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Association Between Change in BMD and Fragility Fracture in Women and Men*

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ABSTRACT: Our objective was to estimate the relationship between longitudinal change in BMD and fragility fractures. We studied 3635 women and 1417 men 50–85 yr of age in the Canadian Multicentre Osteoporosis Study who had at least two BMD measurements (lumbar spine, femoral neck, total hip, and trochanter) within the first 5 yr of the study and fragility fractures (any, main, forearm/wrist, ribs, hip) within the first 7 yr. Multiple logistic regression was used to model the relationship between baseline BMD, BMD change, and fragility fractures. We found that, among nonusers of antiresorptives, independent of baseline BMD, a decrease of 0.01 g/cm^2/yr in total hip BMD was associated with an increased risk of fragility fracture with ORs of 1.15 (95% CI: 1.01; 1.32) in women and 1.34 (95% CI: 1.02; 1.78) in men. The risk of fragility fractures in subgroups such as fast losers and those with osteopenia was better estimated by models that included BMD change than by models that included baseline BMD but excluded BMD change. Although the association between baseline BMD and fragility fractures was similar in users and nonusers of antiresorptives, the association was stronger in nonusers compared with users. These results show that BMD change in both men and women is an independent risk factor for fragility fractures and also predicts fracture risk in those with osteopenia. The results suggest that BMD change should be included with other variables in a comprehensive fracture prediction model to capture its contribution to osteoporotic fracture risk.
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Key words: fragility fracture, BMD change, longitudinal study, women, men

INTRODUCTION

Low BMD, as measured by DXA, is considered an important risk factor for fragility fracture and is widely used in clinical practice to identify those at increased risk for fracture.[1–6] Clinical guidelines[7–9] place great emphasis on a single measurement of BMD despite numerous studies concluding that a single measurement of BMD is not sufficient to assess fracture risk.[6,10–15] Thus, a majority of fragility fractures occur in women who do not have osteoporosis as defined by the WHO criteria (T-score < −2.5), which heavily relies on a single BMD measure as the diagnostic indicator.[16–18] This suggests the need to incorporate risk factors other than a single BMD measurement in the assessment of future fracture risk. In postmenopausal women, the rate of age-dependent bone loss has been shown to be an important risk factor for fracture, independent of baseline BMD.[19–23] No studies, however, have investigated the utility of longitudinal bone change for the prediction of fractures in men or included premenopausal women. Furthermore, the change in BMD may be especially important in assessing the possible need for treatment of those with BMD values that fall in the range of osteopenia (T-score between –1 and –2.5), a subgroup that experiences the majority of fractures.[24]

The Canadian Multicentre Osteoporosis Study (CaMos) is a longitudinal population-based study of women and men ≥25 yr of age, within which approximately two thirds have had at least two BMD measurements over 5 yr and have had incident fractures prospectively recorded over a period of 7 yr. Furthermore, this population includes both users and nonusers of antiresorptive agents. This study therefore offers a unique opportunity to determine the

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relationship between BMD change and fractures in women and men over a broad age range and with a spectrum of baseline BMD values that span normal through osteopenia to osteoporosis. It also allows the relationship to be studied according to whether participants did or did not use antiresorptive agents.

MATERIALS AND METHODS

Participants

CaMos is an ongoing, prospective cohort study of 9423 community-dwelling, randomly selected women (6539) and men (2884), ≥25 yr of age at baseline, living within 50 km of nine Canadian cities (St John's, Halifax, Quebec City, Toronto, Hamilton, Kingston, Saskatoon, Calgary, and Vancouver) that began cohort recruitment in 1997–1998. CaMos objectives, methodology, and sampling framework are described in detail elsewhere.[25] Data collection at baseline included an extensive interviewer administered questionnaire and a clinical assessment. The questionnaire included socio-demographic information, medical and fracture history, family history, dietary intake, physical activity, tobacco smoking, and quality of life determinations. Clinical assessments included height, weight, and BMD by DXA. Year 3 follow-up (among those 40–60 yr of age at baseline) and 5-yr follow-up (in the entire cohort) included an interviewer-administered questionnaire and clinical assessment of height, weight, and BMD.

This study included women and men between 50 and 85 yr of age who reported not using oral or parenteral glucocorticoids for >3 mo at baseline or during the first 5 yr of follow-up. Exclusion of the 1258 women and 790 men not in the 50–85 age group or using glucocorticoids left 5281 women and 2094 men remaining for this analysis. From this study sample, 3635 women and 1417 men had at least two BMD measurements in the first 5 yr and available fracture information in the first 7 yr. The subgroup of the study sample with missing BMD or fracture information will be referred to as the ''excluded'' group.

