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The Definition and Clinical Significance of Nonvertebral Fractures

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Abstract Nonvertebral fractures form the bulk of osteoporotic fractures and yet, other than hip fractures, are often dismissed, particularly in the younger age groups. Thus, less than 30% of women with osteoporotic fractures and less than 10% of men worldwide are receiving appropriate treatment. This article discusses the incidence, cost, and consequences of nonvertebral fractures. Recent evidence suggests these fractures form the bulk of costs to the community and herald an increased risk of refracture and premature mortality that applies to all types of nonvertebral, and not just hip, fractures.

Keywords Fracture · Osteoporosis · Epidemiology · Refracture · Mortality

Clinical Trial Acronyms

DOES	Dubbo Osteoporosis Epidemiology Study
FIT	Fracture Intervention Trial
FOSIT	Fosamax International Trial

Introduction

Osteoporotic fractures have traditionally been considered primarily as those occurring in the spine (vertebral), hip, or wrist. Most epidemiologic studies have focused on hip fractures as, from a population perspective, they are the easiest to study because virtually all are admitted to the hospital. Moreover, they have the most severe consequences in terms of post fracture disability and mortality. Vertebral fractures have also been well described in the literature and are most often the end point of choice for clinical trials. The reason for this is that morphometric vertebral fractures (ie, based on x-ray criteria of vertebral height loss) rather than clinical vertebral fractures (ie, associated with pain) can be fairly easily standardized and, as a group, occur more frequently than other individual fracture types. Wrist fractures have often been dismissed as minor fractures with few long-term sequelae.

However, there is a growing body of evidence to suggest that not only do these three fracture types inadequately represent the spectrum of osteoporotic fractures, they may not even constitute a majority of fractures. Furthermore, the burden of fractures to the individual and community in terms of morbidity, cost, and premature mortality is contributed in large part by fractures not considered in this classic triad.

For these reasons, this review will focus on the more controversial area of nonvertebral fractures including the definition, risk of subsequent fracture and premature mortality, cost and some issues surrounding bone density and treatment. The importance of highlighting the impact of these fractures is the large treatment gap that currently exists internationally whereby less than 30% of women with fractures and less than 10% of men are being treated appropriately.

Definition

The simplest definition of a nonvertebral fracture is a fracture not occurring in the spine and excluding fractures of the skull. Most researchers would also agree that pathologic fractures should be excluded as being unrelated

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to osteoporosis. However, this would still include fractures of the digits and other controversial areas such as the ankle.

Fractures of the digits are often excluded in a nonvertebral fracture definition, presumably because their mode of fracture (often sporting injury, fight, or kicking furniture) does not clearly fit into the classic definition of a low-trauma fracture and the consequences of digit fractures are presumed not to be significant. There is little data on this latter aspect but some recent evidence suggests that excluding or including these fractures with other nonvertebral fractures does not affect increased subsequent fracture or mortality risk [1].

Ankle fractures have also not traditionally been considered as osteoporotic fractures as their incidence does not rise exponentially with age like spine or hip fractures and they often occur after a twisting injury. In addition, ankle fractures occur with an increased risk in heavier rather than lighter women, which is the opposite for other fractures [2]. In our Dubbo cohort, we did not find that ankle fractures in women increased the risk of a subsequent fracture; however, in men they did [3••].

The degree of trauma sustained in the definition of an "osteoporotic" fracture is becoming an interesting issue. Virtually all definitions of osteoporotic fracture have included a low-trauma component (ie, fall from a standing height or less). However, there is increasing evidence that fractures occurring after moderate or even high trauma are associated with low bone density [4] and that the risk of a subsequent fracture is similar following an initial fracture whether it occurs after low or high trauma [5•]. In a study from the Netherlands of clinical fractures, 20% of fractures resulted from trauma greater than that of a standing height or less [6]. In previous work of consecutive fractures treated in the outpatient clinic of a major teaching hospital, approximately half of the fractures were more moderate trauma fractures yet they had similar proportion of risk factors for osteoporosis as the minimal trauma fractures including prior fractures [7].

Thus, although the definition of nonvertebral fractures for epidemiologic purposes often excludes certain fracture types and fractures occurring after more moderate trauma, it is likely that these fractures also contribute significantly to the societal fracture burden including adverse fracture outcomes and should be included in studies in the future. In this context it is interesting that in randomized clinical trials, the definition of nonvertebral fractures has varied including site and degree of trauma, which may contribute to the differences in nonvertebral efficacy seen for different osteoporotic medications [8].

