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LOCOMOTOR DISEASES

Loss of hip bone mineral density over time is associated with spine and hip fracture incidence in osteoporotic postmenopausal women

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Abstract The objective of the study assess the relationship between bone mineral density (BMD) loss over time and fracture incidence in postmenopausal women. This is a posthoc analysis that includes women from the placebo group of two large randomized controlled trials having assessed the efficacy of a new anti-osteoporotic drug. BMD was assessed every 6 months during 3 years at the lumbar spine, the femoral neck and the total proximal femur. Vertebral fractures were assessed using a semiquantitative method. Hip fractures were based on written documentation. All patients received calcium and vitamin D. In the present study that included 1,775 patients (with complete data at baseline and after 3 years), the logistic regression analysis, adjusted for covariates, showed that 3-year change in lumbar BMD was not statistically associated with the new vertebral fractures after 3 years. However, femoral neck and total proximal femur BMD changes was statistically correlated with the incidence of new vertebral fractures ($P < 0.001$). When considering change in BMD after the first year of follow-up, a decrease in total proximal femur BMD was statistically associated with an increase in the incidence of new vertebral fractures during the last 2 years of follow-up ($P = 0.048$). The 3-year change in femoral neck and total proximal BMD was statistically correlated with the incidence of hip and fragility fracture after 3 years (all $P < 0.001$). In this elderly osteoporotic population receiving calcium and vitamin D, a decrease in hip BMD after 1 or 3 year of follow-up, is associated with an increased risk of fracture incidence. However, spine BMD changes do not influence vertebral fracture incidence.

Keywords Bone mineral density · Vertebral fracture · Hip fracture · Osteoporosis · Calcium · Vitamin D · Risk factor · Disease management

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Introduction

Osteoporosis is a disease characterized by a decrease in bone mass and deterioration in skeletal microarchitecture, leading to increased fragility and susceptibility to fracture. It is now widely accepted that one of the major determinants of skeletal weakness results from the bone loss that occurs after menopause. Epidemiologic studies of fracture incidence have shown that, in untreated patients, low bone mineral density (BMD) is consistently correlated with increased fracture risk [1–3]. The rate of bone loss, which is variable among postmenopausal women, has been postulated to be an independent risk factor for fracture [4, 5]. However, few prospective studies have assessed the association between the rate of bone loss and the risk of fracture [6–10]. In three of these studies however, the rate of bone loss was only obtained from the forearm site [6–8]. The

other studies provided conflicting results, some suggesting that BMD change was an independent risk factor for fragility fracture [10, 11] while a study suggest that repeating a measurement of BMD provides little additional value besides the initial BMD measurement for predicting incident fractures [9].

The aim of this study was to assess, in a large osteoporotic population followed regularly for 3 years, the association between BMD changes at the lumbar spine, total proximal femur and femoral neck and the risk of morphometric vertebral, hip and all fragility fractures.

Materials and methods

This post-hoc analysis was performed on data from the placebo arm of the SOTI (Spinal Osteoporosis Therapeutic Intervention study) and the TROPOS (Treatment of Peripheral Osteoporosis) studies [12, 13]. The design and methodology of these two studies were fully described in previous reports [12, 13]. Briefly, ambulatory postmenopausal women were recruited in eleven European countries and in Australia to participate in two prospective, randomized, double-blind, placebo-controlled trials (i.e. SOTI and TROPOS studies) assessing the effect of a new anti-osteoporotic drug. Women were eligible for the SOTI study if they were at least 50 years old, had been postmenopausal for at least 5 years, had at least one prevalent vertebral fracture confirmed by spinal radiography and had a lumbar spine *T*-score below −2.5. In the TROPOS study, the criteria of eligibility were a femoral neck BMD below −2.5, an age of 74 years or older, or an age between 70 and 74 years with at least one additional risk factor for fracture. Calcium and vitamin D supplementation was prescribed throughout the studies. Doses of calcium supplements were up to 1,000 mg of elemental calcium, depending of dietary intake, to maintain a daily calcium intake above 1,500 mg. Doses of vitamin D were 400–800 IU, depending on the baseline serum concentration of 25-hydroxyvitamin D. All participants gave written informed consent before enrolment, and institutional review boards approved these two studies. All participants gave written informed consent before enrolment and these two studies were approved by the appropriate IRBs.

