MedicineToday 2014; 15(11): 18-27

PEER REVIEWED FEATURE
2 CPD POINTS

Osteoporosis and fragility fractures

A practical approach

YVONNE SELECKI MB BS, MPH; JOHN A. EISMAN AO, MB BS, PhD, FRACP

In patients with established osteoporosis or a fragility fracture, lifestyle measures such as exercise, supplements and falls risk reduction have not been shown to prevent further fractures. Specific pharmacological treatments can reduce the risk of fractures and may prolong survival.

Key points

- **Fragility fractures (fractures following minimal trauma) signifying osteoporosis are common in both sexes.**
- **Fragility fractures signal a high risk of further fracture and are associated with high morbidity and increased mortality.**
- **Most Australians with a high fracture risk do not receive treatment to reduce this risk.**
- **Lifestyle changes such as exercise, falls risk reduction and calcium and vitamin D supplementation have not been shown to reduce fracture risk and should not be considered adequate to treat patients with a fragility fracture or established osteoporosis.**
- **Specific osteoporosis treatments can reduce the risk of fractures and may prolong survival; they include hormonal therapies, antiresorptive agents and, for very severe osteoporosis, anabolic therapies.**

Osteoporosis, as evidenced by fragility fractures (bone fractures following minimal trauma), is common with increasing age in both women and men. The presence of a fragility fracture signals an increased risk of further fractures and is associated with both high morbidity and increased mortality (Figures 1a and b).

Fragility fractures can affect almost any bone in the skeleton with the exception of the head and neck. Although spine, hip and wrist fractures are arguably the most common, fractures of the proximal humerus, pelvis, distal femur, proximal tibia and multiple ribs are also associated with an increased risk of further fractures and contribute to the overall clinical burden of fragility fractures. In contrast, stress fractures of the feet and, perhaps unexpectedly, ankle fractures in women may not be associated with osteoporosis.

Much attention has been paid to osteoporosis prevention in the general population with much less attention paid to osteoporosis treatment in patients who have already sustained a fragility fracture. Most recent evidence in Australia suggests that only 20% of patients who are eligible for anti-osteoporosis treatment after a fracture actually receive it. A new focus has developed on fracture liaison services as an optimal approach to 'capturing the fracture' around the time of patient admission to hospital as a way of improving health care and reducing costs.[1,2] Here, we discuss preventive approaches and the management of patients with fragility fractures or high fracture risk.

EPIDEMIOLOGY

At any age, women have approximately double the risk of a fracture compared with men. However, following a fragility fracture, the 'protective' effect of male sex is lost and the risk of a subsequent fracture increases three to fourfold in men compared with twofold in women. A single fragility fracture increases an individual's subsequent fracture risk to that of a person at least 20 years older, highlighting the clinical importance of commencing treatment after any fragility fracture.

Although the likelihood of fracture is higher in older individuals, more fractures occur in

Dr Selecki is Translational Research Medical Officer in Osteoporosis – Bone Biology at the Garvan Institute of Medical Research, Sydney. Professor Eisman is Director of the Clinical Translation and Advanced Education in Osteoporosis – Bone Biology at the Garvan Institute of Medical Research, Sydney; Endocrinologist at St Vincent's Hospital, Sydney; Associate Dean, Clinical Excellence and Research at the School of Medicine Sydney, University of Notre Dame Australia; and Professor (Conjoint) at the University of New South Wales, Sydney, NSW.

the 60 to 75 years age group than in the over 75 year age group because the former make up a larger proportion of the population. Hence, the community burden of fragility fractures falls in the relatively 'young old' rather than the elderly.

COMPLICATIONS OF FRAGILITY FRACTURES

Fragility fractures are associated with premature mortality. This association is most marked in the first five years after a fracture event, and any subsequent fracture increases the risk further for the next five to 10 years. The increase in mortality is greater in men than in women, with an almost threefold increase after most major fractures in men compared with around a twofold increase in women.[3,4] The increased mortality reduces life expectancy by about 10 years in people aged 75 years and over and by about five years in those aged between 60 and 75 years, particularly those with hip and multiple spine fractures. However, as noted previously, because of the much larger size of the population of relatively younger women and men, the potential for life years lost falls predominantly in the under 75 years age group.

Although hip fractures are a significant contributor to the mortality risk after a fragility fracture, they are not responsible for most of the life years lost.[5-8] Nonhip and nonspine fractures comprise at least 50% of all fragility fractures and contribute to 25 to 30% of the premature mortality. There has been considerable discussion as to the mechanism of the excess mortality. Some studies suggest that up to half of the excess deaths could be attributed to comorbidities, but other large-scale population-based studies did not find evidence that comorbidities made any substantive contribution.