The participants were classified as users of antiresorptive agents if they reported regular use of bisphosphonates, selective estrogen receptor modulators (SERMs), calcitonin, or hormone therapy (HT) at baseline or during the 7 yr of follow-up. These data were collected before the publication of the results of the Women's Health Initiative randomized controlled hormone trial,[26] which has dramatically impacted HT use.[27] Of the other antiresorptive agents, cyclical etidronate and alendronate were approved for osteoporosis in Canada in 1995; raloxifene in 1998; and risedronate and salmon calcitonin nasal spray in 2000. Women and men 50–85 yr of age were also categorized according to their osteoporosis status by BMD at baseline (normal, osteopenic, or osteoporotic, as per WHO guidelines) determined from their lumbar spine and/or femoral neck T-scores.

Fracture assessment

Follow-up fractures were identified by self-report in scheduled interviews at year 3 and year 5 and yearly postal questionnaires through year 7. Further information regarding fracture was gathered through a structured telephone interview, which included in-depth questions regarding the fracture site and the circumstances leading to fracture. Low-trauma fractures were any fractures that occurred without trauma or as a result of a fall from standing height or less. Low-trauma fractures were further classified by skeletal site and analyzed separately according to the following categories: any fracture (excluding head, hands, and feet), main fracture (hip, pelvis, vertebrae, ribs, forearm/wrist), forearm/wrist fracture, hip fracture, and rib fracture. Throughout this paper, a fragility fracture will refer to a low-trauma fracture that occurred during the first 7 yr of the study.

BMD

Lumbar spine (L_1–L_4), femoral neck, total hip, and greater trochanter BMD were all measured by DXA using Hologic QDR 1000, 2000, 4500 or Lunar DPX densitometers. Machine calibration was done daily. Daily and weekly quality assurance tests were performed as recommended by the DXA manufacturers. Vertebral exclusions to eliminate confounding focal artifacts, notably degenerative changes, were performed based on principles of the ISCD.[28] Clinical interpretation, including selection of the spine levels for reporting, was based on the standard machine printouts, which included the scan image and the BMD, T-score, and Z-score values for individual and combined vertebral levels. Longitudinal stability was monitored using a spine phantom, local to each site. Of the nine CaMos centers, two used GE Lunar machines and seven used Hologic machines. Lunar data were converted into equivalent Hologic values by standard methods.[29] All densitometers were calibrated at the start of the study and once each year thereafter using a single European Spine Phantom to ensure site-to-site comparability. All Hologic measurements were reanalyzed by the same technician and all Lunar measurements by two technicians. Subsequent BMD measurements were done on the same DXA machine as baseline measurements. DXA measurements were performed at baseline, year 3 (in those 40–60 yr old at baseline), and year 5 for the entire cohort.

Statistical analysis

Individual-level BMD slope estimates were computed for the lumbar spine, femoral neck, total hip, and greater trochanter sites. BMD values at baseline and year 5 were used to compute the BMD change in 67% of our studied sample, BMD values at baseline, years 3 and 5 were used in 32% of our sample, and BMD values at baseline and year 3 were used in 1%. The majority of the participants had BMD values at baseline and year 5 because only those 40–60 yr old had a DXA at year 3. For those with only two BMD measurements, the slope between the two points was used to estimate the rate of BMD change. A simple linear regression was used to estimate the rate of change for those with three BMD measurements. For the latter, we recomputed the BMD change using two BMD values. Results for two-point and three-point assessments were

similar, and therefore, results using all available data are presented. Results will be provided for all antiresorptive agents grouped together because BMD changes were found not to differ between HT and bisphosphonate users (from baseline to year 5 of follow-up) and because these accounted for the majority of the users.

Pearson correlations were estimated between baseline BMD and BMD change to examine possible confounding. Multivariate logistic regression models were used to estimate the effect of BMD change from baseline to year 5 on fragility fractures (years 1–7), independent of baseline BMD. Separate regression models were created for each sex, BMD measurement site, and fracture outcome. Linearity of age was assessed using logistic regression models with age divided into categories. Interactions between age and BMD changes were considered. Covariates considered for inclusion were prevalent low-trauma fracture (before baseline), height, body mass index (weight in kilograms divided by height in meters squared), diabetes, osteoarthritis, and rheumatoid arthritis.

To study the association of BMD change independently from baseline BMD, we generated in turn, univariate logistic models, multivariate logistic models including the covariates listed above (when applicable) and change in BMD without baseline BMD, and finally multivariate logistic models including the list of covariates and both change in BMD and baseline BMD. Both BMD change and baseline BMD were scaled so that ORs were expressed for 0.01 g/cm^2/yr and 0.01 g/cm^2, respectively. The multivariate logistic regression models described were stratified by antiresorptive use (users, nonusers, combined). In view of the fact that it has been shown in randomized control trials that patients with the lowest baseline BMD have the greatest risk of future fracture,[30] we stratified the analyses for the first tertile of baseline total hip BMD (i.e., nonusers with the lowest baseline BMD [<0.8312 g/cm^2 in women; <0.9646 g/cm^2 in men]) as well as by osteoporosis status. Finally, we also stratified the analyses for the first tertile of total hip BMD change (i.e., nonusers losing bone most rapidly [change < −0.0075 g/cm^2/yr in women; < −0.005184 g/cm^2/yr in men]) and refer to these as ''fast losers.'' These models were also generated in combined users and nonusers of antiresorptive agents to predict follow-up fragility fractures for years 6 and 7 (i.e., after all BMD measurements had been made). In the latter case, participants who reported fractures at years 1–5 were excluded. The latter analysis was thought to be potentially useful to establish if our results are underestimating or overestimating the associations between BMD change and fragility fractures.

