MedicineToday
The Peer Reviewed Journal of Clinical Practice

Osteoporosis

Reprint Collection

Formerly MODERN MEDICINE

This supplement is sponsored as an educational service by NOVARTIS

Reprint Collection – Osteoporosis July 2010
ISSN 1443-430X

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SUBSCRIPTION RATES
Prices for Australia include 10% GST.

Standard	$210.00 per year $370.00 for two years
Medical students	$65.00 per year, $120.00 for two years
RMO/Intern introductory offer	$105.00 for one year $195.00 for two years
NZ, PNG, Fiji (Pacific region)	$225.00 per year
Asia	$270.00 per year
Rest of the World	$325.00 per year
Back issues	$17.50 each $8.80 medical students $22.00 overseas

MedicineToday
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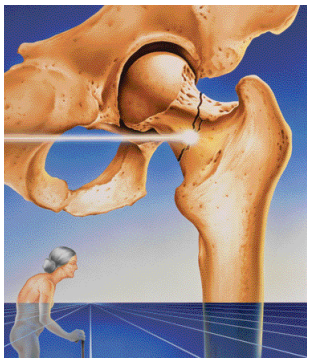

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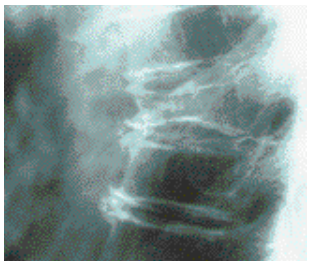

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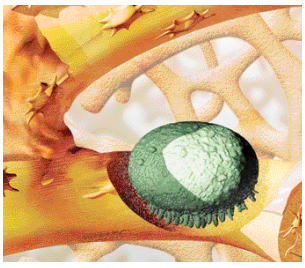

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The articles in this reprint collection were originally published in *Medicine Today*, January 2008 to May 2010, and have been updated. This collection has been sponsored by an unrestricted educational grant from Novartis Pharmaceuticals Australia Pty Ltd. The opinions expressed in the articles are those of the author and not necessarily those of Novartis Pharmaceuticals Australia Pty Ltd. Some products and/or indications mentioned may not be approved for use in Australia. Please review Product Information, available from the manufacturer, before prescribing any agent mentioned in these articles.

Osteoporosis
a constellation of problems

This collection of articles written by Professor Diamond and colleagues describes many aspects of the constellation of problems in osteoporosis.

The first article, cowritten with Dr Golombik, reviews the potential side effects of treatment and describes a World Health Organization fracture risk algorithm. The Australian-developed, Garvan-Dubbo-based Fracture Risk Calculator (available via the website: www.fractureriskcalculator.com) is another risk calculator that has been shown, in both Australian and other international centres, to predict very accurately fracture risk outcomes for both women and men.

The accompanying patient handout, written by the same authors, presents a brief summary of some important and useful points to communicate with patients with osteoporosis.

Some of the secondary causes of osteoporosis, which are important to consider as potentially modifiable factors, are identified in the article cowritten with Dr Tonks. Although some of these factors are indeed modifiable, unfortunately many are not readily modifiable, such as the use of potent oestrogen-blocking therapy in patients with breast cancer. Similarly, the use of exogenous corticosteroids may not be avoidable. However, being aware of these issues helps to identify individuals at greater risk of osteoporosis and therefore worthy of intervention.

The serious impact of osteoporosis and its high incidence in men are stressed in the third article, cowritten with Professor Ebeling. It describes treatment options for men with osteoporosis and indicates how secondary causes should be excluded in this group (as in women). The somewhat more limited information available on antiresorptive therapy in men is also reviewed.

The fourth article, cowritten with Professor Mason, stresses the importance of adequate vitamin D levels and the commonness of vitamin D insufficiency in the community. It reviews the evidence that vitamin D insufficiency can also affect general health, emphasising the importance of ensuring adequate vitamin D status in all individuals.

The focus of the last article, cowritten with Professor White, is how a single bone fragility fracture signals the likelihood of the progressive downward spiral, with further fractures and indeed generally adverse outcomes. It is worth noting that all fragility fractures are associated with adverse outcomes, including further fractures and, importantly, premature mortality. This article also emphasises the potential use of the bisphosphonates in metastatic cancer to bone.

