OSTEOPOROSIS-RELATED MORTALITY: TIME-TRENDS AND PREDICTIVE FACTORS

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ABSTRACT

Osteoporosis is one of the leading causes of handicap worldwide and a major contributor to the global burden of diseases. In particular, osteoporosis is associated with excess mortality. We reviewed the impact of osteoporosis on mortality in a population by defining three categories: mortality following hip fractures, mortality following other sites of fractures, and mortality associated with low bone mineral density (BMD). Hip fractures, as well as other fractures at major sites are all associated with excess mortality, except at the forearm site. This excess mortality is higher during the first 3-6 months after the fracture and then declines over time, but remains higher than the mortality of the normal population up to 22 years after the fracture. Low BMD is also associated with high mortality, with hazard ratios of around 1.3 for every decrease in 1 standard deviation of bone density at 5 years, independently of fractures, reflecting a more fragile population. Finally predictors of mortality were identified and categorised in demographic known factors (age and male gender) and in factors reflecting a poor general health status such as the number of comorbidities, low mental status, or level of social dependence. Our results indicate that the management of a patient with osteoporosis should include a multivariate approach that could be based on predictive models in the future.

Keywords: Bone mineral density, fracture, mortality, mortality indicators, osteoporosis, predictive model, population, time-trends.

BACKGROUND AND OBJECTIVES

Osteoporosis is one of the leading causes of handicap worldwide and a major contributor to the global burden of diseases.[1-3] The impact at the population level is constantly increasing due to aging in societies,[4,5] although some studies have reported a stabilisation or even decline in the incidence of age-adjusted osteoporotic fractures in Western societies, possibly due to increased average body weight, improved functional ability among the elderly, and specific measures to prevent bone loss and reduce the risk of falling.[6-9]

Osteoporotic fractures are associated with a high mortality rate.[10-13] This excess mortality is mostly elevated in the first 3-6 months following the fracture then seems to decline during the first 2 years post-fracture, but does not return to the levels of the general population even 10 years after the fracture.[10,14,15]

Some studies showed that the excess mortality seems to be stable during the last few decades[13,16,17] while others suggested it is decreasing with time, probably due to advances in the surgical management of the fractures, or to preventive measures in the postoperative periods, such as antibiotherapy and anticoagulation, and to pharmacological primary and secondary preventive measures.[14,18-24] Moreover, the decline in age-specific rates of osteoporotic fractures could indirectly lead to a decline in the global mortality burden.

The recent literature addressed the evolution of the outcomes of osteoporotic fractures with time and

focused on potential risk factors associated with mortality. Magnitude of time trends in absolute and relative mortality following fractures differs between studies. Furthermore, and beyond the fracture event, there is emerging evidence that bone mineral density (BMD) is associated independently with increased mortality.

The objective of the current review is to investigate time-trends of mortality associated with different aspects of osteoporosis: hip fractures, other sites of fractures, and low BMD. The association with specific predictive factors is also addressed.

METHODS

A review of the US National Library of Medicine (PubMed database) was performed using the Medical Subject Headings (MeSH) terms: "osteoporosis", "fractures", "bone", "mortality", and "population". A second search using the terms: "bone density", "mortality", and "population" was performed in a subsequent step. The search retrieved 433 articles, 64 of which were retained for the analysis. Studies were retained when relevant to the review objectives and when conducted in a population setting. Studies were excluded when their objective related to the efficacy of anti-osteoporotic treatments, sponsored or not. The studies were divided into three categories: mortality following a hip fracture, mortality following any other fracture, and mortality in low BMD patients regardless of fractures. For each study, the population and study design were identified, as well as the mortality indicator used. For every category, the studies were classified by year of publication.

RESULTS

1. Mortality Following Hip Fractures

Among all osteoporotic fractures, hip fracture is the site most commonly associated with mortality. The highest excess in mortality is during the immediate post-fracture period, especially the first 6 months, but remains high several years after the fracture, as shown in population-based prospective studies.[10,14,25] This could be underestimated in randomised trials where the frail individuals at greatest risk of death are rarely considered suitable.