Incidence of Nonvertebral Fractures

The incidence of nonvertebral fractures is greater than that of vertebral fractures; however, without systematic x-raying of the population, asymptomatic vertebral fractures (~ two thirds of all vertebral fractures) will not be detected. In studies from the DOES, in which there was no systematic spine x-ray, nonvertebral fractures (excluding digits, pathologic, and non-minimal trauma fractures) accounted for 70% of fractures in women and 69% of fractures in men [3••]. The National Osteoporosis Foundation estimates that osteoporosis accounts for 1.5 million nonvertebral fractures in the United States compared with about 550,000 vertebral fractures [9]. Importantly, although the incidence of hip and vertebral fractures increases exponentially with age, this is not the case for many other types of nonvertebral fractures. When non-hip nonvertebral fractures are considered as a group, they dominate the fracture type in the younger ages. For example, in data from DOES, the incidence of non-hip nonvertebral fracture in those 60–69 years of age was 15.4/1000 person-years (95% CI, 12.7–18.8) in women and 7.8/1000 person-years (95% CI, 5.8–10.4) in men compared with a clinical vertebral fracture incidence of 4.2/1000 person-years (95% CI, 2.9–6.1) for women and 1.8/1000 person-years (95% CI, 1.0–3.3) for men in the same age group. By 80+ years the incidence of these fracture types is more similar, so that although the point estimates of the non-hip nonvertebral fractures remain higher than that of either vertebral or hip, the confidence limits overlap [10].

Cost of Nonvertebral Fractures

There have been many studies estimating the cost of fractures, particularly hip fractures, with differing estimates depending on the methods (eg, economic modeling or real-world data, whether calculating only direct costs or including indirect costs, the population studied and so on). Suffice it to say that all studies are in agreement that the cost is huge and predicted to increase with the increase in the aging population and number of fractures. For example, in one study, the estimated cost of osteoporotic fractures in the United States in 2005 was over $19 billion [11].

Importantly for this review, the cost of non-hip non-vertebral fractures has come into recent focus. Hip fractures are undisputedly the most costly of fractures due in part to their requirement for hospitalization, operation, and often long-term care. However, with non-hip nonvertebral fractures accounting for 40% of fractures in one study [11], their overall cost needs special attention. Although non-hip nonvertebral fractures have a lower per-patient cost than either hip or vertebral fractures [11–13], their prevalence is greater. In one study, the ratio of non-hip nonvertebral to hip fractures was 11:1 in those 50–64 years of age and 2:1 in those over 65 years of age. This resulted in 66% of the direct 1-year costs being attributable to non-hip nonvertebral fractures in the 50- to 64-year age group and 36% in the older age group;

hip fracture costs accounted for 21% and 52%, respectively [13]. Thus, the cost of osteoporotic fractures is substantial and growing and contributed to in large part by the nontraditionally considered fractures.

Subsequent Fracture

It is now well recognized that the risk of a subsequent fracture increases substantially following an initial fracture. Following an initial nonvertebral fracture, the risk of any subsequent fracture is increased approximately twofold in women. What is not so well recognized is that this increased risk is greater for men, exists for all initial fracture types and not just those considered more major (eg, hip, pelvis), and that this increased risk varies over time.

There have been two published meta-analyses examining risk of a subsequent fracture [14, 15]. The first of these, published in 2000, synthesized the studies by initial fracture type, of which there were nine of prior wrist fractures, 15 of prior vertebral fractures, and 19 of any prior fracture excluding wrist, vertebrae, and hip [14]. Apart from a prior vertebral fracture predicting a fourfold increase in subsequent vertebral fractures, the other relative risks were remarkably consistent for any combination of initial and subsequent fracture of around 2. However, the majority of data focused on initial wrist and vertebral fractures with less specific conclusions being able to be drawn about other specific fracture types. In addition, the majority of studies were of women, although there were some of men. The second meta-analysis, published in 2004, examined initial and subsequent osteoporotic fracture risk in over 60,000 men and women drawn from 11 international cohorts. The definition of a prior fracture differed between cohorts; in some cohorts all fractures were considered; for others, only the more typical osteoporotic fractures. The findings of this meta-analysis were similar to the previous meta-analysis, of about a twofold increased risk of subsequent hip or osteoporotic fracture following a prior fracture. Interestingly, in this analysis low bone density only explained a small proportion of the risk of subsequent fracture [15].