The articles in this collection, originally published in *Medicine Today* and updated as necessary, cover many of the aspects facing individuals with osteoporosis in the Australian community. In particular, they emphasise the frequency of the condition in men as well as in women, the importance of excluding secondary causes, the range of therapeutic options, and the relative safety and rapid onset of the efficacy of these therapies. MT

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MedicineToday PEER REVIEWED ARTICLE
MedicineToday 2008; 9(1): 12-23
Updated June 2010

Postmenopausal osteoporosis

identifying women at risk and selecting appropriate agents

Postmenopausal osteoporosis is now occurring in epidemic proportions. GPs have the responsibility of identifying women at high risk of osteofragility fractures.

TERRY DIAMOND
FRACP

TERRY GOLOMBIK
PhD

Professor Diamond is an Associate Professor in Endocrinology at the University of New South Wales and Senior Endocrinologist at St George Hospital. Dr Golombik is a Research Fellow, Department of Endocrinology at St George Hospital, Sydney, NSW.

Osteoporosis is one of the most common disorders affecting Australian women, with one in two women over the age of 60 years suffering an osteoporosis-related fracture. The lifetime risk for a woman having a hip fracture is one in six whereas that for breast cancer is one in nine. Osteoporosis-related fractures result in an increased morbidity and premature mortality, adding to significant healthcare costs and resources around the world. The term 'osteoporosis' is emotive and often leads to panic, misunderstanding and incorrect treatment of the disorder. It is often regarded as synonymous with low bone mineral density (BMD), but BMD is only one of the risk factors contributing to osteofragility fracture. It is important to identify women at high risk of osteofragility fractures so they can be effectively treated with appropriate antiosteoporotic therapies and to use strategies that will prevent falls, thereby reducing lifetime fracture risk and associated morbidity.

IN SUMMARY

- **The prevalence of osteofragility fractures in postmenopausal women is rapidly escalating. These fractures lead to an increase in morbidity and premature mortality.**
- **The fracture risk in postmenopausal women should be calculated according to both osteoporotic risk factors and bone mineral density (BMD) T-scores.**
- **Secondary causes of osteoporosis should always be excluded prior to initiating antiosteoporotic therapies.**
- **Specific pharmacological agents are rebatable on the PBS for postmenopausal women aged 70 years or over with a BMD T-score of -3.0 or less (primary prevention) and postmenopausal women with a BMD T-score of -2.5 or less and a prior osteofragility fracture (secondary prevention).**
- **Antiresorptive therapies are considered first-line agents for women with osteofragility fractures.**
- **Anabolic agents should be considered in women who continue to have fractures despite optimal antiresorptive therapies.**
- **Simpler dosing regimens, improved drug tolerability and patient compliance programs encourage women to continue therapies for longer periods of time, thereby enhancing therapeutic outcomes.**

Pathogenesis

Fractures occur as a result of a decrease in bone strength (low BMD and alteration in bone quality) superimposed on a fall or minimal trauma (age-related 'sarcopenia' or reduced strength associated with age-related muscle atrophy; Table 1). Other secondary disorders, apart from ageing and the menopause, may result in an increased likelihood of fracturing (Table 2).

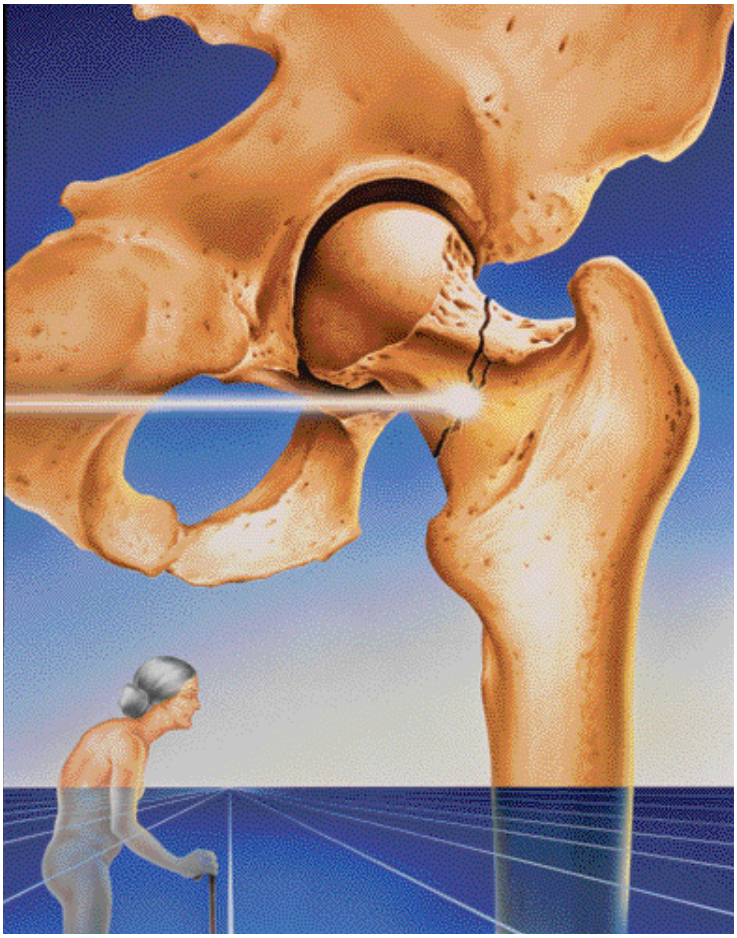
In women, peak bone mass is achieved at the age of 30 to 35 years for cortical bone and earlier for trabecular bone. From the age of 40 years, bone loss occurs at a rate of 0.3 to 0.5% annually, with acceleration during the menopause of about 4 to 6% annually. The cumulative loss over a life time is 40 to 50% of bone mass, predominantly from the spine, hip and distal radius.[1]