Literature in the past two decades showed that most deaths are related to associated comorbidities, reflecting a poor underlying health condition rather than the fracture itself.[5,26,27] It is clear nowadays that the excess deaths after a hip fracture can be attributed to serious underlying comorbidities that are unrelated to osteoporosis, suggesting that a certain proportion of deaths could not be prevented by reducing fractures.[28,29]

The mortality indicators are shown in Table 1 by study and by chronological order of publication. Although the studies have different populations, methodologies, and mortality indicators, there is a clear trend of decreased excess mortality with time within the same cohort, even if this excess remains present up to 22 years after the hip fracture. At 1 year, hazard ratios (HRs) vary from around 3-10; they decline to 5 at 5 years, and to 2.5 at 10 years. There is also a trend for a decline in excess mortality at 1 year by date of study publication, suggesting a decreased association with mortality over the last decade (Figure 1).

2. Mortality Following Fractures at Sites other than the Hip

Osteoporotic fractures at sites other than the hip also lead to a high number of excess deaths.[5,45,46] Most deaths occur within 1 year of fracture, particularly during the first 6 months.[47] Mortality following fractures is higher in men than in women.[5]

The Dubbo study from Australia reported that a high mortality is associated with any type of major fracture compared to the general population,[10] and that this excess mortality persists up to 5 years after all major types of fracture. Many studies, however, showed that mortality rates after forearm fracture are similar to the general population.[10,34]

The mortality indicators are shown in Table 2 by study, by chronological order of publication. Due to the heterogeneity of the studies, a direct comparison cannot be made, but again, in the same cohort, there is a decline in excess mortality with time and higher mortality in males.

3. Predictors of Mortality Following Osteoporotic Fractures

Since the fracture itself cannot explain the excess mortality, many studies addressed the associated risk factors with poor survival. Some factors were associated with the fracture, such as the site of fracture and the timeframe following the fracture. The hip site was associated with the higher mortality rates, but other sites considered as major were also associated to a lesser extent (vertebral,

pelvis, shoulder). Fractures at the forearm were not associated with excess mortality. As for time, the mortality risk was higher in the immediate post-fracture period and declined subsequently, remaining however higher than the normal population up to 10 years after the occurrence of the fracture.

However, most factors were independent from the fracture *per se* and yet predicted excess mortality.[26,37,38,55-57] These can be divided in demographic factors, such as age and male gender, and factors reflecting a poor general health status: the number of co-medications, associated chronic diseases (two or more), Charlson index CI) components and medications, low score on entality status test, not walking outdoors before the fracture, lower handgrip strength, use of walking aids, level of social dependence, and being in an institution. It is noticeable that the CI components encompass several chronic diseases. A comparable mortality with the normal opulations was suggested in the absence of risk factors such as low mentality status, low handgrip strength, and fewer than two associated chronic diseases.[55]

Finally, the non-operative conservative management is also associated with poorer outcome. However, this finding could be due to selection bias; the patients chosen for conservative management may have a lower health status or be at higher mortality risk initially, preventing them from reaching the operative option.

4. Mortality Associated with Low BMD

Except for pulmonary deaths in women with severe vertebral deformities and kyphosis, strong associations of osteoporotic fractures with specific causes of death have not been identified, suggesting an indirect association with underlying comorbid conditions that may also lead to osteoporosis.[46] This is consistent with the notion that low BMD *per se* is associated with excess mortality from various causes.[28,31,45,46,48,49]

Low BMD is responsible for a growing global health burden, only partially representative of the real burden of osteoporosis. In fact a recent meta-analysis showed that global deaths attributable to low BMD increased between 1990 and 2010, and that low BMD could be responsible for at least one-third of deaths attributable to falls, which is third in the list of major health burdens after road injuries and self-harm.[58,59]

BMD was shown to be associated with mortality independently of age, weight, body mass index, smoking status, previous fracture, physical activity, drug use, and presence of chronic diseases. Low BMD was defined in the studies by low values measured by Dual Energy X-ray Absorptiometry or calcaneus quantitative ultrasound. HR was calculated by linear reduction of 1 standard deviation (SD) of bone density or broadband ultrasonic attenuation (Table 3). The risk of mortality at 5 years was inversely correlated with BMD with HRs of 1.16-1.44, except for one study that included a clinical endpoint (height loss), where HRs were higher (3.43).[60-65]

Factors associated with excess mortality in osteoporosis cohorts are mainly CI components and Elixhauser index.[66] The Charlson comorbidity index predicts the 10-year mortality for a patient who may have a range of comorbid conditions, such as myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic lung disease, connective tissue disease, ulcer, chronic liver disease, diabetes, haemiplegia, moderate or severe kidney disease, diabetes with end-organ damage, tumour, leukaemia, lymphoma, moderate or severe liver disease, malignant tumour, metastasis, and AIDS.[67] The Elixhauser comorbidity measure developed a list of 30 comorbidities that are significantly associated with in-hospital mortality and include both acute and chronic conditions, relying on the ICD-9-CM coding manual.[68,69]

Table 1: Summary of studies addressing mortality after hip fracture.

