

Secondary Prevention of Low-Trauma Fractures: In Search of an Effective Solution

Amal Shibli-Rahhal, MD, MS

ABSTRACT

Objective: To review and summarize the literature regarding current approaches to secondary prevention of low-trauma osteoporotic fractures.

Methods: PubMed search and summary of existing literature related to complications and secondary prevention of osteoporotic fractures was performed.

Results: Fragility fractures are associated with high rates of short and long term morbidities and carry a high risk of mortality and fracture recurrence. Several of the currently available anti-osteoporosis medications have been shown to decrease the risk of fracture recurrence in patients with prevalent osteoporotic fractures and some may even decrease mortality. However, only a minority of patients with fragility fractures are adequately evaluated and treated for osteoporosis. Fracture liaison services that ensure identification and risk stratification of patients with fragility fractures and proper evaluation and treatment of osteoporosis have proven effective at enhancing osteoporosis care in these patients, decreasing fracture recurrence and possibly even decreasing long-term mortality, while providing long-term cost savings. Unfortunately, however, this model of care has not been widely adopted and implemented.

Conclusion: Fragility fractures represent a major health care problem for aging populations. Unfortunately, most patients with low-trauma fractures still receive suboptimal osteoporosis care.

Key words: osteoporosis; fracture; fragility; low-trauma; bone density.

Low-trauma fractures are fractures that occur from a trauma equivalent to a fall from standing height or less [1,2]. They can involve any skeletal site, but the most significant are vertebral, pelvic, wrist and hip fractures, which together represent close to 90% of all

low-trauma fractures [3,4]. The overall burden of low-trauma fractures is quite high worldwide and is projected to increase over time [3–6]. In 2010, 3.5 million new low-trauma fractures were reported in the European Union [3]. In the United States, there were more than 2 million fractures in 2005, and it is estimated that more than 3 million fractures will occur in year 2025 [4].

Low-trauma fractures are generally indicative of compromised bone strength—especially when they involve the hip—and are thus often referred to as fragility fractures. While the traditional definition of osteoporosis is a bone mineral density (BMD) T-score of -2.5 or lower, low-trauma fractures of the hip are also diagnostic of osteoporosis, regardless of bone mineral density [2,7–9]. In addition, low-trauma fractures of the vertebrae, the proximal humerus, and the pelvis are considered diagnostic of osteoporosis when combined with T-scores between -1 and -2.5 [2,7]. Bone biopsies and high-resolution peripheral quantitative computed tomography (HR-pQCT) in patients with low-trauma fractures and normal BMD suggest microarchitectural alterations and abnormalities of collagen orientation and crosslinking within the bone matrix [10–12], leading to decreased bone strength.

This review will address the individual and societal costs of low-trauma fractures and issues related to secondary prevention of fractures, with specific emphasis on pharmacotherapy and fracture liaison services.

Impact of Low-Trauma Fractures

Acute and Long-Term Complications

Of all fragility fractures, hip fractures are the ones most likely to result in serious acute complications. The most common acute complications are delirium in up to 50%

From the Department of Internal Medicine, University of Iowa Carver College of Medicine, Iowa City, IA.

of patients and malnutrition in up to 60%, both of which predict slower and less complete recovery [13–16]. Other complications include urinary tract infections in up to 60% of patients in certain reports [17], thromboembolic disease with deep venous thrombosis in around 27% of patients and pulmonary embolism in up to 7% [16], and acute kidney injury in about 15% [18].

In addition, it is not uncommon for patients to suffer from significant long-term functional limitations following fragility fractures. While vertebral fractures do not frequently lead to hospitalization or institutionalization, they often lead to significant physical limitations and chronic pain [19,20] and to negative effects on self-esteem, mood, and body image [21,22]. However, the most remarkable functional decline and limitations are seen after hip fractures [23–25]. In a study of 2800 women and men with hip fracture, Beringer et al found that more than 30% were still institutionalized, and only 40% were able to walk outdoors independently 1 year later. Predictors of poor outcome included male sex, advanced age, cognitive impairment, and presence of comorbidities [23].

It is not surprising then that a fracture is often associated with an overall decline in the individual's quality of life and this has been demonstrated in several studies [26–28]. In the largest study of this type, Tarride et al examined over 23,000 patients with fragility fractures and found a sharp decline in health-related quality of life (HRQOL) immediately after the fracture, which remained below baseline for up to 3 years [26]. The decline was worse in patients with hip and spine fractures compared to other fractures [27].

