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ORIGINAL ARTICLE

Sex-specific associations of vitamin D and bone biomarkers with bone density and physical function during recovery from hip fracture: the Baltimore Hip Studies

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Abstract

Summary Less is known about recovery from hip fracture in men. We found differences in 25-hydroxyvitamin D and bone biomarkers between men and women during the year after hip fracture, underscoring the importance of vitamin D assessment in older men and pharmaceutical treatment to reduce bone resorption after hip fracture.

Purpose Less is known about recovery from hip fracture in men compared to women. We examined differences between men and women in 25-hydroxyvitamin D (25OHD) and bone turnover markers, and associations with bone mineral density (BMD) and physical function, during the year after a hip fracture.

Methods Community-dwelling, ambulatory adults aged 65 years and over (157 men and 154 women) enrolled in the Baltimore Hip Studies 7th cohort were included. We analyzed 25OHD, C-terminal telopeptide (β-CTX-I), procollagen type I N-terminal propeptide (PINP), PTH, and femoral neck BMD at baseline, 2, 6, and 12 months after hip fracture, and short physical performance battery (SPPB) at 2, 6, and 12 months.

Results During admission for hip fracture, median 25OHD levels were 15.2 ng/mL (IQR 10.0) in men compared with 23.9 ng/mL (IQR 13.4) in women and remained lower in men at 2, 6, and 12 months (all $p < 0.001$). β-CTX-I was higher in men on admission, and at 2 and 6 months (all $p < 0.05$), and PINP was higher in men at 6 months ($p = 0.04$), with no significant differences between men and women in PTH. Higher 25OHD and PINP concentrations in women only and lower β-CTX-I and PTH concentrations in both sexes were associated with greater BMD. Higher 25OHD concentrations were associated with higher SPPB scores in both sexes.

Conclusions These findings underscore the importance of vitamin D assessment in older men and missed opportunities in both sexes for vitamin D supplementation and pharmaceutical treatment to reduce bone resorption after hip fracture.

Keywords 25-Hydroxyvitamin D · C-Telopeptide · DXA · Procollagen type 1 amino-terminal propeptide · Short physical performance battery

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Introduction

Hip fractures are debilitating and can lead to significant morbidity and mortality [1]. Because hip fracture is more common in women, the majority of research on risk factors for hip fracture has been conducted in women, despite a higher annual mortality after fracture in men at any given age [2]. In the Osteoporotic Fractures in Men Study (MrOS) cohort, low BMD was a risk factor for hip fracture in men, with acceleration of bone loss after the age of 70 [3]. Several studies have additionally examined serum levels of 25OHD and markers of bone turnover as predictors of hip fracture in men. In MrOS, 25OHD < 20 ng/ml was present in 26% of participants and 25OHD < 30 ng/ml was present in 72% of participants [4]; lower 25OHD levels were associated with higher fracture risk [5]. However, the association between markers of bone turnover and subsequent fracture has been inconsistent in studies of men [6–8].

Even less is known about alterations in 25OHD and bone biomarkers during recovery from hip fracture, a time of active bone healing. Data from the Baltimore Hip Studies have shown high levels of β-CTX-I and PTH in women during the year after hip fracture [9–11]. However, there are no data on 25OHD levels or bone turnover markers over time in men who have sustained a hip fracture, and therefore no comparisons to women to assess potential sex-specific differences in bone metabolism after fracture. This could affect consideration of treatment options post fracture.

We sought to address these gaps in the first study of patients who have sustained a hip fracture to prospectively enroll equal numbers of men and women and obtain serial blood measurements. We compared 25OHD, PINP, β-CTX-I, and PTH in men and women during the year after a hip fracture and examined the relationship between these biomarkers and BMD and physical function during recovery. We have previously shown in this study that men had a statistically significant decline in BMD at the femoral neck during the year following a fracture (−4.60% [95% confidence interval (CI) −7.76%, −0.20%] in adjusted analyses) whereas women did not (−1.62% [95% CI −4.57, 1.32%] in adjusted analyses), and the *p*-value for the interaction term was not statistically significant [12]. We have also shown that women had a better SPPB score at first measurement than men did, but men had greater improvement in SPPB score over time [13]. We hypothesized that, despite higher BMD at the time of fracture, men would have lower 25OHD levels and higher bone turnover than women, shortly after hip fracture and over time. We also hypothesized that there were potential sex-specific differences in the relationship between these biomarkers and BMD and physical function during the year after fracture.

