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Incident Fracture is Associated with a Period of Accelerated Loss of Hip BMD: The Study of Osteoporotic Fractures

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Abstract

Purpose—A prior fracture is one of the strongest predictors of subsequent fracture risk, but the etiology of this phenomenon remains unclear. Systemic bone loss post-fracture could contribute to increased risk of subsequent fractures. Therefore, in this study we investigated whether incident fractures, including those distant to the hip, are associated with accelerated loss of hip bone mineral density (BMD) in elderly women.

Methods—We analyzed data from 3,956 Caucasian women aged ≥65 years who were enrolled in the Study of Osteoporotic Fractures and completed hip BMD measurements at study visit 4 (year 6) and visit 6 (year 10). Clinical fractures between visits 4 and 6 were ascertained from triannual questionnaires and centrally adjudicated by review of community radiographic reports. Subjects provided questionnaire information and clinical variables at examinations for known and potential covariates. Generalized linear models were used to calculate average annual percent change in total hip BMD between visits 4 and 6 for each incident fracture type, and for upper body and lower body fractures combined. A subset of women (n=3,783) was analyzed for annual total hip BMD change between study visits 4 and 5, and between study visits 5 and 6 to evaluate change in total hip BMD during these 2-year intervals.

Results—Women with incident upper body fracture or incident lower body fracture exhibited reductions in total hip BMD of 0.89% and 0.77% per year, respectively, while women who did not fracture exhibited reductions in total hip BMD of 0.66% per year during the 4-year period. Accelerated loss of hip BMD was isolated to the 2-year time interval that included the fracture. Loss of total hip BMD was not affected by the number of days from fracture to follow up DXA.

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Conclusions—Systemic bone loss following fracture may increase the risk of future fractures at all skeletal sites. There is a need for improved understanding of mechanisms leading to apparent accelerated bone loss following a fracture in order to reduce subsequent fracture risk.

Summary

Bone loss following a fracture could increase the risk of future fractures. In this study we found that elderly women who had an upper body fracture or multiple fractures lost more bone at the hip than those who did not fracture. This suggests a possible systemic bone loss response initiated by fracture.

Keywords

Osteoporosis; Fracture Risk Assessment; DXA; Bone Loss; Fracture Healing; Cohort Study

Introduction

Many factors contribute to osteoporotic fracture risk (*e.g.*, age, ethnicity, glucocorticoid use), but the most reliable predictor of fracture risk is a previous fracture of any kind [1–7]. People with a previous history of fracture have a 2–10 fold greater risk of sustaining a future fracture in their lifetime than those with no history of fracture [2, 4–6], even after controlling for bone mineral density [2, 3, 8]. This risk of future fractures increases with the number of prior fractures [2, 8], and is maintained even when the previous fracture occurs at an unrelated skeletal site [2, 4, 7, 9], or early in life [3, 9–12]. This elevated fracture risk is highest in the first 1–2 years following index fracture, then decreases over subsequent years, but remains higher than that of the general population [1, 7, 13]. The etiology of this increased fracture risk remains unclear. Previous studies have shown that increased fracture risk can be partially attributed to a person's poor physical function, risk of falls, or other individual cofactors [14–17]. However, another contributing factor may be that an incident fracture is followed by a systemic loss of bone that over time could lead to an increased risk of subsequent fractures at all skeletal sites [11].

Our research group has reported that in mice, bone fracture or other injuries initiated bone loss at skeletal sites distant from the fracture site, leading to a reduction in trabecular bone volume by 1–2 weeks post-fracture [18, 19]. This bone loss was associated with decreased voluntary movement of mice (mechanical unloading), increased levels of circulating inflammatory cytokines, and increased osteoclast number at early time points (3–4 days) post-injury [19]. This bone loss observed in mice may also occur in elderly individuals post-fracture, since prolonged immobility and inflammation post-fracture in elderly women and men may contribute to fracture risk. However, systemic bone loss following a fracture has not been carefully evaluated in a human clinical cohort. Studies of human subjects have reported that following a hip or tibia fracture, patients lost bone mineral density (BMD) at an accelerated rate at the hip, lumbar spine, and lower extremities [20–25]. These data are consistent with a loss of bone at other skeletal sites following a fracture. However, these previous studies did not quantify bone loss at skeletal sites distant from the fracture site, and BMD loss at these weight bearing sites following hip or tibia fracture could be explained in part by reduced loading during the recovery period after fracture. If accelerated hip BMD

loss were also observed after upper body fractures, this would provide evidence for a systemic bone loss phenomenon due to other mechanisms, since reduced mechanical loading would likely not explain hip BMD loss after these fractures.