Mortality Following Fragility Fractures

Perhaps the most concerning complication, however, is the excess mortality seen after fractures. Several studies have demonstrated excess mortality after vertebral fractures, especially in the year following the fracture [29–33], but the highest increase in mortality was observed following hip fractures. In fact, the 30-day mortality after a hip fracture approximates 7% [23] and the excess 1-year mortality is estimated at 8% to 36% [34,35]. While the highest risk of mortality is seen in the first year following the fracture, the increased risk persists for at least 5 to 6 years [36]. Malnutrition, decreased mobility, male sex,

and the number of coexisting medical comorbidities further increase the risk of mortality [29,32,34,36,37].

Risk of Fracture Recurrence

In both men and women, a fragility fracture at any site increases the risk of subsequent fractures [38–41], and the risk increases with the number of prevalent fractures [42]. Gehlbach et al estimated an 80% increase in the risk of fracture recurrence after 1 fracture, a threefold increase after 2 fractures, and an almost fivefold increase after 3 fractures [42]. The increase in risk is even more pronounced following vertebral fractures specifically, doubling after the first fracture and increasing by up to ninefold after 3 fractures [42, 43]. This increase in risk is highest in the first year following the fracture but may persist for up to 10 years [39,43].

Fracture Impact on Society

Fractures are associated with a high financial burden to society, in terms of direct acute care costs and long-term rehabilitation [3,4,44–48]. In 2010, the direct cost from fractures in the EU was estimated at €24.6 billion [3]. In the US, this cost was around \$14.0 billion in 2002 and \$16.9 billion in 2005 [4,48], and in Canada it was \$1.5 billion in 2011 [47]. These numbers increase substantially when costs associated with long-term post-fracture rehabilitation are included, with an additional estimated yearly cost of €10.7 billion in the EU and \$1.03 billion in Canada [3,47].

While hip fractures account for only about 18% of all low-trauma fractures, they are associated with the highest cost burden, accounting for about 50% to 70% of the total fracture-associated expenditures [3,4,44]. This is likely due to the fact almost all hip fractures require hospitalization, most require surgical repair and rehabilitation, and because they lead to the highest rates of morbidity and mortality.

Can Fracture Recurrence After a Low-Trauma Fracture Be Prevented?

Many approaches to secondary fracture prevention have been proposed, including but not limited to fall prevention, exercise therapy, nutrition therapy, prevention and treatment of sarcopenia, vitamin D and calcium supplementation, and osteoporosis pharmacotherapy [49–53]. Of those, osteoporosis pharmacotherapy has the strongest

and most compelling efficacy data and will be reviewed in the following sections.

Effect of Antiresorptive Therapy After a Fracture

In the Fracture Intervention Trial (FIT), alendronate decreased the risk of new vertebral fractures by about 47% and of hip fractures by about 50% in women with preexisting vertebral fractures [54,55]. Similar fracture protection benefits were demonstrated in the Hip Intervention Program (HIP), where risedronate decreased the risk of hip fractures by 60% in women with prior history of vertebral fractures [56].

The best data regarding secondary prevention of hip fractures however comes from the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) trial, where patients were randomized to zoledronic acid or placebo within 90 days of a hip fracture. Over a median duration of therapy of about 2 years, zoledronic acid decreased the risk of any new clinical fracture by 35%, of new vertebral fractures by 46%, and of recurrent hip fractures by 30% [57].

Effect of Anabolic Therapy After a Fracture

The Fracture Prevention Trial (FPT) compared the effect of teriparatide to placebo in women with at least 1 moderate or 2 mild atraumatic vertebral fractures and showed a 65% reduction in the risk of new vertebral fractures and a 53% reduction in the risk of new non-vertebral fractures [58]. Likewise, the Abaloparatide Comparator Trial In Vertebral Endpoints (ACTIVE) enrolled women with at least 2 mild vertebral fractures, 1 moderate vertebral fracture or history of a low trauma fracture of the forearm, humerus, sacrum, pelvis, hip, femur, or tibia. In this trial, abaloparatide decreased the risk of new vertebral fractures by 85% and of new non-vertebral fractures by 43% compared to placebo [59].

Will Anti-Osteoporosis Therapy After a Low-Trauma Fracture Impact Fracture Healing?