Methods

Participants and study design

The Baltimore Hip Studies (BHS-7) cohort study recruited patients prospectively from eight acute care hospitals located in the Baltimore, Maryland area [14]. Since hip fracture is less common in men than in women, enrollment of men was rolling, with women's enrollment frequency matched within each hospital in a 1:1 ratio. This contemporaneous enrollment strategy within each hospital was designed to minimize the effects of changes in care over time within each hospital and of hospital practice heterogeneity between hospitals on observed differences between men and women. Community-dwelling men and women aged 65 years or older admitted with diagnosis of hip fracture (ICD-9 codes 820.00–820.9) who consented (or whose proxy provided consent) to participate within 15 days of admission were enrolled. Patients were excluded if they had a pathologic fracture, did not speak English, were bedbound for 6 months prior to fracture, lived > 70 miles from the hospital, weighed > 300 pounds (weight restrictions on DXA table), did not undergo surgery, or had hardware in the contralateral hip leaving no unaffected hip for BMD measurement. Between May 2006 and June 2011, 362 hip fracture patients were consented (180 men and 182 women). Twenty-three participants were withdrawn. Five participants did not provide data at the baseline and 2-month follow-up visit and another 18 were removed from the analysis sample as a result of an IRB-requested post procedure audit, leaving a final sample of 339 (168 men, 171 women). The protocol was approved by the IRB at the University of Maryland Baltimore, as well as by each study hospital's IRB.

Blood and DXA measurements were obtained within 15 days of hospital admission and at 2-, 6-, and 12-month post-admission. Other baseline measures were obtained within 22 days of admission and at the same follow-up time points. Performance measures, including the SPPB, were only obtained at the 2, 6, and 12 timepoints. Assessments included fasting morning blood collection, an interview, and physical performance-based measurements conducted at the participant's place of residence. Weight was measured and a sliding caliper was used to measure knee height in order to estimate height. DXA was performed at one of seven study DXA centers located at or near recruitment hospitals.

Biochemical measurements

Fasting serum specimens were collected between 7 and 10 a.m. Samples were processed no later than 1 pm and stored at −80° until assayed together at the end of the study. 25OHD was measured by LC/MS/MS at the Brigham and

Women's Hospital Research Assay Core using standard reference material from the Vitamin D Standardization Program. Sensitivity was 1 ng/mL, and at 10 ng/mL, the intra-assay CV was 6.1% and inter-assay CV was 7.3% for D3 and 7.7% and 8.6% for D2 with a reference range of 30–75 ng/mL. β-CTX-I, PINP, and PTH were measured at The Johns Hopkins Institute for Clinical and Translational Research Clinical Research Unit Core Laboratory. β-CTX-I was measured by ELISA from IDX, with a sensitivity of 20 ng/L, intra-assay CV of 8.2%, inter-assay CV of 10.3%, and reference range of 90–1050 ng/L for postmenopausal women and 50–610 ng/L for men. PINP was measured by RIA from IDS, with a sensitivity of 2.0 µg/L, intra-assay CV of 4.1%, inter-assay CV of 2.7%, and reference range of 16–96 µg/L for postmenopausal women and 22–87 µg/L for men. Intact PTH was measured by ELISA from Alpco, with a sensitivity of 0.9 ng/L, intra-assay CV of 4.1%, inter-assay CV of 2.7%, and reference range of 8.3–68.0 ng/L.

Outcome assessments

Total hip and femoral neck BMD scans were performed of the non-fractured hip. Three of the seven DXA machines used were manufactured by Hologic (Waltham, MA, USA) and four by GE Lunar Prodigy (Madison, WI, USA). Standardized methods were used for quality control (QC), certification of DXA operators, and scanning procedures [14]. These included daily QC plots from each site and annual cross-calibration of machines using a single spine phantom and a variable composition phantom from Bio-Imaging Technologies (Newtown, PA, USA), and monthly review of randomly selected study scans across sites by two expert investigators. We selected femoral neck BMD for analyses because total and femoral neck BMD are highly correlated and femoral neck is used in clinical calculations of fracture risk.

The Short Physical Performance Battery (SPPB) includes balance, walking speed, and chair rise tests and is scored from 0 to 12 points; a higher score indicates better performance [15]. A change of 0.3–0.8 points is considered clinically significant [16].

