Osteoporotic fractures

What is the impact on mortality?

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The risk of excess mortality persists for at least five years after a fracture event, with the highest risk period being the first few years. It is, however, still unclear what proportion of this risk is attributable to the fractures themselves or to underlying frailty and comorbidity. Age, sex, type of fracture and pre-existing comorbidities are some of the predictors of mortality following a fracture.

Key points

- **Mortality risk is increased in the elderly following low trauma hip, vertebral and proximal nonhip nonvertebral fractures.**
- **The mortality risk is further increased following subsequent fractures.**
- **Men have a higher risk of mortality following fractures than women.**
- **Antiresorptive treatment for people with osteoporosis may improve their survival.**
- **Early diagnosis and appropriate treatment for osteoporosis is a cost-effective strategy for the Australian healthcare system.**

ENDOCRINOLOGY TODAY 2018; 7(1): 27-29

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Osteoporosis is a systemic skeletal disorder characterised by reduced bone mass and microarchitectural deterioration resulting in an increased risk of fracture. Increased bone remodelling with ongoing bone loss is a principal factor in the development of osteoporosis due to the long-term imbalance of bone formation and resorption whereby the osteoblastic phase of bone formation is exceeded by the osteoclastic phase of bone resorption.

Osteoporosis is a common problem and its prevalence is increasing with an ageing population. It is estimated that 4.74 million people in Australia over the age of 50 years have osteoporosis or osteopenia. Fractures have a large socioeconomic impact due to the associated increased morbidity and mortality, as well as the fracture-related economic costs. In 2012, it was calculated that the economic cost of osteoporosis in Australia was estimated to exceed $33.6 billion over the next 10 years.[1] Although the impact of fractures on morbidity and costs are well published, there is much less attention on the risk of increased mortality.

Impact of osteoporosis on mortality

Premature mortality after a fracture is well established following hip and vertebral fractures. There is more recent evidence that some of the nonhip nonvertebral osteoporotic fractures are also associated with increased mortality.

Hip fractures

The increased risk of mortality following hip fractures is well documented and consistent across numerous studies including the Dubbo Osteoporosis Epidemiology Study.[2] In a systematic review of 22 studies, excess mortality in the first year following hip fractures ranged from 8.4 to 36%.[3] The Study of Osteoporotic Fractures found that only 14% of the deaths could be causally related to the hip or pelvic fracture.[4] The highest risk of death following a hip fracture was within the first six months after the fracture.[5-7] The increased risk of mortality, however, persists for up to 10 years after a fracture.

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Vertebral fractures

Vertebral fractures are the most common osteoporotic fracture and are also associated with significant morbidity and mortality. Similar to hip fractures, mortality risk is the highest in the first year after a fracture. The excess mortality in the first year after vertebral fractures range from 1.9 to 42%.[8-13] Mortality has been reported to be increased for up to 22 years following a vertebral fracture. Risk of mortality following vertebral fractures is generally lower than that for hip fractures. It has been reported that 28% of all deaths associated with vertebral fractures requiring hospital admission might be causally related to the fracture itself.[14] In the large US epidemiological Study of Osteoporotic Fractures, vertebral fractures were found to be related to increased risk of subsequent cancer and pulmonary death.[9]

Nonhip nonvertebral fractures

Nonhip nonvertebral fractures, such as pelvic, humeral, distal forearm and rib fractures, account for more than 50% of all fractures. However, they are the least well studied. In a prospective cohort from the Dubbo Osteoporosis Epidemiology Study, nonhip nonvertebral fractures, were associated overall with a 20% excess mortality for the first five years after a fracture.[15] Interestingly, in that study, proximal fractures were associated with an increased risk of mortality, whereas distal fractures were associated with an increased risk of mortality only in the group who sustained subsequent fractures.[15]

