Osteoporos Int
DOI 10.1007/s00198-014-3014-9

ORIGINAL ARTICLE

Accelerated bone loss and increased post-fracture mortality in elderly women and men

D. Bliuc · N. D. Nguyen · D. Alarkawi · T. V. Nguyen · J. A. Eisman · J. R. Center

Received: 23 October 2014 / Accepted: 17 December 2014

Abstract
Summary Bone loss, a fracture risk factor, may play a role in post-fracture mortality. We found accelerated bone loss (≥1.31 % bone loss/year for women and ≥1.35 % bone loss/year for men) associated with 44–77 % increased mortality. It remains unclear whether bone loss is a marker or plays a role in mortality.
Introduction Osteoporotic fractures are associated with increased mortality although the cause is unknown. Bone loss, a risk factor for osteoporotic fracture is also associated with increased mortality, but its role in mortality risk post-fracture is unclear. This study aimed to examine post-fracture mortality risk according to levels of bone loss.
Methods Community-dwelling participants aged 60+ from Dubbo Osteoporosis Epidemiology Study with incident fractures were followed from 1989 to 2011. Kaplan-Meier survival curves were constructed according to bone loss quartiles. Cox proportional hazard models were used to determine the effect of bone loss on mortality.
Results There were 341 women and 106 men with ≥2 BMD measurements. The rate of bone loss was similar for women and men (women mean −0.79 %/year, highest bone loss quartile −1.31 %/year; men mean −0.74 %/year, highest quartile −1.35 %/year). Survival was lowest for the highest quartile of bone loss for women ($p<0.005$) and men ($p=0.05$). When analysed by fracture type, the association of bone loss with mortality was observed for vertebral (highest vs lower 3 quartiles of bone loss, women $p=0.03$ and men $p=0.02$) and non-hip non-vertebral fractures in women ($p<0.0001$). Bone loss did not play an additional role in mortality risk following hip fractures. Importantly, overall, rapid bone loss was associated with 44–77 % increased mortality risk after multiple variable adjustment.
Conclusion Rapid bone loss was an independent predictor of post-fracture mortality risk in both women and men. The association of bone loss and post-fracture mortality was predominantly observed following vertebral fracture in both women and men and non-hip non-vertebral fracture in women. It remains to be determined whether bone loss is a marker or plays a role in the mortality associated with fractures.

Keywords BMD measurements · Bone loss · Mortality risk · Osteoporosis · Population

D. Bliuc · N. D. Nguyen · D. Alarkawi · T. V. Nguyen · J. A. Eisman · J. R. Center (✉)
Osteoporosis and Bone Biology Program, Garvan Institute of Medical Research, 384 Victoria St., Darlinghurst, NSW 2010, Australia
e-mail: j.center@garvan.org.au

J. A. Eisman · J. R. Center
Clinical School, St. Vincent's Hospital Sydney, Sydney, NSW, Australia

T. V. Nguyen · J. A. Eisman · J. R. Center
Faculty of Medicine, UNSW, Sydney, Australia

J. A. Eisman
Clinical Translation and Advanced Education, Garvan Institute of Medical Research, and School of Medicine Sydney, University of Notre Dame Australia, Sydney, NSW, Australia

Introduction

There is increasing evidence that all major osteoporotic fractures are associated with increased mortality risk [1–7]. The mechanism that leads to this increased risk is unclear but in general is not considered to be directly associated with the fracture per se, except perhaps for some of the acute mortality following hip fracture.

Published online: 20 January 2015

Indeed, risk factors for mortality risk have been predominantly studied following hip fracture [4, 8, 9]. Comorbid diseases have been hypothesised to play an important role in mediating mortality risk following hip fracture, however the evidence is contradictory [10, 11]. Some studies suggest that part (~50 %) of the excess mortality following hip fracture can be explained by the number and severity of comorbidities [10], while other studies including our own found little or no association between comorbidities and post-fracture mortality [1, 11]. There are few data examining risk factors for the increased mortality risk following other major fractures. Several fracture risk factors such as low bone density and muscle weakness have been associated both independently with mortality and in association with fracture, but they only account for a small proportion of the mortality risk [1, 12].

Bone loss is another known risk factor for fracture that has also been associated with increased risk of mortality in the general population [13, 14]. Kado et al. reported the association of bone loss with all cause mortality, pulmonary and cardiovascular mortality, but not stroke or cancer in elderly women. In that study, a loss of bone mass equivalent to 1 SD was associated with a 30 % increased risk of all cause mortality, and a 60 % increased risk of pulmonary mortality [13]. More recently, a report from the Dubbo Osteoporosis Epidemiology Study indicated that bone loss together with low femoral neck BMD, weight loss and weight fluctuation were independent predictors of mortality risk in the general population in both women and men [14]. However, the specific role of bone loss in mortality risk in the context of a fracture has not been studied.