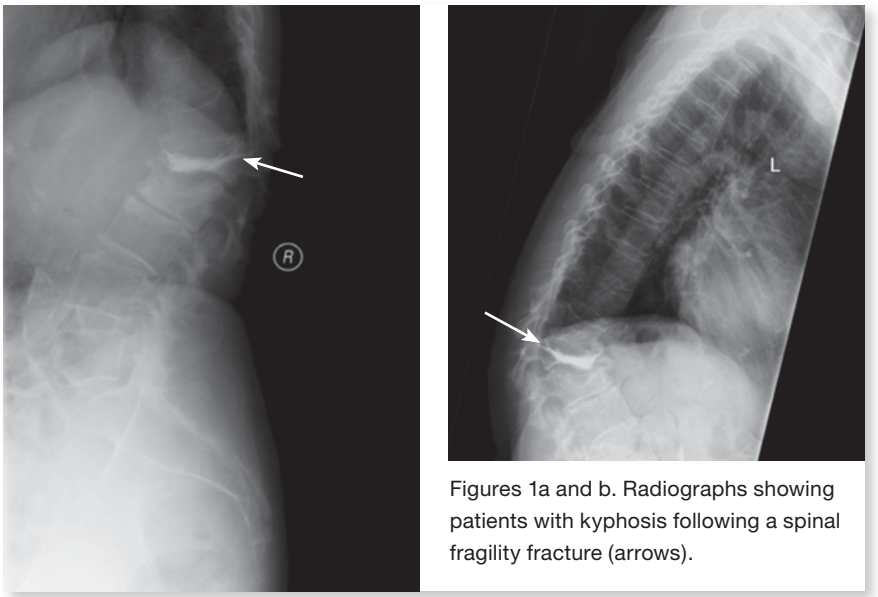
As well as mortality, fractures are associated with considerable morbidity, sustained decreases in quality of life and loss of independence. This is most clearly seen in older individuals with a hip fracture, 25% of whom require nursing home placement.

PREVENTIVE APPROACHES

There has been a major focus on lifestyle measures for prevention of fragility fractures (e.g. exercise, diet, calcium and vitamin D supplementation and fall reduction strategies). However, recent studies have cast doubt on the efficacy and safety of calcium supplementation, exercise and falls risk reduction in people with osteoporosis. RACGP guidelines recommend that 'calcium 1000–1200 mg/day should be taken in conjunction with vitamin D 700–800 IU/day to optimise clinical efficacy'.[9] However if an individual's 25-hydroxyvitamin D level is optimal, there is no evidence to support adding more vitamin D. We will discuss the evidence and recommendations for lifestyle measures.

Vitamin D

Vitamin D is required for normal calcium absorption and normal bone remodelling, but the optimal level of vitamin D is being debated. Studies of vitamin D supplementation in elderly nursing home residents have had positive results, but many of these individuals would have had vitamin D insufficiency, if not frank deficiency. Other studies of vitamin D supplementation in healthy community-dwelling individuals have



Figures 1a and b. Radiographs showing patients with kyphosis following a spinal fragility fracture (arrows).

had equivocal results.[10] This makes sense: if a person has sufficient vitamin D then adding extra would be unlikely to have much if any benefit. In fact, an Israeli study showed that an optimal 25-hydroxyvitamin D level was associated with optimal survival, but that both low and very high levels were associated with decreased survival.[11] This effect was modest for high levels but quite steep for low levels. Hence moderation makes sense.

Nevertheless, low levels of vitamin D (serum 25-hydroxyvitamin D level less than 50 nmol/L) are surprisingly prevalent in Australia, possibly related to our long working hours and strict adherence to sun safe practices, and are not limited to people with darker skin and sun avoidance for religious observation. The effects of all therapeutic agents have been evaluated in conjunction with adequate calcium and vitamin D intake. If a patient has low vitamin D levels and/or a low calcium intake then the aim should be to optimise both.

Recommendation: Provide vitamin D supplements to patients who have osteoporosis and whose 25-hydroxyvitamin D levels are below 50 nmol/L at the end of winter, especially those who are institutionalised.[12]

Calcium

Calcium is considered important to bone health based on obvious physiological principles. Calcium hydroxyapatite constitutes the major component of bone mineral. Calcium is lost in urine, faeces and shed skin and hair at an estimated rate of 250 to 300 mg/day total from all pathways. On the other hand, intestinal calcium absorption from dietary sources or supplements is at best approximately 30% and decreases with age. This has led to the presumption that we require a calcium intake between 800 and 1200 mg daily.

Encouraging calcium intake with supplements if dietary intake is inadequate has been presumed safe and potentially beneficial. However, some recent studies suggest that higher calcium doses have adverse effects on cardiovascular risk, although other similar studies have not shown any such adverse effect.[13] More importantly, there is equivocal evidence of benefit in terms of fracture risk reduction.[12]

Recommendation: The approach to calcium intake is now moderate. A 'reasonable' total calcium intake of 800 to 1200 mg daily from all sources is advised. If that level of intake cannot be achieved from dietary, mainly dairy, sources then supplements could be suggested. The average calcium intake from non-dairy foods is approximately 400 mg/day. There is no evidence for benefit from the additional components of supplements, such as other minerals, for people who do not have an underlying disease or an abnormally restrictive diet. There is a suggestion, based on physiological grounds, that calcium supplements should be taken with a major meal to minimise peak levels of absorption.

Exercise

There is good evidence that weight-bearing exercise has some benefit for bone density preservation. However, no study has shown that this apparent benefit translates to any fracture risk reduction, possibly because of the modest nature of the benefit and the need for continued exercise and activity to maintain it. By contrast, the benefit of exercise is sometimes extrapolated on the unsupported presumption that any benefit would accumulate over time. However, this is neither logical on physiological grounds (unless loading was progressively increased) nor has there been any study to show such a response. In a relatively small study of stronger exercise loading, there was some improvement in bone density but significantly more falls in the exercising group. Thus, it cannot be assumed that exercise is safe and there is no conclusive evidence that it reduces fracture risk.