The Dubbo Osteoporosis Epidemiology study found a 2.0- and 2.2-fold increased mortality risk in women and men, respectively, after major nonhip nonvertebral fractures (pelvis, distal femur, multiple ribs and humerus).[2] Of the nonhip nonvertebral fractures, humerus and distal forearm fractures have been the most studied.[15-21] Evidence of increased mortality following humerus fractures is consistent in the literature. An early study demonstrated a five-year increased relative risk of mortality of 2.1 for men and women aged 60 years and 1.8 for those aged 80 years and over.[22] A study using South Korean data demonstrated an 8.5% and 6.4% one-year mortality rate for men and women, respectively, following humeral fractures in 2012.[19] However, mortality following distal forearm fractures is more controversial. Studies of distal forearm fractures and mortality have variably reported increased mortality, no difference and decreased mortality.[16,18,23-27] Some of the differences may be due to age of participants, size of study and length of follow up.

Predictors of mortality after a fracture

The risk of excess mortality persists for years after a fracture event with the highest risk period being the first five years. The underlying mechanisms of excess mortality after a fracture remain unclear, as some of the risk factors for mortality following a fracture are also independent risk factors of mortality. Most of the studies attempting to address this question have studied hip fractures and there are little data on nonhip nonvertebral and mortality.

Some common predictors of mortality following a fracture

- Increased age
- Male sex
- Pre-exisiting comorbidities
- Proximal fractures
- Low bone mineral density
- Bone loss
- Frailty
- Subsequent fractures

Some of the common risk factors following general low trauma fractures are discussed below (Box). Risk factors associated with fractures secondary to underlying specific conditions such as malignancy and endocrine disorders are beyond the scope of this article.

Age

Age is the primary independent predictor of mortality, with increasing age being associated with increasing fracture-associated mortality. However, compared with a similar aged population, the relative risk of mortality was higher in younger people (age <75 years). This is most probably a reflection of the lower baseline mortality in young people and/or a greater relative frailty in the younger population who sustain hip and vertebral fractures. Furthermore, the number of life years lost is greater in the younger population with fracture. In the younger population (age <75 years), only hip, vertebral and more proximal fractures (e.g. pelvis, humerus, ribs) but not peripheral fractures were associated with increased mortality.[2]

Sex

Despite a higher prevalence of fractures in women, men have a higher risk of mortality following a fracture. In a meta-analysis of 24 studies of patients with hip fractures, the pooled estimate hazard ratio of all-cause mortality was higher in men at both one year (3.7 *vs* 2.9 in women) and 10 years (2.5 *vs* 2.3 in women).[28] Similarly, mortality risk is greater in men following vertebral fractures. Standardised mortality ratios for men were higher than those in women during a two-year follow up in a South Korean study.[19] In the Dubbo study, standardised mortality ratios were higher in men across all fracture sites.[2]

These differences in survival between the sexes after a fracture are not fully understood. It is possible, however, that men who fracture have poorer general health compared with women.[29] In a prospective multicentre cohort study of hip fractures, men generally had poorer health as determined by the American Society of Anesthesiologists score with more comorbidities and greater likelihood of developing complications such as delirium, pneumonia and septicaemia.[30] However, other studies have found no difference between men and women.

Dose effect of fractures

Mortality risk following fractures is also dependent on the number of fractures. The Study of Osteoporotic Fractures found that

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mortality rose with increasing number of prevalent vertebral fractures.[9] Subsequent fractures were associated with a 1.5- to twofold increase in standardised mortality rates in the Dubbo study.[2] Mortality was increased predominantly in the first five years after the initial fracture. However, if there was a subsequent fracture, the mortality remained elevated for 10 years with refracture contributing significantly to the excess mortality.[31]

Pre-existing comorbidities

There have been many studies examining the role of comorbidities on mortality following a fracture with conflicting results.[23,32-35] The Spanish study of hospitalised patients with osteoporotic vertebral fractures demonstrated a clear association between increasing mortality and extent of comorbidities.[32] In the Fracture Intervention Trial, adjustment for comorbidities did not affect any of the mortality hazard ratios.[23]

One study did not find any association between mortality following hip fracture and prefracture comorbidities.[35] In this study, the major causes of mortality were due to the complications of the fracture event, rather than comorbidities.

