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Serial Bone Density Measurement and Incident Fracture Risk Discrimination in Postmenopausal Women

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IMPORTANCE Repeated bone mineral density (BMD) testing to screen for osteoporosis requires resources. For patient counseling and optimal resource use, it is important for clinicians to know whether repeated BMD measurement (compared with baseline BMD measurement alone) improves the ability to discriminate between postmenopausal women who will and will not experience a fracture.

OBJECTIVE To assess whether a second BMD measurement approximately 3 years after the initial assessment is associated with improved ability to estimate fracture risk beyond the baseline BMD measurement alone.

DESIGN, SETTING, AND PARTICIPANTS The Women's Health Initiative is a prospective observational study. Participants in the present cohort study included 7419 women with a mean (SD) follow-up of 12.1 (3.4) years between 1993 and 2010 at 3 US clinical centers. Data analysis was conducted between May 2019 and December 2019.

MAIN OUTCOMES AND MEASURES Incident major osteoporotic fracture (ie, hip, clinical spine, forearm, or shoulder fracture), hip fracture, baseline BMD, and absolute change in BMD were assessed. The area under the receiver operating characteristic curve (AU-ROC) for baseline BMD, absolute change in BMD, and the combination of baseline BMD and change in BMD were calculated to assess incident fracture risk discrimination during follow-up.

RESULTS Of 7419 participants, the mean (SD) age at baseline was 66.1 (7.2) years, the mean (SD) body mass index was 28.7 (6.0), and 1720 (23%) were nonwhite individuals. During the study follow-up (mean [SD] 9.0 [3.5] years after the second BMD measurement), 139 women (1.9%) experienced hip fractures, and 732 women (9.9%) experienced major osteoporotic fracture. In discriminating between women who experience hip fractures and those who do not, AU-ROC values were 0.71 (95% CI, 0.67-0.75) for baseline total hip BMD, 0.61 (95% CI, 0.56-0.65) for change in total hip BMD, and 0.73 (95% CI, 0.69-0.77) for the combination of baseline total hip BMD and change in total hip BMD. Femoral neck and lumbar spine BMD values had similar discrimination for hip fracture. For discrimination of major osteoporotic fracture, AU-ROC values were 0.61 (95% CI, 0.59-0.63) for baseline total hip BMD, 0.53 (95% CI, 0.51-0.55) for change in total hip BMD, and 0.61 (95% CI, 0.59-0.63) for the combination of baseline total hip BMD and change in total hip BMD. Femoral neck and lumbar spine BMD values had similar ability to discriminate between women who experienced major osteoporotic fracture and those who did not. Associations between change in bone density and fracture risk did not differ by subgroup, including diabetes, age, race/ethnicity, body mass index, or baseline BMD T score.

CONCLUSIONS AND RELEVANCE The findings of this study suggest that a second BMD assessment approximately 3 years after the initial measurement was not associated with improved discrimination between women who did and did not experience subsequent hip fracture or major osteoporotic fracture beyond the baseline BMD value alone and should not routinely be performed.

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Supplemental content

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Fractures will be experienced by 1 out of 2 postmenopausal white women in their remaining lifetime.[1] Bone mineral density (BMD) is well recognized as a strong predictor of fracture risk. The United States Preventive Services Task Force (USPSTF) recommends screening for osteoporosis with BMD measurement in women aged 65 years or older.[2] For postmenopausal women younger than 65 years, the USPSTF recommends selective osteoporosis screening based on clinical risk factors and formal clinical risk assessment tools. However, the USPSTF does not make recommendations regarding the interval of BMD testing owing to limited evidence. Repeated BMD testing to screen for osteoporosis requires resources. However, whether repeated BMD testing improves fracture prediction beyond that provided by baseline BMD is controversial.

Two previous studies found that repeat measurement of BMD 4 to 8 years after the baseline scan did not meaningfully improve the ability to distinguish who experienced incident fracture from who did not.[3,4] However, previous studies have limitations, including analysis of data from both men and women together[4] and the lack of younger postmenopausal women in the study population.[3,4] Important knowledge gaps also exist regarding whether certain risk subgroups may derive more benefit from undergoing repeated BMD testing after 3 years compared with a single baseline BMD test in terms of predicting risk of incident fracture. For instance, repeat BMD testing may have greater value in higher-risk individuals, such as those with advanced age, lower body mass, white vs black race/ethnicity, or diabetes.