In the current study, we investigated loss of hip BMD in older Caucasian women with and without incident fracture(s). We hypothesized that women who sustained an incident fracture at any skeletal site would exhibit a greater loss of total hip BMD than women who did not fracture. This result would be consistent with a systemic bone loss response initiated by an incident fracture, which could have important implications for identification and treatment of those at risk for subsequent osteoporotic fractures.

Methods

Participants

The multi-center Study of Osteoporotic Fractures (SOF) enrolled a total of 9,704 primarily Caucasian women 65 years old from September 1986 to October 1988, with follow-up clinical visits approximately every 2 years. Women were recruited from population-based listings in four areas of the United States [26]. Women were excluded if they were unable to walk without assistance from another person or had a history of bilateral hip replacement. Our study cohort consisted of 3,956 SOF participants who had measurements of hip BMD between study visit 4 (1992–1994) and study visit 6 (1997–1998) and who had not experienced a fracture during the 2 years prior to visit 4 (Fig. 1).

Measurements

Participants completed a questionnaire and were interviewed during study visit 4 and asked about health status, medication use, education, smoking history, intention to lose weight, and falls during the previous year. A selected medical history was obtained, including a history of physician diagnosis of fracture since the age of 50 years, stroke, diabetes, hypertension, Parkinsonism, dementia, coronary heart disease, chronic obstructive lung disease, and cancer (except skin cancer). Physical activity was assessed using a modified version of the Harvard Alumni Questionnaire [27, 28] and was expressed as a weighted score of kilocalories expended per week. To assess functional disability, women were asked whether they had any difficulty performing any of five independent activities of daily living (IADLs) [29]. Tests of physical function included grip strength (using a handheld Jamar dynamometer) and walking speed (time in seconds to walk 6 meters at usual pace). Body weight was recorded with a balance beam scale at both examinations. Height was measured using a standard held-expiration technique with a wall-mounted Harpenden stadiometer (Holtain, U.K.). Height and weight were used to calculate standard BMI. Medication use was determined at study visits 4, 5, and 6 by asking participants to bring with them to the clinic visit current prescription and over-the-counter medications used in the last 30 days. If a participant forgot to bring in one or more medications, this information was obtained via telephone or return visit. All medications recorded by the clinics were stored in an electronic medications inventory database [30]. At study visits 4 and 6, BMD of the proximal femur was measured using dual energy x-ray absorptiometry with cross-calibration between instruments (QDR 1000; Hologic, Waltham, MA) using density phantoms; a subset of women ($n = 3,783$) also

had hip BMD measured at visit 5 (study year 8). Spine BMD at these time points was available only for a subset of women (<400), therefore change in spine BMD was not calculated.

Fractures

After study visit 4, participants were contacted about falls and fractures every 4–6 months by postcard or telephone. Reported fractures were adjudicated by a study physician from community x-rays and medical records. All participants with single or multiple fractures of the upper body (humerus, elbow, wrist, hand, vertebral, rib, finger, face, clavicle, neck, forearm, scapula, skull) or lower body (ankle, foot, toe, lower leg, hip, heel, pelvis, knee, tailbone) from visit 4 to visit 6 were included in our analyses. All participants with no incident fractures from visit 4 to visit 6 were included as non-fracture controls.