The histological characteristics of osteoporosis include decreased cortical thickness and decreased number and size of trabeculae, with preservation of osteoid seams. Bone formation and resorption is normally a coupled process occurring continuously at various sites on bone surfaces. Resorption precedes formation and bone turnover is maintained with many active units (Figure 1). During the menopause, oestrogen withdrawal results in high bone turnover. Bone resorption (which is maximal on endocortical surfaces) exceeds formation, eroding medullary cavities and perforating trabecular plates. This uncoupling in bone turnover is due to receptor activator of nuclear factor KB (RANK) ligand, a protein expressed by osteoblastic stromal cells. RANK ligand binds RANK receptors on osteoclasts, causing differentiation, activation and increased bone resorption. A reduction in circulating levels of insulin-like growth factor-1 contributes to the osteoblast dysfunction and reduced bone formation noted in periosteal bone with ageing.

Impact of osteoporosis

The burden of osteoporosis-related fractures is escalating around the world due to the increasing life expectancy of women (beyond 80 years of age). Moreover, the effect of globalisation on developing countries such as China and other Asian countries has led to dietary and lifestyle changes that contribute to the osteoporosis syndrome. It is predicted that the number of hip fractures worldwide will rise from 1.7 million in 1990 to 6.3 million in 2050.[2]

Postmenopausal osteoporosis



Osteoporosis is one of the most common disorders affecting Australian women, with one in two women over the age of 60 years suffering an osteoporosis-related fracture. It is important to identify women at high risk of osteofragility fractures so they can be effectively treated with appropriate antiosteoporotic therapies, and to advise patients on a 'healthy bone lifestyle'.

In Europe, it is estimated that 643,000 osteoporosis-related hip fractures occur annually,[3] compared with 1.5 million osteoporosis-related fractures (including 700,000 vertebral and 250,000 hip fractures) in the USA.[4] In Australia, data from three prospective cohort studies (conducted in Geelong, Tasmania and Dubbo) estimate that 65,000 osteoporosis-related fractures occur annually, with a direct cost to the community of approximately $1.9 billion.[5]

Hip fracture is the most catastrophic of the osteoporotic fractures, resulting in chronic pain, disability and increased mortality (20 to 25% of women die within the first 12 months' post-fracture). At least 40% of survivors are unable to

Table 1. Factors contributing to osteofragility fractures

Decreased bone density

Low peak bone mass

- Genetics
- Calcium, phosphorus and vitamin D deficiency
- Anorexia and nutritional disorders
- Oestrogen deficiency
- Lifestyle factors (e.g. lack of weight-bearing exercise, smoking)

Increased bone loss

- Ageing
- Menopause
- Calcium and vitamin D deficiency
- Medications
- Secondary causes of osteoporosis

Decreased bone quality

- Bone size and geometry
- Mineral and matrix composition
- Microarchitecture
- Bone porosity and thinness
- Accumulation of microdamage

Increased falls

- Older age
- Sarcopenia (loss of muscle strength)
- Slow reflexes
- Poor cognition, vision, gait or balance
- Medications
- Disease states