Exercise has not been formally evaluated in any adequately powered randomised intervention study. Rather the evidence suggests that, as with lifestyle and other interventions, there is a critical optimum that may yield some benefit while minimising the risk of harm.[14] There is also limited or no evidence of efficacy of strength or balance training for reducing fracture risk or of safety (with respect to training-related falls and injuries). The RACGP guidelines state that 'general practitioners could recommend sensible, moderate levels of physical activity throughout life as part of a healthy lifestyle. However, no studies have demonstrated any efficacy in fracture risk reduction or addressed side effects, such as injuries'.[9]

Recommendation: Aim for moderate weight-bearing exercise on a regular basis for general health reasons rather than for any bone-related benefit.

Falls risk reduction

As with exercise, the concept of falls risk reduction is based on epidemiological data showing that patients at higher risk of falls are at higher risk of fractures. However, randomised studies of falls risk reduction strategies have not shown fracture risk reduction.[14,15] This lack of demonstrable benefit may relate to small study size or subjects studied (as benefit would be expected only in those at highest risk of falling), or it may be that the strategies reduce falls risk but do not prevent those falls that are severe enough to result in fractures. Moreover, interventions to reduce falls risk are not cheap. Hence, although reducing falls is a reasonable goal in patients at highest risk, the current data do not support a focus on falls risk reduction strategies. Nevertheless, there is evidence of some benefit in fracture reduction from review of medications to minimise problems such as hypotension and from cataract surgery to improve vision, both probably acting through reducing major falls risk.

Recommendation: Reducing falls risk has an obvious benefit on injurious falls but there is little or no evidence that falls risk reduction strategies have a clinically important impact on fracture risk.

1. LIFESTYLE MEASURES TO REDUCE FRACTURE RISK

- Optimise calcium intake and vitamin D levels
  - Maintain an adequate calcium intake (three serves of dairy or equivalent high-calcium foods per day). If this is not possible then calcium supplements 600 mg daily day may be prescribed, ideally taken with a large meal
  - If adequate safe exposure to sunlight is not possible then prescribe vitamin D supplements to maintain serum 25-hydroxyvitamin D levels above 50 nmol/L
- Cease smoking
- Avoid excess alcohol
- Maintain a healthy body weight. Underweight is a risk for osteoporosis and obesity may increase fracture risk in falls
- Consider high-intensity weight-bearing exercise, which may help reduce bone loss, as part of a healthy lifestyle. However, there is limited evidence for efficacy in fracture risk reduction or for safety regarding side effects, such as exercise-related injuries
- Consider fall reduction strategies focused on improved balance, which can reduce injurious falls. However, as for exercise, there is limited evidence for efficacy in fracture risk reduction or for safety regarding side effects, such as training-related injuries

Moderation: the Goldilocks principle

Taken together these data (or lack of data) on the benefits and safety of lifestyle interventions suggest that healthy lifestyle recommendations should be moderate. They could include adequate calcium intake (neither too high nor too low) and sunlight (neither too much nor too little) and reasonable weight-bearing exercise (neither too much nor too little). If individuals cannot achieve the nutrition or sunlight exposure goals then supplements could be considered. Similarly, for those at high risk of falling, falls risk reduction strategies could be recommended.

Recommended lifestyle interventions are summarised in Box 1. However, it must be recognised that these recommendations are not supported by evidence of fracture risk reduction. Hence, lifestyle interventions alone are not sufficient to reduce further fractures in patients who have had a fragility fracture or in those with established osteoporosis.

WHO SHOULD RECEIVE OSTEOPOROSIS TREATMENT?

In patients with established osteoporosis, effective anti-osteoporosis pharmacotherapy not only approximately halves subsequent fracture risk but also reduces the risk of premature mortality by as yet ill-defined mechanisms unrelated to fracture risk reduction.[16,17] A key question is what is meant by established osteoporosis? Essentially it is defined as severely low bone density (Figures 2a and b) and especially prior fragility fractures.

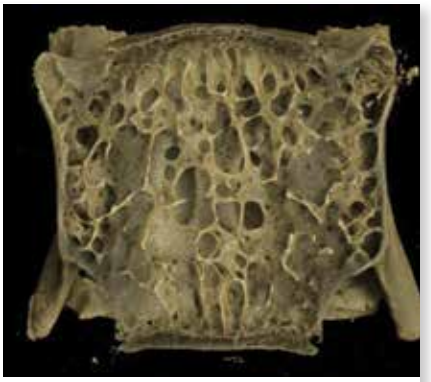
Osteoporosis

Osteoporosis has been somewhat arbitrarily defined as a bone mineral density (BMD), usually measured at one of the lumbar spine or proximal femoral sites, of 2.5 standard deviations (or more) below mean normal values in young people. The further an individual's values are below that arbitrarily defined cut-off point, the worse is their osteoporosis and the proportionally greater their risk of fragility fractures. However, spinal BMD values may be spuriously elevated because of arthritic conditions, including osteoarthritis, and hence most risk estimates are based on proximal femur (femoral neck or total hip) BMD.

BMD values between one and 2.5 standard deviations below mean young normal values have been termed osteopenia. However, this range includes a significant minority (perhaps 16%) of otherwise healthy young people. In reality, there is no clear cut-off point to differentiate osteoporosis from normal. Rather, with progressively lower bone density values, the risk of fracture exponentially increases.

There is good evidence that more fragility fractures occur in the larger proportion of people with BMD values above (albeit close to) the osteoporosis cut-off point than in the higher risk but much smaller proportion with BMD values below (i.e. worse than) the osteoporosis cut-off point.