Fracture types were defined as: 1. Hip – femoral neck, intertrochanteric, and other fractures of the head and the neck of the femur. 2. Wrist – distal radius and/or ulna, lunate, scaphoid, trapezoid, trapezium, capitate, hamate, pisiform, triquetral fractures. 3. Skull – frontal, occipital, parietal, temporal, and sphenoid fractures. 4. Face – nasal, maxilla, zygomatic (malar), lacrimal, concha, and vomer fractures. 5. Neck – cervical spine fractures. 6. Clavicle fractures. 7. Scapula fractures. 8. Humerus fractures. 9. Elbow – ulnar olecranon, trochlea, epicondyle, and capitulum fractures. 10. Forearm – medial shafts of the radius and ulna. 11. Hand – metacarpal fractures. 12. Finger – phalanges (proximal, middle, distal) fractures. 13. Rib fractures. 14. Vertebral – thoracic and lumbar spine fractures. 15. Pelvis – sacroiliac joint, ilium, ischium, pubis, and acetabular (central, anterior, posterior) fractures. 16. Tailbone – coccyx and/or sacrum fractures. 17. Knee – patellar fractures. 18. Lower Leg – tibia and/or fibula fractures. 19. Ankle – distal tibia and fibula (malleolus) fractures. 20. Foot – talus, navicular, cuneiform, cuboid, and metatarsal fractures. 21. Toe – phalanges fractures. 22. Heel – os calcis fractures.

Statistical Analysis

Baseline characteristics (visit 4) were compared across groups based on number of incident fractures (0, 1, >1) using chi-squared tests for categorical data and analysis of variance for continuous data.

Mean annual percent change in total hip BMD was calculated during the approximately 4-year period between visit 4 and visit 6 for participants with incident fractures by individual skeletal site, and for participants with any upper body fracture or any lower body fracture. Fractures of the neck (n=1), forearm (n=1), scapula (n=1), skull (n=2), heel (n=1), and tailbone (n=2) were not analyzed individually due to insufficient numbers, though these fractures were included in the grouped upper body fracture or lower body fracture analyses. Linear regression was used for the multivariable adjusted models to compare each fracture group separately to the non-fracture group. Models were adjusted for potential confounders that were related to fracture incidence by univariate analysis at $p < 0.10$, including age, walking speed, bisphosphonate or estrogen use, glucocorticoid use, and total hip BMD at visit 4. Results are presented as adjusted mean percent change in total hip BMD.

To determine the effect of days from fracture to follow-up visit on percent change in total hip BMD, days from fracture to follow up visit were categorized into quartiles and a linear regression analysis was performed. Adjusted means and p for trends were calculated to show the relationship between days from fracture and change in total hip BMD for upper body fractures and for lower body fractures. Multivariable models adjusted for potential confounders were also performed.

For women with hip BMD measurements at visits 4, 5, and 6 ($n = 3,783$), data were further analyzed in 2-year intervals (visit 4–5 or visit 5–6) using repeated measures linear mixed models analysis with participant ID as the random effect. This was done to assess whether annual percent change in total hip BMD over a 2-year interval during which a fracture occurred was different from the annual percent change in total hip BMD during the previous 2-year period or during the subsequent 2-year period. Among those who had an upper body or lower body fracture during the visit 4–5 interval, their annual percent change in total hip BMD was compared to their annual percent change in BMD during the visit 5–6 interval. For those who fractured during the visit 5–6 interval, comparisons were made between their annual percent change in total hip BMD during this fracture time period and the earlier, visit 4–5 interval. Annual percent change in BMD between the visit 4–5 interval and the visit 5–6 interval were also compared to those who did not fracture. Models were adjusted for age, walking speed, medication use, and total hip BMD at visit 4.

Results

Baseline characteristics at visit 4 were similar for women without fracture ($n = 3,424$) and those with one ($n = 470$) or multiple ($n = 62$) incident fractures, with the exception that those with incident fracture(s) tended to be older, smaller (lower height and weight), have slower walking speed, and have lower total hip BMD (Table 1). Women with one or more incident fracture also had lower total hip T-score, and were more likely to have had a previous fracture since the age of 50. For women who did not fracture, 571 (16.7%) were classified as osteoporotic based on T-score ≤ -2.5 ; for women with 1 fracture, 123 (26.2%) were classified as osteoporotic; for women with >1 fracture, 19 (30.2%) were classified as osteoporotic.

