

Osteoporotic Fracture – When Repairing the Fracture is not enough

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Abstract

Osteoporotic fractures are a major public health problem in most Western countries. Due to their ageing population, Asia and South America will soon feel the burden of this issue. Osteoporotic/low trauma fractures are associated with increased morbidity and mortality and are often followed by further fractures. Effective and well-tolerated bone protective medication such as bisphosphonates and denosumab are readily available and has been shown to prevent further fractures. As the molecular biology of bone turnover is now well-characterised, more specific targeted therapies are currently undergoing clinical trial.

Despite these advances in pharmacotherapy secondary prevention of osteoporosis following low trauma fracture is often not implemented. Reasons for this include lack of appreciation of the importance of a low trauma fracture as a predictor of morbidity and mortality, lack of time on the part of treating clinicians and uncertainty regarding whose role it is to address secondary fracture prevention. However, many would suggest that best-practice surgical repair of an osteoporotic fracture also involves measures to prevent the next one. Such measures include bone mineral density assessment by dual x-ray absorptiometry, commencement of bone protective therapy and falls prevention strategies. This multi-faceted secondary prevention programme requires close cooperation between the orthopaedic surgical, nursing and physiotherapy team and a medical team with expertise in bone health. This occurs infrequently. The role of a Fracture Liaison Service built around a dedicated Fracture Liaison Coordinator will be discussed as this is probably the most effective strategy to ensure consistent secondary prevention of osteoporosis following low trauma fracture.

Keywords: Osteoporosis; Secondary prevention; Fracture liaison service; Fracture liaison coordinator

The Public Health Burden of Osteoporosis

Osteoporotic fractures are a major public health issue in most Western countries and will become an increasing problem in Asia and South America due to population ageing [1]. Almost two million people in Australia (population 24 million) are affected by osteoporosis (OSP) with an annual cost to the Australian community estimated at AUD7.4 billion [2]. According to the World Health Organization (WHO) definition of OSP (bone mineral density T-score < -2.5, ie 2.5 standard deviations below that for young normal controls as measured by dual x-ray absorptiometry, DXA), approximately 11% of men and 27% of women aged 60 years or over are osteoporotic [3].

The major complication of OSP is low trauma fracture (LTF, trauma equivalent to a fall from a standing height). Fracture incidence in Australian men and women aged 50 years and over was 1248 and 1916 per 100 000 person-years, respectively [4]. Lifetime fracture risk in a person aged 50 years was 27% for men and 44% for women, respectively [4]. Patients sustaining a LTF of the hip had a 33% mortality rate in the subsequent 12 months, with up to one third of such people requiring admission to residential care [5,6]. Regardless of anatomic site, a LTF was associated with an increased risk of another fracture for up to 10 years, by which time up to 60% of surviving women and men had sustained a subsequent fracture [7]. A LTF was associated with increased mortality, especially in men [8], which

persisted for five years following fracture at any site and for up to 10 years following hip fracture [9].

In light of the increased morbidity and mortality following LTF, clinicians should be actively screening such patients for OSP by DXA, instituting effective bone-protective therapy and providing lifestyle and falls prevention advice to prevent further fracture. However, this is not being done [10-12]. At 12 months post-fracture, only 16% of patients who had been admitted to a major university teaching hospital in Sydney, Australia for management of the fracture had been commenced on bone-protective therapy [10]. A study of 88 000 post-menopausal community dwelling Australian women found that 29% reported a history of at least one LTF, but less than one-third were on bone protective treatment [13].

Pharmacologic Treatment

The following discussion will cover current issues regarding the drug treatment of OSP. However, the important role of exercise as part of a multi-faceted programme to prevent further LTF will not be discussed here as it has been recently extensively reviewed [14,15].

Bisphosphonates

Bisphosphonates (BPs) such as alendronate (ALN), risedronate (RSD) and zoledronate (ZLD) have been shown to reduce fracture risk and are first-line treatments for OSP, especially following LTF [16]. Administration of IV ZLD within 90 days following surgical repair of a fractured hip and continued annually for a total of three years reduced

the risk of vertebral and non-vertebral fractures, but also improved patient survival by 28% – possibly due to a beneficial effect on cardiovascular events and pneumonia [17]. A prospective cohort study, the Dubbo Osteoporosis Epidemiology Study, examined over 2000 community dwelling people from April 1989 to May 2007, and found that OSP treatment with BPs was associated with reduced mortality in women and possibly men [18].