Table 2. Secondary causes of osteoporosis

Endocrine disorders and oestrogen deficiency

- Oestrogen deficiency
  - Primary/secondary pituitary failure
  - Hyperprolactinaemia
  - Primary ovarian failure
  - Surgical menopause
  - Chromosomal disorders (Turner's syndrome)
  - Functional hypogonadism (overexercise)
- Corticosteroid excess
  - Cushing's syndrome
  - Corticosteroid therapy
- Primary hyperparathyroidism
- Thyrotoxicosis
- Type 1 diabetes mellitus

Gastrointestinal and nutritional disorders

- Malabsorption
  - Coeliac disease
  - Gastric/bowel resection
  - Inflammatory and infiltrative bowel disease
  - Crohn's disease
- Malnutrition
- Anorexia
- Vitamin D and calcium deficiency
- Vitamin B_{12} deficiency
- Chronic liver disease
  - Primary biliary cirrhosis
  - Haemochromatosis

Haematological disorders and others

- Malignancy
  - Multiple myeloma and monoclonal gammopathy of undetermined significance
  - Leukaemias
  - Lymphomas
  - Systemic mastocytosis
- Toxins and drugs
  - Alcohol
  - Iron and aluminium excess
  - Antiepileptic agents
  - Thyroxine excess
  - Aromatase inhibitors
  - Methotrexate
  - Proton pump inhibitors
  - Glitazones
- Collagen disorders
  - Osteogenesis imperfecta
  - Marfan's syndrome
  - Ehlers–Danlos syndrome
- Homocystinuria
- Idiopathic hypercalciuria
- Chronic disorders
  - Cardiorespiratory
  - Renal
- Inflammatory arthropathies
- Post-transplant

walk independently again, 60% require assistance for more than 12 months post-fracture and 25 to 30% are totally dependent and require permanent nursing home care.[6,7] Vertebral fractures are usually undiagnosed and follow a protracted course, resulting in progressive height loss, chronic back pain, loss of self-esteem, depression and death (Figure 2).[8] The five-year mortality for vertebral fracture is similar to that of hip fracture.

Identifying women at risk

Although osteoporosis is a preventable and treatable condition, many affected individuals remain undertreated. In an Australian study, 69,358 postmenopausal women who had attended 927 primary care physicians completed surveys. Of these women, 57,088 reported the presence of a postmenopausal fracture or risk factors and 29% had at least one self-reported fracture. Fewer than one in three women were receiving specific therapies for osteoporosis and only 40% had been told they had osteoporosis.[9]

After the menopause all women should be assessed clinically to determine the need for BMD testing.[10,11] Major risk factors for osteofragility fractures in postmenopausal women include those that are modifiable (e.g. alcohol consumption, smoking, low bodyweight, poor nutrition, eating disorders, lack of exercise, low dietary calcium, vitamin D deficiency and frequent falls) and those that are fixed (e.g. ageing,

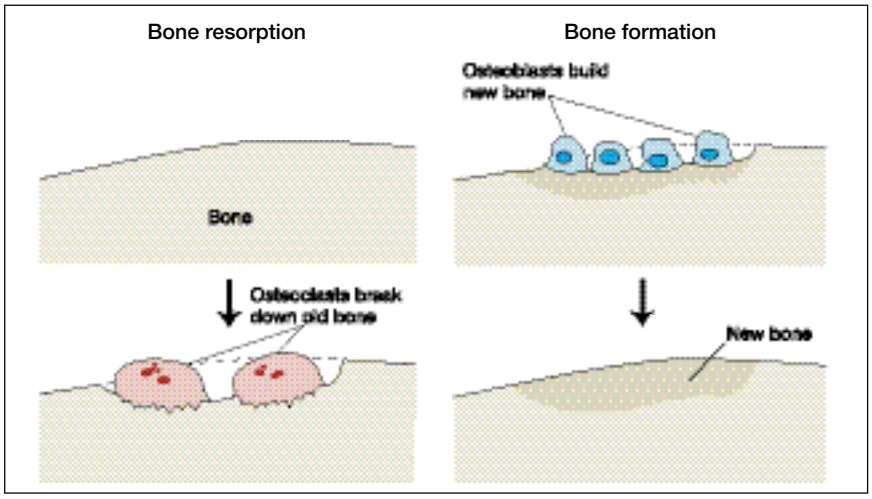
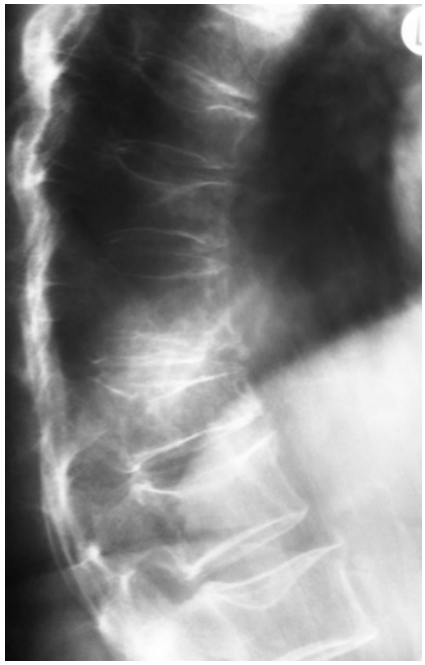