The objectives of the present study were to use data from a large prospective cohort that included younger and older postmenopausal women to evaluate whether, compared with baseline BMD alone, a second BMD measurement approximately 3 years after the initial measurement was associated with a better ability to distinguish women who would experience a subsequent fracture from women who would not. We also determined whether the association of change in BMD with fracture risk varied across risk subgroups defined by age, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), race/ethnicity (white vs black), or a diagnosis of diabetes. We hypothesized that the repeat BMD measurement 3 years after baseline would not be associated with an improved ability to estimate subsequent risk of major osteoporotic fracture (MOF) or hip fracture beyond that of baseline BMD alone.

Key Points

Question Is a second bone mineral density (BMD) measurement approximately 3 years after the initial baseline measurement associated with improved subsequent fracture risk discrimination in postmenopausal women?

Findings This cohort study of 7419 postmenopausal women found that a second BMD assessment approximately 3 years after the initial measurement was not associated with improved risk discrimination, beyond the initial BMD assessment, between women who did and did not experience hip fracture or major osteoporotic fracture.

Meaning The findings of this cohort study suggest that a second BMD measurement approximately 3 years after the initial measurement was not associated with improved accuracy of fracture risk assessment beyond a baseline bone mineral density measurement and should not routinely be performed in postmenopausal women.

Methods

Women's Health Initiative Study Participants

We used data from the Women's Health Initiative (WHI) Study, which recruited 161 808 postmenopausal women aged 50 to 79 years at 40 clinical centers in the US.[5] Participants were free from serious cardiac, pulmonary, renal, and hepatic conditions. The WHI observational study examined potential risk factors and natural course of important causes associated with morbidity and mortality in postmenopausal women. The 3 placebo-controlled WHI clinical trials tested hormone therapy, calcium plus vitamin D supplementation, and dietary modification (low-fat eating pattern). At baseline, weight and height were measured and BMI was calculated. Each institution obtained institutional review board committee approval to conduct this study. All participants provided written informed consent that was obtained in a manner consistent with the Common Rule requirements. No one received compensation or was offered any incentive for participating in this study.

After completion of the main WHI study (1993-2005), all women who were still participating in WHI were invited to join to join the WHI Extension 1 Study (2005-2010). In the WHI Bone Density Substudy, participants at 3 of the 40 clinical centers (Tucson/Phoenix, Arizona; Pittsburgh, Pennsylvania; and Birmingham, Alabama) were invited at the time of WHI enrollment to undergo BMD measurement using standardized protocols. Of the 11 363 who underwent baseline BMD measurement of the lumbar spine and hip, 9304 underwent both baseline and year 3 BMD measurements. We excluded data from 843 participants who reported using bisphosphonates, calcitonin, selective estrogen receptor modulators, or a combination of those medications) prior to their year 3 BMD measurement (eFigure 1 in the Supplement). We also excluded data from 16 participants who did not attend follow-up visits following their year 3 BMD measurement, 537 participants who reported a history of MOF at study baseline or between BMD measurements, and 489 participants for whom covariate data (regarding hormone use, history of fracture, or BMI) were missing. Therefore, the analytic sample for this study consisted of 7419 participants. The timing of assessments and outcomes are summarized in eFigure 2 in the Supplement.

Assessment of Incident Fracture

Fractures were self-reported on annual questionnaires. All self-reported hip fractures were adjudicated using medical records. The validity of information regarding fractures obtained by self-report is good in WHI and is higher for hip (78%) and forearm/wrist (81%) fractures than for clinical spine fractures (51%).[6] We defined MOF as hip, spine, radius, ulna, wrist,

upper arm, or shoulder fracture. The validity of the self-reported MOF category at the exact site was 80.4%.[6]

BMD and Appendicular Lean Mass Measurement

The BMD and appendicular lean mass (sum of lean mass of the arms and legs) were measured using dual-energy x-ray absorptiometry (DXA) with Hologic QDR2000 or 4500W machines (Hologic, Inc) at WHI study baseline and follow-up year 3. The DXA quality assurance procedures included cross-clinic use of hip and spine phantom scans, further evaluation of scans with specific problems, and review of a random sample of all scans.[7]