The aim of this study was to determine whether rapid bone loss is associated with increased risk of mortality in individuals with osteoporotic fractures.

Methods

Study population, setting and design

The study population included women and men over the age of 60 with incident osteoporotic fractures who were enrolled in the Dubbo Osteoporosis Epidemiology Study. The methodology of this study has been extensively described elsewhere [1, 15, 16]. Briefly, this ongoing prospective study started in April 1989, and recruited over 60 % of the eligible 60+ population in the City of Dubbo. Dubbo is a semi-rural city of 32,000 people, with a relatively stable population and with its own radiological services, thus constituting an ideal setting for epidemiological study. One of the main aims of Dubbo Osteoporosis Epidemiology Study was to record all fractures occurring in the community through a systematic review of all x-ray records. Approximately half (754/1295) of all the individuals with incident fractures identified agreed to participate into a detailed ongoing assessment. The study was approved by the St. Vincent's Hospital Human Research Ethics Committee. After signing the informed consent form, participants attend regular ~2–3 yearly clinic visits for data collection and measurements.

The characteristics of the fracture cohort have been previously described [1, 15]. This study included only individuals who had sustained at least one osteoporotic fracture and who had a minimum of two BMD measurements. Thus, from the whole incident fracture cohort of 528 women and 187 men, 341 (65 %) women and 106 (57 %) men were eligible for the current analysis. The selected sample had the same age, gender and fracture type distribution as the whole fracture cohort.

Assessment of outcomes and risk factors

Fracture ascertainment

All fracture events occurring from April 1989 onwards were identified through the two and, at some times, three radiological services in Dubbo as previously reported. The circumstances of the fracture were obtained through direct interview. Only minimal trauma fractures (following a fall from standing height or less) were included. High trauma fractures, pathological fractures (e.g., cancer, Paget's disease) as well as fractures of the head, fingers and toes were excluded. Participants were also classified according to initial fracture type into: hip, vertebral and non-hip non-vertebral fracture.

Data ascertainment

1. BMD measurements — BMD (g/cm^2) was measured at the femoral neck by DXA using a GE LUNAR Densitometer (Madison, WI) at baseline and 2 yearly thereafter. All participants who had at least 2 BMD measurements were included in the study. Bone loss was assessed in two ways: overall bone loss, irrespective of timing of the fracture event, using all BMD measurements; and partial i.e., to assess bone loss in relation to the fracture event using at least 2 BMD measurements prior to fracture or 2 measurements post-fracture. The average number of BMD measurements was 5 (±2) for women and 4 (±2) for men. The coefficient of reliability for our institution was 0.96 at the femoral neck in normal subjects.

2. Clinical data	Information on lifestyle factors, as well as comorbidities, falls history and medication were self-reported and were collected through direct interview by a study coordinator. Participants were classified according to the number of comorbidities into four groups: none, 1, 2 and 3 or more. Comorbidities were also classified according to the type of the disease. Alzheimer, depression and epilepsy were grouped under neurological diseases, ischemic heart disease, myocardial infarction, cardiac arrhythmia and cardiac failure were included in cardiovascular disease and asthma and emphysema were included in the respiratory diseases. Hypertension, diabetes and rheumatoid arthritis were analysed separately.
3. Mortality data	Mortality status is ascertained continuously during the study follow-up through systematic searches of funeral director lists, local newspapers and Dubbo media reports. Deaths certificates were obtained from the New South Wales Registry of Births, Deaths, and Marriages.

Statistical analysis

The incidence of mortality was calculated as the number of deaths per 100 person-years of follow-up, assuming the occurrence of death followed the Poisson distribution. The time to follow-up used for the calculation of person-years was calculated for each participant from the date of initial fracture to death or end of study (1 January 2011).

The annual percentage change in BMD was calculated for each participant using a linear regression model. Polynomial models to examine bone loss did not improve goodness of fit over the linear model. Therefore, in order to preserve a larger sample size, linear models were preferred. For this model, a linear regression equation was used for each participant in order to determine the individual intercept and slope. The rate of bone loss was calculated as the ratio of the slope to the intercept.

Participants were then classified according to quartile of bone loss.

All BMD measurements were included in the bone loss calculation regardless of the time of fracture.

Mortality risk was assessed initially using Kaplan-Meier survival curves with participants stratified according to quartiles of bone loss into either four groups and subsequently two groups: the highest quartile vs. the lower three quartiles of bone loss.

Cox proportional hazards models were used to determine the effect of bone loss on mortality after adjusting for age at fracture, baseline femoral neck BMD, history of falls, number and type of comorbidities and osteoporosis treatment. The assumption of the proportional hazards model was checked for each risk factor. Backward and forward stepwise regressions were used to build the multivariate model. The Akaike information criterion was used to determine the most parsimonious model.