The Bayesian Information Criterion (BIC)[31] was used to provide approximate Bayes Factors to compare the associations between baseline BMD, BMD change, and fragility fractures when comparing models with and without BMD change and/or baseline BMD, when all covariates are included and forced in the model. In doing so, the BIC leads to Bayesian posterior probabilities for each of four models: all covariates, all covariates and BMD change, all covariates and baseline BMD, and all covariates and BMD change and baseline BMD. Comparisons (ratios) between the posterior probabilities for the best model including BMD change and the model including baseline BMD but excluding BMD change indicates the relative importance of using BMD change in a model estimating the risk for fragility fractures as opposed to a model with baseline BMD alone. The BIC comparisons were produced for nonusers of antiresorptive agents. The comparisons in the nonusers were also produced for those with the lowest baseline BMD, the fast losers, and stratified by baseline osteoporosis status (normal, osteopenic, and osteoporotic).

RESULTS

Baseline characteristics

Baseline characteristics of the participants included in the study sample are shown in Table 1. Women who were excluded (met the age and drug criteria for inclusion but were lacking repeated BMD and/or fracture information) were on average older, shorter, lighter, and had lower baseline BMD values at all hip sites compared with the study sample. They also had more comorbidities at baseline (osteoarthritis, rheumatoid arthritis, and diabetes) than the women included in the study sample: 29.9% compared with 19.2%, respectively. A greater proportion of excluded women were menopausal and more had experienced prevalent low-trauma fractures but fewer were taking antiresorptive agents. Excluded men were on average older, shorter, and lighter compared with the study sample, were similar with respect to BMD, but more had diabetes.

Among women using antiresorptive agents at baseline, 92.6% used HT alone. However, at year 7, of the 2464 women who reported using antiresorptives at baseline or during follow-up, 42.2% reported using only HT, 28.4% only bisphosphonates, 18.3% used HT and bisphosphonates (not necessarily at the same time), and 10.9% used combinations of other antiresorptives with or without HT and bisphosphonates (not necessarily at the same time). In men at year 7, 195 of the 208 who used antiresorptive agents were taking bisphosphonates.

The mean BMD change per year in the lumbar spine was a gain of 0.004 g/cm^2 in women, corresponding to a change of 0.42%/yr from baseline, and a gain of 0.006 g/cm^2 in men, corresponding to a change of 0.56%/yr from baseline. The mean changes in femoral neck and total hip were the same, with a loss of 0.002 g/cm^2/yr corresponding to a change per year from baseline of −0.26% in femoral neck in both women and men and to −0.27% and −0.25% in total hip in women and men, respectively. The mean change in the trochanter was a loss of 0.001 g/cm^2/yr, corresponding to a change per year from baseline of −0.12% in women and −0.14% in men. In men and in women and at all skeletal sites, the SD of BMD change was ~0.01 g/cm^2.

The cumulative incidence of low-trauma fracture at various skeletal sites is depicted in Fig. 1. Women had a higher cumulative incidence than men at all fracture sites except for the rib. Women in the older age group (65–85 yr) had a cumulative incidence approximately twice that of the younger group (50–64 yr). Thus, when the rate of BMD loss