Visit 4 was conducted from 8/31/1991 to 12/29/1994; visit 6 was conducted from 1/3/1997 to 2/8/1999. The mean time between the visit 4 and visit 6 BMD assessments was $1,626 \pm 203$ days (range: 1,036–2,286 days). Because of the wide range of time between visit 4 and visit 6, average annual percent change in total hip BMD was calculated by normalizing each subject's total percent change in total hip BMD by that subject's number of years between visits. The mean time from incident fracture to follow-up BMD assessment was 857 ± 496 days (range: 16–2,028 days) for women with a single upper body fracture, 821 ± 496 days (range: 16–1,861 days) for women with a single lower body fracture, and 852 ± 482 days (range: 46–2,028 days) for women with multiple fractures.

Subjects with an incident upper body fracture or multiple fractures at either the upper or lower body had a greater loss of total hip BMD during the 4-year time period (study visit 4 to 6) compared to the BMD change in those who did not fracture (Table 2). This greater

reduction in BMD was maintained even after controlling for age, walking speed, medication use, and baseline total hip BMD. For example, women who sustained a vertebral fracture (-1.26% per year) had a loss of total hip BMD that was 91% greater than that of women without fracture (-0.66% per year). Subjects with incident hip fractures lost an average of 1.10% per year of total hip BMD; loss of total hip BMD with incident fractures at other lower body skeletal sites was not significantly increased compared to women who did not fracture. Loss of total hip BMD was significantly greater for women with any upper body single fracture (-0.89% per year) compared to women who did not fracture; loss of total hip BMD was not significantly greater for women with any lower body single fracture (-0.77% per year), though this may be due to low statistical power or inclusion of fracture sites such as the toe. No significant differences were observed in loss of total hip BMD between women with a single upper body fracture and those with a single lower body fracture ($p = 0.59$). No significant differences were observed in the average annual percent loss of total hip BMD based on days from incident upper body or lower body fracture to follow-up BMD measurement (Table 3).

Annual percent loss of total hip BMD was significantly greater during the 2-year interval that included a fracture compared to the 2-year interval before the interval that included the fracture or the 2-year interval after the interval that included a fracture (Table 4). For subjects with an incident fracture during study visits 5 to 6, average annual percent total hip BMD loss during the 2-year fracture interval was -1.23% per year for those with upper body fractures and -1.20% per year for those with lower body fractures. For these same subjects, average percent total hip BMD loss during the previous 2-year interval before the fracture interval was -0.51% per year for those with upper body fractures ($p = 0.007$) and -0.37% per year for those with lower body fractures ($p = 0.036$). For subjects with a fracture during study visits 4 to 5, average percent total hip BMD loss during the 2-year fracture interval was -1.00% per year for those with upper body fractures and -1.31% per year for those with lower body fractures. For these same subjects, average percent total hip BMD loss during the subsequent 2-year interval after the fracture interval was -0.76% per year for those with upper body fractures ($p = 0.527$) and -0.09% per year for those with lower body fractures ($p = 0.003$). Average annual loss of total hip BMD was significantly greater during the 2-year fracture interval compared to those that did not have any fracture.

Discussion

In this study in elderly Caucasian women, we found that incident fracture was associated with a period of accelerated loss of total hip BMD, even when the fracture was at a distant skeletal site (e.g., vertebra); the effect size of hip BMD loss was similar for upper body fractures and lower body fractures. We also found that the accelerated loss of hip BMD was isolated to the 2-year time interval that included the fracture, and that the percent loss of total hip BMD was not affected by the number of days from the fracture to follow up DXA. Altogether, these data are consistent with the hypothesis of systemic bone loss initiated by fracture.