BMD was measured by dual energy X-ray absorptiometry (DXA) at baseline and after 3 years of follow-up at the lumbar spine (region of interest L2–L4), total proximal femur and femoral neck. All the scans were analyzed centrally and BMD *T*-scores were calculated according to the centralized European normative data (D.O. Slosman, Geneva, Switzerland). A quality control program including daily quality controls was conducted throughout the studies [14]. The coefficients of variation for BMD measurement were 1.47% at the lumbar spine, 1.62% at the femoral neck, and 1.24% at the total proximal femur.

Vertebral fractures were assessed by the same team in a central facility throughout the 3-year studies (C. Roux and J. Fetchenbaum, Paris, France) with a semiquantitative visual assessment of each vertebra, from T4 to L4 [15] (L5 vertebra was assessed as fractured or not fractured) [15]. The semiquantitative grading scale was as follow: grade 0, normal; grade 1, a decrease in the height of any vertebra of 20–25%; grade 2, a decrease of 25–40%; and grade 3, a decrease of 40% or more. A new fracture was defined by a change in the score of a vertebra from grade 0 to 1 or more. Hip fractures were based on written documentation (radiograph, radiological report, copy of the hospitalization/emergency department report). During the study, major non-vertebral fractures were reported by study investigators based on written documentation provided and documented in the source document (radiograph, radiological report, copy of the hospitalization/emergency department report). Only documented non-vertebral fractures were taken into account in the statistical analysis. Fractures of the coccyx, skull, jaw, face, phalanx (fingers and toes), and ankle were not regarded as being related to osteoporosis and were not considered. Vertebral and major non-vertebral fractures were considered as fragility fracture.

Statistical analysis

Patients were included in this particular analysis only if they had vertebral X-rays and all sites BMD performed at baseline and after 3 year. The association between changes in BMD and fracture incidence (vertebral, hip and all fragility fracture) was assessed through a logistic regression analysis with age, body mass index (BMI), BMI change after 3-year, number of prevalent vertebral fractures and baseline BMD as covariates. Covariates were categorized for the present analysis (e.g. age > 70 years, BMI < 25 kg/m^2, BMI change < -1 kg/m^2, baseline BMD *T*-score < 2.5, presence or absence of prevalent vertebral fracture). Odds ratio (OR) and the related 95% confidence interval (95% CI) was assessed for a cut-off of BMD decrease of 3%. We also assessed the risk to experience at least one new fracture in different groups stratified for different BMD changes (i.e. quartiles of BMD change).

Results

Baseline characteristics of this study population are presented in Table 1. Out of the 3,358 women available at baseline, complete information after 3 years of follow-up was available for 1,775 subject. After 3 years, 369 women (20.7%) experienced a new vertebral fracture, 40 (2.2%)

Table 1 Baseline characteristics of the patients included in this study

	Total study population ($n = 3358$) [Mean (SD)]	Included in this study ($n = 1775$) [Mean (SD)]
Age (years)	75.1 (6.4)	73.3 (6.1)
Body mass index (kg/m^2)	25.6 (4.1)	25.7 (4.0)
Bone mineral density (g/cm^2)		
Lumbar spine	0.778 (0.150)	0.777 (0.148)
Total hip	0.661 (0.100)	0.674 (0.094)
Femoral neck	0.565 (0.075)	0.574 (0.073)
Number of previous vertebral fractures	1.29 (2.19)	1.18 (1.96)