TABLE 1. BASELINE CHARACTERISTICS OF THE STUDY SAMPLE AND EXCLUDED GROUP

	Women				Men			
	Study sample				Study sample			
Baseline variable	*No fragility fracture (n = 3271)*	*Fragility fracture* (n = 364)*	*All (n = 3635)*	*Excluded (n = 1646)*	*No fragility fracture (n = 1342)*	*Fragility fracture* (n = 75)*	*All (n = 1417)*	*Excluded (n = 677)*
Age (yr)	64.2 (8.1)	67.5 (8.3)	64.5 (8.2)	69.9 (8.8)	63.8 (8.2)	65.2 (8.2)	63.9 (8.2)	69.6 (9.2)
Height (cm)	159.8 (6.1)	159.1 (6.6)	159.7 (6.2)	158.2 (6.8)	173.4 (6.8)	175.1 (7.5)	173.5 (6.9)	171.5 (7.1)
Weight (kg)	69.2 (13.2)	69.3 (13.1)	69.2 (13.2)	67.9 (14.5)	82.5 (12.8)	81.7 (12.6)	82.5 (12.8)	79.3 (15.3)
BMD (g/cm^2)								
Lumbar spine L_1–L_4	0.930 (0.17)	0.848 (0.16)	0.921 (0.17)	0.907 (0.18)	1.054 (0.17)	0.958 (0.17)	1.049 (0.18)	1.052 (0.18)
Femoral neck	0.703 (0.12)	0.645 (0.11)	0.697 (0.12)	0.669 (0.12)	0.800 (0.12)	0.728 (0.13)	0.796 (0.12)	0.782 (0.14)
Total hip	0.857 (0.14)	0.780 (0.13)	0.849 (0.14)	0.810 (0.15)	1.011 (0.14)	0.912 (0.15)	1.006 (0.14)	0.984 (0.17)
Greater trochanter	0.640 (0.11)	0.582 (0.11)	0.635 (0.11)	0.606 (0.12)	0.780 (0.12)	0.696 (0.13)	0.775 (0.12)	0.767 (0.14)
Osteoarthritis or rheumatoid arthritis	444 (13.6%)	93 (25.6%)	537 (14.8%)	348 (21.1%)	69 (5.1%)	6 (8.0%)	75 (5.3%)	46 (6.8%)
Diabetes	163 (5.0%)	25 (6.9%)	188 (5.2%)	177 (10.8%)	98 (7.3%)	3 (4.0%)	101 (7.1%)	98 (14.5%)
Menopause	3051 (93.3%)	351 (96.4%)	3402 (93.6%)	1604 (97.5%)	—	—	—	—
Any prevalent fragility fracture*	605 (18.5%)	129 (35.4%)	734 (20.2%)	387 (23.5%)	224 (16.7%)	16 (21.3%)	240 (16.9%)	116 (17.1%)
Antiresorptive users	1015 (31.0%)	85 (23.4%)	1100 (30.3%)	362 (22.0%)	1 (1.3%)	0 (0.0%)	1 (0.1%)	3 (0.4%)

Continuous variables are expressed as mean (SD).

* Any fragility fracture excluding head, hand, and feet (years 1–7).

increases in the older age groups, the cumulative incidence of fragility fractures also increases.

Rate of BMD change

The Pearson correlations between baseline BMD and BMD change ranged from −0.18 at the femoral neck to −0.08 at the lumbar spine in women and from −0.05 at the femoral neck to 0.14 at the lumbar spine in men, excluding the possibility of any strong confounding. Similar correlations were seen when analyses were stratified by antiresorptive use. The main parameters of interest were the adjusted ORs together with 95% CIs for each decrease of 0.01 g/cm^2/yr (one SD) in the rate of BMD change. In the multivariate models, adjustments were made for baseline BMD, age, fracture before baseline, height, body mass index, and, when sample size permitted, for osteoarthritis, rheumatoid arthritis, and diabetes.

Hip fracture results are presented only for women between 65 and 85 yr of age because of a low number of hip fractures in younger women and in younger and older men. The results of the multivariate linear regression assessing the relationship between BMD change and follow-up fracture in users and nonusers of antiresorptive agents are shown in Fig. 2 for women and in Fig. 3 for men.

In women not using antiresorptive agents, the highest association with BMD change was with hip fractures (Fig. 2). A decrease of 0.01 g/cm^2/yr in the greater trochanter increased low-trauma hip fracture risk by 2.39-fold (95% CI: 1.15; 4.95); a decrease of 0.03 g/cm^2 (3 SD) per year lead to a 13.65-fold increase risk. In contrast with nonusers, ORs of users of antiresorptive agents were closer to 1 (Fig. 2). This contrast between users and nonusers is particularly striking in main and forearm/wrist fractures.

In men who were nonusers of antiresorptive agents, the strongest association between BMD change and fragility fracture was with BMD changes at the total hip (Fig. 3), where a decrease of 0.01 g/cm^2/yr was associated with an increase in any fragility fracture by 1.60-fold (95% CI: 1.20; 2.14). A decrease of 0.03 g/cm^2/yr in any of the three hip BMD sites was associated with a fracture risk increase of close to 3.4-fold. Because of the small number of men on antiresorptive therapy, the only fracture risk we could estimate was for any fragility fracture. The ORs for any fragility fracture for male users of antiresorptive agents were closer to 1 or <1 (Fig. 3).