Year	Population	Follow-up after hip fracture	Mortality Indicator	Reference
1991	Medicare hip fractures population, USA	90 days 1 year	CF 12.6% CF 23.7%	Fisher et al.[30]
1996	9,704 ambulatory women aged 65 years or older enrolled in the SOF	5.9 years	RR 2.4	Browner et al.[31]
1997	578 community-dwelling females aged 70 and older, USA	5 years	Excess death 9%	Magaziner et al.[31]
2000	6,459 women aged 55-81 years participating in the FIT, USA	3.8 years	RR 6.68	Cauley et al.[32]
2001	Residents aged 60 years and older	5 years	Men: Mortality ratio 540%, excess death rate 57 Women: Mortality ratio 500%, excess death rate 32	Iacovino et al.[33]
2004	Hospital setting, Sweden	1 year 5 years	RR 10.2 (men) RR 9.1 (women) RR 5.8 (men) RR 5.4 (women)	Johnell et al.[34]
2004	Prospective, 7,512 volunteer ambulatory women aged 75 and older, France (EPIDOS study)	3.9 years	RR 2 MR 112.4 per 1,000 woman-years, compared with 27.3 per 1,000 woman-years for the non-fractured	Empana et al.[25]
2007	43,165 veterans, USA	1 year	Mortality odds: 12% in women 32% in men	Bass et al.[35]
2009	Prospective cohort from the Dubbo Osteoporosis Epidemiology Study of community-dwelling women and women aged 60 years and older, Australia	10 years	SMR 2.43	Bliuc et al.[10]
2009	786,717 hip fractures aged 65 and older, Medicare, USA	1 year	MRs 32.5% (men) 22% (women)	Brauer et al.[20]
2010	South Korea NHI claims database 9,817 hip fractures	1 year	SMR 2.85	Kang et al.[36]
2010	Prospective cohort hip fractures, Taiwan	1 year	MR 31% men 16% women Mortality 8-times higher than age-adjusted general population	Vaseenon et al.[37]
2010	National Hospital Discharge Register 41,000 hip fractures, Denmark	1 year	CM 37.1% men 26.4% women SMR in the <75 years 7.9 men 7.3 women SMR in the >75 years 3.3 men 2.6 women	Kannegaard et al.[38]
2011	Cohort 6,782 hip fractures in women, UK	1 year	MRs 13.3% in women <65 years 31% in women >65 years	Karantana et al.[39]
2012	Population-based health survey, women aged 65 years and more, Norway	3 months 2.8 years	HR 6.5 HR 1.9	Gronskag et al.[40]

Table 1 continued.

Year	Population	Follow-up after hip fracture	Mortality Indicator	Reference
2013	Population-based cohort of 63,257 middle-aged and elderly Chinese men and women in Singapore	5 years	HR 1.64 (men) HR 1.58 (women)	Koh et al.[41]
2013	5,180 hip fractures, Norway	1 year	SMR 3.64 (men) SMR 2.78 (women)	Finnes et al.[18]
2013	Dubbo Osteoporosis Epidemiology Study, Australia	 1 year 5 years 10 years	RS 0.83 in women 0.63 in men 0.59 in women 0.48 in men 0.31 in women 0.36 in men	Frost et al.[42]
2013	National Insurance Database 143,595 hip fractures, Taiwan	1 year 2 years 5 years 10 years	SMR 9.67 SMR 5.28 SMR 3.31 SMR 2.89	Wang et al.[43]
2013	Population-based cohort study, 2,901 residents, USA	22 years	SMR 1.2	Melton et al.[44]
2014	81,867 first hip fracture patients (nationwide), Norway	1 year	SMR 4.6 men SMR 2.8 women	Omsland et al.[14]

CF: case fatality; SOF: Study of Osteoporotic Fractures; FIT: Fracture Intervention Trial; RR: Relative Risk; EPIDOS: Epidemiology of Osteoporosis Study; MR: mortality rate; NHI: National Health Insurance; SMR: standardised mortality ratio; CM: cumulative mortality; HR: hazard ratio; RS: relative survival.