Covariates

Socio-demographic variables of interest included age and race. BMI and Charlson Comorbidity Index [17, 18], excluding mild liver disease, were also calculated. For participants with missing Charlson Comorbidity Index ($n=1$) or BMI ($n=1$), values were imputed to sex-specific means. Participants were asked about prednisone, multivitamin, and calcium supplement use in the six months prior to baseline and oral and intravenous bisphosphonate, teriparatide, calcitonin, testosterone, estrogen, and vitamin D supplement use in the six months prior to baseline and at each study visit. Once taking a bisphosphonate, individuals were classified as persistent users for all subsequent time points due to the long duration of effects of bisphosphonates on bone turnover markers.

Statistical analysis

Baseline descriptive statistics were used to examine the distribution of demographic and clinical characteristics, and biomarkers by sex. Significant differences between men and women were assessed using *t*-tests for continuous measures and chi-squared tests or Fisher's exact tests for categorical measures. Unadjusted longitudinal regression models estimated by generalized estimating equations (GEE) accounting for repeated measures by subject were constructed to examine the differences in biomarkers over time by sex. For the analysis of 25OHD over time, an additional sensitivity analysis was performed excluding participants taking 10,000 IU of vitamin D or more after enrollment, to assess if post-fracture vitamin D supplementation differences by sex affected findings. Unadjusted and fully adjusted longitudinal analysis by GEE was performed examining the relationship between each biomarker and femoral neck BMD and SPPB over time. We incorporated the baseline, 2-, 6-, and 12-month DXA scan data into each model to model change in femoral neck BMD in parallel with change in each biomarker. For SPPB, changes were modeled using 2-, 6-, and 12-month data. These models should be interpreted as the average change in population femoral neck BMD (in g/cm^2) or SPPB (in points) per unit increase in biomarker during 12 months after hip fracture. Models in which men and women were analyzed separately are presented to provide a clinical context for the estimated magnitude of differences between men and women. The primary model included both men and women and included interaction terms to test for potential effect modification over time by sex. Statistical significance of the *p*-value for the interaction term in this model supports differences between men and women. Adjusted models included age, race, BMI, Charlson Comorbidity Index, prednisone use, and bisphosphonate use. All models with the BMD outcome additionally included an indicator to account for inter-site and machine differences [19]. All biomarkers were log-transformed for analysis and back-transformed for data presentation. *p*-values less than 0.05 were considered statistically significant. Analyses were performed using SAS version 9.4 (Cary, NC, USA) and all statistical tests were 2-sided.

Results

Table 1 illustrates the baseline characteristics of the 156 men and 149 women from the BHS 7th cohort who had at least one biomarker measurement, after excluding one

man taking testosterone and five women taking estrogen. Men and women had similar mean age (80.5 and 81.4 years, respectively) and BMI (25.6 and 24.9 kg/m^2, respectively), with 92% White across both sexes. Men had a higher mean Charlson Comorbidity Index, were less likely to have taken prednisone, a bisphosphonate, a multivitamin, or calcium and had a higher mean femoral neck BMD in the hip contralateral to the fracture. Men and women both had low physical function at 2 months after the fracture, as assessed by the SPPB.

Figure 1 displays longitudinal trends of 25OHD, β-CTX-I, PINP, and PTH over baseline, month 2, month 6, and month 12 after hip fracture. Men had significantly lower 25OHD concentrations than women did at every time point measured ($p < 0.001$ for all comparisons). Shortly after the admission for hip fracture, median 25OHD levels were 15.2 ng/mL (IQR 10.0 ng/mL) in men compared with 23.6 ng/mL (IQR 13.4 ng/mL) in women. Concentrations were 20.9 ng/mL (IQR 13.6 ng/mL) vs 29.5 ng/mL (IQR 15.8 ng/mL) at 2 months after the fracture, 20.8 ng/mL (IQR 14.6 ng/mL) vs 30.5 ng/mL (IQR 14.5 ng/mL) at 6 months, and 23.9 ng/mL (IQR 13.3 ng/mL) vs 30.6 ng/mL (IQR 11.3 ng/mL) at 12 months. In addition, the prevalence of 25OHD levels below discrete thresholds at baseline was higher in men than in women, at 93% vs 77% with levels < 30 ng/mL, 72% vs 37% < 20 ng/mL, and 22% vs 10% < 10 ng/mL (Supplemental Table). These differences by sex persisted through the 12-month follow-up, including in a sensitivity analysis in which participants taking 10,000 IU or