Figure 4 compares the ORs for any fragility fractures for a decrease of 0.01 g/cm^2/yr in total hip BMD, stratifying by different subgroups or stages of osteoporosis. The association between BMD change and fragility fractures was strongest in women who were most rapidly losing total hip bone mass (i.e., in women in the first tertile of BMD change; Fast losers). Depending on the skeletal site, between 42% and 74% of women 50–54 yr old and between 40% and 50% of the women 80–85 yr old were included in the fast loser category (data not shown). In men, the strongest association with fractures was with those in the lowest baseline BMD (i.e., in the first tertile of baseline BMD). BMD change, however, was also strongly associated

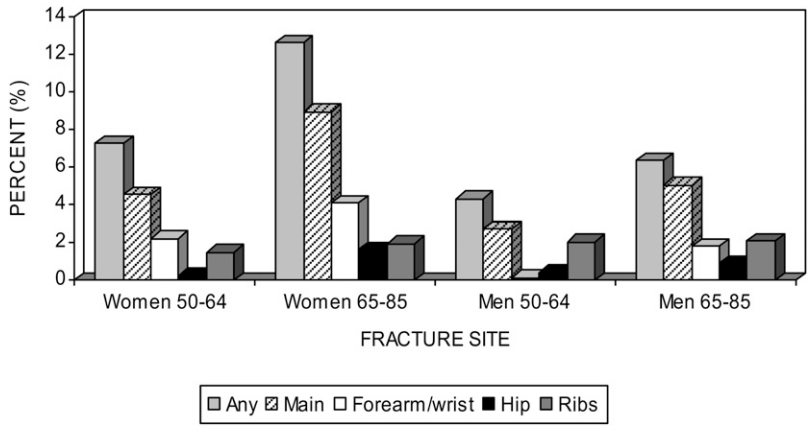

FIG. 1. Cumulative incidence of fragility fractures over 7 yr in women and men who are taking and not taking antiresorptive agents.

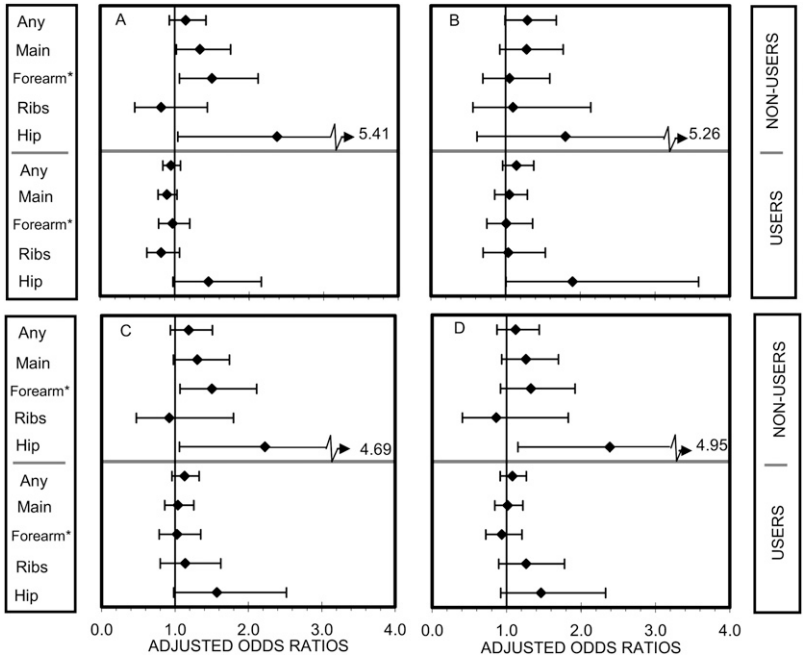

FIG. 2. Adjusted ORs and 95% CIs for a BMD decrease of 0.01 g/cm^2/yr in women using or not using antiresorptive therapies in estimating fragility fracture. (A) Lumbar spine. (B) Femoral neck. (C) Total hip. (D) Trochanter. Forearm includes forearm and wrist fractures.

with fragility fractures in men with osteopenia. Figure 4 shows that, when considering only fragility fractures occurring in years 6 and 7, after the determination of the BMD measurements for assessment of change had been completed, the association between BMD change and incident fractures was similar or stronger than the association with fractures reported in years 1–7.

Baseline BMD

In all multivariate models, a decrease of 0.01 g/cm^2 in baseline BMD was associated with an increase in fracture risk. In women not using antiresorptive agents, the ORs ranged from 1.01 (95% CI: 0.99; 1.04) for fragility forearm/wrist fractures at the baseline lumbar spine BMD to 1.20 (95% CI: 1.06; 1.37) for fragility hip fractures at the baseline femoral neck BMD. In men who were not taking antiresorptive agents, the ORs ranged from 1.03 (95% CI: 0.98; 1.08) for fragility ribs fractures to 1.11 (95% CI: 1.03; 1.20) for fragility forearm/wrist fractures at the baseline greater trochanter BMD. Similar results were obtained with antiresorptive users.