Other Covariates

Information regarding age, race/ethnicity, educational level, history of previous fracture, tobacco smoking, socioeconomic status, and medication use was obtained using a baseline self-assessment questionnaire. The RAND 36-item health survey physical functioning construct was calculated (range from 0 to 100, with higher scores indicating more favorable health state).[8] Physical activity level (total metabolic equivalent task hours per week) was assessed using the WHI validated physical activity questionnaire.[9,10]

Statistical Analysis

We used Cox proportional hazards regression to determine the associations between change in BMD and first incident fracture. Hip fractures and MOF each served as primary outcomes (dependent variables) of separate models. The primary independent variable was expressed per 1 SD decrease in total hip BMD, in which BMD was expressed as absolute BMD change. Secondary independent variables were change in femoral neck BMD and change in lumbar spine BMD. On the basis of prior publications, we adjusted the models for age, race/ethnicity, history of fracture (prior to study baseline or during follow-up but prior to the year 3 DXA), physical activity level, BMI (year 3), physical function level, and number of falls in the last year. Proportional hazards models were additionally stratified within the model by current use of hormone therapy (self-use in the observational study or active study arm of the WHI Hormone Therapy Trial) and WHI Study component (clinical trial, observational study). We made the decision a priori to stratify by age (<65, 65-74, ≥75 years), diabetes, race/ethnicity (black vs white), BMI category (<25, 25 to <30, ≥30), and baseline BMD T score. We verified the proportional hazards assumption; there were no violations of proportionality. In the models, missing categorical covariate data were given a separate missing category; no imputation was performed.

In sensitivity analyses, we excluded women using bone-active medications (bisphosphonates, teriparatide, denosumab, selective-estrogen receptor modulators, proton pump inhibitors, systemic corticosteroids, diabetes medications, selective serotonin reuptake inhibitors, loop diuretics, or aromatase inhibitors) at any time during follow-up. We used unconditional logistic regression models to examine baseline BMD and BMD change as estimators of hip fracture risk and MOF risk. We calculated the area under the receiver operating characteristic curve (AU-ROC) for baseline BMD alone, change in BMD, and the combination of baseline BMD and BMD change to discriminate women who experienced fracture from women who did not. These logistic regression models were minimally adjusted to account for current use of hormone therapy and WHI study component. Data analysis was conducted between May 2019 and December 2019 using SAS for Windows, version 9.4 (SAS Institute Inc) to perform statistical analyses. A 2-sided $P < .05$ was considered statistically significant.

Results

During the study follow-up (mean [SD], 9.0 [3.5] years after the second BMD measurement), 139 women (1.9%) experienced 1 or more hip fractures, and 732 women (9.9%) experienced 1 or more MOF. At baseline, the mean (SD) age of participants was 66.1 (7.2) years, mean (SD) BMI was 28.7 (6.0), and 1720 participants (23%) were nonwhite (**Table 1**). The numbers of incident hip and MOF events during study follow-up are summarized in eTable 1 in the Supplement.

Association of Change in BMD Between Baseline and Year 3 With Incident Hip Fracture Risk and MOF Risk

In models adjusted for age, race/ethnicity, history of fracture, physical activity level, BMI, physical function level, frequency of falls, hormone use, and baseline BMD, each 1 SD decrease in total hip absolute BMD (vs baseline) was associated with a 1.3-fold increase in the risk of hip fracture (adjusted hazard ratio [aHR], 1.29; 95% CI, 1.08-1.54 per 1 SD decrease in BMD; $P = .004$) (**Table 2**). By contrast, each 1 SD lower total hip or femoral neck baseline BMD was associated with 1.8-fold higher risk of hip fracture in the fully adjusted model (aHR, 1.80; 95% CI, 1.45-2.24). Associations of baseline femoral neck BMD and change in femoral neck BMD with hip fracture risk were of a similar magnitude (eTable 2 in the Supplement). Baseline lumbar spine BMD and change in lumbar spine BMD were not significantly associated with hip fracture risk although associations between lumbar spine BMD and hip fracture risk were similar in magnitude to those between total hip and femoral neck BMD and hip fracture risk.

For estimating risk of MOF, greater change in BMD at each of the 3 BMD measurement sites (total hip, femoral neck, and lumbar spine) was associated with a modest increase in risk of fracture; aHRs per 1 SD decrease in absolute BMD were 1.11 (95% CI, 1.03-1.20) for total hip BMD change, 1.18 (95% CI, 1.09-1.28) for femoral neck BMD change, and 1.12 (95% CI, 1.04-1.21) for lumbar spine BMD change. By contrast, baseline BMD was more strongly associated with increased risk of MOF, with aHRs ranging from 1.39 (95% CI, 1.28-1.51) for baseline lumbar spine BMD to 1.51 (95% CI, 1.37-1.67) for baseline femoral neck BMD.