The PBS guidelines recommend anti-osteoporosis treatment following a 'minimal trauma fracture' with 'established osteoporosis'. The PBS does not specifically



Figures 2a and b. Microcomputed tomography scans of osteoporotic bone.

Images courtesy of Nancy Mourad, Garvan Institute of Medical Research, Sydney, NSW.

define 'minimal trauma fracture' nor the BMD criteria for 'established osteoporosis'. Where the PBS does list a BMD T-score of –2.5 or less as a criterion for treatment it is for anyone aged over 70 years, regardless of fracture history.

Fragility fractures

Fragility fractures can be defined operationally as fractures that have occurred after relatively minor trauma (no obvious trauma or a fall from no more than standing height). This is subjective as patients often factor in their age when assessing whether they expected a fracture and hence do not always recognise a fragility fracture. We ask patients, 'If you were in your 20s and healthy, would you have expected to have fractured in the circumstances?' Unless patients can confidently say 'yes', we recommend presuming the fracture is a fragility fracture until osteoporosis has been considered and effectively excluded.

Future fracture risk

A number of tools have been developed to predict future fracture risk to underpin and support clinical decision-making, treatment recommendations and risk communication with individual patients. At the Garvan Institute, we have developed the Garvan Fracture Risk Calculator (available at www.garvan.org.au/bone-fracture-risk). This tool uses the individual's sex, age, bone density (or weight), history of prior fractures (since age 50 years) and falls (in the past year) to estimate risk.[18,19] It has been validated in several centres worldwide.[20,21] It can be used to communicate risk to an individual, reassuring those with low risk and encouraging active treatment for those at high risk.

The WHO Fracture Risk Assessment Tool (FRAX) is a more complicated fracture risk calculator used by some radiology services. It has been shown to be less accurate than the Garvan Fracture Risk Calculator.[21-25]

MANAGEMENT OF PATIENTS WITH HIGH FRACTURE RISK

Investigations

For patients with established osteoporosis or fragility fractures, clinical management should exclude contributory factors such as malabsorption (especially coeliac disease), low vitamin D levels, premature hypogonadism, myeloma or endocrine disorders such as thyrotoxicosis, thyroid hormone over-replacement, hyperparathyroidism or Cushing syndrome.[26] These conditions increase the risk of osteoporosis, and many may be clinically silent so require specific consideration.

Measurements of serum calcium, 25-hydroxyvitamin D and parathyroid hormone levels are useful baseline tests. If the results suggest any abnormalities or there are any clinical indicators, such as being underweight, then exclusion of coeliac disease is recommended. If any other abnormalities are suggested by pathology results then expert review may be appropriate.

Treatment

Steps in management of patients with a high fracture risk include:

- correction of any contributing conditions
- consideration of lifestyle measures (despite the limited evidence for benefit)
- osteoporosis-specific pharmacotherapy.

Osteoporosis-specific pharmacotherapy is required and appropriate in patients with a T-score less than –2.5 and those with a prior fracture but is often neglected, a serious oversight in current osteoporosis management. Effective antiosteoporosis treatments reduce the risk of fractures and may prolong survival. They are generally well tolerated with a low risk of significant side effects. As noted in the RACGP guidelines, there is seldom any rationale for not strongly recommending such treatment after any fragility fracture, as it is approved by the Pharmaceutical Benefits Advisory Committee and covered by the PBS.[9] The specific treatments available include hormonal therapies, antiresorptive (i.e. antiosteoclast) agents and, for very severe osteoporosis, anabolic therapies that can increase bone mass and density.

When considering the need for pharmacological treatment for patients whose BMD is in the osteopenic range but who have not had a fragility fracture, calculation of absolute fracture risk may be particularly useful. Age and other risk factors may indicate the need for treatment, but the efficacy of pharmacotherapy for the treatment of osteopenia in those who have not had a fragility fracture has not been established.[27] PBS guidelines reserve subsidised treatment of patients with osteopenia (T-score of -1.5 or less) for those at risk of glucocorticoid-induced osteoporosis (taking prednisolone

7.5 mg daily or equivalent for three months or longer).

HORMONAL THERAPIES

Just as menopause in women and hypogonadism in men are associated with excessive bone loss, so can hormonal therapy (oestrogenic or androgenic) partially reverse and certainly stop further bone loss.

Oestrogen or testosterone therapy

Oestrogen therapy in postmenopausal women has been shown to reduce the risk of fracture, including hip fracture.[28] However, there is evidence for adverse effects, including an increased risk of breast cancer diagnosis and possibly cardiovascular events, which limit the utility of this therapy based on risk–benefit considerations. However, recent re-analyses suggest that the risks have been overestimated.[29]

Testosterone replacement in men with hypogonadism may improve bone density but no large studies have been carried out to demonstrate antifracture efficacy. Testosterone may be associated with an increased risk of prostate cancer. Moreover, some recent studies suggest increased cardiovascular risk with the initiation of testosterone replacement.[30]

Given these concerns, simple oestrogen or testosterone therapy is usually limited to individuals who present with sex hormone deficiency symptoms, with any bone effect being seen as a side benefit.

Other hormonal therapies

Partial or selective oestrogen antagonists, such as tamoxifen and raloxifene, have been shown to protect against bone loss. Raloxifene has been shown to reduce fracture risk, especially for spine fractures.[31,32] Although oestrogen antagonists have not been formally compared (head-to-head) with oestrogen treatments, they appear to have weaker effects on bone than oestrogen per se. Importantly, these agents reduce breast cancer risk and recurrence.

