely low serum calcium and PTH levels. They involve several organs (1). Among them, the skeleton has been a focus because of potential deleterious effects of persistent exposure to low or undetectable PTH. Skeletal features of hypoparathyroidism include low bone turnover with greater volume and width of the trabecular compartment and lower cortical porosity (7). Histological findings in the hypoparathyroid skeleton comprise reduction of the mineralizing surface and reduced indices of bone turnover (7). By dual X-ray absorptiometry (DXA), these skeletal abnormalities are evident as normal or above average bone mineral density (BMD) and trabecular microarchitecture [as evaluated by trabecular bone score (TBS)], compared to healthy subjects (7,8). Assessment of bone quality by high-resolution peripheral quantitative computed tomography show higher trabecular number at tibia and reduced cortical porosity at both tibia and radius (9). To date, there are no clear data elucidating how these skeletal characteristics could potentially relate to clinically relevant reduction or increase in bone fragility in hypoparathyroidism. Indeed, there are no definitive data on the prevalence of fragility fracture in hypoparathyroidism (10). According to Underbjerg et al, discrepancy exists between the risk of upper extremities fractures in the non-surgical (higher risk) *vs* the postsurgical hypoparathyroid subjects, compared to the general population. A study in 104 patients with idiopathic hypoparathyroidism showed higher prevalence of vertebral fractures (VF) compared to healthy subjects, particularly in association with postmenopausal status and

anticonvulsant therapy (11). Other studies reported inconsistent results in the prevalence of VF and non-VF in hypoparathyroid *vs* control subjects (12-14).

Vertebral fracture assessment (VFA) is an established, reliable and accurate methodology for the diagnosis of VF in patients with osteoporosis and other metabolic bone disease (15-19). As such, VFA is recommended for the evaluation of VF in adult patients and children with different metabolic bone disease by national and international consensus statements and guidelines (19-21). When analyzed by radiologists with the requisite expertise in the evaluation of vertebral morphology, VFA has significant advantages compared to the conventional X-ray (16,22). The VFA methodology is associated with lower radiation exposure, easier and faster spine image acquisition, and the lack of the parallax effect that increases vertebral distortion and therefore the rate of misdiagnosis with routine vertebral X-ray.

To our knowledge, no study has yet assessed the prevalence of VF in postmenopausal women with chronic postsurgical hypoparathyroidism. In particular, VFA has not been employed in this cohort of patients. The primary aim of the study was to assess this issue by comparing postmenopausal hypoparathyroid women with a cohort of age-matched healthy women. We also evaluated risk factors for VF in postmenopausal women with chronic hypoparathyroidism.

Materials and Methods

Participants

We studied 50 postmenopausal women with chronic postsurgical hypoparathyroidism (mean age 65.4 ± 9 years) and 40 age-matched healthy postmenopausal women (mean age 64 ± 8.5 years) as the control group. Hypoparathyroid subjects were recruited between November 2017 and December 2019 among those consecutively referred to the Unit of Internal Medicine and Metabolic Bone Disease, Sapienza University of Rome and meeting inclusion and exclusion criteria. The diagnosis of chronic postsurgical hypoparathyroidism was established by the persistent presence of serum calcium and PTH levels below normal for at least 1 year after neck surgery

in association with requirements for calcium and/or active vitamin D supplementation.

Inclusion criteria were postmenopausal women with chronic hypoparathyroidism, as previously defined. Exclusion criteria were previous use of teriparatide or recombinant human PTH(1-84); glucocorticoid use within the past 2 years; history of Cushing syndrome, uncontrolled thyroid disease, malabsorption syndrome, significant liver disease, creatinine clearance <30 mL/min, other chronic disorders of mineral metabolism, comorbidities known to reduce BMD, and increase fracture risk.

Healthy postmenopausal women were recruited among personnel of the hospital and ambulatory women referred in the same period to our center by general practitioners for a menopause-screening program. In this group, medical history, physical examination, and laboratory exams excluded disorders of bone and mineral metabolism, as well as comorbidities known to reduce BMD and increase fracture risk; they did not take medications affecting bone and mineral metabolism.