In sensitivity analyses limited to participants who did not report using bone-active medications at any time during follow-up, the magnitudes of the aHRs were not substantially altered although the CIs around the point estimates of the associations sometimes included 1.0 (eTable 3 in the Supplement).

Table 1. Sociodemographic and Clinical Characteristics of the Study Population at the Second BMD Measurement[a]

Characteristic	Participants, No. (%)		
	All (n = 7419)	With major osteoporotic fracture outcome	Without major osteoporotic fracture outcome
Age, mean (SD), y	66.1 (7.2)	68.1 (7.1)	65.9 (7.2)
<65	3239 (44)	251 (34)	2988 (45)
65-74	3124 (42)	335 (46)	2789 (42)
≥75	1056 (14)	146 (20)	910 (14)
Race/ethnicity			
White	5699 (77)	642 (88)	5057 (76)
African American	1116 (15)	47 (6)	1069 (16)
Hispanic	434 (6)	34 (5)	400 (6)
Other/unknown	170 (2)	9 (1)	161 (2)
Educational level ≥college degree	2287 (30.8)	227 (31)	2060 (31)
BMI, mean (SD)	28.7 (6.0)	28.5 (6.2)	28.7 (6.0)
<25	2191 (30)	221 (30)	1970 (30)
25 to <30	2625 (35)	269 (37)	2356 (35)
≥30	2603 (35)	242 (33)	2361 (35)
Appendicular lean mass, mean (SD), kg	14.8 (2.8)	14.7 (2.8)	14.8 (2.8)
Falls in the last year[b]			
0	5176 (70)	450 (62)	4726 (71)
>0 to <2	1729 (23)	205 (28)	1524 (23)
≥2	347 (5)	62 (9)	285 (4)
History of fracture (any fracture before year 3 BMD measurement, other than major osteoporotic fracture)	2466 (33)	339 (46)	2127 (32)
Current smoker	501 (7)	46 (6)	455 (7)
Physical activity, mean (SD), MET h/wk	11.5 (13.9)	11.2 (13.2)	11.5 (14.0)
0	1323 (18)	139 (19)	1184 (18)
>0 to <5	1824 (25)	180 (25)	1644 (25)
5 to <12	1652 (22)	154 (21)	1498 (22)
≥12	2620 (35)	259 (35)	2361 (35)
Physical function, mean (SD)[c]	77.2 (22.1)	73.3 (24.0)	77.6 (21.9)
≤60	1603 (22)	200 (27)	1403 (21)
>60 to <90	2625 (35)	260 (36)	2365 (35)
≥90	3191 (43)	272 (37)	2919 (44)
Current estrogen therapy use (oral or transdermal)[d]	3454 (47)	314 (43)	3140 (47)
Medication use			
Antidiabetic[e]	646 (9)	80 (11)	566 (9)
Proton pump inhibitor	532 (7)	70 (10)	462 (7)
Systemic corticosteroid	17 (<1)	5 (<1)	12 (<1)
Thiazolidinedione	63 (<1)	11 (2)	52 (<1)
Loop diuretic	457 (6)	68 (9)	389 (6)
Selective serotonin reuptake inhibitor	527 (7)	76 (10)	451 (7)
Aromatase inhibitor	5 (<1)	0	5 (<1)
BMD measurements, mean (SD)			
Total hip			
BMD, g/cm^2	0.874 (0.139)	0.825 (0.131)	0.879 (0.139)
T score	−0.655 (1.053)	−1.000 (1.028)	−0.617 (1.049)
≤−2.5	240 (3)	47 (6)	193 (3)
Annualized BMD absolute change	0.002 (0.011)	0.001 (0.012)	0.002 (0.011)
Annualized BMD percent change	0.197 (1.333)	0.108 (1.430)	0.206 (1.322)
Femoral neck			
BMD, g/cm^2	0.738 (0.127)	0.692 (0.113)	0.743 (0.127)
T score	−1.115 (1.036)	−1.464 (0.971)	−1.076 (1.036)

(continued)

Table 1. Sociodemographic and Clinical Characteristics of the Study Population at the Second BMD Measurement[a] (continued)