Another option is tibolone, which is rendered inactive on absorption but is then metabolised to active compounds in various body tissues. In bone it exerts oestrogen-like actions and has been shown to reduce the risk of fractures, including hip fractures.[33] It does not stimulate the breast or uterus and was shown to reduce initial breast cancer diagnoses but not breast cancer recurrence. It reduces hot flushes and vaginal dryness and may improve libido. In some but not all studies it was associated with low but increased cardiovascular risk, which has limited its use.[34]

Almost all oestrogen-related therapies have been reported to be associated with increased risk of deep vein thrombosis. This needs to be kept in mind, particularly if the patient becomes immobilised or if extended inactivity is possible or planned (e.g. during travel).

ANTIRESORPTIVE THERAPIES

Bisphosphonates

The bisphosphonates were the first anti-osteoporosis therapies to be fully evaluated for antifracture efficacy in large-scale, randomised, placebo-controlled trials. They include alendronate, risedronate and zoledronic acid, which have all been shown to reduce the risk of spine and nonspine fractures as well as hip fractures.[35–41]

The bisphosphonates are relatively well tolerated, although the oral formulations are occasionally associated with upper gastrointestinal symptoms. Orally administered bisphosphonates are very poorly absorbed even when taken exactly as prescribed – while the patient is fasting, with plain water and 30 to 60 minutes before any food. The recommended dosage is, however,

2. SIDE EFFECTS OF BISPHOSPHONATES

Avascular necrosis of the jaw

Avascular necrosis was first described as a side effect of bisphosphonates in people being treated with very high dosages of these drugs for metastatic bone malignancy, often combined with high doses of corticosteroids. This situation is quite distinct from the much lower bisphosphonate doses used in osteoporosis. The distinction is important for two reasons:

- the risk of avascular necrosis is much lower in people being treated for osteoporosis, perhaps one in 10,000 person years of treatment
- if avascular necrosis does occur in people being treated for osteoporosis, it is likely to be much less severe than in individuals receiving cancer therapy.[42,43]

Moreover, management of avascular necrosis of the jaw has improved with more conservative dental approaches and is associated with better outcomes. The major current concern is that many dentists refuse to do required dental work on patients who have been taking bisphosphonates. The Australian Dental Association no longer supports this position, but the recommendation to complete any dental work before commencing treatment remains. Good dental hygiene is considered to reduce the risk further. Considering the low incidence of avascular necrosis of the jaw, avoidance of dental work is not required.

Atypical femoral fractures

Atypical femoral fractures have been reported in people taking long-term bisphosphonate therapy. These fractures have unique features: they are nearly transverse fractures with cortical thickening and a cortical beak at the fracture site, and they can be bilateral.

In initial reports, they seemed to be more common in people who had relatively mild osteoporosis or perhaps only osteopenia at the start of treatment. They may also be more common in patients of Asian ethnicity.

Nevertheless, atypical femoral fractures are still very rare; their incidence in a Kaiser Permanente study was approximately 100th the incidence of typical hip fractures and perhaps 1000th that of all fragility fractures combined.[44-46] Thus, for any individual, the risk–benefit ratio still favours the use of bisphosphonates. For patients who have a high risk of fracture and for whom the consequences of fracture would be serious, the benefits of bisphosphonates outweigh the small risk of atypical fracture.

based on that low absorption. A new enteric-coated formulation of risedronate has two advantages: it is less likely to cause upper gastrointestinal symptoms and it can be taken with food. Both the oral bisphosphonates (alendronate and risedronate) are now available as once a week dosing, with risedronate also available as once a month dosing. Zoledronic acid is administered annually as an intravenous infusion.

All bisphosphonates have sustained efficacy, such that they are less affected by modest variations in adherence to therapy. Zoledronic acid given intravenously reduces the problem of poor compliance. In a randomised controlled trial in patients after hip fracture, zoledronic acid not only reduced subsequent fracture risk but also reduced mortality.

Two side effects of bisphosphonates – avascular jaw necrosis and atypical femoral fractures – have generated considerable concern (see Box 2).[42-46] The risk of avascular jaw necrosis led to recommendations that patients complete any dental work before commencing bisphosphonate treatment. However, this risk in people being treated for osteoporosis is low, perhaps one in 10,000 person years of treatment, and avoidance of dental work is not required.

It has become common to cease bisphosphonate treatment after five years – the so-called 'drug holiday'. This has been advocated because of concern about the side effect of atypical femoral fractures. However, these fractures are uncommon, perhaps one atypical fracture for more than 100 typical femoral fractures averted. In fact, there is little evidence in support of drug holidays unless the bone density deficit is relatively small (i.e. BMD values rise above the osteoporotic threshold with therapy). Even in these patients, follow up must be maintained to reinstitute therapy if and when the bone density starts to decline again. A recent follow-on analysis of the FLEX study, which led to the development of the drug holiday concept, showed that one in every three women who still had osteoporosis by BMD measurement suffered fractures in the five years after ceasing bisphosphonate treatment.[47]

Recommendation: Bisphosphonates are well-tolerated, effective drugs with benefits in fracture risk reduction and may prolong healthy survival. The concept of a drug holiday has no place in women or men with osteoporosis by BMD criteria.