Postmenopausal status was defined as having no menstrual period for more than 1 year in both groups. Women with known VF were excluded from recruitment in both groups. History of spinal injury was assessed while collecting the medical history in all subjects.

In all subjects, a complete physical examination was done. We measured height to the nearest 0.001 m by a standard stadiometer and weight by a calibrated bathroom scale to the nearest 0.1 kg with subjects wearing light clothing and no shoes. Body mass index (BMI) was calculated in any subject by the weight expressed in kilogram, divided by height in squares meter.

The study was approved by the Sapienza University of Rome Ethics Committee, and all subjects gave written informed consent. The research was carried out complying with the World Medical Associations Declaration of Helsinki—Ethical Principles for Medical Research involving Human Subjects.

Areal bone mineral density

Areal BMD was measured by DXA (QDR 4500; Hologic, Waltham, MA, USA) at the lumbar spine (L1-L4), total hip, and femoral neck in all subjects. Fractured L1-L4 vertebrae were excluded from BMD measurement. The coefficients of variation are 1.0% at lumbar spine, 1.5% at femoral neck, and 1.7% at total hip (23). Areal BMD was expressed in grams per square centimeter (g/cm^2) and in T-score units. T-score values ≤ -2.5 at any skeletal site were considered for the diagnosis of osteoporosis; T-score values ≤ -1 and ≥ -2.5 were considered to be osteopenic.

Trabecular bone score

Lumbar spine TBS was assessed using de-identified DXA files from L1-L4 scans using the TBS iNsight software (version 3.0.2.0; Medimaps group, Geneva, Switzerland). The TBS was calculated as the mean value of the individual measurements for the vertebrae L1-L4 and excluding any vertebra excluded from BMD calculation. TBS was calculated as the sum of the squared gray-level differences between pixels at a specific distance and angle and then calculated as the slope of the log-log transform of this variogram (23). TBS thresholds were considered based on data from meta-analysis by Harvey et al corresponding to 1.23 and 1.31 (23,24). We defined values above 1.31 as normal pattern (low risk of fracture), between 1.31 and 1.23 as partially degraded micro-architectural pattern (intermediate risk), and below 1.23 as degraded pattern (high risk of fracture) (23).

Vertebral fracture assessment

The presence of VF was assessed by DXA images of the lateral thoracic and lumbar spine using the Lunar-iDXA densitometer (Lunar iDXA TM, GE Healthcare, Madison, WI, USA; enCORETM 2009 software version 13.20.033). To obtain the images of the spine, the patient is positioned in the left lateral decubitus, similarly to the standard spine radiograph, with the knees and hips flexed at 90° angle and the arms flexed with both hands joined. The position allows having the spine parallel to the table and avoids artificial angulation of the vertebrae. Scanning time is approximately 120 to 240 sec.

An experienced skeletal radiologist analyzed the spine DXA images according to the algorithm-based qualitative approach (ABQ) (25). The ABQ is a qualitative method for assessing VF that implies the visualization of the center of the endplate within the vertebral ring to detect any concave depression (26). The radiologist considers both the vertebral shape and the appearance of the end plate to differentiate clearly VF from other non-VF deformities (eg, developmental variant, degenerative change, etc).

After the qualitative reading, vertebral morphometry was performed. The enCORETM Software version 13.5 (Encore Software, San Jose, CA, USA) automatically places 6 points in each vertebral body from L4 to T8 to calculate the anterior (HA), middle (HM), and posterior (HP) heights and their ratios (HA/HP, HM/HP), and the average height of each vertebra. The same radiologist reviewed the vertebral morphometry and, when necessary, manually corrected marker position that were automatically placed, according to Hurxal (27). Vertebral heights

were manually measured from T7 to T4 if adequately visualized.

Based on these measurements, vertebrae were classified as normal (<20% reduction) or fractured (>20% reduction). Fractured vertebrae were graded as grade 1 (mild, 20%-25% reduction), grade 2 (moderate, 25%-40% reduction), or grade 3 (severe, >40% reduction) according to the Genant et al criteria (28). Fractured vertebrae were also defined as wedge, biconcave, or crush fractures.