Characteristic	Participants, No. (%)		
	All (n = 7419)	With major osteoporotic fracture outcome	Without major osteoporotic fracture outcome
≤−2.5	590 (8)	100 (14)	490 (7)
Annualized absolute change	−0.000 (0.012)	−0.001 (0.011)	−0.000 (0.012)
Annualized percent change	−0.028 (1.550)	−0.182 (1.561)	−0.011 (1.548)
Lumbar spine			
BMD, g/cm^2	1.015 (0.173)	0.968 (0.168)	1.020 (0.173)
T score	−0.728 (1.563)	−1.068 (1.525)	−0.690 (1.563)
≤−2.5	896 (12)	124 (17)	772 (12)
Annualized absolute change	0.006 (0.017)	0.006 (0.018)	0.006 (0.016)
Annualized percent change	0.621 (1.696)	0.619 (1.974)	0.621 (1.663)

Abbreviations: BMD, bone mineral density; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); MET, metabolic equivalent task.

[a] Values are taken from the last known value at the year 3 BMD measurement. Missing data: educational level (47 participants); appendicular lean mass (6 participants); falls (167 participants); fracture (648 participants); smoking (86 participants); diabetes (5 participants).

[b] Falls in the past year is a calculated rate based on a weighted mean of self-report intervals occurring in the year prior to BMD measurement.

[c] RAND 36-item health survey physical functioning construct, range 0 to 100.

[d] Self-initiated or trial-assigned.

[e] Antidiabetic use includes self-report of diabetes being treated with medication.

Table 2. Association of Annualized Absolute Total Hip BMD Change With Risk of Hip Fracture and Risk of Major Osteoporotic Fracture[a]

Measure	Hip fracture		Major osteoporotic fracture	
	1 SD decrease, HR (95% CI)	*P* value	1 SD decrease, HR (95% CI)	*P* value
Baseline BMD[b]	1.80 (1.45-2.24)	<.001	1.50 (1.37-1.64)	<.001
Absolute change				
Unadjusted	1.38 (1.17-1.63)	<.001	1.13 (1.05-1.21)	.002
Adjusted	1.21 (1.02-1.44)	.03	1.07 (1.00-1.16)	.06
Adjusted + BMD	1.29 (1.08-1.54)	.004	1.11 (1.03-1.20)	.005

Abbreviations: BMD, bone mineral density; HR, hazard ratio.

[a] For change in BMD, 1 SD decrease in absolute BMD corresponded to 0.011372 g/cm^2 at the total hip, 0.011696 g/cm^2 at the femoral neck, and 0.016676 g/cm^2 at the lumbar spine. All models are stratified by current hormone use (yes/no) and Women's Health Initiative Study component (clinical trial/observational study) and adjusted for age, race/ethnicity, history of fracture, physical activity, body mass index, physical function, falls in the last year, and, in BMD-adjusted models (adjusted + BMD), baseline BMD.

[b] HR per 1 SD lower baseline BMD.

Association of Continuous Absolute Change in BMD With Incident Hip Fracture Risk and MOF Risk Stratified by Diabetes, Age, Race/Ethnicity, and BMI

Associations between absolute change in total hip BMD (but not femoral neck or lumbar spine BMD) and hip fracture risk appeared to be more pronounced in white participants (HR, 1.32; 95% CI, 1.10-1.60) vs African American participants (HR, 0.59; 95% CI, 0.26-1.31) (*P* = .05 for interaction) (**Table 3**). Associations between change in femoral neck BMD and hip fracture risk appeared to be more pronounced in participants with diabetes (*P* = .04 for interaction), but this interaction was not significant when change in total hip or lumbar spine BMD was substituted for change in femoral neck BMD (eTable 4 in the Supplement).

Interaction of Continuous Annualized Absolute BMD Change and Baseline BMD T Score With Fracture Risk

We did not find evidence of an interaction between baseline BMD T score category and BMD change for estimating fracture outcomes (Table 3; eTable 4 in the Supplement).