Subsequent Fracture Risk in Women Compared with Men

The differences between men and women in their fracture risk were examined recently. It has been consistently demonstrated that the absolute risk of an *initial* fracture is approximately twofold higher in women than in men across all age groups [3, 16]. However, following an initial fracture, the absolute risk for a *subsequent* fracture was similar for men and women across all age groups. In other words, the relative risk of a subsequent fracture increased 1.6- to 2.4-fold for women but was substantially higher, 2.8- to 4.3-fold in men [3••]. This finding equated to a risk equivalent to an initial fracture risk for a woman 10 years older and for a man 20 years older. Thus, the protective effect of male sex for initial fracture risk was lost after an initial fracture. These findings are consistent with earlier studies [17, 18] and were recently verified in another sample [1].

Role of Type of Fracture

As alluded to above, whereas much of the older literature concentrated on fractures of the forearm, hip, and spine, recent focus has included other peripheral limb fractures. The overall findings are that fractures at virtually any site are predictive of subsequent fracture, albeit with differing levels of risk. Moreover, even the more minor initial fractures herald an increased risk of a more major subsequent fracture such as a hip or vertebral fracture.

The risk of a subsequent hip fracture following an initial hip fracture has been well documented in several large studies. One recent large Danish population-based cohort study of 169,145 hip fracture cases found a 2.2-fold increased relative risk of a subsequent hip fracture that did not normalize until 15 years [19]. Although incidence rates vary across nations, this approximate twofold risk of subsequent hip fracture following an initial hip fracture appears fairly stable across studies [20–22].

The risk of a subsequent hip fracture following a wrist fracture has also been studied in several samples. In general, the relative risks for subsequent hip fracture following wrist fracture are less than that observed following an initial hip fracture with one study reporting a nonsignificant risk of 1.29 (0.88–1.89) [23] and others around 1.5 [18, 24, 25] with one study as high as 2.0 [17]. However, in those studies that have looked at all subsequent fractures and not just restricted to hip fracture outcome including the Manitoba study [23], wrist fractures were associated with an increased risk of subsequent fracture of 1.5- to twofold [1, 3••, 14, 17].

In the DOES, the relative risk of any subsequent fracture ranged between 1.4- to 2.8-fold for women, with the lowest risk following lower limb fractures and the highest risk following a hip fracture. For men, these risks ranged from 2.9 for lower limb fractures to 4.9 for hip fractures. In our study, there were a couple of fracture types that were not predictive of subsequent fracture. These included ankle fractures in women and rib fractures in men. Ankle fractures are often associated with a twisting force and heavier women are at increased risk; thus, they have not been traditionally considered as osteoporotic [2, 26]. Nevertheless, we were unable to demonstrate an increased subsequent fracture risk in women even when stratified by degree of injury, although they were significant in men. Similarly, rib fractures were

not associated with subsequent fracture in men in our study, although they were in women. This finding for rib fractures is consistent with a European study [27]; however, in a US population study, rib fractures in men were predictive of subsequent fracture [28].

Despite these couple of exceptions, the most important point from our and other studies is that the site of subsequent fracture does not appear to differ by initial fracture site. Thus, even a more minor fracture heralds increased risk of a more major fracture [1, 3••, 17].

Timing of Subsequent Fracture

It is becoming more apparent that the risk of a subsequent fracture does not remain constant over time. The risk is highest in the first year or two post initial fracture and then gradually declines over the next 10 years [3••, 25, 29–31]. This change in risk seems to exist for all fracture types with the length of the increased risk ranging between studies, probably primarily based on population size and length of follow-up. In the large Danish hip fracture study, the greatest risk of a subsequent hip fracture was observed within the first year post fracture and then gradually declined. In that study the cumulative incidence of a second hip fracture was 9% at 1 year and 15% after 5 years. The risk did not return to population initial risk until 15 years, but by 10 years the increased risk was minor [19]. The importance of this observation is that the window for maximum effective intervention is very close to the initial fracture. In the Dubbo cohort, approximately 41% of fractures in women and 52% fractures in men occurred within the first 2 years post initial fracture [3••]. These findings are similar in other studies [1]. Based on life tables analyses, of those surviving 10 years, 40–60% had sustained another fracture.

Thus, the greatest risk of a refracturing lies close in time (within the first few years) to the initial fracture. Yet the risk of subsequent fracture still remains elevated above population risk for at least 10 years, by which time almost half of those surviving will have sustained another fracture.