All statistical analysis was performed using SAS version 9 [17].

Results

Characteristics of the fracture cohort

There were 341 women and 106 men with incident osteoporotic fracture who had at least two bone density measurements. Age at fracture was similar for women and men [78.0 (±7.5) for women and 78.9 (±7.6) for men). Approximately half of the fractures were non-hip non-vertebral fractures (53 % in women and 46 % in men) followed by vertebral (34 % in women and 37 % in men) and hip fracture (13 % in women and 17 % in men).

Women were followed on average for 17 years (interquartile range 12.6–21.1) and men for 13.6 years (interquartile range 8.8–19.3). During this interval, 214 women and 80 men died yielding an incidence of mortality of 7.1 deaths/100 person-years of follow-up (95 % CI, 6.2–8.1) for women and 12.2 deaths/100 person-years follow-up (95 % CI, 9.8–15.2) for men. Individuals who died were older, had lower femoral neck BMD, a higher rate of bone loss and were less likely to have received anti-resorptive treatment (Table 1). The number of comorbidities was identical amongst those who died and those alive at the end of follow-up. However, hypertension and diabetes were less prevalent and cardiovascular and neurological diseases more prevalent amongst men who died compared to those who are alive.

Bone loss

Women had on average 6 (±2) and men 5 (±2) BMD measurements during the study period. Women lost approximately 0.79 % bone mass/per year (interquartile range −1.31, −0.02) and men lost 0.74 % bone mass/per year (interquartile range −1.35, 0.07). The rate of bone loss did not differ according to the 3 types of fracture (hip, vertebral and non-hip non-vertebral) in women ($p=0.92$) or men ($p=0.13$).

Age at fracture, baseline BMD, weight, number of comorbidities as well as first fracture type distribution was similar across quartiles of bone loss for both women and men (Table 2). However, the number of deaths was significantly higher for those in the highest quartile of bone loss, compared with the lower three quartiles ($p=0.0006$ for women and $p=0.04$ for men). Participants with higher rates of bone loss were also less likely to have had previous therapy with bisphosphonates (women 5 %

Table 1 Characteristics of the fracture cohort

Variable	Women		Men	
	Dead (n=214)	Alive (n=127)	Dead (n=80)	Alive (n=26)
Age at fracture, yrs	79.3 (7.6)*	76.0 (7.6)	80.0 (7.7)**	75.5 (6.6)
Femoral neck BMD[b] g/cm^2	0.72 (0.11)*	0.79 (0.11)	0.86 (0.12)**	0.89 (0.15)
Rate of bone loss[b] (%/year)	−0.86 (2.10)	−0.67(1.46)	−0.88 (11.76)**	−0.32 (1.55)
Fracture type[a]				
Hip	34 (10)	11 (3)	15 (14)	3 (3)
Vertebral	70 (21)	45 (13)	30 (28)	9 (8)
Non-hip non-vertebral	110 (32)	71 (21)	35 (33)	14 (13)
Bisphosphonate use[a]	31 (9)**	35 (10)	1 (0.9)**	5 (5)
Diseases[a]				
None	48 (14)	26 (8)	19 (18)	2 (3)
1	75 (22)	47 (14)	29 (27)	10 (9)
2	64 (19)	26 (8)	24 (23)	9 (8)
≥3	27 (8)	28 (8)	8 (8)	5 (5)
Cardiovascular[a]	70 (21)	33 (10)	23 (22)**	10 (9)
Hypertension[a]	116 (34)	71 (21)	26 (25)**	13 (12)
Diabetes[a]	13 (4)	9 (3)	6 (6)	1 (0.9)
Respiratory[a]	21 (6)	20 (6)	14 (13)	6 (6)
Neurological[a]	44 (14)	27 (8)	19 (18)**	2 (2)
Cancer[a]	26 (8)	19 (6)	14 (13)**	8 (8)
Rheumatoid arthritis[a]	15 (4)	5 (1)	4 (4)	0 (0)

BMD bone mineral density, *yrs* for years number represents number (percent) of the whole cohort

[a] No. (%)

[b] Mean (SD)

*p<0.0001; **p<0.001

for those with rapid bone loss vs 24 % for those with lower rates of bone loss, p=0.0004; and men 0 % for those with rapid bone loss vs. 8 % for those with lower rates of bone loss, p=0.10).