experienced a hip fracture and 502 (28.2%) experienced a new fragility fracture. After 3-year of follow-up, in univariate analysis, the BMD changes at the femoral neck and total proximal femur, but not at the lumbar spine, were significantly associated with new vertebral fracture incidence ($P < 0.001$). The logistic regression analysis, including age, BMI, BMI change, prevalent vertebral fracture and baseline BMD as covariates, confirms that 3-year change in lumbar BMD changes was not statistically associated with the new vertebral fractures after 3 years ($P = 0.78$; Table 2). However, femoral neck and total proximal femur BMD changes was statistically associated with the incidence of new vertebral fractures ($P < 0.001$; Table 2). We have performed analysis in the two cohorts (SOTI and TROPOS) separately as in the pooled study group. Results were similar for the central value of the OR's, although 95% CI were larger and consequently sometimes not significant in the smaller SOTI study group.

From the logistic regression, besides BMD changes, prevalent vertebral fracture was independently associated with new vertebral fracture (data not shown). In separate models, initial BMD has been removed or substituted for final BMD without meaningful difference for the association with fracture incidence (data not shown). The incidence of morphometric vertebral fracture in each quartile of total proximal femur BMD changes was 26.0% (Q1), 20.3% (Q2), 15.4% (Q3) and 15.7% (Q4) ($P < 0.0001$; Fig. 1). The risk to experience new vertebral fractures in patients in the lowest quartile of total proximal femur BMD change (<−5.27%) is increased by 66% (95% CI 28–114%, $P < 0.001$) compared to patients in the highest quartiles (>+0.66%). The use of absolute BMD changes (in g/cm^2) confirms the trends of our results obtained with relative changes. Femoral neck and total proximal femur, but not lumbar BMD changes were statistically associated with the incidence of new vertebral fractures ($P < 0.001$). For example, for each decrease of 10 g/cm^2 in total proximal femur BMD, the OR (95% CI) for the association with new vertebral fracture was 1.08 (1.05–1.12).

When considering all fragility fracture during the 3 year of follow-up, femoral neck and total proximal femur, but not lumbar BMD changes, were statistically associated with the incidence of fractures ($P < 0.001$; Table 2).

Forty women (2.2%) have experienced a hip fracture during the 3 years of follow-up. The logistic regression analysis, including age, BMI, BMI change, prevalent vertebral fracture and baseline BMD as covariates, showed that 3-year change in femoral neck and total proximal femur BMD was statistically associated with the incidence of hip fracture after 3 years ($P < 0.01$; Table 2). Patients within the first quartile of femoral neck BMD change (<−5.49%) have experienced 22 hip fractures (4.6%) compared to 7 fractures (1.5%) in patients within the fourth quartile (>+0.68%). The risk to experience a hip fracture in patients with the highest femoral neck BMD less is then more than 3-fold greater than in patients within the smallest BMD less ($P = 0.005$).

When considering change in BMD after the first year of follow-up, the logistic regression analysis showed that change in total proximal femur BMD were significantly associated with new vertebral fracture assessed during years 2 and 3 (Table 3). However, changes in lumbar spine

Table 2 Results of the logistic regression analysis for the prediction of new fractures over 3 years, adjusted for age, body mass index, body mass index change over time, number of prevalent vertebral fractures and baseline bone mineral density

Fracture level	BMD change after 3 years (<−3% vs. ≥−3%)	OR (95% CI)	*P*-value
Vertebral fracture	Lumbar spine	0.93 (0.74–1.24)	0.78
	Total hip	1.66 (1.30–2.12)	<0.0001
	Femoral neck	1.83 (1.44–2.33)	<0.0001
Hip fracture	Lumbar spine	1.48 (0.76–2.86)	0.23
	Total hip	2.69 (1.27–5.68)	0.009
	Femoral neck	3.25 (1.48–7.11)	0.003
Any fragility fracture	Lumbar spine	1.08 (0.85–1.36)	0.50
	Total hip	1.47 (1.18–1.84)	0.0005
	Femoral neck	1.58 (1.27–1.96)	<0.0001