Table 1 Baseline characteristics of participants

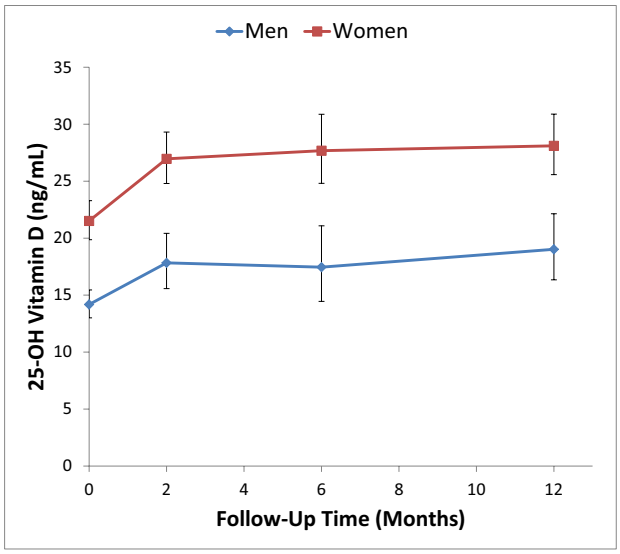
	Men $N=156$	Women $N=149$
Age in years, mean (SD)	80.5 (7.6)	81.4 (7.7)
Caucasian race, *n* (%)	140 (92)	136 (92)
BMI (kg/m^2), mean (SD)	25.6 (4.6)	24.9 (5.7)
Charlson comorbidity index*, mean (SD)	2.5 (1.9)	1.7 (1.6)
Fracture type, *n* (%)		
Femoral neck	69 (44)	80 (54)
Intertrochanteric	68 (44)	55 (37)
Other	18 (12)	14 (9)
Surgical management, *n* (%)		
Internal fixation	93 (60)	76 (51)
Arthroplasty	57 (37)	68 (46)
Other	5 (3)	5 (3)
Prednisone use, *n* (%)	8 (6)	20 (14)
Bisphosphonate use, *n* (%)	11 (7)	35 (24)
Calcium supplement use, *n* (%)	40 (27)	100 (68)
Multivitamin use, *n* (%)	94 (64)	115 (78)
Baseline femoral neck BMD, mean (SD)**	0.74 (0.14)	0.68 (0.13)
SPPB at 2 months, mean (SD)***	3.0 (2.7)	3.6 (2.6)