Timing of BMD measurements in relation to fracture and effect on bone loss

For this study, all BMD measurements were considered regardless of the timing of fracture. While the majority of the participants had at least one BMD measurement before the fracture and one after the fracture, approximately 25 % of the cohort had BMD measurements only prior to the fracture (85/341 women and 43/106 men). The rate of bone loss in this group was greater than the rest of the cohort; however the difference was significant only in women. Most importantly, mortality risk was significantly higher in this group compared with the rest of the cohort, presumably because they had died prior to obtaining a post-fracture bone density scan. However, excluding this group as part of sensitivity analysis did not alter the overall results. The effect of the fracture event on the rate of bone loss could be compared only in the group of participants (101 women and 39 men) who had at least 2 BMD measurements prior and 2 BMD measurements post-fracture. The rate of bone loss was similar pre- and post-fracture in women [mean (SD) −0.33 (1.45) and −0.38 (1.67), p=0.11 pre- and post-fracture interval, respectively] and in men [mean (SD) −0.76 (1.59) and −0.62 (2.22), p= 0.75 pre- and post-fracture interval, respectively].

Although bone loss was not significantly different pre- and post-fracture, we also analysed bone loss in those subjects who had had at least 2 bone density scans prior to fracture (266/341 women and 74/106 men) in case the fracture event may have had some influence on bone loss post-fracture. Interestingly, the association between bone loss and mortality was higher in this subgroup compared to the overall group (age-adjusted HR 1.83 [95% CI, 1.30–2.58] and 2.71 [95% CI, 1.42–5.16] for women and men, respectively).

Kaplan-Meier survival curves

The effect of bone loss on mortality risk was evaluated using Kaplan-Meier survival curves. This was performed initially with participants stratified in 4 groups corresponding to the 4 quartiles of bone loss and then in 2 groups: the highest quartile (most rapid bone loss) vs. the lower 3 quartiles (Fig. 1 panel I).

Table 2 Participants characteristics according to quartiles of bone loss

	Bone loss, %/year			
	Women		Men	
	Most rapid quartile (≥−1.31)	Least rapid 3 quartiles (<−1.31)	Most rapid quartile (≥−1.35)	Least rapid 3 quartiles (<−1.35)
Number	86	255	26	80
Age at fracture[a], yrs	78 (8)	77 (7)	77 (8)	77 (8)
Deaths, no. (%)	64 (74)*	150 (59)	22 (85)*	58 (73)
Femoral neck BMD[a] g/cm^2	0.74 (0.13)	0.75 (0.11)	0.83 (0.12)	0.88 (0.12)
Weight[a], kg	62 (12)	65 (12)	73 (11)	78 (11)
Fracture type, no. (%)				
Hip	13 (15)	32 (13)	5 (19)	13 (16)
Vertebral	30 (35)	85 (33)	11 (42)	28 (35)
Non-hip non-vertebral	43 (50)	138 (54)	10 (38)	39 (49)
Comorbidities, no. (%)				
None	14 (16)	60 (24)	7 (27)	14 (18)
1	28 (33)	94 (37)	10 (38)	29 (36)
2	32 (37)	58 (23)	6 (23)	27 (34)
3 or more	12 (14)	43 (17)	3 (12)	10 (13)
Cardiovascular, no (%)	25 (29)	78 (31)	7 (27)	26 (33)
Hypertension, no. (%)	55 (64)*	132 (52)	9 (35)	30 (38)
Diabetes, no. (%)	5 (6)	17 (7)	3 (12)	4 (5)
Respiratory, no. (%)	14 (16)	27 (11)	3 (12)	17 (21)
Neurological, no. (%)	18 (21)	53 (21)	3 (12)	18 (23)
Cancer, no. (%)	11 (13)	34 (13)	6 (23)	16 (20)
Bisphosphonate use, no. (%)	4 (5)*	62 (24)	0 (0)	6 (8)

[a] Mean (SD)

*$p<0.005$ correspond to a statistically significant difference between highest quartile of bone loss and lower 3 quartile