Denosumab

Denosumab is a human monoclonal antibody to receptor activator of nuclear factor kappa-B ligand (RANKL), a key regulator of osteoclast development, survival and activity. It reduces osteoclast numbers and activity with associated improvements in BMD and reductions in fracture risk.[48-50] It has similar efficacy to other antiresorptive agents but, as with bisphosphonates, there have not been head-to-head randomised controlled trials of efficacy. Denosumab is given as a subcutaneous injection twice a year, which is convenient and has potential benefits in adherence monitoring. It is well tolerated but has the potential for similar side effects to the bisphosphonates, such as avascular necrosis of the jaw, at least when used in high doses for metastatic bone malignancy, and for atypical bone fractures in longer-term treatment. The rapid reversibility of effect by about seven months after

each injection may be an advantage in these contexts. It is an excellent first-line choice with comparable efficacy and safety to the bisphosphonates.

Strontium ranelate

Strontium ranelate is a unique therapy that has been reported to have both antiresorptive and bone anabolic actions. Because strontium accumulates in the skeleton, about half of the increase in BMD associated with its use is attributable to the greater radiodensity of the strontium atom. It has been shown to reduce fracture risk.[51-53] Although the apparent decrease in fracture risk is somewhat less than that reported with other agents, there have not been head-to-head comparisons.

Strontium ranelate is generally well tolerated although some individuals report gastrointestinal upset. There have been reports of increased risk of deep venous thrombosis, although it is not clear if this is truly related to the drug. Recently, a 'black box' warning has been issued in regard to cardiovascular risk and it is suggested that strontium ranelate should not be used in older individuals, especially those with known cardiovascular risk. It is also not clear that this risk is truly drug-related, but health agencies have taken a cautious approach. The TGA recommends strontium ranelate be used only when other antiresorptive drugs are not tolerated.

ANABOLIC AGENTS

Teriparatide is a recombinant analogue of human parathyroid hormone. Although constant high levels of parathyroid hormone result in bone loss, intermittent bursts of the hormone result in an anabolic effect. Teriparatide given by subcutaneous injection daily has been shown to improve bone density and reduce fracture risk in both men and women with very low BMD, including glucocorticoid-associated osteoporosis.[54-56] The reduction in fracture risk may be greater than with antiresorptive agents but there have not been head-to-head comparisons in terms of anti-fracture efficacy.

Teriparatide is generally well tolerated, although some patients complain of leg cramps. In studies in rats given teriparatide from weaning to old age, osteosarcoma was observed. It is not clear that this is relevant to human treatment given the relatively very high dose and lifelong administration in the rat studies. In humans, there is no evidence of any increased risk of osteosarcoma in postmarketing surveillance. Nevertheless, teriparatide is not recommended in patients before puberty nor in anyone with a history of bone radiotherapy, bone cancer or Paget's disease of bone. Obtaining informed consent for its use requires discussion of these rodent data with patients.

When the rodent data on teriparatide became available, the drug's pivotal human studies were ceased at 18 months in women and 11 months in men. After careful review of the rodent data and, despite agreement on their limited relevance to humans, the TGA limited teriparatide use to a duration of 18 months and only once in a person's lifetime.

Largely because of cost, teriparatide use in Australia is restricted to patients with severe osteoporosis (T-score less than –3.0) and fractures occurring despite at least a year of antiresorptive therapy. Importantly, its use should be followed by long-term effective antiresorptive therapy or the benefit achieved will be gradually lost.

Recommendation: Teriparatide should be considered in individuals with persistently low BMD and a fracture despite adherence to prior bisphosphonate therapy. Its use should be followed by maintenance antiresorptive therapy.

CONCLUSION

Osteoporosis is common in all ageing communities, including Australia. Although more common in women, it is a significant and largely overlooked health issue for men. Osteoporosis can be diagnosed by bone densitometry but often first presents with fragility fractures.

Lifestyle change is widely advocated as part of a general health approach to osteoporosis. However, some recommendations, such as increased exercise, carry a risk of adverse effects, including falls and fractures. Moreover, no lifestyle change has been shown to materially reduce fracture risk. Perhaps the greatest risk is that lifestyle recommendations are mistakenly adopted as an alternative to proven effective pharmacotherapy. Anti-osteoporosis pharmacotherapy can markedly reduce the risk of fragility fractures and there is evidence that it can prolong survival. It is generally well tolerated with a low risk of significant side effects.

Despite the major impact of osteoporosis on morbidity and mortality and the evidence for the efficacy of antiosteoporosis therapy, most Australians who are at high risk, even after fragility fractures, do not receive treatment to reduce their risk of a further fracture. Focused intervention is required to improve health and survival outcomes. MT

REFERENCES

A list of references is included in the website version (www.medicinetoday.com.au) and the iPad app version of this article.

COMPETING INTERESTS. Dr Selecki: None. Professor Eisman has received consulting and research support from Amgen, Aspen, Lilly, Merck Sharp and Dohme, Novartis, Sanofi-Aventis and Servier.