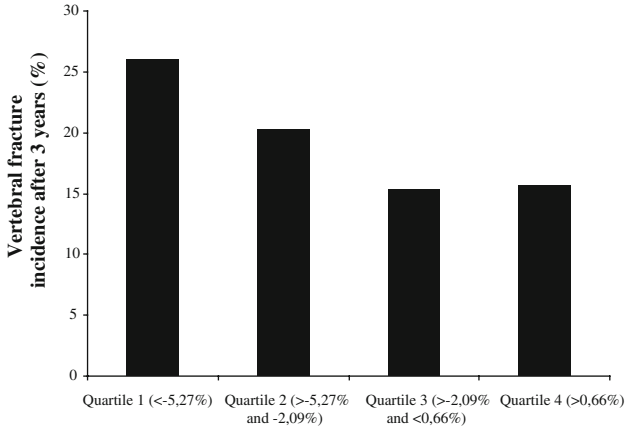

Fig. 1 Vertebral fracture incidence stratified for quartiles of total proximal femur BMD changes after 3 years

Table 3 Results of the logistic regression analysis for the prediction of new fractures over years 2 and 3, adjusted for age, body mass index, body mass index change over time, number of prevalent vertebral fractures and baseline bone mineral density

Fracture level	BMD change after 1 years (<−3% vs. ≥−3%)	OR (95% CI)	*P*-value
Vertebral fracture	Lumbar spine	1.05 (0.81–1.37)	0.66
	Total hip	1.31 (1.00–1.72)	0.048
	Femoral neck	1.04 (0.80–1.36)	0.73
Hip fracture	Lumbar spine	0.84 (0.39–1.82)	0.67
	Total hip	1.48 (0.62–3.52)	0.37
	Femoral neck	1.53 (0.66–3.53)	0.31
Any fragility fracture	Lumbar spine	1.07 (0.84–1.35)	0.56
	Total hip	1.26 (0.99–1.62)	0.06
	Femoral neck	1.02 (0.80–1.30)	0.83

and femoral neck BMD after 1 year were not significantly associated with new vertebral, hip or fragility fracture the last 2 years of follow-up.

Discussion

We show, in the present study, an association between the changes in total proximal femur and femoral neck BMD and morphometric vertebral fracture incidence, in untreated patients, followed for 3 years.

Previous studies having assessed the association between bone loss and the risk of fractures have been mainly performed using measurement of the forearm [6–8]. In the most recent one including 671 postmenopausal women, the authors showed that the rate of short-term (mean 2.7 years) bone loss was significantly associated with future (mean 10.7 years) fracture independently of age, previous fractures, maternal history of fracture, physical activity, grip strength, falls, and baseline BMD [8]. The conflicting results obtained by the other studies (i.e. some suggesting that BMD loss over time should be considered as a risk factor for fracture while other suggesting that BMD loss provide little additional value over that provided by initial BMD measurement) could probably be partly explained by differences in study population (e.g. age, sex, site of BMD measurement, initial BMD value) [9–11].

To the best of our knowledge, only one study has assessed the relationship between changes in BMD at the hip and spine and vertebral fracture risk in elderly women in the general population [11]. In univariate analysis, BMD measured at the femoral neck was consistently a significant independent predictor of hip fracture, and the discriminant power was better than that measured at the lumbar spine. Furthermore, the effect of lumbar spine BMD on vertebral fracture was more pronounced than its effect on nonvertebral fractures. Interestingly, in multivariate analysis, the authors showed that bone loss at the femoral neck, but not at the lumbar spine, was a predictor of symptomatic fracture risk in elderly women, independent of baseline BMD and age, a finding consistent with our current results.