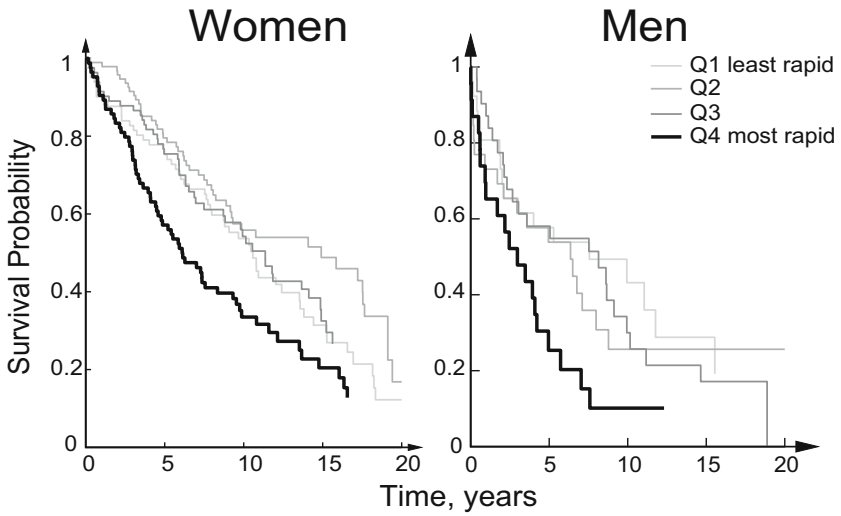

Fig. 1 Kaplan-Meier survival curves according to bone loss for all types of fracture. I-Stratification according to all quartiles of bone loss **a** Women (q1≥−0.02 % bone mass/year; −0.01>q2>−0.67 % bone mass/year; −0.67>q3>−1.31 % bone mass/year; q4≤−1.31 bone mass/year) **b** Men (q1≥0.07 % bone mass/year; 0.06>q2>−0.57 % bone mass/year; −0.56>q3>−1.35 % bone mass/year; q4≤−1.35 bone mass/year). II-Stratification according to most rapid quartile of bone loss versus least rapid three quartiles **a** Women (≤−1.31 bone mass/year vs >−1.31 bone mass/year) **b** Men (≤−1.35 bone mass/year vs>−1.35 bone mass/year)

For both women and men, the curve corresponding to the highest quartile of bone loss separated from the rest, indicating that mortality risk was highest for the highest quartile of bone loss compared to the lower three quartiles of bone loss. Given that the survival curves corresponding to the lower 3 quartiles of bone loss were intertwined indicating similar mortality rates, the participants were stratified into 2 groups only: highest quartile vs lower three quartiles. As expected, survival rates were significantly lower for the highest quartile of bone loss in both women and men ($p<0.0001$ for women and $p=0.05$ for men) (Fig. 1 panel II).

Effect of fracture type on mortality risk

In the group of participants with hip fracture, higher rates of bone loss were not associated with higher mortality rates for either women or men ($p=0.7$ for women and $p=0.8$ for men) (Fig. 2 panel I).

By contrast, for the group with an initial clinical vertebral fracture, those in the highest quartile of bone loss had a significantly higher mortality rate than those in the lower three quartiles ($p=0.03$ for both women and men) (Fig. 2 panel II). Similarly, in the group of women with non-hip non-vertebral fracture, those in the highest quartile of bone loss had a significantly higher mortality rates compared to those with lower bone loss rates ($p<0.0001$). For men with non-hip non-vertebral fractures, those with higher rates of bone loss appeared to have higher mortality rates than those with lower bone loss rates; however, this did not reach statistical significance ($p=0.26$), most likely due to the small number of people in this group ($n=49$) (Fig. 2 panel III). It is notable that the greatest mortality rates overall post-fracture for all fracture types were observed in the first 5 years post-fracture for both women and men consistent with previous reports [1].

Age-adjusted hazard ratios of mortality according to fracture type confirmed the above results. The highest quartile of bone loss was significantly associated with mortality risk for vertebral fracture [age-adjusted HR 2.54 (1.50–4.29) and 3.32 (1.39–7.93) for women and men, respectively], and non-hip non-vertebral fracture in women [age-adjusted HR 1.78 (1.18–2.70) for women and 1.19 (0.52–2.70) for men]. Increased rates of bone loss did not play a significant role in mortality risk following hip fracture [1.03 (0.47–2.25) and 1.72 (0.46–6.46) for women and men, respectively].

Predictors of mortality risk post-fracture

The highest quartile of bone loss was associated with 44–77 % increased mortality risk after adjusting for age, baseline femoral neck BMD and comorbidities [adjusted HR 1.44 (95% CI, 1.07–1.95) and 1.77 (95% CI, 1.04–3.01) for women and men, respectively]. Increasing age (+5 years) was independently associated with mortality risk [adjusted HR 1.54 (95 % CI, 1.39–1.71 and 1.66 (95 % CI, 1.38–1.99) for women and men, respectively], while lower femoral neck BMD was an independent mortality risk predictor only in women [adjusted HR 1.30 (95 % CI, 1.11–1.52)] as was rheumatoid arthritis in women [HR 1.81 (95 % CI, 1.06–3.10)].

Discussion

In this cohort of women and men with osteoporotic fractures, bone loss was associated with an increased risk of mortality. This association was independent of age, baseline femoral neck BMD, number and types of comorbidities in both women and men. The impact of rapid bone loss on mortality risk varied according to initial fracture type in both genders. The effect of bone loss on mortality risk was manifest following clinical vertebral fractures in both women and men. For non-hip non-vertebral fractures the association was only significant in women. However, following hip fractures rapid bone loss did not contribute further to the increased mortality for either women or men.