Figure 1. The normal bone remodelling process. a (left). Bone resorption – antiresorptive agents act at this level by inhibiting osteoclasts. b (right). Bone formation – anabolic agents act at this level by stimulating osteoblasts.



PHOTOLIBRARY

Figure 2. Lateral thoracic X-ray demonstrating an osteoporotic vertebral compression fracture. Note the marked decrease in anterior vertebral height of the fractured vertebra as compared to the normal anterior vertebral heights in the unfractured vertebrae above and below the fracture.

personal history of prior fracture during adulthood, fragility fracture in a first degree relative, race/ethnicity, secondary causes of osteoporosis, and current use of oral corticosteroids for more than three months).[12] The more risk factors a woman has, the higher her risk of osteofragility fractures. Individuals with five or more risk factors have a fracture risk increase of as much as 17-fold.

BMD and fracture risk

The prevalence of fractures is more common in individuals with bone densitometric evidence of osteoporosis. However, more than 90% of hip fractures occur following a fall, highlighting the importance of other fracture-related risk factors. It is estimated that 25% of all fractures occur in women aged 80 years and older (these women account for only 10% of the population).

The most commonly used measurement to diagnose osteoporosis and predict fracture risk is BMD.[13] A low BMD is an established predictor of fracture risk in older adults. There is a gradient of increasing fracture risk with decreasing BMD, such that for every one standard deviation decrease in age-adjusted BMD, fracture risk increases about twofold.[14] The current WHO criteria for establishing the diagnosis of postmenopausal osteoporosis is based on a BMD threshold defined by a T-score of -2.5 or less (the T-score is the number of standard deviations below the average BMD of a young, healthy adult of the same sex). Severe osteoporosis is defined as a BMD T-score of -2.5 or less in the presence of one or more fragility fracture. Although dual energy x-ray absorptiometry (DXA) is the current usual method for assessing BMD at the hip and spine, several different techniques including quantitated computed tomography (QCT) have been developed to measure BMD at other skeletal sites.

In Australia, BMD testing is rebatable on the PBS based on the individual's risk profile. The criteria for BMD testing include postmenopausal women aged 70 years and over and regardless of risk factors, young postmenopausal women with one or more risk factors and postmenopausal women presenting with fractures (clinical or morphometric).

Combining BMD and other risk factors

Estimates of fracture risk increase significantly when BMD is combined with other risk factors.[15,16] Age is a strong BMD-independent risk factor for fracture: at any BMD value, older adults are at a higher risk for fracture than younger adults.

A history of prior fracture increases the relative risk for subsequent fracture at these sites. The risk of vertebral fracture increases 4.4-fold after a vertebral fracture, the risk of wrist fracture increases 3.3-fold after a wrist fracture, and the risk of hip fracture increases 2.3-fold after a hip fracture. A previous fracture at one site will increase the risk of fracture at any other site by about 2- to 2.5-fold.

Unfortunately, although BMD is an important tool for assessing the risk of osteoporosis-related fractures, it does not capture all of the qualities of bone that may contribute to fracture risk. In a recent Australian study, half the burden of fragility fractures in the