Intra-operator precision for VFA has been assessed previously and resulted in coefficients of variation and root mean square standard deviations of 1.4% and 0.28 mm for HA, 1.5% and 0.27 mm for HM, 1.7% and 0.35 mm for HP, 1.9% and 0.37 mm for average height, 2.0% and 0.019 for HA/HP ratio, and 2.6% and 0.023 for HM/HP ratio (16).

Nonvertebral fractures

Major low-trauma fractures (femur, proximal humerus, or distal forearm) occurring after the menopause were recorded in all subjects by medical history. In case of fractures, an expert radiologist reviewed the X-ray images.

FRAX®

The assessment of the individual 10-year fracture risk for major fractures and hip fractures utilized the clinical risk factors and femoral neck BMD. The FRAX® tool for Italy (<http://www.shef.ac.uk/FRAX>) were used and calculation was made at recruitment. Hence, the presence of VF was not included in the calculation. High risk for 10-year probability of major osteoporotic fracture was defined for FRAX® values $\geq 20\%$ and for hip fracture $\geq 3\%$ (29).

Statistical analysis

Results are presented as mean values $\pm$ SD. Between-group comparisons of demographic, clinical, and densitometric characteristics, as well as prevalence of fractures were assessed using Wilcoxon rank sum test with continuity correction and Fisher's exact test for dichotomous variables. Prevalence of VF is expressed as percentage of fractured over the total number of subjects in both groups. Comparisons between hypoparathyroid women with and without VF were made as far as the same parameters and using the same statistical tests.

A stepwise logistic regression analysis including age, years since menopause, years since diagnosis, BMI, presence of symptoms, serum calcium levels, L1-L4, neck and total hip BMD, TBS, and FRAX® values as covariates was used to identify potential predictors of VF.

The R package version 3.5.0 (R Core Team, 2018) was used for statistical calculations, and *P*-values < 0.05 were considered significant.

Results

Table 1 reports the characteristics of patients with hypoparathyroidism and the control group. There were no differences in demographic and anthropometric characteristics of the two groups. Almost half of the women in the hypoparathyroid group reported hypocalcemia-associated symptoms, mostly expressed as neuromuscular. As expected, serum calcium and PTH levels were significantly lower in the hypoparathyroid *vs* the control group (*P* < 0.0001 for both). Additionally, medical history was negative for any significant injury to the spine in all subjects.

Mean L1-L4 and total hip BMD and T-score values were normal in both groups, while the control group had mean neck T-score values in the osteopenic range (Table 1). Additionally, BMD and T-score values at all sites were significantly higher in the hypoparathyroid women (the difference in L1-L4 T-score values reached near significance: *P* = 0.06). Conversely, no between-group difference was found in terms of TBS values. In both groups, these values (1.20 ± 0.13 in the hypoparathyroid and 1.16 ± 0.17 in healthy women) fitted in the classification of degraded microarchitecture (high fracture risk). In both groups, the 10-year probability of fracture, assessed by FRAX®, was not above accepted threshold values. However, there was a trend toward significantly higher values in the hypoparathyroid group when FRAX® was assessed without femoral neck BMD (8.2 ± 5.7 for major fractures and 2.6 ± 2.9 for hip fractures *vs* 6.8 ± 4.4 and 2.1 ± 2.4 , respectively; *P* = 0.06). Conversely, no between-group differences were observed for FRAX® values assessed with femoral neck BMD. In particular, parental history of femur fracture was reported in 7/50 (14%) hypoparathyroid women and in 1/40 (2.5%) healthy subjects (*P* < 0.05); smoking was reported in 8/50 (16%) women in the hypoparathyroid and 2/40 (5%) in the control group (*P* < 0.05); no cases of glucocorticoid therapy in both groups were reported.