The association between bone loss and mortality risk in the general population has been previously reported, including in the Dubbo Osteoporosis Epidemiology Study [13, 14]. In the latter study, baseline femoral neck BMD, a high rate of bone loss, weight loss and weight fluctuation were independent predictors of all cause mortality in both women and men, irrespective of whether they had had a fracture, and contributed to ~36 % and 22 % of deaths in women and men, respectively [14]. The current study extended the findings of the previous study by taking into account both the fracture event and the fracture type. In this analysis, a high rate of bone loss was an independent predictor of fracture-associated mortality risk. A rate of bone loss greater than −1.36 % per year was associated with increased post-fracture mortality after accounting for age, baseline femoral neck BMD as well as number and type of comorbidities.

This is the first study to our knowledge that has explored the role of bone loss in mortality risk following different types of osteoporotic fractures. Interestingly, although the rate of bone loss was similar for hip, clinical vertebral and non-hip non-vertebral fracture, the association between bone loss and mortality risk varied with the type of initial fracture. This association was strongest for clinical vertebral fractures. In this group, rapid rate of bone loss was associated with 2.5–4.5-fold increased risk of mortality in women and men, and the relationship was not altered after accounting for other risk factors such as age, baseline femoral neck BMD or number of comorbidities. Similar to vertebral fractures, rapid bone loss was associated with increased mortality risk following non-hip non-vertebral fractures. However, the relationship of bone