continued

Table 3. Investigations to exclude secondary causes of osteoporosis

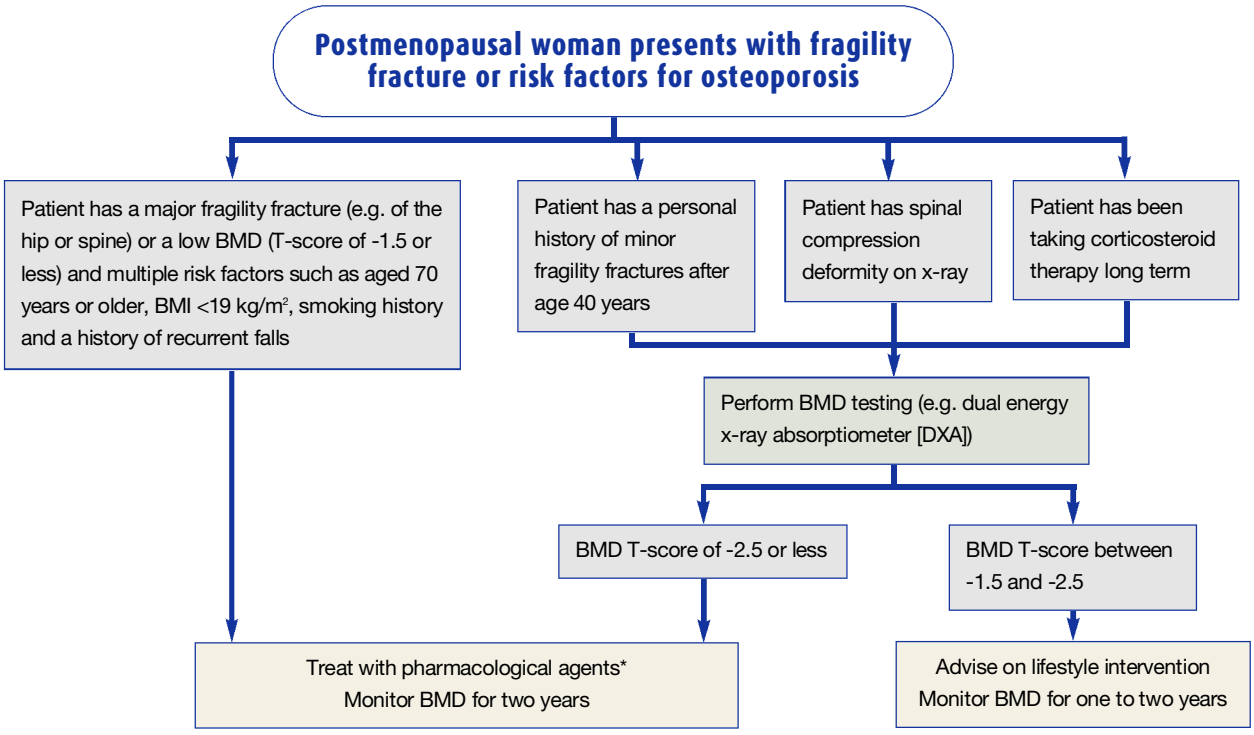
- Full blood count, erythrocyte sedimentation rate and protein electrophoresis to exclude myeloma and haematological disorders
- Serum chemistry (calcium, phosphorus, creatinine, liver functions)
- Serum 25-hydroxyvitamin D and parathyroid hormone to differentiate primary from secondary hyperparathyroidism and exclude vitamin D deficiency
- Thyroid stimulating hormone to exclude thyrotoxicosis
- Follicle stimulating hormone and oestradiol to differentiate primary from secondary hypogonadism
- 24-hour urinary calcium excretion to differentiate between familial hypocalciuric hypercalcaemia and hyperparathyroidism
- 24-hour urinary free cortisol to exclude Cushing's syndrome
- Anti-tissue transglutaminase antibody to exclude coeliac disease
- Bone turnover markers (CTx and NTx telopeptides of type 1 collagen) to measure the response of antiresorptive agents
- Bone marrow and trephine biopsy with tetracycline labelling to exclude malignancy or an infiltrative bone disorder and to semiquantitate bone mass, turnover and mineralisation rates

community occurred in women without densitometric evidence of osteoporosis.[17] Other diagnostic approaches (such as microcomputed tomography, magnetic resonance imaging and markers of bone turnover) may in the future help better the understanding of the relation between bone architecture and fracture risk. Until such tools are readily available, BMD testing combined with multiple risk factor assessment should be used to determine the global fracture risk in an individual and the need for antiosteoporotic therapies.

Clinical management

The gold standard of treatment in osteoporosis is to reduce fracture risk and improve outcomes in women at high risk. It is important to exclude secondary causes of osteoporosis before recommending a

An approach to managing postmenopausal women with or at risk of a fragility fracture



*Certain antiosteoporotic agents are rebatable on the PBS for postmenopausal women.