Bisphosphonates are preferentially deposited in bone where they are taken up by osteoclasts, the cells responsible for bone resorption. This results in inhibition of osteoclast activation and stimulation of osteoclast apoptosis [19]. Much attention has focused on the association of BPs with the potentially devastating complication of osteonecrosis of the jaw (ONJ). A recent Australian case control study found the odds ratio for developing delayed dental healing when taking an oral BP was 13.1 (95% confidence interval, CI 4.4 to 39.3; $P < 0.001$) [20]. However, the absolute risk of ONJ at the doses used for treatment of OSP is estimated by the American Society of Bone and Mineral Research (ASBMR) as 1:10 000-1:100 000 [21]. The small absolute risk of ONJ means the benefit-to-risk ratio of BP therapy is high when used to treat OSP in patients who have sustained a LTF [19].

There has also been concern the anti-resorptive effect of BPs may impair fracture healing if given too close to the time of fracture. However, as previously discussed, administration of IV ZLD, the most potent BP currently available, within two weeks following hip fracture appeared to lower mortality with no adverse effects on fracture healing [22]. A randomized controlled trial found that alendronate at a dose of 70 mg weekly (the dose used to treat OSP) improved pin fixation in cancellous bone in elderly female patients with OSP who had sustained a pertrochanteric fracture [23]. This was accompanied by a twofold increase in extraction torque required to remove the pins implanted in cancellous bone [23]. A detailed review concluded the use of BPs in experimental animal models was overall associated with increased callus size and mineralization, reduced callus remodeling and improved mechanical strength with no negative impact on fracture healing [24].

There has been recent concern about the risk of atypical femoral fracture (AFF) with long-term BP use. Such fractures usually occur just distal to the lesser trochanter but proximal to the supracondylar flare, are associated with minimal/low trauma and are transverse in orientation and non-comminuted, possibly with a medial spike [25]. However, a nationwide Swedish study found the increased absolute risk was only 5 cases per 10 000 patient-years (95% CI, 4 to 7) [26]. While post-hoc analyses should be interpreted with caution, a careful secondary analysis of three large randomised BP intervention trials failed to identify an increased risk of atypical fractures of the femoral shaft [27]. The recent ASBMR Taskforce has estimated the absolute risk of AFFs in patients on BPs at 3.2-50 cases per 100 000 person-years, but recognized that long-term use may be associated with higher risk, say 100 per 100 000 person-years [28]. Again, as for ONJ, the small absolute risk of AFF means the benefit-to-risk ratio of BP therapy for the treatment of OSP is high in those who have previously sustained a LTF.

Denosumab

Careful unravelling of the complex molecular biology of bone turnover has resulted in denosumab, a monoclonal antibody specifically blocking Receptor Activator of Nuclear Factor kappa-B

Ligand (RANKL), a crucial cytokine promoting osteoclastogenesis. Denosumab is administered subcutaneously every six months [29]. This is the first “targeted therapy” in the field of bone disease and has been shown to reduce vertebral and hip fractures with few side effects [29]. The shorter in vivo biologic effect of denosumab compared to IV ZLD may explain the minimal risk of ONJ observed following long-term use of denosumab in patients with post-menopausal OSP [30].

Other Agents

Strontium ranelate has been shown to reduce vertebral and non-vertebral fracture risk [31,32]. However, recent concern about an increased risk of myocardial infarction has tempered enthusiasm for this drug [33]. A nested case control study using the United Kingdom Clinical Practice Research Datalink did not find an increased risk of first definite myocardial infarction, hospitalisation with myocardial infarction or cardiovascular death in patients who had used strontium ranelate [34]. However, the effective fracture risk reduction and low incidence of side effects seen with both BPs and denosumab make strontium ranelate a second line agent in the treatment of OSP.