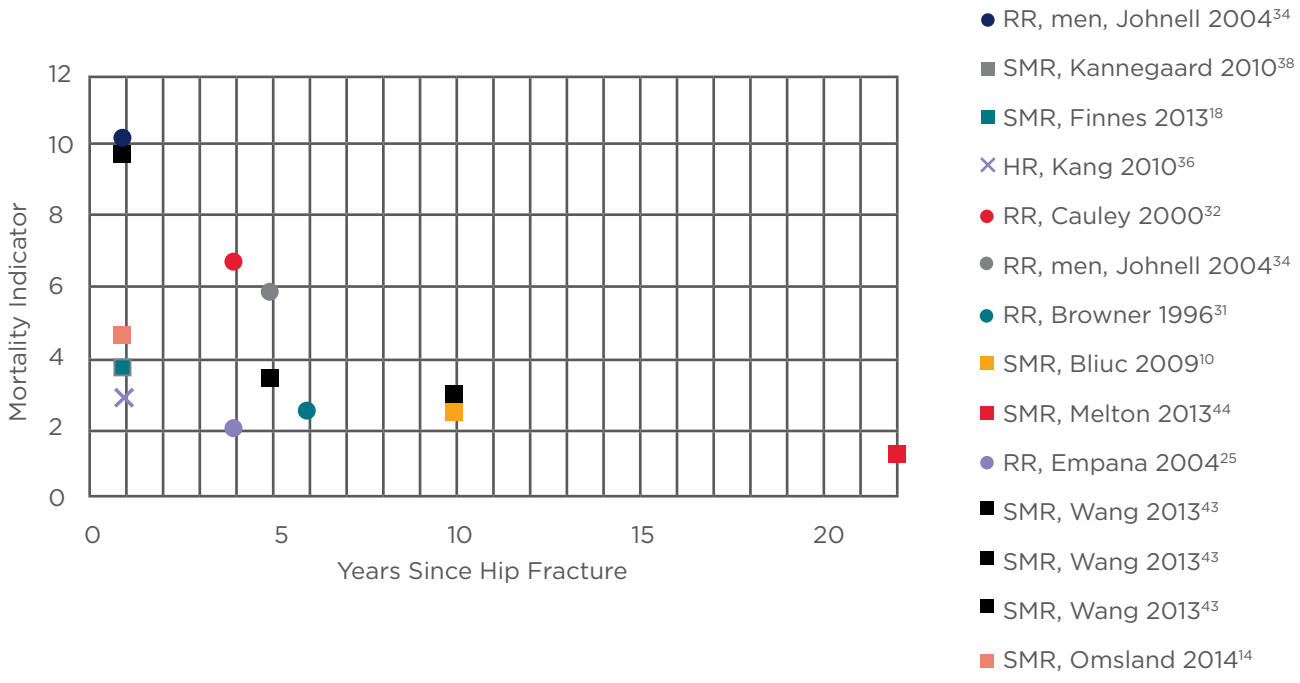

Figure 1: Mortality indicators after hip fracture by study and by time to fracture.
Mortality indicators are derived from different studies and different populations. RR (dots): relative risk, defined as the ratio of the probability of an event (mortality) occurring in an exposed group (fracture) to the probability of the event in a comparison non-exposed group (population). SMR (squares): standardised mortality ratio, defined as the ratio of the observed deaths in the study group (fracture) to expected deaths in the general population. HR (cross): hazard ratio, defined in survival analysis as the ratio of probability of death in the fracture arm compared to the non-fracture arm.

Table 2: Summary of studies addressing mortality after fracture at sites other than the hip.