In our study, lumbar spine BMD changes are not associated with fracture incidence. It has previously been shown that the presence or the worsening of degenerative conditions of the spine (osteophytes, end plate sclerosis) increase with age and could contribute to the artefacts in lumbar spine BMD measurement [16], hence decreasing the accuracy of fracture risk prediction. Moreover, it has been shown that microarchitectural deformities in the vertebra, which are not visually evident, could accumulate over time and contribute to the apparent increase in the lumbar spine BMD and ultimately lead to fracture [17, 18]. We should also acknowledge that the observation that rate of spine BMD change is not predictive of spine fractures is potentially confounded by the high prevalence of baseline and incident vertebral fractures in this study population. As a matter of fact, new fractures affecting the lumbar spine would be expected to produce an artefactual increase in lumbar spine BMD. However, it should be pointed out that our results are not consistent with the previous suggestions that the sensitivity of discrimination of fracture risk could be site specific.

Besides the association with fractures, greater bone loss could be a marker of underlying poor health. In the study of Nguyen et al. [11], it has been shown that a significantly higher rate of bone loss was associated with a highest mortality rate. Greater bone loss would be expected to be associated with cumulative macro- and microarchitectural damage resulting in weaker bone than suggested by overall BMD alone. It has also been shown that bone loss after

menopause could be at least partly attributed to an increased bone turnover rate and that previous longitudinal studies have shown that high bone turnover is associated with an increased rate of bone loss and an increased mortality rate [19].

We have also shown that a change in hip BMD, observed after only 1 year of follow-up was associated with the future vertebral fracture risk. Such information, if confirmed, could be of great interest to better select patients with the highest risk of fractures (i.e. that require the initiation of a pharmacological treatment) by combining this with previously well-known risk factors (i.e. age, gender, baseline BMD,…). However, in the real clinical practice, because of the variability in the measurement of BMD, it should be acknowledged that a 1-year change in BMD of less than 2% could not be considered as relevant. As a matter of fact, even if the coefficients of variation for BMD measurement were below 1.7% in this study, we should acknowledge that such coefficients of variation could be larger in clinical practice.

Simplistic or utopian extrapolation of our results would suggest that a treatment that would increase BMD, at least at the hip, would automatically decrease the risk of fracture. Unfortunately, a lot of discrepancies have been observed in the strength of the association between changes in BMD observed with anti-osteoporotic drugs (alendreonate, risedronate, raloxifene, teriparatide and strontium ranelate) and fracture incidence [20–29].

Our study has strengths and limitations. Our sample size was large and our cohort has been followed with strict obligation of randomized controlled trial. All fractures were prospectively assessed and radiographically confirmed. The repetition of spine radiographs every year allowed an optimal ascertainment of vertebral fractures because only a small proportion of them reach clinical attention. BMD has been assessed at all relevant site. BMD was assessed with strict quality control [14]. However, it should be acknowledged that the imprecision in the measurement of BMD that could be observed in clinical practice could modify the association between changes in BMD and reduction in fracture risk. In addition, women were community-dwelling Caucasian volunteers, and our findings may not be generalized to other populations. Thus, our results should be confirmed in longitudinal studies. Number of individual excluded from this study, because of the absence of the assessment of all clinical outcomes or covariates is high and could have bias the results. For example, individuals with new spine or hip fractures would be expected to have increased mortality or be more likely to withdraw from the study before the 3 year time point. In our study, we have pooled the data of two cohorts and this could potentially have influenced our results. However, these cohorts differ mainly by age, BMD and number of prevalent vertebral fractures. Since all our analyses have been adjusted for these confounders, we do not believe that it could have biased our results. At least, our study population was postmenopausal osteoporotic women treated with calcium and vitamin D. Besides the fact that the exact influence of these supplements on BMD changes and fracture risk is still debated, it should be acknowledge that our results could not be generalized to real untreated osteoporotic women. However, it should be pointed out that experts have recently recommended calcium and vitamin D supplementation to all elderly osteoporotic women [30].

In conclusion, bone loss observed at the hip is associated with an increased risk of morphometric vertebral and hip fracture, independently of other well-know predictors such as BMD and prevalent vertebral fracture.

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