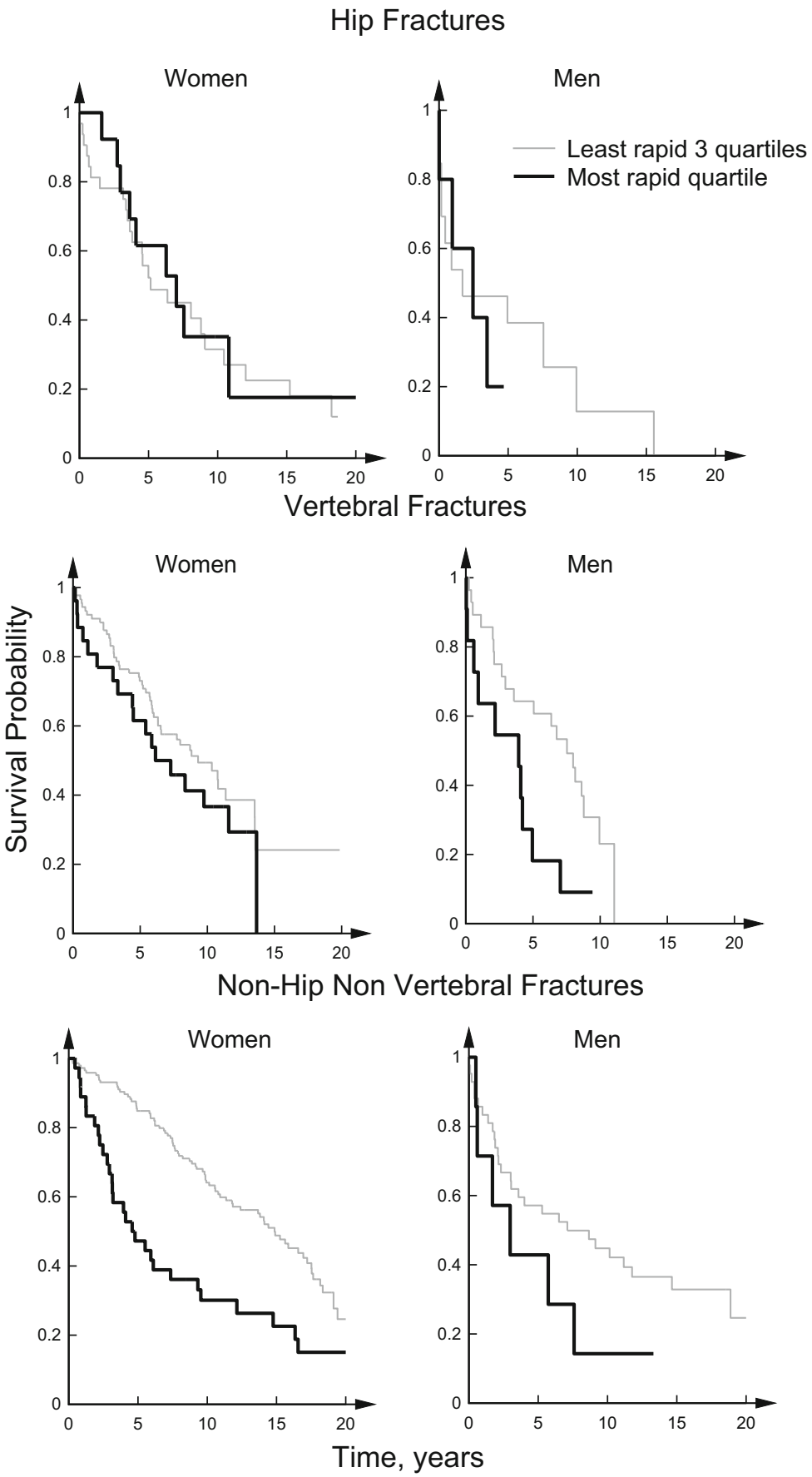

Fig. 2 Kaplan-Meier survival curves according to fracture type and two groups of bone loss: most rapid versus the least rapid three quartiles of bone loss: **a** Women. **b** Men I-Hip fractures, II-Vertebral fractures and III-Non-hip non-vertebral fractures

loss and mortality in this group of fractures was present only in women.

By contrast, bone loss did not play an additional role in the mortality risk associated with hip fracture. Although, this group of individuals had an increased mortality risk, with a 40–45 % total mortality at 5 years post-fracture, the number of deaths was similarly high amongst those with rapid bone loss and those who had lower rates of bone loss, suggesting that other factors may play a role in mortality risk following hip fractures [8, 10].

The mechanism of increased post-fracture mortality with accelerated bone loss is not fully understood. It is possible that bone loss is simply a marker of poor health and ageing, and that the underlying condition that contributed to bone loss may also explain the high mortality risk. Several papers have described the geriatric frailty syndrome characterised by deterioration in physical function, inactivity, susceptibility to falls, fractures and increased mortality risk [18, 19]. The mechanism behind this physical decline has been hypothesised to be a chronic inflammatory state, characterised by high levels of cytokines such as IL-6, IL-1, IL-11 and TNF [20]. These pro-inflammatory factors have been shown to have a direct role in the maturation of osteoclast precursors and the activation of mature osteoclasts, and thus may possibly contribute to more rapid bone loss. The association between bone loss and inflammation has been demonstrated in chronic inflammatory diseases [21]. On the other hand, these pro-inflammatory factors have been associated with atherogenesis [22] and risk of cardiovascular mortality [23]. Thus, an altered immune state may explain both the accelerated bone loss and increased mortality risk.

Another possibility is that bone loss itself may produce some factors detrimental to health. Bone loss occurs through increased bone turnover, and there is an evidence that with increased turnover, there is a release of heavy metals such as lead from the bone [24, 25], which may subsequently predispose to cardiovascular diseases. One study has shown that the lead concentrations increases significantly in whole blood after menopause, an increased bone turnover state, compared to the concentrations before menopause [26], while another study reported increased cardiovascular mortality in women with high levels of blood lead concentrations [27].

This study has several strengths. Firstly, the long follow-up of over 20 years means that the majority of the individuals bone loss was based on three or more rather than two BMD measurements. This enabled us to evaluate the slope of the change rather than the difference between two BMD measurements, hence a higher reliability of the results. The long follow-up was also essential for capturing a large number of events which further made possible exploration of the association of bone loss with mortality risk for different types of fractures, and separately for women and men. However, there are some limitations. The study population is almost entirely Caucasian, and thus these findings cannot be directly extrapolated to other populations or ethnic groups. Secondly, given the high mortality risk following fracture, it was not possible to compare the effect of bone loss prior to and post-fracture in order to determine which was better at predicting mortality risk, although in the sample where this was measurable, bone loss was similar pre- and post-fracture.

In summary, this study has shown that women and men who had high rates of bone loss and had experienced a low trauma fracture had a higher mortality risk than those with a lower rate of bone loss.

Importantly, this association remained statistically significant after adjusting for age, baseline femoral neck BMD, number and type of comorbidities and was present for all types of fractures except hip fractures. The effect of bone loss on mortality risk in men was less clear and depended on initial fracture type. The association between bone loss and mortality risk was strongest following clinical vertebral fractures and possibly for the first 5 years following non-hip non-vertebral fractures. . Similar to women, bone loss did not add independently to the high mortality risk following hip fracture. The mechanism by which bone loss might be linked to increased post-fracture mortality is not known. Nevertheless, this study suggests that bone loss is a contributor to the determination of post-fracture mortality risk and supports the idea that therapy to prevent bone loss may also have an effect on reducing mortality risk.

Conflicts of interest D.B., N.D. N. and T.V. N. have no competing interests to declare. J.A.E. has consulted for and/or received research funding from Amgen, deCode, Eli Lilly, Merck Sharp and Dohme, Novartis, sanofi-Aventis, and Servier. J.R.C. has been supported by and/or given educational talks for Merck Sharp and Dohme, Amgen, and Sanofi-Aventis.