Data are shown as n (%) unless otherwise indicated

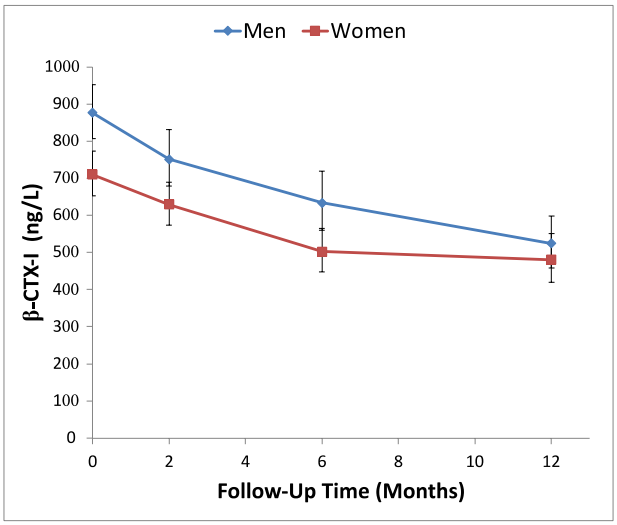
*Excluding mild liver disease

**Available for 120 men and 125 women

***Available for 100 men and 97 women

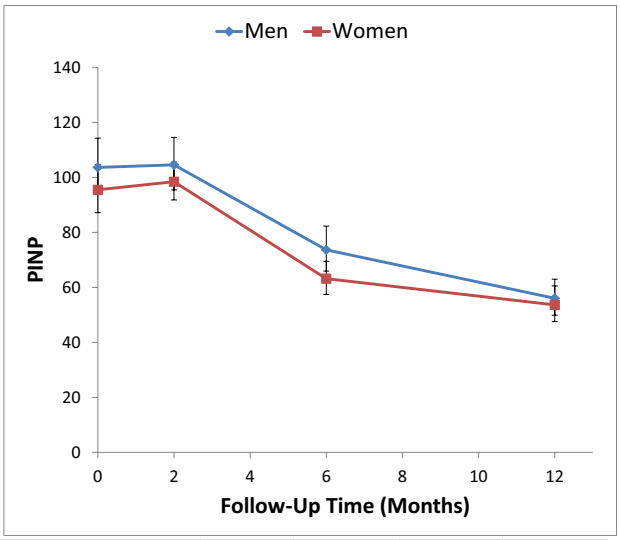


	0	2	6	12
Men (ng/mL)	15.2	20.9	20.8	23.9
Women (ng/mL)	23.6	29.5	30.5	30.6

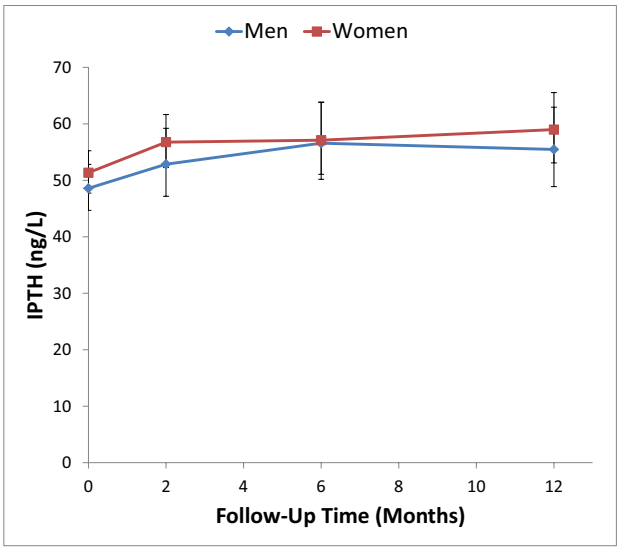


	0	2	6	12
Men (ng/L)	840	735	640	495
Women (ng/L)	700	675	440	430

Fig. 1 Mean 25OHD, β-CTX-I, PINP, and PTH levels at each time point, stratified by sex. Error bars represent 95% confidence intervals. Mean estimates and confidence intervals were obtained from GEE models. Median levels from raw data for each time point are presented below each graph. $N=152$ at baseline, 95 at 2 months, 76 at 6 months, and 68 at 12 months for men. $N=145$ at baseline, 108 at 2 months, 78 at 6 months, and 69 at 12 months for women



	0	2	6	12
Men (µg/L)	109.6	105.5	72.2	56.9
Women (µg/L)	92.3	92.7	62.4	53.6



	0	2	6	12
Men (ng/L)	51.1	51.3	56.7	53.8
Women (ng/L)	50.1	54.0	56.1	57.1

Fig. 1 (continued)

more of ergocalciferol vitamin D supplementation were excluded (9 participants at 2 months, 9 at 6 months, and 3 participants at 12 months).

β-CTX-I concentrations declined in both men and women after hip fracture. Men had significantly higher β-CTX-I levels than women did during the first 6 months after hip fracture ($p < 0.05$) with no significant difference at 12 months ($p = 0.10$). Median β-CTX-I levels were 0.84 ng/mL (IQR 0.55 ng/mL) in men and 0.70 ng/mL (IQR 0.55 ng/mL) in women on admission. At 2 months post-fracture, β-CTX-I levels were 0.74 ng/mL (IQR 0.47 ng/mL) in men and 0.68 (IQR 0.38 ng/mL) in women, 0.64 ng/mL (IQR 0.45 ng/mL) in men and 0.44 ng/mL (IQR 0.39 ng/mL) in women at 6 months, and 0.50 ng/mL (IQR 0.37 ng/mL) in men and 0.43 ng/mL (IQR 0.44 ng/mL) in women at 12 months. These results were not affected by exclusion of participants taking a bisphosphonate or teriparatide.

Concentrations of PINP declined after two months in both sexes, with a statistically significantly higher level in men at six months ($p = 0.04$). For PINP, the median value after fracture was 109.6 µg/L (IQR 86.9 µg/L) in men and 92.3 µg/L (IQR 66.5 µg/L) in women. At 2 months, PINP was 105.5 µg/L (IQR 68.3 µg/L) in men and 92.7 µg/L (IQR 48.8 µg/L) in women. By 6 months, PINP was 72.2 µg/L in men (IQR 52.1 µg/L) and 62.4 µg/L (IQR 34.6 µg/L) in women. At 12 months, PINP was 56.9 µg/L (IQR 36.9 µg/L) in men and 53.6 µg/L (IQR 34.9 µg/L) in women.