Baseline BMD vs Change in BMD vs a Combination of These Factors in Discriminating Women Who Experienced Hip Fracture or MOF From Women Who Did Not

Overall, compared with baseline total hip BMD alone, absolute change in total hip BMD (year 3 minus baseline) and the combination of baseline BMD and change in BMD had an almost identical ability to discriminate women who experienced hip fracture from women who did not (adjusted for current hormone use and WHI study component) (**Table 4**). Overall, AU-ROC values were 0.71 (95% CI, 0.67-0.75) for baseline total hip BMD, 0.61 (95% CI, 0.56-0.65) for change in total hip BMD, and 0.73 (95% CI, 0.69-0.77) for the combination of baseline total hip BMD and change in total hip BMD. The AU-ROC values were similar among the 3 age subgroups (<65 years, 65-74 years, and ≥75 years) although AU-ROC values for the discrimination of hip fracture were slightly lower among women 65 years or older than among women younger than 65 years. AU-ROC values for femoral neck BMD and lumbar spine BMD for the discrimination of

Table 3. Interaction of Annualized Absolute Total Hip BMD Change and Subgroups With Risk of Hip Fracture and Risk of Major Osteoporotic Fracture[a]

Subgroup	Hip fracture		Major osteoporotic fracture	
	1 SD decrease, HR (95% CI)	*P* value for interaction	1 SD decrease, HR (95% CI)	*P* value for interaction
Diabetes				
Yes	1.72 (1.18-2.51)	.09	1.12 (0.93-1.35)	.90
No	1.19 (0.98-1.45)		1.11 (1.02-1.20)	
Age, y				
<65	1.87 (1.22-2.85)	.74	1.09 (0.96-1.24)	.11
65-74	1.05 (0.82-1.36)		1.05 (0.94-1.17)	
≥75	1.41 (1.09-1.83)		1.31 (1.13-1.54)	
Race/ethnicity				
African American	0.59 (0.26-1.31)	.05	0.90 (0.68-1.17)	.14
White	1.32 (1.10-1.60)		1.10 (1.02-1.20)	
BMI				
<25	1.27 (0.95-1.71)	.63	1.10 (0.94-1.28)	.81
25 to <30	1.51 (1.16-1.95)		1.15 (1.01-1.30)	
≥30	1.08 (0.77-1.50)		1.08 (0.96-1.21)	
Baseline T score				
≤−2.5	0.98 (0.63-1.51)	.14	1.13 (0.87-1.48)	.96
>−2.5 to <−1.0	1.23 (0.96-1.57)		1.09 (0.97-1.23)	
≥−1.0	1.43 (1.09-1.86)		1.10 (0.99-1.22)	
HT use				
Yes	1.38 (1.03-1.84)	.63	1.22 (1.09-1.37)	.04
No	1.26 (1.02-1.56)		1.04 (0.95-1.15)	

Abbreviations: BMD, bone mineral density; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HR, hazard ratio; HT, hormone therapy.

[a] Hazard ratios, 95% CIs, and interaction *P* values were derived from a survival model with fracture outcome as a function of annualized absolute change in BMD, the subgroup of interest, and their interaction. Models are stratified by current hormone use (yes/no) and Women's Health Initiative Study component (clinical trial/observational study) and adjusted for age (omitted from the models stratified by age), race/ethnicity, BMI, history of fracture, and baseline BMD. For change in BMD, 1 SD decrease corresponded to 0.011372 g/cm^2 at the hip, 0.011696 g/cm^2 at the femoral neck, and 0.016676 g/cm^2 at the lumbar spine. For age, BMI, and baseline BMD T-score subgroups, *P* value is from a separate model testing interaction of annualized absolute change in BMD by trend across subgroup levels.

Table 4. Comparison of AU-ROC Statistics in Models Adjusted for Baseline Total Hip BMD, Absolute Yearly BMD Change, or Their Combination, Overall and by Age Group[a]

Fracture site	AU-ROC (95% CI)		
	Baseline BMD	BMD change	Baseline BMD + BMD change
Hip fracture			
Overall	0.71 (0.67-0.75)	0.61 (0.56-0.65)	0.73 (0.69-0.77)
Age, y			
<65	0.66 (0.54-0.79)	0.69 (0.58-0.80)	0.73 (0.62-0.83)
65-74	0.67 (0.61-0.73)	0.55 (0.47-0.62)	0.67 (0.61-0.74)
≥75	0.64 (0.57-0.71)	0.62 (0.53-0.70)	0.69 (0.62-0.76)
Major osteoporotic fracture			
Overall	0.61 (0.59-0.63)	0.53 (0.51-0.55)	0.61 (0.59-0.63)
Age, y			
<65	0.58 (0.54-0.61)	0.53 (0.49-0.56)	0.58 (0.54-0.61)
65-74	0.61 (0.58-0.64)	0.53 (0.50-0.56)	0.61 (0.58-0.64)
≥75	0.60 (0.55-0.65)	0.58 (0.53-0.63)	0.63 (0.58-0.68)

Abbreviations: AU-ROC, area under the receiver operating characteristic curve; BMD, bone mineral density.