One major question regarding the use of anti-osteoporosis drugs in patients with a recent fracture is the effect that treatment might have on bone healing after fracture or fracture-repair surgery. With antiresorptive agents in particular, the main concern is whether suppression of bone turnover may lead to delayed bone healing, since healing requires

callus remodeling. A small prospective study evaluated fracture healing in 196 patients treated for a distal radius fracture, 153 of whom were on a bisphosphonate at the time of the fracture. While bisphosphonate use was associated with a longer time to radiographic union, the time to union was only 6 days longer in the bisphosphonate group (55 days versus 49 days to union in the bisphosphonate and control groups, respectively), and has generally not been felt to be clinically significant [60]. The most reassuring data regarding this question however, comes from the HORIZON trial where 2127 men and women were randomized to zoledronic acid or placebo within 90 days of a hip fracture. No difference in healing between the 2 groups was seen, regardless of the time of initiation of zoledronic acid (within 2 weeks of fracture, between 2 and 4 weeks, between 4 and 6 weeks or after 6 weeks) [61].

The stimulation of bone turnover that occurs with anabolic agents is generally thought to accelerate bone healing. In animal studies, teriparatide has been found to enhance callus formation and mechanical strength [62–64], but there is no definitive data in humans to prove this effect [65].

In summary, there is strong evidence demonstrating the effectiveness of bisphosphonates and anabolic agents at decreasing the risk of fracture recurrence in patients with preexisting vertebral fractures. Zoledronic acid has also been shown to decrease the risk of fracture recurrence after a hip fracture. Anti-osteoporosis therapy after a fracture has no clinically significant effect on fracture healing.

The Gap Between Science and Practice

Practice Guidelines Versus Actual Practice

Based on the data presented above, multiple professional societies and expert groups have developed guidelines emphasizing the importance of evaluation and treatment for osteoporosis following a low-trauma fracture, especially those of the hip and spine [8,9,66–69]. In a 2009 multidisciplinary workshop of the International Society of Fracture Repair, an in-depth review of existing data showed no evidence for a negative effect of anti-osteoporosis drugs on fracture healing. As a result, it was recommended not to withhold osteoporosis therapy until fracture healing has occurred, and to initiate treatment

before patient discharge from the fracture ward in order to improve follow-up [70].

However, despite these expert guidelines and the availability of several effective agents to decrease the risk of fracture and fracture recurrence, evaluation and treatment of patients for osteoporosis after a low-trauma fracture are very low. Several large-scale studies involving older patients with fractures in North America, Europe, Asia, and Australia have shown that the rates of BMD measurement or drug therapy for osteoporosis after a fragility fracture do not exceed 25% to 30% [71–80]. While treatment trends over time may have shown some improvement, they remain overall disappointing. For example, in a study of over 150,000 patients who sustained a fracture between 1997 and 2004, Roerholt et al found that around 20% of women were started on therapy after a vertebral fracture in 1997, while 40% received therapy in 2004. Among women with hip fracture, 3% received treatment in 1997 and 9% in 2004 [71]. Furthermore, when osteoporosis treatment rates are examined more closely, most of the patients who receive treatment after a fracture are those who were being treated prior to the fracture, so treatment is simply continued in them. New osteoporosis therapy is initiated in only 5% to 15% of patients who are not already on osteoporosis therapy at the time of fracture [72,73,77,81,82].

Analyses of prescription patterns suggest that patients with vertebral fractures are more likely to receive treatment compared to those with hip fractures [71,82], and that women are much more likely to receive therapy than men [71,74,77,83–88]. Other factors that decrease the chance of receiving therapy include black race [84], low income [74], older age, presence of multiple comorbidities, and polypharmacy [83].

Barriers to Care: Where Are We Failing?

The large discrepancy between science and practice when it comes to secondary prevention of fractures is quite puzzling and has been the subject of several investigations. A major barrier to proper care seems to be the lack of ownership of the problem by the orthopedic surgeons and medical providers, and the less than ideal collaboration between the 2 services in coordinating and providing secondary prevention [89–94]. The orthopedic

surgeons are one of the first points of contact with health care for a patient with a low-trauma hip fracture. They are mainly charged with providing acute fracture care and often cannot provide long-term osteoporosis care, which would be more suitable for a medical specialist. However, while the acute care surgical team is not best suited to treat osteoporosis, it is still very important that they initiate patient referral to a provider who can provide long-term osteoporosis care. This transition of care—of lack of it—seems to be one of the major missing links, leading to patient loss [88] and suboptimal secondary prevention.

However, patient referral may not be a sufficient solution and interestingly, a medical consultation during an acute admission for hip fracture does not seem to increase the frequency of osteoporosis diagnosis [95]. This points to a deficiency in knowledge, and as a matter of fact, studies do suggest a problem with under-recognition of the connection between low-trauma fractures and underlying osteoporosis among medical and surgical providers alike [92,93,96]. In a survey of orthopedic surgeons and consultant physicians involved in the care of patients with low-trauma hip fractures, only 24% of respondents felt that osteoporosis therapy was indicated. The majority of providers thought that treatment with a bisphosphonate was indicated only if low BMD was present, rather than in all patients with low-trauma hip fractures [92]. This is further illustrated by the fact that only a minority of patients with a low-trauma fracture are formally given the diagnosis of osteoporosis [75,80,97] or are told that they have osteoporosis [79].