We observed significantly greater loss of total hip BMD during the 4-year period that included an incident fracture of the vertebra (-1.26% per year), clavicle (-1.85% per year),

and hip (−1.10% per year) compared to those that did not fracture (−0.66% per year). Incident fractures to other skeletal sites did not result in significantly greater average annual total hip BMD loss than in nonfracture controls, though some fracture types exhibited a trend toward increased total hip BMD loss, including the humerus (−1.00% per year, $p=0.077$), elbow (−1.18% per year, $p=0.053$), and pelvis (−1.11% per year, $p=0.177$). It is possible that differences in the magnitude of total hip BMD loss could be partly due to the size of the bone that is fractured. A fracture to a larger bone may result in a greater amount of interfragmentary surface area, which correlates to a greater comminution severity [31, 32]. These measures suggest a more severe injury, which may involve greater injury-induced inflammation, soft tissue damage, etc., that may result in a greater subsequent bone loss at the hip and other skeletal sites. This is further supported by the BMD changes observed among individuals who had multiple fractures from visit 4 to visit 6; these women on average lost 1.30% per year total hip BMD during this time interval.

Dirschl et al. reported considerable loss of BMD at the contralateral hip (−5.4%) and lumbar spine (−2.4%) one year after a hip fracture in elderly patients [20]. Karlsson et al. reported BMD loss one year after fracture of 2–4% in the contralateral hip and 7% in the lower extremities collectively, but no significant loss in the upper extremities [21]. Similarly, Magaziner et al. reported a 4.9% decrease in BMD at the femoral neck and 3.5% decrease in BMD at the total hip one year after a hip fracture in elderly women [23], and Rathbun et al. reported a 4.90% decrease in BMD at the femoral neck and a 4.16% decrease in BMD at the total hip in older men within one year of hip fracture [24, 25]. In our study, in which there was a longer interval between baseline and follow-up BMD measurement, we observed a 1.10% per year mean loss of total hip BMD during the 4-year period that included a hip fracture; it is possible that this figure is underestimated since women with more disabling fractures (such as hip fractures) were less likely to return for follow-up visits because of their higher risk of death in the interim and their poorer health status. If this were the case, our results might have underestimated the rate of total hip BMD loss in our population for hip fracture patients. Importantly, our study is unique in that we report significant decreases in hip BMD following upper body fractures. Loss of hip BMD following a lower extremity fracture may be partially attributed to decreased activity and mechanical loading of the lower limbs. However, because disuse is less likely to be a contributor to hip BMD loss following an upper body fracture, hip bone loss following an upper body fracture may be driven by other non-mechanical mechanisms. In our studies of post-fracture bone loss in mice, we observed considerable systemic inflammation as well as mechanical unloading at early time points post-fracture, along with increased osteoclastogenesis in trabecular bone [19]. These same mechanisms may contribute to post-fracture bone loss in people, since immobility and injury-induced inflammation are operative in this population. If this phenomenon were confirmed by prospective studies, this would represent a novel etiology contributing to the increased risk of subsequent fractures following an index fracture and would underscore the need to both identify and treat subjects at risk for osteoporotic fractures.

Our analysis of total hip BMD loss in the 2-year time intervals before, during, and after an incident fracture showed that accelerated loss of hip BMD is isolated to the time interval during which the fracture occurred. If accelerated bone loss had been observed in the time intervals before and after the interval in which the fracture occurred, it could be concluded

that people experiencing greater bone loss are more likely to experience fractures. However, since accelerated bone loss was only observed in the time interval that included a fracture, this interpretation is less likely to be true. Instead, these data are in agreement with our hypothesis of a systemic bone loss response initiated by an incident fracture. However, given the nature of the SOF study design, BMD measurements directly after the fracture with longitudinal follow-up is not available, therefore it cannot be discerned whether the accelerated bone loss occurred immediately before the fracture versus after the fracture.

Based on available data, our finding that average annual percent loss of total hip BMD did not differ as a function of the number of days between the fracture and follow-up BMD measurement suggests that systemic bone loss occurs soon after an incident fracture, and is not recovered over the next 1–4 years. If the bone loss had occurred a considerable time after the fracture, we would expect to see significantly less bone loss for women who had a follow-up visit shortly after the fracture. Alternatively, if there were bone loss shortly after a fracture followed by a recovery of BMD, we would expect to see significantly less bone loss in women who had a follow-up visit several years after the fracture. Prospective studies with frequent BMD measurements after fracture are needed to confirm the time course of bone loss and potential recovery following an incident fracture.