Furthermore, a large-scale retrospective analysis of US Medicare claims data found a mortality hazard ratio of 1.37, compared with controls, in patients with vertebral fractures and a Charlson comorbidity index (a scoring index using 19 categories of comorbidities with higher scores indicating greater comorbidity) of 0 suggesting that at least a significant part of the mortality increase was unrelated to comorbidity.[33] Interestingly, the survival of these patients was comparable with their matched controls for the first 12 to 24 months then got progressively worse after the first two years, which is a different pattern from other studies.

Bone mineral density

Low bone mineral density (BMD) is a well-documented risk factor for fractures. Lower BMD is also independently associated with higher nontrauma-related mortality.[36,37] The Study of Osteoporotic Fractures reported a 1.19-fold increase in mortality for every standard deviation decrease in proximal radius bone density.[36] Lower BMD was associated with an increased risk of myocardial infarction in a cohort study of men and women.[38] Adjustments for smoking, hypertension, hypertriglyceridaemia and diabetes did not weaken the association in this study. A meta-analysis reported that a 1.17-fold increase in total mortality and 1.13-fold increase in cardiovascular mortality per standard deviation decrease in BMD at all sites.[39] There was no significant association between lower BMD and stroke mortality.

Bone loss and bone remodelling

Bone loss is a known risk factor for fracture and has also been found to be associated with increased mortality in the general population. The Study of Osteoporotic Fractures found that for each standard deviation increase in BMD loss at the hip, there was a 1.3-fold increase in all-cause mortality, after adjustment for risk factors and baseline BMD.[40] The Dubbo Osteoporosis Epidemiology Study found accelerated bone loss to be an independent predictor of postfracture mortality.[41] Compared with the lowest quartile, the highest quartile of bone loss was associated with the poorest survival. Interestingly, this study found similar findings in men.[41] It is postulated that osteoporosis and atherosclerosis share common pathophysiological mechanisms suggesting interplay between bone cells and the vascular system.

Frailty

An alternative hypothesis that has been suggested is that a fracture is a signal of frailty, and the observed increased mortality may reflect the frail cohort so identified, rather than any causal relationship between the fracture event and mortality. A study of the Australian Department of Veterans' Affairs databases found that prefracture residential aged care residence was the strongest predictor for mortality.[42] Admission criteria to residential aged care in Australia includes some degree of functional and/or cognitive limitation. Most of the studies attempting to elucidate this question have, however, studied hip fractures and there are little data on nonhip nonvertebral and frailty.

Effects of treatment on mortality

Antiresorptive treatment may possibly reduce the mortality risk following a fracture. In an analysis of the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) trial, a 28% reduction in mortality was seen in the zoledronic acid treatment arm. Only 8% of this reduction could be accounted for by a reduction in subsequent fractures.[43]

Analyses from cohort studies of Canada, Australia and Denmark have also shown reduced mortality during follow up in participants treated with bisphosphonates.[44-47] A meta-analysis of eight randomised controlled trials reported an overall 11% reduction in mortality with treatment.[45] However, the HORIZON trial was the only study that had a significant reduction in mortality in its own right.[48]

Conclusion

The treatment of people with osteoporotic fractures results in high economic costs. In addition, there is significantly increased morbidity and mortality associated with minimal trauma fractures, although whether this is attributable to fractures or underlying frailty and morbidity is still uncertain. Preventing osteoporotic fractures by early diagnosis and appropriate treatment may be an important and cost-effective priority for the Australian healthcare system. **ET**

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A list of references is included in the online version of this article (www.endocrinologytoday.com.au).

COMPETING INTERESTS: None.

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