Funding This work was supported by the National Health Medical Research Council Australia (NHMRC project ID; DB 1073430, JRC 1008219, DA, TVN, JRC and JAE 1070187). The authors are solely responsible for the contents of this paper, and do not reflect the views of NHMRC. Other funding bodies are Osteoporosis Australia-Amgen grant; the Bupa Health Foundation (formerly MBF Foundation); the Ernst Heine Foundation; and untied grants from Amgen, Merck Sharp & Dohme, sanofi-Aventis, Servier, and Novartis.

Role of the sponsor The study sponsors had no role in the study design; collection, analysis and interpretation of the data; the writing of this report; or the decision to submit this paper for publication.

References

1. Bliuc D et al (2009) Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. JAMA 301(5):513–21

2. Center JR et al (1999) Mortality after all major types of osteoporotic fracture in men and women: an observational study. Lancet 353(9156):878–82
3. Huntjens K et al (2010) Risk of subsequent fracture and mortality within 5 years after a non-vertebral fracture. Osteoporos Int
4. Empana JP, Dargent-Molina P, Breart G (2004) Effect of hip fracture on mortality in elderly women: the EPIDOS prospective study. J Am Geriatr Soc 52(5):685–90
5. Kado DM et al (2003) Incident vertebral fractures and mortality in older women: a prospective study. Osteoporos Int 14(7):589–94
6. Shortt NL, Robinson CM (2005) Mortality after low-energy fractures in patients aged at least 45 years old. J Orthop Trauma 19(6):396–400
7. Johnell O et al (2004) Mortality after osteoporotic fractures. Osteoporos Int 15(1):38–42
8. Kannegaard PN et al (2010) Excess mortality in men compared with women following a hip fracture. National analysis of comedications, comorbidity and survival. Age Ageing 39(2):203–9
9. Alegre-Lopez J et al (2005) Factors associated with mortality and functional disability after hip fracture: an inception cohort study. Osteoporos Int 16(7):729–36
10. Tosteson AN et al (2007) Excess mortality following hip fracture: the role of underlying health status. Osteoporos Int 18(11):1463–72
11. Vestergaard P, Rejnmark L, Mosekilde L (2007) Increased mortality in patients with a hip fracture-effect of pre-morbid conditions and post-fracture complications. Osteoporos Int 18(12):1583–93
12. Browner WS et al (1993) Association between low bone density and stroke in elderly women. The study of osteoporotic fractures. Stroke 24(7):940–6
13. Kado DM et al (2000) Rate of bone loss is associated with mortality in older women: a prospective study. J Bone Miner Res 15(10):1974–80
14. Nguyen ND et al (2007) Bone loss, weight loss, and weight fluctuation predict mortality risk in elderly men and women. J Bone Miner Res 22(8):1147–54
15. Center JR et al (2007) Risk of subsequent fracture after low-trauma fracture in men and women. JAMA 297(4):387–94
16. Simons LA et al (1990) The Dubbo study: an Australian prospective community study of the health of elderly. Aust N Z J Med 20(6):783–9
17. (2006) Base SAS: 9.1.3 Procedures Guide. 2nd ed Cary, NC: SAS Publishing
18. Ensrud KE et al (2007) Frailty and risk of falls, fracture, and mortality in older women: the study of osteoporotic fractures. J Gerontol A Biol Sci Med Sci 62(7):744–51
19. Ensrud KE et al (2009) A comparison of frailty indexes for the prediction of falls, disability, fractures, and mortality in older men. J Am Geriatr Soc 57(3):492–8
20. Ershler WB, Keller ET (2000) Age-associated increased interleukin-6 gene expression, late-life diseases, and frailty. Annu Rev Med 51: 245–70
21. Redlich K, Smolen JS (2012) Inflammatory bone loss: pathogenesis and therapeutic intervention. Nat Rev Drug Discov 11(3):234–50
22. Jones KG et al (2001) Interleukin-6 (IL-6) and the prognosis of abdominal aortic aneurysms. Circulation 103(18):2260–5
23. Selim G et al (2006) Inflammation predicts all-cause and cardiovascular mortality in haemodialysis patients. Prilozi 27(1):133–44
24. Gulson B et al (2002) Skeletal lead release during bone resorption: effect of bisphosphonate treatment in a pilot study. Environ Health Perspect 110(10):1017–23
25. Gulson BL et al (1998) Mobilization of lead from the skeleton during the postnatal period is larger than during pregnancy. J Lab Clin Med 131(4):324–9
26. Silbergeld EK, Schwartz J, Mahaffey K (1988) Lead and osteoporosis: mobilization of lead from bone in postmenopausal women. Environ Res 47(1):79–94
27. Khalil N et al (2009) Association of blood lead concentrations with mortality in older women: a prospective cohort study. Environ Health 8:15