The strengths of this study include the analysis of a large population of elderly women with comprehensive longitudinal BMD measures, incident fracture adjudication, and relevant covariates for osteoporosis. This allowed us to analyze BMD change over the time interval during which an incident fracture occurred, and adjust for time between BMD measures and time from incident fracture to follow-up BMD measurement. The limitations of this study include the fact that our study population included only Caucasian women in North America, so the generalizability of these data to other countries, ethnic groups, or men is unclear. Additionally, this study investigated bone loss in an older population (women greater than 65 years old), in which there is a steeper trajectory of bone loss than in the general population, and other co-morbid diseases may not be accounted for. Another limitation is that BMD was evaluated over a time interval that included an incident fracture, but we are unable to evaluate specifically when bone loss happened with respect to the incident fracture. Additionally, subjects had different time intervals between BMD assessments, and between incident fractures and follow-up BMD assessment. To account for this limitation, data were normalized for each subject to determine average annual percent change in total hip BMD. Another limitation of this study is that we have longitudinal BMD measures only at the hip, therefore we cannot speculate on BMD changes at other skeletal sites or for the whole-body. However, these results are still extremely important, as loss of BMD at the hip over time could result in a greater risk of incident hip fracture, and hip fractures are associated with the highest morbidity and mortality of any fracture site in the elderly population. Finally, it is important to note that data analyzed in this study were collected over 20 years ago (1992–1998), therefore there are possible cohort effects that may limit applicability to other populations.

Conclusions

Incident fracture was associated with a greater reduction in total hip BMD during the 4-year period in which the fracture occurred in elderly Caucasian women compared to those that did not fracture. These data may suggest that systemic bone loss following fracture contributes to subsequent fracture risk; future prospective studies could be designed to confirm this observation. Improving our understanding of mechanisms leading to accelerated bone loss following a fracture may lead to therapeutic strategies aimed at reducing subsequent fracture risk and improving the long-term skeletal health of osteoporotic patients.

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Figure 1:

Flowchart of study sample selection for the study of loss of total hip BMD associated with incident fractures.

Table 1:

Distribution of baseline characteristics at visit 4.

Characteristic, mean $\pm$ SD or n (%)	Number of incident fractures			
	0 (N= 3424)	1 (N= 470)	>1 (N= 62)	p-value
Age (y)	75.6 $\pm$ 4.0	75.9 $\pm$ 4.5	77.5 $\pm$ 4.1	<0.001
Height (cm)	158.8 $\pm$ 5.9	158.2 $\pm$ 6.3	157.7 $\pm$ 7.0	0.0481
Weight (kg)	67.2 $\pm$ 12.3	66.0 $\pm$ 12.8	64.1 $\pm$ 12.0	0.0307
Self reported health (fair--very poor)	496 (14.5)	76 (16.2)	12 (19.3)	0.3702
Walking speed (m/s)	1.00 $\pm$ 0.20	0.99 $\pm$ 0.20	0.93 $\pm$ 0.18	0.0528
Walk for exercise	1874 (54.9)	245 (52.2)	34 (54.8)	0.5643
Current smoker	169 (4.9)	27 (5.7)	4 (6.4)	0.6639
Alcohol drinks per week				0.9341
<1 per week	2666 (77.9)	367 (78.2)	48 (76.2)	
2–13 per week	562 (16.4)	79 (16.8)	12 (19.0)	
14+ per week	194 (5.7)	23 (4.9)	3 (4.8)	
Total hip BMD (g/cm ²)	0.76 $\pm$ 0.13	0.71 $\pm$ 0.13	0.69 $\pm$ 0.13	<0.001
BMI (kg/m ²)	26.6 $\pm$ 4.6	26.4 $\pm$ 4.7	25.7 $\pm$ 4.2	0.1785
Total hip T-score	-1.50 $\pm$ 1.05	-1.86 $\pm$ 1.05	-2.04 $\pm$ 1.08	<0.001
Any fracture since age 50	1327 (38.9)	240 (51.1)	35 (56.4)	<0.001
Involuntary weight loss >2kg since last visit	537 (15.7)	70 (14.9)	12 (19.3)	0.6494
Bisphosphonate/estrogen use	707 (20.6)	87 (18.5)	11 (17.7)	0.4894
Glucocorticoid use	240 (7.0)	44 (9.4)	6 (9.7)	0.1439
Time between visit 4 and 6 (yrs)	4.4 (0.5)	4.5 (0.5)	4.6 (0.5)	0.002