Osteoporosis and fragility fractures
A practical approach

YVONNE SELECKI MB BS, MPH; **JOHN A. EISMAN** AO, MB BS, PhD, FRACP

REFERENCES

1. Eisman JA, Bogoch ER, Dell R, et al; ASBMR Task Force on Secondary Fracture Prevention. Making the first fracture the last fracture: ASBMR task force report on secondary fracture prevention. J Bone Miner Res 2012; 27: 2039-2046.
2. Akesson K, Marsh D, Mitchell PJ, et al; IOF Fracture Working Group. Capture the fracture: a best practice framework and global campaign to break the fragility fracture cycle. Osteoporos Int 2013; 24: 2135-2152.
3. Bliuc D, Nguyen ND, Nguyen TV, Eisman JA, Center JR. Compound risk of high mortality following osteoporotic fracture and refracture in elderly women and men. J Bone Miner Res 2013; 28: 2317-2324.
4. Bliuc D, Nguyen ND, Milch VE, Nguyen TV, Eisman JA, Center JR. Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. JAMA 2009; 301: 513-521.
5. Frost SA, Nguyen ND, Black DA, Eisman JA, Nguyen TV. Risk factors for in-hospital post-hip fracture mortality. Bone 2011; 49: 553-558.
6. Söderqvist A, Ekström W, Ponzer S, et al; Stockholm Hip Fracture Group. Prediction of mortality in elderly patients with hip fractures: a two-year prospective study of 1,944 patients. Gerontology 2009; 55: 496-504.
7. Ioannidis G, Papaioannou A, Hopman WM, et al. Relation between fractures and mortality: results from the Canadian Multicentre Osteoporosis Study. CMAJ 2009; 181: 265-271.
8. Radley DC, Gottlieb DJ, Fisher ES, Tosteson AN. Comorbidity risk-adjustment strategies are comparable among persons with hip fracture. J Clin Epidemiol 2008; 61: 580-587.
9. Royal Australian College of General Practitioners. Clinical guideline for the prevention and treatment of osteoporosis in postmenopausal women and older men. Sydney: RACGP; 2010. Available online at: http://www.racgp.org.au/your-practice/guidelines/musculoskeletal/osteoporosis (accessed October 2014).
10. Scragg R. Do we need to take calcium with vitamin D supplements to prevent falls, fractures, and death? Curr Opin Clin Nutr Metab Care 2012; 15: 614-624.
11. Saliba W, Barnett O, Rennert HS, Rennert G. The risk of all-cause mortality is inversely related to serum 25(OH)D levels. J Clin Endocrinol Metab 2012; 97: 2792-2798.
12. Nowson CA, McGrath JJ, Ebeling PR, et al; Working Group of Australian and New Zealand Bone and Mineral Society, Endocrine Society of Australia and Osteoporosis Australia. Vitamin D and health in adults in Australia and New Zealand: a position statement. Med J Aust 2012; 196: 686-687.
13. Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. BMJ 2011; 342: d2040.
14. Cameron ID, Gillespie LD, Robertson MC, et al. Interventions for preventing falls in older people in care facilities and hospitals. Cochrane Database Syst Rev 2012; (12): CD005465.
15. Frick KD, Kung JY, Parrish JM, Narrett MJ. Evaluating the cost-effectiveness of fall prevention programs that reduce fall-related hip fractures in older adults. J Am Geriatr Soc 2010; 58: 136-141.
16. Center JR, Bliuc D, Nguyen ND, Nguyen TV, Eisman JA. Osteoporosis medication and reduced mortality risk in elderly women and men. J Clin Endocrinol Metab 2011; 96: 1006-1014.
17. Bolland MJ, Grey AB, Gamble GD, Reid IR. Effect of osteoporosis treatment on mortality: a meta-analysis. J Clin Endocrinol Metab 2010; 95: 1174-1181.
18. Nguyen ND, Frost SA, Center JR, Eisman JA, Nguyen TV. Development of prognostic nomograms for individualizing 5-year and 10-year fracture risks. Osteoporos Int 2008; 19: 1431-1444.
19. Nguyen ND, Frost SA, Center JR, Eisman JA, Nguyen TV. Development of a nomogram for individualizing hip fracture risk in men and women. Osteoporos Int 2007; 18: 1109-1117.
20. van Geel TA, Nguyen ND, Geusens PP, et al. Development of a simple prognostic nomogram for individualising 5-year and 10-year absolute risks of fracture: a population-based prospective study among postmenopausal women. Ann Rheum Dis 2011; 70: 92-97.
21. Langsetmo L, Nguyen TV, Nguyen ND, et al; Canadian Multicentre Osteoporosis Study Research Group. Independent external validation of nomograms for predicting risk of low-trauma fracture and hip fracture. CMAJ 2011; 183: E107-E114.
22. van Geel TA, Eisman JA, Geusens PP, van den Bergh JP, Center JR, Dinant GJ. The utility of absolute risk prediction using FRAX and Garvan Fracture Risk Calculator in daily practice. Maturitas 2014; 77: 174-179.
23. Bolland MJ, Siu AT, Mason BH, et al. Evaluation of the FRAX and Garvan fracture risk calculators in older women. J Bone Miner Res 2011; 26: 420-427.