Bisphosphonates and denosumab work predominantly on the osteoclast to reduce bone resorption. The other approach to address low bone mass is to stimulate the osteoblast to increase bone formation. The only true bone anabolic agent currently in clinical use is teriparatide (recombinant human parathyroid hormone) [35]. This agent results in potent osteoblastic stimulation which leads to a marked increase in bone density and reduced fracture risk [35]. While the bone anabolic effect of teriparatide is complex, a novel mechanism may be increased heterogeneity of Type I collagen fibril orientation which makes teriparatide-treated bone more resistant to fracture than a more homogeneous structure [36]. However, the need for daily subcutaneous administration and the high cost of this drug limits its usefulness. Interestingly, the potent bone anabolic effect may be of clinical utility in promoting bone healing following fracture. One hundred and two post-menopausal women with a dorsally angulated distal radial fracture in need of closed reduction but not surgery, were randomly assigned to eight weeks of once-daily injection of placebo, 20 µg teriparatide (the current dose for treatment of OSP) or 40 µg teriparatide within 10 days of fracture. Both doses of teriparatide reduced the time to first radiographic appearance of complete cortical bridging [37].

The arrival of the next generation of bone anabolic agents which specifically block the effect of sclerostin, a key negative regulator of bone formation is eagerly awaited and may revolutionise the treatment of bone disease [38]. Drugs that block cathepsin K, an enzyme released by osteoclasts which degrades type I collagen, the predominant collagen in bone are currently undergoing clinical trial and will further widen the range of medications available to treat OSP [39].

Secondary Fracture Prevention

Despite the wide availability of an increasing range of pharmacologic agents clearly shown to reduce fracture risk, less than 30% of patients following LTF are commenced on effective bone protective therapy [10-12]. There are many reasons for this unacceptable gap in clinical care. These include lack of appreciation of the importance of a LTF as a predictor of morbidity and mortality, lack of time on the part of treating clinicians, uncertainty regarding whose role it is to address secondary fracture prevention, poor communication between hospitals and primary care physicians,

concern that anti-resorptive drugs might impair fracture healing and lack of training regarding the use of bone protective therapy in orthopaedic surgical curricula [1].

Many interventions have sought to address this important gap in best practice clinical care. A randomised controlled trial found that patients allocated to an “osteoporosis case manager” following LTF were 4.7 times more likely (adjusted odds ratio, 4.7; 95% CI, 2.4-8.9; $P < 0.001$) to be taking BP therapy at six months [40]. Direct intervention where patients following LTF were offered investigation and treatment for OSP was more effective than a less direct “information based” approach [41]. A public health education campaign combined with provision of written information to patients post-LTF encouraging OSP management by their usual primary care provider was associated with an increased number of serum 25-OH vitamin D assays and DXA scans but failed to improve prescription of bone protective therapy [42]. In contrast active identification and management of OSP following LTF significantly reduced re-fracture rates at four years [43].

Despite these efforts which have been mirrored worldwide a recent retrospective observational cohort study based on United States administrative insurance claims data in those aged 50 years and over admitted with a hip fracture from January 1, 2002 to December 31, 2011 reported the Kaplan-Meier estimated probability of OSP medication use within 12 months following discharge was still only 28.5% [44]. Disturbingly, the rate declined from 40.2% in 2002 to 20.5% in 2011. The median time to commencement of bone protective therapy was 69 days with most commencing treatment within 12 months of the fracture [44].

Effective secondary prevention of OSP requires concerted involvement of the orthopaedic surgeon as he/she is usually the first clinician involved in fracture care. A prospective randomized trial found that compared with “usual” care, patients were twice as likely to be taking treatment for OSP management six months following fracture if it was initiated by the attending orthopaedic surgeon with follow-up in a dedicated orthopaedic OSP clinic [45]. Fracture care by the orthopaedic surgeon should be followed by efforts to prevent subsequent fracture such as a falls prevention assessment, an exercise programme to improve muscle tone and strength and commencement of bone protective therapy with BMD assessment by DXA for risk stratification and provision of a baseline to guide therapy [46]. While some of these interventions may be outside the skill-set of most orthopaedic surgeons they are easily accessible by referral to rheumatology, endocrinology or geriatric medicine colleagues who have an interest in bone disease. The ASBMR Task Force Report on Secondary Fracture Prevention even suggested this should constitute an “obligation” as part of best practice post-fracture clinical and ethical care to prevent further morbidity and mortality [1].