'healthy bone lifestyle' and/or the use of specific pharmacological therapies.[18]

Exclusion of secondary causes of osteoporosis

Most women with osteofragility fractures will suffer from postmenopausal osteoporosis and can be managed with appropriate antiosteoporotic agents. The 10 to 20% of women who have an underlying secondary cause need appropriate investigations (Table 3). They often present with a BMD Z-score of less than -2.0 (the Z-score is the number of standard deviations below the average BMD of age-matched healthy women). Treatment of their primary disorder (e.g. thyrotoxicosis, primary hyperparathyroidism or Cushing's syndrome) may yield significant increases in BMD, thereby reversing the process causing osteoporosis and reducing fracture risk. For example, spinal BMD can increase by as much as 20% in women with primary hyperparathyroidism treated by a successful parathyroidectomy.

Lifestyle intervention ('healthy bone lifestyle')

A 'healthy bone lifestyle' consists of an optimal amount of calcium (more than 1200 mg daily) and vitamin D_3 supplements (more than 800 IU daily, aiming for a serum 25-hydroxyvitamin D level of more than 50 to 70 nmol/L), weight-bearing exercises and avoidance of tobacco and alcohol. The use of external hip protectors should be considered in elderly institutionalised women, including those in nursing homes. These modalities slow bone loss and also reduce fracture rates in elderly women.

In a recent meta-analysis, calcium supplementation and calcium in combination with vitamin D were associated with a 12% reduction in fractures of all types (17 randomised trials, n = 52,625).[19] A systematic review also showed that vitamin D_3 supplementation (doses of 700 to 800 IU per day) was associated with a 26% reduction in hip fracture in adults aged 60 years and older (three randomised trials, n = 5572).[20] This was related to the positive effects of vitamin D_3 on the gut (increasing calcium absorption), bone (preventing secondary hyperparathyroidism and bone resorption) and muscle (reducing risk of falls). Vitamin D deficiency/insufficiency (serum 25-hydroxyvitamin D level below 50 nmol/L) is not uncommon in Australia and should be actively identified and treated. A 'healthy bone lifestyle' should be recommended as adjuvant therapy to all women receiving antiosteoporotic agents.

Pharmacological interventions

Various clinical guidelines for managing patients who have or are at risk for

Table 4. Fracture reduction with bisphosphonate therapy*,[23-25]

Intervention	Relative risk reduction (95% CI)	Number of trials (patients)	NNT†
Vertebral fracture (primary endpoint)			
Alendronate (5-40 mg)	48% (35-57)	8 (9360)	7-27
Ibandronate (2.5-20 mg)	62% (41-75)	1 (2946)	20
Risedronate (2.5-5 mg)	36% (23-46)	5 (2604)	9-20
Zoledronic acid (5 mg)	70% (62-76)	1 (7765)	13
Hip fracture (primary endpoint)			
Alendronate (5-40 mg)	39% (8-60)	8 (9360)	91
Ibandronate (2.5-20 mg)	No data	No data	No data
Risedronate (2.5-5 mg)	30% (10-40)	1 (9331)	91
Zoledronic acid (5 mg)	41% (17-58)	1 (7765)	91
Nonvertebral fracture (secondary endpoint)			
Alendronate (5-40 mg)	49% (31-62)	6 (3723)	24
Ibandronate (2.5-20 mg)	Nonsignificant data	1 (2946)	No data
Risedronate (2.5-5 mg)	27% (13-49)	7 (12,958)	31
Zoledronic acid (5 mg)	25% (13-36)	1 (7765)	37

* Data were not from head-to-head studies; † NNT = number needed to treat to prevent one osteoporotic fracture.