Table 2:

Percent annual change in total hip BMD by incident fracture between study visit 4 and visit 6

Fracture Type	N	Mean annual percent change in Total Hip BMD		
		Unadjusted (95%CI)	Multivariateadjusted (95%CI) ¹	Multivariateadjusted (95%CI) ²
None	3424	-0.67 (-0.71, -0.63)	-0.67 (-0.71, -0.63)	-0.66 (-0.70, -0.62)
Humerus	43	-1.02 (-1.40, -0.64)	-1.00 (-1.37, -0.63)	-1.00 (-1.37, -0.63)
Elbow	21	-1.22 (-1.75, -0.68) *	-1.26 (-1.79, -0.74) *	-1.18 (-1.70, -0.66)
Wrist	77	-0.76 (-1.04, -0.48)	-0.73 (-1.00, -0.45)	-0.68 (-0.95, -0.40)
Hand	13	-0.92 (-1.60, -0.24)	-0.94 (-1.61, -0.27)	-0.88 (-1.54, -0.22)
Vertebral	28	-1.34 (-1.81, -0.87) **	-1.29 (-1.75, -0.83) **	-1.26 (-1.72, -0.81)*
Rib	34	-0.67 (-1.09, -0.25)	-0.68 (-1.10, -0.27)	-0.72 (-1.13, -0.31)
Finger	16	-0.92 (-1.54, 0.31)	-0.98 (-1.58, -0.37)	-1.00 (-1.61, -0.38)
Face	15	-0.70 (-1.34, -0.07)	-0.60 (-1.22, -0.02)	-0.61 (-1.23, +0.01)
Clavicle	6	-1.84 (-2.84, -0.83) *	-1.87 (-2.85, -0.88) *	-1.85 (-2.83, -0.87) *
Any Upper Body Single Fracture [†]	260	-0.93 (-1.09, -0.78) **	-0.92 (-1.07, -0.77) **	-0.89 (-1.05, -0.74) **
Ankle	58	-0.69 (-1.02, -0.37)	-0.73 (-1.05, -0.42)	-0.69 (-1.00, -0.37)
Foot	47	-0.69 (-1.05, -0.33)	-0.65 (-1.00, -0.30)	-0.65 (-1.00, -0.30)
Toe	19	-0.27 (-0.83, +0.29)	-0.28 (-0.83, +0.27)	-0.27 (-0.82, +0.28)
Lower leg	14	-0.77 (-1.43, -0.12)	-0.66 (-1.31, -0.02)	-0.65 (-1.29, -0.01)
Hip	38	-1.31 (-1.71, -0.91) **	-1.17 (-1.56, -0.77) *	-1.10 (-1.49, -0.71)*
Pelvis	14	-1.20 (-1.86, -0.54)	-1.18 (-1.82, -0.53)	-1.11 (-1.75, -0.47)
Knee	14	-0.63 (-1.31, -0.05)	-0.62 (-1.29, +0.04)	-0.59 (-1.26, +0.07)
Any Lower Body Single Fracture [‡]	210	-0.83 (-1.00, -0.66)	-0.80 (-0.97, -0.63)	-0.77 (-0.94, -0.60)
Multiple Fractures - Upper Body Only [†]	25	-1.51 (-2.00, -1.02) ***	-1.39 (-1.87, -0.91) **	-1.42 (-1.90, -0.93) **
Multiple Fractures - Upper or Lower Body ^{†‡}	62	-1.42 (-1.73, -1.11) ***	-1.31 (-1.61, -1.00) ***	-1.30 (-1.60, -0.99) ***

*
p<0.05**
p<0.01***
p<0.001¹
adjusted for age²
adjusted for age, walking speed, bisphosphonate or estrogen use, glucocorticoid use, height, weight, and total hip BMD at visit 4[†]
Includes humerus, elbow, wrist, hand, vertebral, rib, finger, face, clavicle, neck, forearm, scapula, and skull fractures[‡]
Includes ankle, foot, toe, lower leg, hip, pelvis, knee, heel, and tailbone fractures

Table 3:

Annual percentage change in total hip BMD from visit 4 to visit 6 by quartiles of days from incident fracture to follow-up visit.