Year of publication	Population	Site of Fracture	Follow-up after fracture	Mortality Indicator	Reference
1993	Rochester residents, USA	Vertebral	5 years	Survival 61% (76% in normal population) Relative survival 0.81	Cooper et al.[48]
1998	Population-based survey, 6,480 subjects, Europe EPOS	Vertebral deformities	2.3 years	Rate Ratio 1.3 in men, 1.9 in women	Ismail et al.[49]
2000	6,459 women aged 55-81 years participating in the Fracture Intervention Trial, USA	Clinical Vertebral Fractures	3.8 years	RR 8.64	Cauley et al.[32]
2003	598 normal population, Sweden (EVOS)	Vertebral deformities	10 years	HR 2.4 in men HR 2.3 in women	Hasserius et al.[50]
2003	677 patients, Finland	Osteoporosis + Vertebral fractures	3.2 years	HR 4.4	Jalava et al.[51]
2004	2,847 fractures, Sweden	Spine	1 year 5 years	RR 10 RR 4.3	Johnell et al.[34]
2004	2,847 fractures, Sweden	Shoulder	1 year 5 years	RR 4 (men) RR 2.7 (women) RR 2.1 (men) RR 1.4 (women)	Johnell et al.[34]
2004	2,847 fractures, Sweden	Forearm	1 year 5 years	RR 1.1 (men) RR 1.8 (women) RR 1.2 (men) RR 1.9 (women)	Johnell et al.[34]
2005	2,847 fractures, Sweden	Vertebral deformities	22 years	111.7/1000 py in men (73.4/1000 py in normal population) 95.1/1,000 py in women (62.0/1,000 py in normal population)	Hasserius et al.[52]
2009	Prospective cohort from the Dubbo Osteoporosis Epidemiology Study of community-dwelling women and women aged 60 years and older, Australia	Major	5 years	SMR 1.65	Bliuc et al.[10]
2010	629 patients, Osteoporosis Screening Execise, Japan	Vertebral	10 years	SR 69%	Ikeda et al.[53]
2010	National Claim Registry, Korea	Vertebral	2 years	SMR 2.53 (men), 1.86 (women) Mortality rates 20.61% (men), 10.48% (women)	Lee et al.[54]
2013	2,901 fractures, Olmsted county, USA		22 years	SMR 1.2 But mainly in the first 5 years following the fracture	Melton et al.[44]

EPOS: European Prospective Osteoporosis Study; RR: relative risk; EVOS: European Vertebral Osteoporosis Study; HR: hazard ratio; SMR: standardised mortality ratio; SR: survival rate.

Table 3: Summary of studies addressing mortality associated with low BMD.

Year of publication	Population	Site of BMD	Follow-up	Mortality Indicator	Reference
2002	5,816 women, aged 70 years and above, USA	Quantitative Ultrasound of calcaneus	5 years	HR 1.16	Bauer et al.[60]
2006	275 postmenopausal elderly women, Brazil	Femur dual energy X-ray absorptiometry	5 years	HR 1.44 (total mortality) HR 1.28 (cardiovascular mortality)	Pinheiro et al.[61]
2010	3,145 community dwelling people aged 65 years and above, China	Height Loss >2 cm, correlated with low BMD	5 years	HR 3.43	Auyeung et al.[62]
2011	1,429 ambulatory postmenopausal female volunteers aged over 50 years, Japan	Lumbar spine BMD	4.5 years	HR 1.39	Shiraki et al.[63]
2013	Prospective population-based observational study on 390 white North European women aged 48 at study start, Sweden	Distal forearm BMD	3.4 years	RR 1.36	Svejme et al.[65]

BMD: bone mineral density; RR: relative risk; HR: hazard ratio.
The mortality risk indicators were calculated by 1 standard deviation reduction of bone density or broadband ultrasonic attenuation.

DISCUSSION AND CONCLUSION

We reviewed population studies addressing osteoporosis-related mortality, and identified a trend towards decreasing mortality over time. This review has some limitations. The included studies present a high degree of heterogeneity: different populations, different methodologies. The mortality indicators were highly heterogeneous, which also limits the comparisons. This heterogeneity may result in biased interpretation of comparability between populations at the same time point, between different populations at different time points, but also within the same populations at different time points. When separated by decades, confounding factors such as higher life expectancy may interfere with the interpretation of trends of crude mortality rates.

When considering major endpoints such as mortality, the patient should be viewed as a whole and their prognosis cannot be summarised by a single risk factor figure or a single health event. Otherwise healthy and fit patients do not seem to have increased mortality subsequent to the fracture. Male sex, age, site of fracture, the immediate post-fracture period, and poor general health status seem to be universally accepted risk factors for excess mortality.

Some risk factors, when taken individually, may be subject to controversies in different studies. Obesity for example is traditionally associated with lower fracture rates, but recent data from the GLOW study[70] suggest that obesity is associated with higher fracture rates at some specific sites such as the ankle[26] and also with longer hospital stays and poorer functional status.[71]

Due to the important contribution of comorbidities to mortality associated with osteoporosis, a general multivariable approach is suggested to predict mortality, rather than individual indicators such as BMD. Predictive models, similar to models used in cardiovascular diseases, may be developed for more patient-tailored preventive programmes in the future.

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