Risk of Mortality

It has long been acknowledged that there is an increased risk of mortality following hip fractures, consistent in numerous studies. Vertebral fractures have also been associated with increased premature mortality [32, 33]. However, it is only recently becoming appreciated that the increased premature mortality extends beyond these two fracture types to virtually all fractures and across all ages [1, 34, 35••]. Moreover, a subsequent fracture results in a further increase in mortality [35••].

Hip Fractures

The increased mortality following hip fractures has been widely reported. The cumulative mortality 1 year following a hip fracture ranges from 20% to 40% [19, 32, 36, 37], with higher mortality rates observed in men compared with women. The excess mortality remains elevated above an age- and sex-matched population mortality for at least 10 years and possibly longer [19, 35••, 37]. A recent meta-analysis of 39 cohort studies in women and men estimated that following a hip fracture in an 80-year-old woman, there was an excess annual mortality of 8% at the end of the first year and 18% at 5 years. For men these estimates were 18% and 26%, respectively [37]. The higher mortality in men post hip fracture than women has been reported in a number of studies [32, 36]. One recent study examining the cause of this gender difference found that it was not due to a difference in the number of comorbidities or medications but was unable to identify a specific cause. The greatest difference in mortality between the sexes occurred in the first few weeks post hip fracture [36]. Although more hip fractures occur in the old, the relative increase in mortality has generally been found to be greater in the younger person, with standardized mortality ratios ranging up to threefold higher in the younger (60-year-old) compared with the older (80+) age groups [32, 34, 38]. When considered in terms of years of life lost, these differences become more stark, with 10–11 life years lost in the younger age groups compared with 0.8–1.3 life years lost in the older age groups.

Non-hip Peripheral Fractures

Increased premature mortality following non-hip peripheral fractures has now been reported in a couple of studies. In initial work from the DOES with 5-year follow-up, we reported increased mortality following all major fractures (a group of fractures including proximal humeral, multiple rib, pelvis, distal femur, and proximal tibia/fibula) [32]. Subsequent 18-year follow-up data from the same study confirmed the increased mortality for these fractures but also demonstrated an increased mortality following minor fractures in older (> 75 years) but not younger age groups [35••]. The mortality increase ranged from 1.4-fold for minor fractures in women to twofold for major fractures in men, with the standardized mortality ratios being higher in men then women for all fracture types. By comparison, the increased standardized mortality ratios for hip fractures in that study were 2.5-fold for women and 3.5-fold for men. These findings are consistent with other studies [1, 34, 38], although forearm fractures have not been universally found to be associated with an increased premature mortality [33,

34]. These differences may relate to different age groups and length of study follow-up.

Timing of Mortality

The greatest mortality increase has been consistently found to occur in the first 1–2 years following the fracture for both hip and non-hip fractures [1, 34, 35••, 38, 39]. In one study of nonvertebral fractures, absolute mortality risk declined from 12% in the first year to 6% in the subsequent 2–5 years. Over a longer period of follow-up, the majority of the deaths have occurred within the first 5 years post fracture, with mortality rates then declining toward the background population mortality, except for hip fractures in which the increased mortality has been demonstrated for at least 10 years as described above [35••, 39]. The importance of the fractures traditionally thought to be less significant (ie, non-hip nonvertebral fractures) can be considered in the light of recent mortality findings in a population sample of all fractures over 18 years. The group of non-hip nonvertebral fractures constituted approximately half of the total number of fractures and preceded over 40% of all deaths. This group of fractures was estimated to contribute to 28% of all excess deaths in women and 31% of all excess deaths in men [35••].

Role of Subsequent Fracture

The role of subsequent fracture on mortality risk has been recently examined in the DOES. Perhaps, not surprisingly, although the excess mortality risk declined over the first 5 years following an initial fracture to reach population mortality rates, the occurrence of a subsequent fracture again increased the mortality risk. The mortality risk following this subsequent fracture was increased 2.2-fold for women and 3.5-fold for men and was higher than that associated with just one fracture. Moreover, although this mortality risk declined over the next 5 years, similar to that following the initial fracture, it did not completely reach population mortality levels [35••].

Thus, given the high frequency of subsequent fracture and mortality following all types of osteoporotic fractures, these two adverse outcomes need to be considered together in ongoing studies as they clearly impact upon each other and are closely linked.