The median PTH value on admission was 51.1 ng/L (IQR 27.0 ng/L) in men and 50.1 ng/L (IQR 26.6 ng/L) in women. PTH levels did not differ significantly between men and women at any time point.

Table 2 demonstrates the longitudinal association of each biomarker with femoral neck BMD. Higher 25OHD concentrations during recovery from hip fracture were associated with higher BMD in women (0.012 g/cm^2 higher for every 10 ng/mL higher 25OHD level, 95% CI 0.001, 0.022, $p = 0.03$), but not in men (− 0.013 g/cm^2, 95% CI − 0.031, 0.005, $p = 0.16$), after accounting for DXA machine type and adjustment for age, race, BMI, Charlson Comorbidity Score and prednisone and bisphosphonate use, with a p-value of 0.03 for interaction by sex. Higher β-CTX-I and PTH during over the year post fracture were associated with lower BMD in both sexes (− 0.019 g/cm^2 for every 500 ng/L higher β-CTX-I level, 95% CI − 0.033, − 0.005, $p = 0.01$ and − 0.012 g/cm^2 for every 30 ng/L higher PTH level, 95% CI − 0.021, − 0.003, $p = 0.009$ in adjusted models), with no significant interactions detected between men and women. Higher PINP concentrations were associated with higher BMD only in women (0.020 g/cm^2 for every 50 µg/L higher PINP level, 95% CI 0.020, 0.030, $p = 0.02$), with a p-value of 0.004 for interaction by sex in the adjusted model.

Higher 25OHD concentrations during the year post fracture were associated with higher SPPB scores when men and women were analyzed together, both for crude (0.40, 95% CI 0.11–0.70, $p = 0.007$) and adjusted (0.26, 95% CI 0.01–0.51, $p = 0.04$) analyses (Table 3). p-values for interaction by sex were not statistically significant. β-CTX-I, PTH, and PINP were not associated with SPPB in men or women in adjusted analyses.

Table 2 Average change in population femoral neck BMD in g/cm^2 per unit increase in biomarker during 12 months after hip fracture

		Men		Women		Combined men and women		
		BMD change in g/cm^2	95% CI	BMD change in g/cm^2	95% CI	BMD change in g/cm^2	95% CI	*p*-value Interaction
25OHD, per 10 ng/mL	Crude	−0.018	−0.037, 0.002	0.009	−0.004, 0.023	−0.009	−0.021, 0.002	0.02
	Adjusted	−0.013	−0.031, 0.005	0.012*	0.001, 0.022	0.001	−0.009, 0.011	0.03
β-CTX-I, per 500 ng/L	Crude	−0.024*	−0.043, −0.005	−0.011	−0.032, 0.009	−0.013	−0.028, 0.001	0.39
	Adjusted	−0.023*	−0.041, −0.003	−0.014	0.031, 0.004	−0.019*	−0.033, −0.005	0.78
PTH, per 30 ng/L	Crude	−0.009	−0.021, 0.006	−0.015	−0.030, 0.003	−0.009*	−0.021, 0	0.60
	Adjusted	−0.006	−0.018, 0.009	−0.018*	−0.027, 0.006	−0.012*	−0.021, −0.003	0.24
PINP, per 50 µg/L	Crude	−0.005	−0.015, 0.005	0.015	−0.005, 0.035	0.005	−0.005, 0.015	0.07
	Adjusted	−0.005	−0.020, 0.005	0.020*	0.020, 0.030	0	−0.010, 0.010	0.004

All models adjusted for DXA machine type (Hologic or Lunar)

Additional covariates included in adjusted model: age, race, BMI, Charlson Comorbidity Index, prednisone use, and bisphosphonate use. Combined model additionally adjusted for sex

p-value is for interaction of biomarker by sex

*$p < 0.05$

Table 3 Average change in population SPPB per unit increase in biomarker during 12 months after hip fracture