Interestingly, we observed a 16% prevalence of VF, assessed by VFA in hypoparathyroid *vs* 7.5% in healthy women. Seven fractured hypoparathyroid patients had 1 VF; 1 patient had 2 VFs. Five patients (62.5%) had grade 1 wedge VF; 2 (25%) had grade 2 wedge, and 1 (14.3%) grade 2 wedge and grade 2 biconcave VF (Fig. 1). All fractured healthy women had 1 VF; 2 subjects (66.7%) had grade 1 wedge, and 1 (33.3%) had grade 2 biconcave VF. As per the International Society for Clinical Densitometry guidelines, grade 1 VF were not followed up

Table 1. Clinical and densitometric characteristics (mean values $\pm$ SD) in hypoparathyroid and healthy women

Characteristics	Hypoparathyroid women (n = 50)	Healthy women (n = 40)	P-value ^a
Age, years	65.4 $\pm$ 9	64.2 $\pm$ 8.6	NS
Height, cm	160 $\pm$ 7	160 $\pm$ 5.9	NS
Weight, kg	67.7 $\pm$ 10.9	66.9 $\pm$ 9.5	NS
BMI, kg/m ²	26.3 $\pm$ 4.2	26.3 $\pm$ 4.3	NS
Time since menopause, years	16.5 $\pm$ 8	14.8 $\pm$ 9.8	NS
Time since diagnosis, years	19 $\pm$ 10.7	—	—
Hypocalcemia-associated symptoms, n (%)	20 (40%)	—	—
Neuromuscular	20 (40%)	—	—
Neuropsychiatric	2 (4%)	—	—
Serum total calcium, mg/dL (nr 8.4-10)	8.5 $\pm$ 0.3	9.6 $\pm$ 0.4	<0.0001
Serum PTH, pg/mL (nr 6.5-36.6)	7 $\pm$ 4.2	26.5 $\pm$ 6.6	<0.0001
L1-L4 aBMD, g/m ²	1.028 $\pm$ 0.160	0.945 $\pm$ 0.126	0.05
T-score	-0.3 $\pm$ 1.5	-0.9 $\pm$ 1	0.06
Femoral Neck aBMD, g/m ²	0.952 $\pm$ 1.286	0.703 $\pm$ 0.1	<0.05
T-score	-0.7 $\pm$ 1.2	-1.4 $\pm$ 0.9	<0.02
Total Hip aBMD, g/m ²	0.921 $\pm$ 0.147	0.842 $\pm$ 0.104	<0.02
T-score	-0.2 $\pm$ 1.2	-0.8 $\pm$ 0.8	<0.05
TBS	1.20 $\pm$ 0.13	1.16 $\pm$ 0.17	NS
FRAX® Without Neck BMD (%)			
Major fractures	8.2 $\pm$ 5.7	6.8 $\pm$ 4.4	0.06
Hip fractures	2.6 $\pm$ 2.9	2.1 $\pm$ 2.4	0.06
FRAX® with Neck BMD (%)			
Major fractures	6.3 $\pm$ 3	6.1 $\pm$ 3.3	NS
Hip fractures	1.3 $\pm$ 1.2	1.5 $\pm$ 1.4	NS

^aAssessed using Wilcoxon rank sum test with continuity correction and Fisher exact test

Abbreviation: nr, normal range.

by conventional X-rays (19). All fractured subjects in both groups were asymptomatic for VF.

No femur fractures were recorded in either group; 2 (4%) nonvertebral, nonfemur fractures were recorded in the hypoparathyroid group and none in the control group.

In the hypoparathyroid group, there was no difference between subjects with and without VF in terms of demographics, anthropometric and clinical characteristics, serum calcium, DXA parameters, TBS, and FRAX® values (Table 2). In the hypoparathyroid group, among those with VFs, 50% had symptoms of hypoparathyroidism *vs* 38% among those without VF.

The logistic regression analysis showed that the presence of VF was not independently associated with any of the aforementioned demographic, anthropometric, clinical, and DXA parameters, nor with serum calcium, TBS, and FRAX® with neck BMD values. We observed a trend toward a significant independent association of VF with FRAX® without femoral neck BMD values for major fractures (odds ratio = 1.11, *P* = 0.09) and for hip fractures (odds ratio = 1.27, *P* = 0.06).

Five of 50 (10%) and 2/50 (4%) subjects in the hypoparathyroid and 2/40 (5%) and none in the control group

were using antidepressant and anticonvulsant drugs, respectively (all *P*s are nonsignificant).