[a] For BMD site of total hip. All logistic regression models are adjusted for current hormone use (yes/no), and Women's Health Initiative Study component (clinical trial/observational study). Major osteoporotic fractures include hip, spine, lower arm/wrist, and upper arm/shoulder.

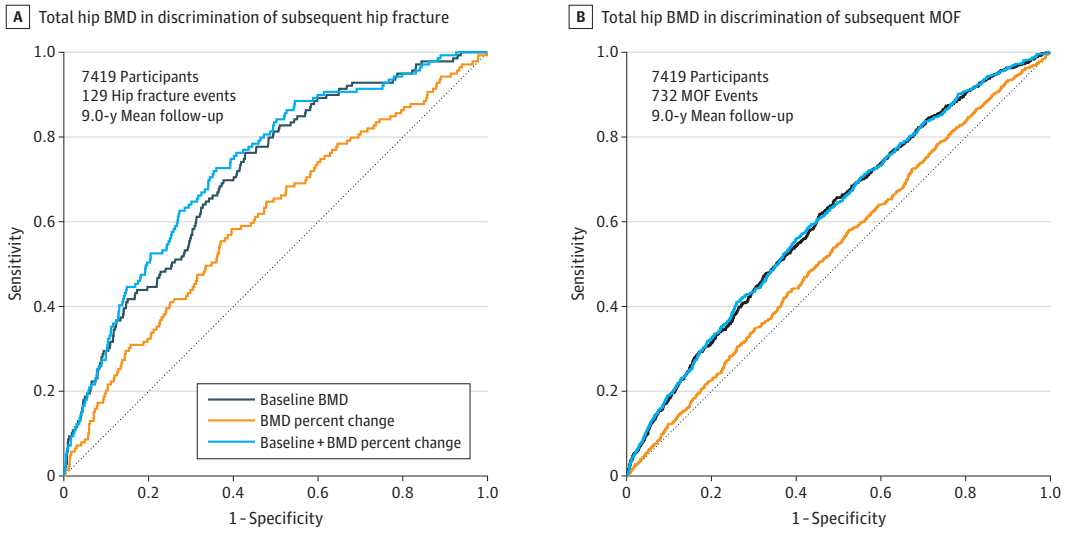
hip fracture and of MOF were very similar to those for total hip BMD (eTable 5 in the Supplement).

The AU-ROC values were lower for MOF than for hip fractures. However, similar to findings with hip fracture, baseline BMD alone, absolute change in BMD (year 3 minus baseline), and the combination of baseline BMD and change in BMD had almost identical ability to discriminate women who experienced MOF from women who did not (AU-ROC values ranged from 0.53 to 0.61). The AU-ROC values were similar among the 3 age subgroups (<65 years, 65-74 years, and ≥75 years). The AU-ROCs for baseline total hip BMD (0.61; 95% CI, 0.59-0.63), total hip BMD change (0.53; 95% CI, 0.51-0.55), and the combination of baseline BMD with BMD change (0.61; 95% CI, 0.59-0.63) were similar to one another in appearance (**Figure**, A and B). The patterns of the AU-ROCs for femoral neck and lumbar spine BMD (eFigures 3A-D in the Supplement) were similar to those for total hip BMD.

Discussion

In this prospective study of a large cohort of postmenopausal women, compared with baseline BMD alone, change in BMD and the combination of change in BMD with baseline BMD did

Figure. Receiver Operating Characteristic Curves for Total Hip Bone Mineral Density (BMD) in Discrimination of Hip Fracture and Major Osteoporotic Fracture



Curves are adjusted for Women's Health Initiative trial assignment and hormone therapy use. MOF indicates major osteoporotic fracture.

not have a better ability to discriminate women who experienced subsequent hip fracture or MOF from women who did not. To our knowledge, this is the first prospective study that addressed this issue in a study cohort that included younger postmenopausal US women. Forty-four percent of our study population was younger than 65 years. Whereas both baseline BMD and change in BMD were associated with incident fracture independent of each other, lower baseline BMD (1 SD lower) was more strongly associated with increased fracture risk than was the 3-year absolute change in BMD (per 1 SD). In addition, associations between change in BMD and fracture risk did not vary by clinical characteristics, including diabetes, age category, race/ethnicity, or BMI.