Fracture Liaison Services—A Potential Solution to Enhance Secondary Fracture Prevention

What is a Fracture Liaison Service?

Several solutions have been proposed to remedy the main barriers that interfere with proper secondary treatment of osteoporosis, namely patient education, provider education, and the initiation of programs to enhance coordination and continuity of care between treating teams. Taken together, these interventions have been modestly effective at increasing the odds of BMD measurement and initiation of osteoporosis therapy [98, 99]. Interventions that focused mainly on provider and/or patient education were the least

effective, especially when they did not rely on direct in-person interactions, and programs intended to enhance transitions of care were more effective [96,99,100].

These programs are commonly referred to as fracture liaison services (FLS). They aim to identify patients with low-trauma fractures, provide risk assessment and education to the patient, and in some cases provide the patient with post-fracture osteoporosis care. These services typically require a dedicated case manager, who is often a clinical nurse specialist, ideally supported by a medical practitioner with expertise in the treatment of osteoporosis. The FLS case manager uses predetermined protocols that facilitate patient identification, risk assessment and management [101]. Some programs are hospital-based, identifying and evaluating patients while still hospitalized for their hip fracture, and others are based in clinics, aiming to provide services after discharge from the initial acute hospitalization [96,99–101].

How Effective Are Fracture Liaison Services?

Several FLS models have been proposed and tested, with some limited to patient identification and risk stratification, and others more intensive, involving initiation of BMD testing or BMD testing and osteoporosis treatment. In a meta-analysis of FLS programs, Ganda et al grouped programs into 3 categories: Type A programs involved patient identification, assessment and treatment, type B programs involved patient identification and assessment only without treatment, and type C programs involved patient identification combined with alerting of the patients and providers to the need to assess and treat. The effectiveness of the programs in terms of BMD testing and initiation of therapy increased with intensity. Type A programs were the most effective with BMD testing and treatment initiation rates of 79.4% and 46.4% respectively, followed by type B programs which had BMD testing and treatment initiation rates of 59.5% and 40.6% respectively, then type C programs which had BMD testing and treatment initiation rates of 43.4% and 23.4% respectively [100].

The most intensive programs have also been shown to significantly decrease the risk of fracture recurrence, with a reduction in the rate of re-fracture from 19.7% to 4.1% within 4 weeks [102], and a 37.2 % reduction within 3 years [103,104]. Additionally, intensive FLS programs

involving pharmacotherapy with a bisphosphonate may be associated with a reduction in mortality after a hip fracture. Beaupre et al evaluated the mortality benefit associated with oral bisphosphonate therapy in the setting of a FLS and demonstrated an 8% decline in mortality per month of oral bisphosphonate use, and an approximate 60% reduction per year of use in comparison to patients who did not receive treatment [105]. This finding was consistent with the reduction in mortality seen with zoledronic acid in the HORIZON trial, which was in part attributable to decreased re-fracture rates, but primarily due to reduction in the occurrence of pneumonia and arrhythmias in patients receiving the drug [57,106].

While fracture liaison services may be associated with increased immediate costs—such as the costs of hiring a case manager, BMD testing and pharmacotherapy, and in some cases a data management system—several cost-effectiveness analyses have shown associated long-term cost savings [107–109]. This is not surprising given that they decrease re-fracture rates, leading to a decline in the very costly immediate and long-term fracture care costs.

Summary

In summary, fragility fractures present a major health care problem for aging populations, leading to significant costs and high morbidity and mortality. Assessment and treatment of osteoporosis following a fragility fracture can decrease the risk of fracture recurrence, long-term costs, morbidities, and possibly mortality. In the last decade, several national and international initiatives have been created to promote and encourage secondary prevention of fragility fractures [110–113]. However, these programs have all been voluntary and there are currently no reliable mechanisms to ensure broad implementation of secondary fracture prevention interventions. As a result, and while several isolated secondary prevention programs have shown great success, most patients with low-trauma fractures still receive suboptimal osteoporosis care.

Corresponding author: Amal Shibli-Rahhal, MD, MS, Dept. of Internal Medicine, University of Iowa Hospitals and Clinics, Iowa City, IA 52242.

Financial disclosures:

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