A powerful example of what can be achieved is the Kaiser Southern California Healthy Bones Program (Kaiser SCAL). A key tenet of this programme was that orthopaedic surgeons became OSP “champions” in a multi-disciplinary team of healthcare professionals involving endocrinology, family practice, internal medicine, rheumatology, gynecology, physical therapy, disease/care management, radiology and nursing education. The programme was facilitated by an electronic medical records system which allowed tracking of DXA scans, LTFs and bone protective medications [47]. Over five years this resulted in a 247% increase in DXA scan usage from 21 557 per year in 2002 to 74 770 per year in 2006 with a 135% increase in prescription of bone protective therapy from 33 208 in 2002 to 78 058 in 2006 [47].

Importantly, the expected number of hip fractures was 2510 in 2006 while the observed number was 1575, representing a 37.2% reduction with a saving of USD 30.8 million for 2006.

The American Orthopaedic Association has attempted to address this issue on a wider scale via the “Own the Bone” programme which sought to interrupt the common scenario of orthopaedic fracture care followed by rehabilitation with little attention to secondary fracture prevention which in turn resulted in a further LTF with worsening morbidity and even mortality [48,49]. The programme included the following facets: nutritional counselling, advice regarding physical activity and lifestyle changes, diagnosis and treatment of OSP and communication strategies directed at patients and primary care physicians [49].

However, the most effective intervention worldwide has been the use of a dedicated Fracture Liaison Service (FLS) where patients who suffer a LTF are identified, assessed and treated for OSP under the watchful eye of a fracture liaison coordinator (FLC) who facilitates smooth progression of bone health care [1,50]. Ideally this approach should create a seamless continuum of care bridging the current gaps between the acute fracture care team (orthopaedic surgeon, physiotherapist, nursing staff), the specialist medical team with expertise in bone health (rheumatologist, endocrinologist, geriatrician) and the general practitioner who is responsible for ongoing care of the patient once they return to the community. Such a service should exist at all centres managing LTFs as it has been shown to reduce re-fracture rates [43] and be cost effective with an incremental cost per quality adjusted life year (QALY) gained (incremental cost-effectiveness ratio - ICER) of AUD17 291 – well below the current maximum willingness to pay for one QALY gained of AUD50 000 [51]. This does not necessarily require frequent attendance by the patient at a hospital clinic as recent evidence from a randomized controlled trial suggests the main role of a FLS may be initiation of bone protective therapy with regular but infrequent follow-up by the FLS [52].

Detailed algorithms for the detection, prevention and treatment of osteoporosis have been published by many professional societies, for example the National Osteoporosis Foundation in the United States [53] and the Royal Australian College of General Practitioners [54]. However, a pragmatic approach which should be implemented as part of post-fracture care in anyone aged 50 years or older with a LTF is as follows [42]:

- 1) referral for a DXA scan to allow risk stratification and to obtain a baseline BMD;
- 2) arranging a serum 25-OH vitamin D assay aiming for a serum level > 60 nmol/l;
- 3) commencement of a bisphosphonate or denosumab in anyone with osteoporosis (T-score < -2.5) and probably in those with osteopenia (T-score between -1.0 and -2.5); and
- 4) discussion of falls prevention strategies.

Conclusion

Osteoporotic fractures are a major public health problem that will further stretch the health care budgets of many countries over the coming years due to an ageing population. Despite a wide range of effective and well-tolerated bone protective pharmacologic therapies secondary prevention of OSP is often not implemented. It can be argued that best practice surgical repair of an osteoporotic fracture

also involves measures to prevent the next one. This requires close cooperation between the orthopaedic surgical, nursing and physiotherapy team and a medical team with expertise in bone health. A Fracture Liaison Service built around a dedicated Fracture Liaison Coordinator is probably the most cost-effective, generalisable and successful strategy to implement effective secondary prevention following low trauma fracture.

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