BMD change versus baseline BMD in estimating fracture risk

Using the BIC as an approximate Bayes factor, we compared models including BMD change with models including baseline BMD in nonusers of antiresorptive agents. In women, when adjusted for all covariates, the model including lumbar spine BMD change was 2.8, 6.2, and 8.1 times more likely to better estimate the risk of main, hip, and forearm/wrist fragility fractures, respectively, than the same model but replacing BMD change by baseline BMD. Similarly, a model with total hip change was 1.4 times more likely to be a better model than the same model with baseline BMD to estimate the risk of forearm/wrist fragility fractures. A model including greater trochanter

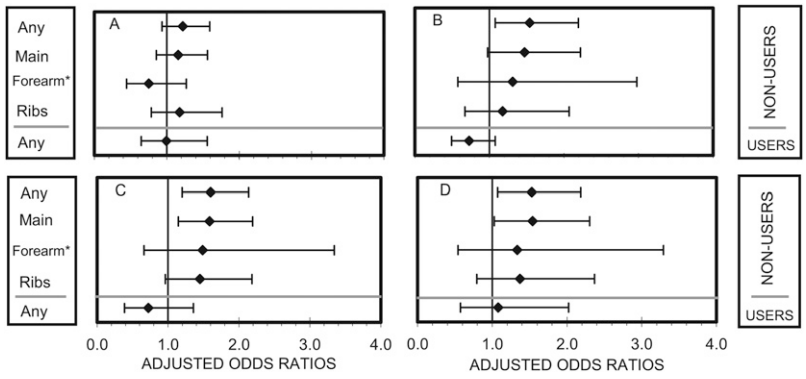

FIG. 3. Adjusted ORs and 95% CIs for a BMD decrease of 0.01 g/cm^2/yr in men using or not using antiresorptive therapies in estimating fragility fracture. (A) Lumbar spine. (B) Femoral neck. (C) Total hip. (D) Trochanter. Forearm includes forearm and wrist fractures.

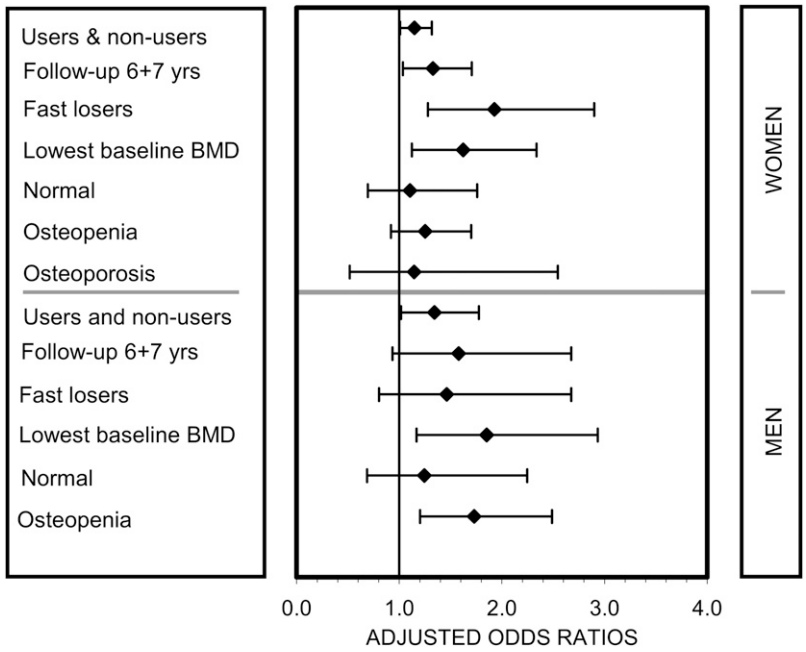

FIG. 4. Adjusted ORs and 95% CIs for a total hip BMD decrease of 0.01 g/cm^2/yr in women and men in estimating any fragility fracture. Users and nonusers refer to the use of antiresorptive agents. ''Follow-up 6+7 yrs'' is predicting any incident fragility fractures in years 6 and 7 only and includes users and nonusers of antiresorptive agents. Only nonusers of antiresorptive agents are included in the following subgroups: fast losers (first tertile of BMD change), those with the lowest baseline BMD (first tertile of baseline BMD); normal, osteopenic, and osteoporotic participants. ''Fast losers'' are in the lowest tertile of BMD change (BMD change < -0.0075 g/cm^2/yr in women; BMD change < -0.005184 g/cm^2/yr in men). ''Lowest baseline BMD'' are in the lowest tertile of baseline BMD (BMD < 0.8312g/cm^2 in women; BMD < 0.9646 g/cm^2 in men).

change was also 2.2 times better to estimate the risk of fragility hip fractures than the same model with baseline BMD.

In contrast to the results in women, in men there was only one situation in which the adjusted model including BMD change was better than one including baseline BMD: total hip change was 2 times better at predicting any fragility fracture than was baseline total hip BMD. However, adjusted models with total hip and greater trochanter BMD change were both equally good compared with their baseline BMD equivalents at estimating the risk of ribs fractures.

Table 2 provides, for each of the subgroups studied, the ratios of the adjusted model probabilities for estimating fracture risk in those who were not using antiresorptive therapy. A model with BMD change and other covariates, with or without baseline BMD, was generally better than a model with baseline BMD and other covariates for the prediction of fragility fractures in nonuser women who were in the first tertile (fast losers) of BMD change (7 of 12 cases) or in the osteopenic subcategory (11 of 12 cases). The risk of fragility fracture in nonuser men with osteopenia was better estimated with a model including BMD change than a model without it (six of eight cases). Also, in five of eight cases, models with BMD change were better at estimating the risk of fragility fractures for men who had the lowest baseline BMD (first tertile of baseline BMD).