Discussion

We report for the first time data on the use of VFA in postsurgical hypoparathyroidism. Our study demonstrates that, despite normal BMD values at all sites, VFs are detected in a clinically relevant and higher proportion of postmenopausal women with chronic postsurgical hypoparathyroidism than matched euparathyroid control subjects. Compared to healthy age-matched women, hypoparathyroid women have higher BMD values at all sites and similar TBS values. The TBS scores for both groups were in the “degraded” range suggesting that predictability for VF by DXA would underestimate the true incidence of VF in both groups. Our results are in line with those observed by Mendonca et al showing a higher prevalence of morphometric VFs by X-ray in a small cohort of postmenopausal women with chronic postsurgical hypoparathyroidism (12). The authors described a 60% prevalence of VFs, with many having normal BMD. Interestingly, 6 out of the 17 patients had multiple VFs (12). Apart from

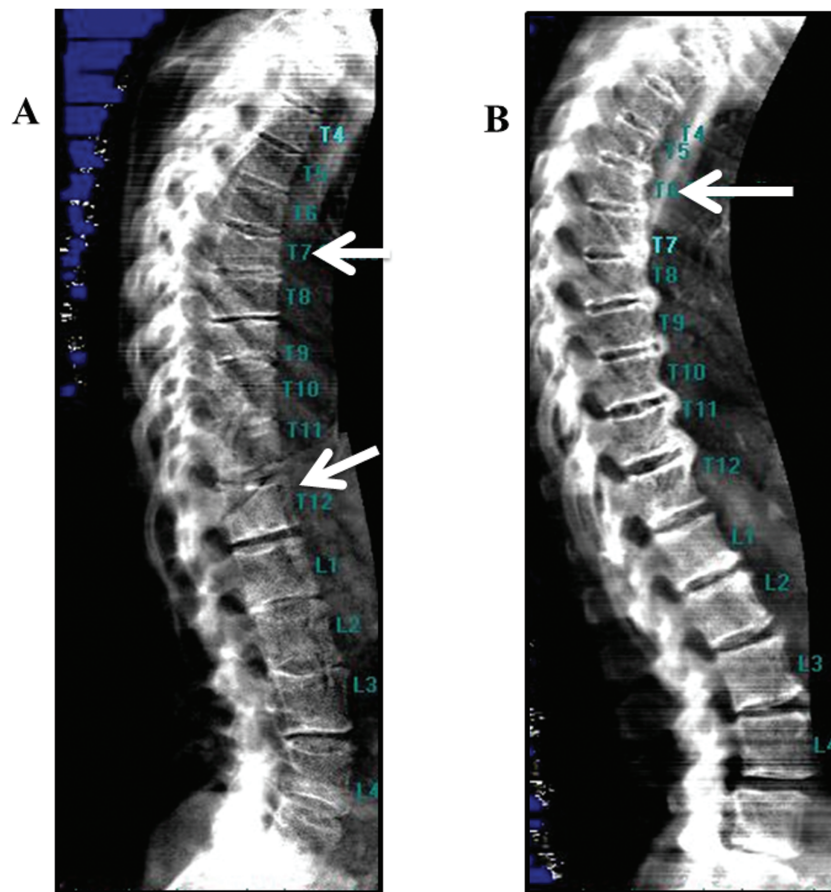


Figure 1. VFA images of patients with chronic postsurgical hypoparathyroidism showing mild biconcave and moderate biconcave VF (A, arrows; T12 and T7, respectively) and mild wedge VF (B, arrow).

BMI that was significantly higher in the Mendonca et al's experience compared to ours, the prevalence of other clinical risk factors for fractures was not evaluated in that study (12). Hence, the higher prevalence of VFs could be due to these other factors. Chawla et al reported a prevalence of VF in idiopathic hypoparathyroidism of about 18% (12). A retrospective analysis of 120 patients with chronic hypoparathyroidism from different causes also reported an 18% prevalence of fractures involving the axial and nonaxial skeleton (30). Our study, using a different approach, confirms the aforementioned reports of fragility fractures in hypoparathyroidism.