24. Sandhu SK, Nguyen NK, Center JR, Pocock NA, Eisman JA, Nguyen TV. Prognosis of fracture: evaluation of predictive accuracy of the FRAX algorithm and Garvan nomogram. Osteoporos Int 2010; 21: 863.
25. Pluskiewicz W, Adamczyk P, Franek E, et al. Ten-year probability of osteoporotic fracture in 2012 Polish women assessed by FRAX and nomogram by Nguyen et al. Conformity between methods and their clinical utility. Bone 2010; 46: 1661-1667.
26. Bours SP, van Geel TA, Geusens PP, et al. Contributors to secondary osteoporosis and metabolic bone diseases in patients presenting with a clinical fracture. J Clin Endocrinol Metab 2011; 96: 1360-1367.
27. Eriksen EF. Treatment of osteopenia. Rev Endocr Metab Disord 2012; 13: 209-223.
28. Cauley JA, Robbins J, Chen Z, et al; Women's Health Initiative Investigators. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. JAMA 2003; 290: 1729-1738.
29. Shapiro S, de Villiers TJ, Pines A, et al. Risks and benefits of hormone therapy: has medical dogma now been overturned? Climacteric 2014; 17: 215-222.
30. Finkle WD, Greenland S, Ridgeway GK, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. PLoS One 2014; 9: e85805.
31. Cummings SR. The paradox of small changes in bone density and reductions in risk of fracture with raloxifene. Ann N Y Acad Sci 2001; 949: 198-201.
32. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA 1999; 282: 637-645.
33. Cummings SR, Ettinger B, Delmas PD, et al; LIFT Trial Investigators. The effects of tibolone in older postmenopausal women. N Engl J Med 2008; 359: 697-708.
34. Lobo RA. Menopause and stroke and the effects of hormonal therapy. Climacteric 2007; 10 Suppl 2: 27-31.
35. Wells GA, Cranney A, Peterson J, et al. Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev 2008; (1): CD001155.
36. Stevenson M, Jones ML, De Nigris E, Brewer N, Davis S, Oakley J. A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis. Health Technol Assess 2005; 9: 1-160.
37. Karpf DB, Shapiro DR, Seeman E, et al. Prevention of nonvertebral fractures by alendronate. A meta-analysis. Alendronate Osteoporosis Treatment Study Groups. JAMA 1997; 277: 1159-1164.
38. Watts NB, Josse RG, Hamdy RC, et al. Risedronate prevents new vertebral fractures in postmenopausal women at high risk. J Clin Endocrinol Metab 2003; 88: 542-549.`
39. McClung MR, Geusens P, Miller PD, et al; Hip Intervention Program Study Group. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med 2001; 344: 333-340.
40. Reid IR, Black DM, Eastell R, et al; HORIZON Pivotal Fracture Trial and HORIZON Recurrent Fracture Trial Steering Committees. Reduction in the risk of clinical fractures after a single dose of zoledronic acid 5 milligrams. J Clin Endocrinol Metab 2013; 98: 557-563.
41. Boonen S, Eastell R, Su G, et al. Time to onset of antifracture efficacy and year-by-year persistence of effect of zoledronic acid in women with osteoporosis. J Bone Miner Res 2012; 27: 1487-1493.
42. Grbic JT, Black DM, Lyles KW, et al. The incidence of osteonecrosis of the jaw in patients receiving 5 milligrams of zoledronic acid: data from the health outcomes and reduced incidence with zoledronic acid once yearly clinical trials program. J Am Dent Assoc 2010; 141: 1365-1370.
43. Pazianas M, Miller P, Blumentals WA, Bernal M, Kothawala P. A review of the literature on osteonecrosis of the jaw in patients with osteoporosis treated with oral bisphosphonates: prevalence, risk factors, and clinical characteristics. Clin Ther 2007; 29: 1548-1558.
44. Feldstein AC, Black D, Perrin N, et al. Incidence and demography of femur fractures with and without atypical features. J Bone Miner Res 2012; 27: 977-986.
45. Dell RM, Adams AL, Greene DF, et al. Incidence of atypical nontraumatic diaphyseal fractures of the femur. J Bone Miner Res 2012; 27: 2544-2550.
46. Silverman SL, Ott SM, Dell RM. Bisphosphonates and atypical femoral fractures. N Engl J Med 2010; 363: 1083; author reply 1084-1085.
47. Bauer DC, Schwartz A, Palermo L, et al. Fracture prediction after discontinuation of 4 to 5 years of alendronate therapy: the FLEX study. JAMA Intern Med 2014; 174: 1126-1134.
48. Papapoulos S, Chapurlat R, Libanati C, et al. Five years of denosumab exposure in women with postmenopausal osteoporosis: results from the first two years of the FREEDOM extension. J Bone Miner Res 2012; 27: 694-701.
49. Boonen S, Adachi JD, Man Z, et al. Treatment with denosumab reduces the incidence of new vertebral and hip fractures in postmenopausal women at high risk. J Clin Endocrinol Metab 2011; 96: 1727-1736.
50. Cummings SR, San Martin J, McClung MR, et al; FREEDOM Trial. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 2009; 361: 756-765.
51. Seeman E, Devogelaer JP, Lorenc R, et al. Strontium ranelate reduces the risk of vertebral fractures in patients with osteopenia. J Bone Miner Res 2008; 23: 433-438.
52. O'Donnell S, Cranney A, Wells GA, Adachi JD, Reginster JY. Strontium ranelate for preventing and treating postmenopausal osteoporosis. Cochrane Database Syst Rev 2006; (4): CD005326.
53. Reginster JY, Seeman E, De Vernejoul MC, et al. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) study. J Clin Endocrinol Metab 2005; 90: 2816-2822.
54. Miller PD, Delmas PD, Lindsay R, et al; Open-label Study to Determine How Prior Therapy with Alendronate or Risedronate in Postmenopausal Women with Osteoporosis Influences the Clinical Effectiveness of Teriparatide Investigators. Early responsiveness of women with osteoporosis to teriparatide after therapy with alendronate or risedronate. J Clin Endocrinol Metab 2008; 93: 3785-3793.
55. Sambrook PN. Anabolic therapy in glucocorticoid-induced osteoporosis. N Engl J Med 2007; 357: 2084-2086.
56. Watts NB. Efficacy of teriparatide and alendronate on nonvertebral fractures. J Clin Endocrinol Metab 2003; 88: 1402-1403; author reply 1403.