DISCUSSION

After achievement of peak bone mass, bone loss occurs throughout life; however, the rate of loss varies and may differ in women and men, may differ at different skeletal sites, and may vary according to age. Thus, recent studies have found accelerated rates of bone loss in women during perimenopause and cortical bone loss in men >75 yr of age.[32] We also recently reported that the highest loss in the lumbar spine and hip sites was seen during the menopausal transition (in women) and at age >65–70 yr at hip

TABLE 2. RATIOS OF THE ADJUSTED MODEL PROBABILITIES FOR ESTIMATING FRACTURE RISK IN NONUSERS: MODEL INCLUDING BMD CHANGE VS. MODEL INCLUDING BASELINE BMD (WITHOUT BMD CHANGE)

Subgroup	Ratio = probability (model with BMD change) / probability (model with baseline BMD)	Women			Men	
		Any	*Main*	*Forearm/wrist*	*Any*	*Main*
Fast losers	L_1–L_4	0.2	0.6	0.8	0.1	0.1
	Femoral neck	**3.8**	**33.7**	**7.2**	0.1	0.1
	Total hip	**3.8**	0.8	**5.9**	0.1	0.1
	Greater trochanter	0.5	**1.8**	**2.5**	0.1	0.1
Lowest baseline BMD	L_1–L_4	0.3	**2.0**	**5.6**	*	**22.0**
	Femoral neck	0.3	0.1	0.5	0.2	0.3
	Total hip	**1.6**	**1.3**	**4.4**	**1.5**	**1.2**
	Greater trochanter	**2.0**	0.1	0.9	**1.3**	0.4
Normal	L_1–L_4	**1.1**	**1.3**	**2.3**	0.8	**1.2**
	Femoral neck	0.1	0.5	0.8	**1.2**	0.8
	Total hip	0.1	0.8	0.8	0.6	0.8
	Greater trochanter	0.3	**1.2**	**1.1**	0.5	1.0
Osteopenia	L_1–L_4	0.8	**1.6**	**2.4**	**3.8**	**1.9**
	Femoral neck	**2.8**	**3.7**	**2.3**	0.6	**2.3**
	Total hip	**1.5**	**5.0**	**7.9**	**1.7**	**4.3**
	Greater trochanter	**1.4**	**2.6**	**1.6**	0.4	**1.5**
Osteoporosis	L_1–L_4	**4.3**	**2.5**	—	—	—
	Femoral neck	0.2	0.1	—	—	—
	Total hip	0.1	0.1	—	—	—
	Greater trochanter	0.3	0.1	—	—	—

In bold, ratios > 1 indicates that models including BMD change are better at estimating fracture risk than a model without it but with baseline BMD. The numbers of ribs and hip fractures in women and men and forearm/wrist fractures in men did not permit us to do the analysis by subsample and sex. "Fast losers" are in the lowest tertile of BMD change (BMD change < -0.0075 g/cm^2/yr in women; BMD change < -0.005184 g/cm^2/yr in men). "Lowest baseline BMD" are in the lowest tertile of baseline BMD (BMD < 0.8312g/cm^2 in women; BMD < 0.9646 g/cm^2 in men).

* Model with covariates and baseline BMD has a zero probability of being correct to predict any fracture.

sites for both women and men.[33] This study suggests that loss of BMD over time is associated with fragility fractures in both women and men who are not treated with antiresorptive agents, independent of baseline BMD. For the majority of the fracture sites and BMD changes, the adjusted ORs imply that a decrease in BMD is associated with an increase in fracture risk, and this increased risk is of clinical importance. Furthermore, the same pattern is observed in both women and men and, although many results taken individually were inconclusive, the consistency in the direction of association overall suggests that the results were not caused by chance.

With the exception of randomized controlled trials, all studies that have looked at the associations between the loss of bone and fracture risk have been among postmenopausal women.[19–23] These studies all reported associations between a high rate of loss and incident fracture. Earlier studies had assessed BMD using single-energy densitometers,[22,23] and three of the studies used peripheral BMD[20,22,23]; hence, the magnitude of the association may not be directly comparable to this study.

In 966 postmenopausal women from the Dubbo Osteoporosis Epidemiology Study followed over an average of 10.7 yr,[21] it was found that, for each 5%/yr loss of femoral neck BMD, the associated hazard ratio for suffering a fragility fracture was 1.4 (95% CI: 1.1, 1.8). The rate of femoral neck bone loss was associated with hip, symptomatic vertebral, and proximal humerus fractures, but not with forearm, wrist, rib, and pelvis fractures, independent of femoral neck BMD and age.