VFA methodology is safe and has been effectively applied to several metabolic bone diseases. It is currently recognized as a reliable and appropriate methodology for VF diagnosis. To this end, it may be used as alternative to conventional radiography in several metabolic bone disease (16,19).

Schousboe et al recently demonstrated the positive impact of VFA in clinical practice by reporting that its use significantly increases prescription of anti-osteoporosis drugs as compared to using DXA alone (30). The most recent

official position statements of the International Society of Densitometry give the same clinical indications for VFA as it does for lateral spine X-ray imaging. These indications are T-score < -1.0 and at least 1 of the following: age ≥ 70 (women), ≥80 years (men); height loss, prior VF; and chronic glucocorticoid therapy (www.iscd.org). The Genant semi-quantitative method of morphometric measurement is recommended for VF diagnosis by VFA (www.iscd.org). Experience of the radiologist is of utmost importance for applying this approach that allows a distinction between VF and vertebral deformities not associated with fracture, developmental abnormalities, or merely short vertebral height (31). This is of particular importance in the diagnosis of mild VF for which inter-operator disagreement is frequently reported by clinical studies (26,32). The use of VFA and the systematic application of the aforementioned methods for VF diagnosis, as well as the experience of the radiologist, are therefore major strengths of our study. In addition, we applied the ABQ method for the evaluation of images, thus increasing the specificity of the diagnosis of VF (31). A recent systematic review and meta-analysis by Yang et al reported a 28% prevalence of VF

Table 2. Clinical and densitometric characteristics (mean values $\pm$ SD) of hypoparathyroid women with and without vertebral fractures

Characteristics	Hypoparathyroid women without VF (n = 42)	Hypoparathyroid women with VF (n = 8)	P-value ^a
Age, years	65.5 $\pm$ 8.3	69.9 $\pm$ 9.8	NS
Height, cm	159.5 $\pm$ 6.6	161.7 $\pm$ 8.4	NS
Weight, kg	68.5 $\pm$ 11.5	63.7 $\pm$ 6	NS
BMI, kg/m ²	26.7 $\pm$ 4.3	24.5 $\pm$ 3	NS
Time since menopause, years	15.5 $\pm$ 7.2	21 $\pm$ 12	NS
Time since diagnosis, years	18.4 $\pm$ 9.5	22.5 $\pm$ 19	NS
Hypocalcemia-associated symptoms, n (%)	16 (38%)	4 (50%)	NS
Serum total calcium, mg/dL (nr 8.4-10)	8.6 $\pm$ 0.1	8.7 $\pm$ 0.5	NS
L1-L4 aBMD, g/m ²	1.024 $\pm$ 0.159	1.038 $\pm$ 0.166	NS
T-score	-0.3 $\pm$ 1.4	-0.4 $\pm$ 1.6	NS
Femoral Neck aBMD, g/m ²	0.991 $\pm$ 1.37	0.715 $\pm$ 0.073	NS
T-score	-0.7 $\pm$ 1.2	-1.2 $\pm$ 0.6	NS
Total Hip aBMD, g/m ²	0.936 $\pm$ 0.152	0.847 $\pm$ 0.082	NS
T-score	-0.1 $\pm$ 1.2	-0.7 $\pm$ 0.7	NS
TBS	1.20 $\pm$ 0.14	1.23 $\pm$ 0.08	NS
FRAX® without Neck BMD (%)			
Major fractures	7.5 $\pm$ 4	11.8 $\pm$ 9.5	NS
Hip fractures	2.2 $\pm$ 1.9	4.7 $\pm$ 5.3	NS
FRAX® with Neck BMD (%)			
Major fractures	6 $\pm$ 3.3	7.4 $\pm$ 3	NS
Hip fractures	1.1 $\pm$ 1.2	2 $\pm$ 1.7	NS

^aAssessed using Wilcoxon rank sum test with continuity correction and Fisher exact test; nr: normal range

by VFA in asymptomatic postmenopausal women, mostly not associated with osteoporosis as assessed by DXA (33). The authors suggested that VFA should be implemented in the routine assessment of fracture risk in postmenopausal women (33). As the vast majority of grade 1 VF are usually asymptomatic, we can conclude that VFA is a valid methodology for assessment of VF of various grades. Accordingly, our study demonstrates that, as in other metabolic bone diseases, screening with VFA during DXA examination represents a valid, safe, and cost-effective method to complete the assessment of the vertebral spine in postmenopausal women with hypoparathyroidism. VFA may have even greater clinical relevance, given that in hypoparathyroidism BMD is typically above average.