	Annual Percentage Change in Total Hip BMD	
Any Upper Body Single Fracture (n = 260)[‡]	Age-adjusted (95%CI)	MV-adjusted (95%CI)^I
Q1 (16–358 days)	–1.02 (–1.41, –0.63)	–0.98 (–1.37, –0.60)
Q2 (358–839 days)	–1.04 (–1.43, –0.65)	–1.04 (–1.42, –0.65)
Q3 (839–1208 days)	–0.88 (–1.27, –0.49)	–0.86 (–1.24, –0.48)
Q4 (1208–1861 days)	–0.79 (–1.18, –0.40)	–0.82 (–1.20, –0.44)
p-trend	0.338	0.446
Any Lower Body Single Fracture (n = 210)[‡]	Age-adjusted (95%CI)	MV-adjusted (95%CI)
Q1 (46–451 days)	–0.63 (–1.06, –0.21)	–0.63 (–1.04, –0.21)
Q2 (451–857 days)	–1.27 (–1.70, –0.85)	–1.31 (–1.74, –0.89)
Q3 (857–1258 days)	–0.74 (–1.16, –0.32)	–0.70 (–1.12, –0.28)
Q4 (1258–2028 days)	–0.68 (–1.10, –0.26)	–0.64 (–1.05, –0.23)
p-trend	0.698	0.579

^I adjusted for age, walking speed, bisphosphonate or estrogen use, glucocorticoid use, height, weight, and total hip BMD at visit 4

[‡] Includes humerus, elbow, wrist, hand, vertebral, rib, finger, face, clavicle, neck, forearm, scapula, and skull fractures

[‡] Includes ankle, foot, toe, lower leg, hip, pelvis, knee, heel, and tailbone fractures

Table 4:

Annual percent change in total hip BMD during the 2-year interval in which a fracture occurred (Fracture Interval), and the prior or subsequent 2-year intervals. All data are adjusted for age, bisphosphonate or estrogen use, glucocorticosteroid use, height, weight and total hip BMD at visit 4.

	n	Average annual % change in total hip BMD (mean (95%CI))			p-value [#]
		2-year Interval Before Fracture Interval	2-year Interval During Which Fracture Occurred	2-year Interval After Fracture Interval	
Fracture during Visit 5 – Visit 6		Visit 4 – Visit 5	Visit 5 – Visit 6		
Upper body single fracture [†]	133	−0.51 (−0.89, −0.14)	−1.23 (−1.60, −0.85) [*]		0.007
Lower body single fracture [‡]	98	−0.37 (−0.90, 0.16)	−1.20 (−1.73, −0.66) [*]		0.036
Fracture during Visit 4 – Visit 5			Visit 4 – Visit 5	Visit 5 – Visit 6	
Upper body single fracture [†]	119		−1.00 (−1.48, −0.52) [*]	−0.76 (−1.24, −0.28)	0.527
Lower body single fracture [‡]	98		−1.31 (−1.79, −0.82) [*]	−0.09 (−0.57, 0.40) [*]	0.003
No fracture during Visit 4 – Visit 6	n	Visit 4 – Visit 5	Visit 5 – Visit 6	p-value	
	3292	−0.56 (−0.62, −0.49)	−0.72 (−0.79, −0.66)	0.001	

^{*} Significantly different ($p < 0.05$) from the No Fracture group during the same time interval (V4-V5 or V5-V6)

[#] p-values indicate significant differences ($p < 0.05$) between intervals (V4-V5 vs. V5-V6)

[†] Includes humerus, elbow, wrist, hand, vertebral, rib, finger, face, clavicle, neck, forearm, scapula, and skull fractures

[‡] Includes ankle, foot, toe, lower leg, hip, pelvis, knee, heel, and tailbone fractures