Hillier et al.[19] prospectively followed 4124 women ≥65 yr of age (mean age at baseline, 72 yr) from the Study of Osteoporotic Fractures, where bone loss was determined by BMD of the total hip. They found a small but important increased fracture risk associated with the rate of bone loss independent of baseline BMD. They concluded that, in healthy, older, postmenopausal women, repeating a measurement of BMD up to 8 yr later provides little additional value over that provided by the initial BMD measurement for predicting incident fractures. However, their findings were based on women initially >65 yr of age and therefore did not include younger women or women in the menopausal transition, where the greatest BMD loss occurs.[33,34]

In contrast with Hillier et al.,[19] we found that a model with BMD change (with or without baseline BMD), compared with a model with baseline BMD, was better at estimating the risk for fragility fractures in women and men with osteopenia not using antiresorptives and in the subgroups with lower baseline BMD or with accentuated BMD loss. There is a theoretical basis for assuming that the rate of bone loss, the age at which it begins, and its duration will have profound effects on bone structural integrity, bone strength, and therefore fracture risk. Rapid remodeling can dramatically impact trabecular integrity by causing an increase in the number of active remodeling sites, thereby increasing the number of trabeculae with areas of focal weakness and decreasing trabecular connectivity.[35] Measurement of a bone resorption marker may therefore be a surrogate for longitudinal bone loss[36]

in which case it might be appropriate to consider treating a woman with osteopenia who has biochemical evidence of elevated bone resorption with an antiresorptive. Alternatively, the measure of the rate of bone loss by DXA may supplement the information gained from measurement of biochemical markers so the two together may give a much more accurate assessment of fracture risk that either alone. Further studies will have to be done to examine these issues.

In this study, the rates of bone change at both the lumbar spine and hip regions in both men and women who are not using antiresorptive agents was associated with fragility fractures, independent of baseline BMD, age, and other risk factors. A combination of low BMD, high rate of bone loss, and age may provide a powerful combination for the stratification of fracture risk and may identify those women who are fracturing at BMD levels higher than those traditionally considered at risk for osteoporotic fracture.

In general, across all BMD sites, ORs for BMD change are closer to one for those using antiresorptive agents compared with nonusers. Therefore, in those who are using antiresorptive agents, the association between BMD change and fractures appeared to be weak or inconclusive. However, it is still possible that BMD change is important in view of the fact that the CIs do not rule out an effect. It has been reported that, although in women with osteoporosis, each 1% improvement in spine BMD (by DXA) is expected to reduce vertebral fracture risk by ~4%, randomized trials of antiresorptive agents show that 1–6% improvements in spine BMD reduce vertebral fracture risk by 35–50% or greater.[37] Less than 20% of the decreased spine fracture risk produced by alendronate or raloxifene can apparently be explained by improvement in spine BMD.[37] Furthermore, Sarkar et al.[30] showed that, although BMD changes after raloxifene therapy were poorly predictive of reduction in vertebral fracture, baseline BMD was predictive. The effect of drugs on nonspine fracture risk seems to be even more complex and cannot be predicted from changes in DXA BMD. Long-term use of antiresorptive treatments may thus alter the quality of bone ways that are not captured by changes in BMD as measured by DXA.[35]

Strengths of this study included the use of a randomly selected population-based cohort that was followed prospectively, the quality control that was routinely performed to ensure longitudinal reliability of all the BMD measures, and the inclusion of men as well as women. Furthermore, the broad age range, which included women in the perimenopausal period, allowed us to include this rapid and important period of bone loss in our analyses as well as a second relatively rapid period of bone loss we recently identified[33] in older participants.

Limitations of the study included possible selection bias. Participants who had to be excluded because they lacked a second BMD value or fracture information had mean BMD measurements at baseline that were lower than in the participants without an incident fracture, but they showed higher BMD values at baseline than those with an incident fracture. Excluded women also had more health problems and were older and shorter. Furthermore, we were unable to determine the dose or duration of treatment of the antiresorptive agents used. Another limitation was that the time of BMD measurement often overlapped with the occurrence of fracture. However, our results with incident fractures (i.e., fractures occurring at years 6 and 7), despite including users of antiresorptive agents, showed that the ORs were even further away from 1, leading to an increase in fracture risk. This therefore supports and strengthens our results using both concurrent and incident fractures. Last, there were a relatively small number of fragility fractures resulting in wide CIs and some uncertainty in the direction and magnitude of effect.

In summary, our study showed that there is an association between the rapidity of bone loss and fragility fractures in those not taking antiresorptives agents, suggesting that rate of BMD change is independent of baseline BMD as a risk factor for subsequent fragility fracture. Rapid bone loss is an important risk factor for fragility fractures in subgroups of the population such as those who lose bone faster or those with osteopenia. The weak or inconclusive associations between rates of BMD loss and risk of fractures in antiresorptive users suggest that prevention of BMD loss may not be the sole or most important mechanism for fracture protection in those taking antiresorptive agents.

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