Differently from previous studies, we observed low values of TBS in hypoparathyroid women (8,23). Noteworthy, low TBS values were registered in both the hypoparathyroid and the control group of postmenopausal women of our cohort, with no significant between-group difference. This point and the geographical differences

between the previous and the current cohort of hypoparathyroid women suggest the possible presence of country-specific differences in TBS reference data that definitely need confirmation by future research (8,23).

With reference to fracture risk, clinical risk factors for fragility fracture, as denoted by the FRAX® tool, seem to be associated with VF in postmenopausal hypoparathyroid women of our cohort. As femoral neck BMD was substantially normal in this group, it was not surprising that adding this parameter to the FRAX® calculation removed this association. Conversely, we observed that none of the skeletal characteristics of the hypoparathyroid skeleton nor factors associated with the disease itself were significantly associated with an increased risk of fracture. Although the difference was not statistically significant, it is important to note that the half of the hypoparathyroid women with VF had hypocalcemia-associated symptoms *vs* 38% of those without VF.

To our knowledge, these results represent the first report on the assessment of fracture by VFA in hypoparathyroidism.

Our data agree with those recently presented by Formenti et al showing that poorly controlled disease represents 1 of the risk factors for VF in a cohort of 71 female and male patients aged 29 to 87 years with hypoparathyroidism from different causes (34). We did not specifically evaluate factors associated with disease control, but serum calcium at the time of recruitment and hypocalcemia-associated symptoms were dichotomous variables. Hence, more data are needed to address this point. It could be indeed hypothesized that “classical” clinical risk factors for fracture, together with those associated with the disease itself, may be associated with fracture risk in patients with chronic hypoparathyroidism. Given the limits of BMD in assessing fracture risk in hypoparathyroidism, studies evaluating which of the clinical and eventually biochemical factors are associated with VF will help to define the fracture risk profile in these patients. Skeletal parameters other than BMD and TBS need to be investigated to define mechanisms of perturbation of the trabecular compartment that may predispose to fracture. Finally, it would be of interest to investigate whether the results of our study may be applied to premenopausal women and men. In the hypothesis that disease control may significantly affect fracture risk, we cannot exclude that VF may be more common in hypoparathyroid premenopausal women and men *vs* euparathyroid age- and sex-matched subjects.

Limitations of our study are the relatively small number of patients of our cohort with consequent low absolute number of fracture events (both VF and non-VF). This point may have altered our ability of capturing important other factors associated with fragility fractures. Nevertheless, this was not part of the primary aim of the study. Additionally, as VF were asymptomatic and no previous imaging of the spine was available, we could not rule out the possibility that VF have occurred before the diagnosis of chronic postsurgical hypoparathyroidism. Although it was not a very large cohort, the study was designed to investigate prevalence of VF in a homogeneous group of patients, namely postmenopausal hypoparathyroid women. This allowed us to exclude confounding factors such as sex and menopause in the assessment of fracture risk. Finally, our results may not be extended to chronic hypoparathyroidism from all causes, as only postsurgical cases were included in our analysis.

In conclusion, our results demonstrate that, despite normal or above average BMD at all sites, VFs are common in postmenopausal women with chronic postsurgical hypoparathyroidism. VFA is a reliable methodology for assessment of VF and its application during the DXA exam should be recommended in these patients. Future studies are needed to assess specific factors associated with VF in chronic postsurgical hypoparathyroidism.

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Disclosures: SM served as speaker for Abiogen, Amgen, Bruno Farmaceutici, Diasorin, Eli Lilly, Shire, Sandoz, and Takeda. He served in advisory board of Abiogen, Kyowa Kirin, Pfizer, UCB. JPB serves as speaker for Amgen and Radius. He is a consultant for Takeda. All other authors declare no conflict of interests.

Data Availability: The data sets 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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