		Men		Women		Combined men and women		
		SPPB change	95% CI	SPPB change	95% CI	SPPB change	95% CI	*p*-value Interaction
25OHD, per 10 ng/mL	Crude	0.29	−0.17, 0.74	0.52*	0.12, 0.91	0.40*	0.11, 0.70	0.45
	Adjusted	0.21	−0.19, 0.61	0.29	−0.05–0.62	0.26*	0.01, 0.51	0.54
β-CTX-I, per 500 ng/L	Crude	−0.53	−1.07, 0.02	−0.25	−0.90, 0.40	−0.40	−0.83, 0.02	0.52
	Adjusted	−0.07	−0.52, 0.38	−0.12	−0.67, 0.43	−0.09	−0.45, 0.26	0.88
PTH, per 30 ng/L	Crude	0.04	−0.19, 0.27	−0.02	−0.03, 0.003	0.02	−0.22, 0.17	0.45
	Adjusted	0.08	−0.17, 0.34	0.14	−0.17, 0.46	0.13	−0.07, 0.32	0.96
PINP, per 50 µg/L	Crude	−0.57*	−0.93, −0.20	−0.24	−0.75, 0.28	−0.44*	−0.75, −0.14	0.30
	Adjusted	−0.30	−0.66, 0.06	0.10	−0.42, 0.61	−0.13	−0.43, 0.18	0.38

Covariates included in adjusted model: age, race, BMI, Charlson Comorbidity Index, prednisone use, and bisphosphonate use. Combined model additionally adjusted for sex

p-value for interaction of biomarker by sex

*$p < 0.05$

Discussion

In a study designed to detect sex differences in the serum biomarkers of 25OHD, β-CTX-I, PINP, and PTH and their associations with BMD and physical function of men and women who had sustained a hip fracture, we found clinically meaningful differences in concentrations of 25OHD, β-CTX-I, and PINP between men and women for at least 6 months after hip fracture, despite similar changes over time of each biomarker. Moreover, increasing concentrations of biomarkers of vitamin D status (25OHD) and bone formation (PINP) were associated with higher femoral neck BMD only in women, whereas decreasing concentrations of biomarkers of bone resorption—β-CTX-I and PTH—were associated with higher BMD in both sexes. Increasing 25OHD concentrations were associated with better physical function in both sexes. These findings provide insights into mechanisms of bone remodeling underlying sex-specific differences in the year following hip fracture, while highlighting the importance of vitamin D supplementation and pharmaceutical treatment to reduce bone resorption regardless of the patient's sex.

Both men and women in our study had high rates of vitamin D deficiency and insufficiency, which was worse in men

than women and persisted over time. There have been no studies that have measured 25OHD concentrations over time in men compared to women after hip fracture, but studies have shown a high prevalence of vitamin D deficiency and insufficiency measured after acute fragility fracture [20], a high prevalence of frailty in individuals who sustain a hip fracture [21], and lower rates of replacement of vitamin D in men than in women after hip fracture [22]. Men in our study had more comorbidities and could have had lower vitamin D intake and absorption as well as reduced sun exposure compared to women. Whereas higher vitamin D concentrations were associated with higher BMD only in women, the association with improved physical function was present in both sexes. Clinical trials of vitamin D supplementation have had mixed results, although some, but not all, trials restricted to older individuals with low vitamin D concentrations have demonstrated improvements in fracture risk and reduction in falls [23–25], and observational evidence in women following hip fracture finds more falls in those with extremely low vitamin D levels [26]. The US Preventive Services Task Force found inadequate evidence to estimate the benefit of vitamin D supplementation on prevention of fractures in community-dwelling men or postmenopausal women, though studies of participants with vitamin D deficiency were excluded from review [27]. The Endocrine Society, National Osteoporosis Foundation, and American Geriatrics Society all recommend 800 to 1000 IU per day of vitamin D for prevention of falls and fractures in older adults [28–30]. Our data suggest that there are missed opportunities for treatment of vitamin D deficiency in hip fracture patients who are at risk for a subsequent hip fracture, particularly in men with comorbidities, who are more likely to have severe vitamin D deficiency.

The implication that there are missed opportunities for treatment of vitamin D deficiency post hip fracture is supported by the PTH data. PTH levels did not differ significantly between men and women, with mean and median levels trending toward the upper limit of the reference range throughout follow-up. This is likely a reflection of secondary hyperparathyroidism due to vitamin D deficiency in both sexes. Our data suggest that lowering PTH levels during recovery, presumably through vitamin D supplementation, would benefit BMD in both sexes.