Cause of Increased Mortality

The cause of the increased premature mortality post fracture has been debated and remains unresolved. The greatest study in this area has been in relation to hip fractures. There have been a number of studies linking premorbid health to the increased mortality post hip fracture. Dementia, "frailty," comorbid conditions, muscle weakness, and low bone density have all been associated with mortality, particularly in the context of hip fracture [40–43]. Low bone density has been demonstrated to be a risk factor for mortality independent of fracture as has bone loss [44, 45]. For example, in one large US study of medicare beneficiaries, much of the early (within 6 months) hip fracture mortality was attributed to frailty including prefracture health status, functional status, and comorbid conditions [41]. However, other studies have found little or no association between underlying health and mortality [33, 46–48]. For example, in a recent large Danish study of hip fracture subjects, adjustment for comorbidities, despite being higher in the fracture cases, did not markedly affect mortality risk; thus, the authors concluded that the major cause of mortality was linked to the fracture event rather than to the underlying causes [46].

In the Dubbo study [35••], there were a number of factors independently associated with the increased mortality post fracture including subsequent fracture, advancing age, and quadriceps weakness in both sexes, as well as low bone density, increased sway, and smoking in women and decreased physical activity in men. Notably, in this study comorbidities were not associated with the increased mortality and the other factors only accounted for part of the increase. Examination of death certificates revealed causes similar to those of the general Australian population with fractures and/or osteoporosis only mentioned 13% of the time.

Osteoporosis Treatment and Mortality

In the light of the controversy surrounding the increased premature mortality, recent findings regarding the association between osteoporosis treatment and mortality reduction are interesting with potentially extremely important clinical significance. The randomized trial of zoledronic acid post hip fracture resulted in 28% mortality reduction that could only be partially explained (8% of the 28%) by a reduction in subsequent fracture [49••]. A meta-analysis of eight randomized studies concluded that osteoporosis treatment resulted in an 11% mortality reduction, although only the above-mentioned study was significant in its own right [50]. However, supporting these findings are a couple of cohort studies of hip fractures subjects with reported mortality risk reductions of over 50% related to osteoporosis treatment (primarily bisphosphonates) [51, 52].

With osteoporosis treatments having been demonstrated to effectively decrease subsequent fracture by up to 50% and perhaps the fracture-associated mortality by even 10%, the imperative to recognize the adverse impact of all osteoporotic fractures becomes paramount so that early treatment can be appropriately initiated.

Role of Bone Density

It has been clearly demonstrated that the risk of fracture increases both with increasing age and lower bone mineral density. However, the bulk of the population has a T-score above the World Health Organization osteoporotic cutoff of −2.5 and, thus, more fractures occur in the osteopenic than the osteoporotic group [53, 54]. Moreover, it has recently been demonstrated that of repeat or subsequent fractures, over 40% occurred in the osteopenic group for both men and women [55•]. The clinical importance of this comes in considering treatment. Most randomized studies of osteoporosis treatment have recruited subjects with bone density T-scores lower than −2.5. However, in those trials in which T-scores have been higher, retrospective analysis suggests that the treatment benefit in terms of reduction of subsequent nonvertebral fracture is less with higher T-scores. For example, in the FIT study, alendronate had no benefit if the T-sore was greater than −2.0 [56]. Similar results were found in post hoc analysis of the international trial of alendronate (FOSIT) [57] and in the elderly arm of the risedronate study of hip fractures in which bone density status was only known in the minority [58]. With low bone density being a risk factor for mortality as well as subsequent fracture, it suggests that treatment to prevent fracture and possibly mortality should be targeted to those with lower bone density.

Conclusions

This article has highlighted a number of issues surrounding nonvertebral fractures, with emphasis on the non-hip nonvertebral fractures that have been less well studied to date. Although hip fractures have the most devastating consequences, non-hip nonvertebral fractures are common accounting for up to 50% of all fractures. They dominate the fractures seen in the younger elderly population. All fractures and not just hip and vertebral fractures are associated with significant cost, and increased risk of a subsequent fracture of around twofold but varying for initial fracture type. Importantly, the subsequent fracture risk is highest in the first few years post fracture and even minor fractures result in subsequent hip (and vertebral) fractures. There is now growing evidence that increased premature mortality occurs following all osteoporotic fractures, albeit higher for hip fractures and that like the increased subsequent fracture risk, this increased premature mortality occurs soon after a fracture with the risk slowly decreasing down to the background population risk over 5 years but up to 10 years for hip fracture. The cause of the increased mortality, whether due in part to underlying health and/or the fracture itself, is not clear. However, with early evidence that osteoporosis treatment not only decreases subsequent fracture, but may also decrease mortality, the current neglect of people with fractures so that less than 30% of women and 10% of men are receiving appropriate treatment is unconscionable. Treatment, when indicated, should be initiated early for maximum benefit.

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