Our results regarding the lack of benefit of repeat BMD beyond baseline BMD alone in fracture discrimination are generally consistent with previous studies that were restricted to older adults.[3,4] First, among the older women and men participating in the Framingham Osteoporosis Study, Berry and colleagues[4] found that adding percent change in femoral neck BMD (4 years later) did not meaningfully improve performance (AU-ROC) of baseline BMD alone in discriminating hip fractures during a 12-year follow-up period. In that study, the AU-ROC value was 0.71 for the model with baseline femoral neck BMD and 0.72 for the model with both baseline BMD and change in BMD. In that study,[4] participants were older (mean age, 75 years) than in the present study. In a second study, Hillier and colleagues[3] used data from the Study of Osteoporotic Fractures (mean participant age, 72 years) to evaluate repeat BMD measurement after 8 years, with 5 years of subsequent follow-up. The AU-ROC values were identical for initial total hip BMD, repeat total hip BMD, and initial total hip BMD plus change in total hip BMD for discrimination of incident nonspine fractures (AU-ROC, 0.65) as well as for discrimination of incident hip fractures (AU-ROC, 0.73-0.74).

Our results are also generally consistent with studies performed outside of the US regarding associations between change in BMD independent of baseline BMD and fracture risk. Leslie and colleagues[11] examined data from women aged 40 years or older in Manitoba who received a second BMD scan a mean of 4 years after the baseline BMD test and follow-up for incident fractures for 2.7 years following the second BMD test. In that study, BMD change expressed as a continuous measure was not associated with fracture risk after consideration of baseline BMD. Similarly, Nguyen and colleagues[12] examined data from 966 women aged 60 years or older with a follow-up period of approximately 11 years. In that study, the association between femoral neck bone loss and risk of atraumatic fracture (relative hazard, 1.4; 95% CI, 1.1-1.8 per 5% loss) was modest in comparison with the association between baseline femoral neck BMD and fracture risk (relative hazard, 2.0; 95% CI, 1.7-2.2 per SD).

Our analyses approached the potential utility of repeating BMD measurements to estimate risk of fracture in 2 different ways: (1) we found that the repeated BMD measure did not improve the ability to distinguish women who will experience a fracture from women who will not, quantified as AU-ROC values, and (2) we found only modest associations (HRs) between 3-year change in BMD fracture risk. The present results suggest that routinely repeating measurement of BMD 3 years after baseline does not have high clinical utility, especially in context of the competing demands and time constraints of the busy clinical practice setting.

Our results have clinical implications given the need to inform the optimal frequency of BMD testing. Clinicians should be aware that although change in BMD a mean of 3 years after baseline is significantly associated with fracture risk, the magnitude of this risk is modest, and change in BMD does not add meaningfully to distinguish women who experience subse-

quent fracture from women who do not. Moreover, there are public health consequences of the cost and resources required to perform BMD scans that may not provide meaningfully important information for clinical decision-making regarding fracture prediction. Previous publications using data from the WHI study have provided valuable information on predicting fracture risk during the ensuing 5 years using various clinical risk factors. By contrast, the present study was novel because it did not seek to build fracture prediction tools, but rather it directly addressed the key clinical decision-making question, Does a repeated measure of BMD 3 years after baseline provide meaningful information beyond the baseline BMD measurement?

Limitations and Strengths

The limitations of our study included the observational study design; we controlled for numerous relevant confounders, but the possibility of residual confounding remains. As mentioned above, fractures were self-reported. The strengths of this study included the prospective follow-up, the large number of participants, and the detailed information regarding osteoporosis risk factors.

Conclusions

Our results support our initial hypothesis that a second BMD assessment conducted 3 years after the initial measurement would not be meaningfully associated with the risk of hip fracture or major osteoporotic fracture beyond the baseline BMD value alone. Thus, our evidence suggests that repeated BMD testing 3 years after baseline BMD in postmenopausal women should not be routinely performed. This information will inform future guidelines regarding the interval for repeated BMD testing in untreated postmenopausal women. Our findings further suggest that resources should be devoted to increasing the underuse of baseline BMD testing among women aged 65 and 85 years, one-quarter of whom do not receive an initial BMD test.[13]

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