β-CTX-I, a marker of bone resorption, and PINP, a marker of bone formation, were higher at the time of fracture in both sexes and declined over time, reflecting higher initial activity in response to fracture healing. Men in our cohort displayed an overall decline in BMD in their contralateral hip, whereas women did not [12], consistent with higher relative bone resorption. It is possible that the relatively higher levels of β-CTX-I in men throughout the year after fracture differentially affected fracture healing and BMD in the contralateral hip. Our data also show that lower β-CTX-I levels were associated with higher BMD in both sexes. More than 90% of men in this study were not taking bisphosphonates either before or during the study period [31], which is consistent with estimates from other studies [32–34].

Our data support a need for improved recognition of the importance of bisphosphonate initiation in men, to inhibit bone resorption and decrease BMD loss in the contralateral hip, with the goal of prevention of additional fractures. Correction of vitamin D deficiency should be performed prior to initiating osteoporosis therapy. In the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Recurrent Fracture Trial, initiation of vitamin D and IV zoledronic acid reduced both recurrent fracture risk and mortality following hip fracture [35]. However, post hoc analyses from HORIZON show the need to pay specific attention to men during recovery from hip fracture, based on analyses showing that men had less BMD benefit from zoledronic acid than women did over the first 12 months after hip fracture [36]. Evaluation of these and other interventions are recommended during or after hospitalization for hip fracture, in programs such as a Fracture Liaison Service, which is supported by the American Orthopaedic Association, the International Osteoporosis Foundation, and an ASBMR Task Force as a cost-effective way to prevent recurrent fracture [37, 38].

We are unable to determine whether the relationship between vitamin D and SPPB is causal. Data from randomized trials have not been conclusive regarding the impact of vitamin D on physical function and falls, although the degree of vitamin D insufficiency was far less in many of these trials than in our study population [23]. In addition, we did not detect associations between β-CTX-I, PINP, or PTH and physical function, which supports the specificity of their associations with bone.

Our study has several strengths. To our knowledge, this is the first study to assess bone biomarkers in men compared to women during recovery from hip fracture. Recruitment was matched by date and hospital to minimize the effects of changes in care over time and differences in practice across hospitals on any differences detected between sexes. This resulted in inclusion of men and women of similar age, race, and BMI. We collected data using standardized protocols and validated assays in samples collected at four times over the course of one year after hip fracture, and we performed analyses that allowed simultaneous comparisons of 25OHD and three bone biomarkers in clinical use.

However, our study also has limitations. Attrition was 53% by 12 months after the fracture, despite monthly phone calls to maintain contact. To mitigate the effects of missingness on model estimates at later time points, we used models that limit bias from missing data. Our study included predominantly white participants in a single metropolitan area, which could limit generalizability

to non-white hip fracture patients and to patients in other regions. We did not have information on vitamin D content of multivitamins and dietary vitamin D intake nor of denosumab, which was approved by the FDA one year prior to the recruitment of the last participant. We did not consider chronic kidney disease in our analyses. We did examine PTH levels, which may be affected early in the process of chronic kidney disease-mineral and bone disorder, throughout the 12-month recovery period and performed analyses of the relationship between PTH and femoral neck BMD and SPPB outcomes. The β-CTX-I and PTH assays were performed in serum, and the methodologies used for these assays are not transposable to current assays. In addition, our study was observational, limiting causal inferences.

Conclusions

We undertook a comparison of men and women recovering from hip fracture to assess whether levels of 25OHD and bone biomarkers, their values over time, and their associations with BMD and physical function differed during the year after hip fracture. Our findings underscore the importance of vitamin D assessment in older men, as well as missed opportunities in both sexes for vitamin D supplementation and therapy to reduce bone resorption after hip fracture.

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Data availability BHS-7 data have potentially identifiable patient health information. Limited de-identified datasets and analysis codes are available to investigators upon request and approval from the study leadership group.

Declarations

Conflicts of interest Anne R. Cappola, Danielle S. Abraham, Jeffrey M. Kroopnick, Yi Huang, Marc C. Hochberg, Michelle Shardell, Gregory E. Hicks, and Denise Orwig declare no conflicts of interest. Ram R. Miller is a full-time employee of the Novartis Institutes for BioMedical Research. Jay Magaziner serves on the Multidisciplinary Advisory Board for the Own the Bone Program of the American Orthopedic Association and the Board of the Fragility Fracture Network.

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