Table 5. Bisphosphonates: potencies and indications*

Bisphosphonate	Relative potency	Route	Indications and availability‡	Regimens	
				Osteoporosis treatment§	Other indications
Etidronate	1x	Oral	Etidronate alone: Paget's disease, heterotopic ossification	Not indicated for osteoporosis treatment or prevention	See full PI
			Etidronate plus calcium: Osteoporosis, prevention of high dose corticosteroid associated bone loss	Etidronate 400 mg daily for 2 weeks of every 3-monthly cycle; calcium carbonate 1.25 g daily for other 76 days. PBS-listed for established osteoporosis in patients with fracture due to minimal trauma	See full PI
Clodronate	10x	Oral	Tumour-induced hypercalcaemia, osteolytic lesions (breast cancer, multiple myeloma)	Not indicated for osteoporosis treatment or prevention	See full PI
Pamidronate	100x	IV	Tumour-induced hypercalcaemia, symptomatic Paget's disease, osteolytic metastases from breast cancer and advanced multiple myeloma	Not indicated for osteoporosis treatment or prevention	See full PI
Alendronate	1000x	Oral	Confirmed osteoporosis, prevention of osteoporosis in postmenopausal women and patients on long term corticosteroids, Paget's disease	70 mg once weekly. PBS-listed for osteoporosis in patients aged 70 years and older with confirmed osteoporosis and in patients with fracture due to minimal trauma	See full PI
Ibandronate	5000x	Oral	Metastatic bone disease from breast cancer (also intravenous infusion, but private hospital authority required). Infusion 3 mg/3 mL every three months is TGA approved for use in the treatment of postmenopausal osteoporosis but is not available	150 mg once monthly (off-label use). (This dose is registered overseas for osteoporosis treatment and prevention in postmenopausal women)	See full PI
Risedronate	5000x	Oral	Osteoporosis, prevention of osteoporosis due to long term corticosteroids, Paget's disease	35 mg once weekly. PBS-listed for osteoporosis in patients aged 70 years and older with confirmed osteoporosis and in patients with fracture due to minimal trauma, and for corticosteroid-induced osteoporosis	See full PI
Zoledronic acid	10,000x	IV	Solution: Osteoporosis in postmenopausal women, patients aged over 50 years with low trauma hip fracture; to increase BMD in men with osteoporosis and in patients on long term corticosteroids; prevention of corticosteroid-induced BMD	Single annual IV 5 mg infusion dose administered over 15 minutes. PBS-listed for osteoporosis in patients aged 70 years and older with confirmed osteoporosis and in patients with fracture due to minimal trauma, and for corticosteroid-induced osteoporosis	See full PI
			Injection concentrate: Tumour-induced hypercalcaemia, prevention of skeletal related events in advanced bone malignancy	Not indicated for osteoporosis treatment or prevention	

* This table has been prepared according to TGA guidelines. These agents may be used for different indications and at different dosages at the discretion of the prescribing physician.
† Relative potency by in vitro testing. ‡ As of 1 June 2010. § See full PI for each product.

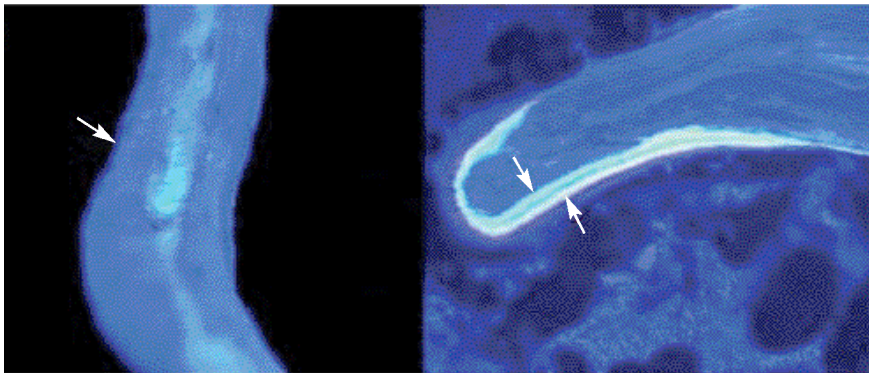
osteoporosis are available (see the flowchart based on PBS guidelines on page 8). The general agreement is that older adults with osteoporosis are candidates for treatment, but all guidelines recognise that some patients who do not have osteoporosis would benefit from treatment. There are no data to suggest that pharmacological agents will reduce the lifetime fracture risk in premenopausal women with no history of fracture and a BMD T-score of less than -3.0.

In Australia, specific pharmacological agents are rebatable on the PBS for postmenopausal women with osteoporosis. Women aged 70 years or older with a BMD T-score of -3.0 or less (primary prevention) and postmenopausal women with BMD T-score of -2.5 or less and a prior osteofragility fracture (secondary prevention) qualify for PBS rebate. These criteria are based on patients' absolute fracture risk and effectiveness of antiosteoporosis therapies. It has been calculated that for an agent to be cost effective, 10 to 20 women would need to be treated to prevent one vertebral fracture and 20 to 40 women to prevent one hip fracture.

The pharmacological therapies for osteoporosis are classified as antiresorptive (or antiresorptive; those agents that inhibit or slow the bone resorption phase of the bone remodelling cycle) and anabolic (those agents that stimulate new bone formation as demonstrated by increased double-tetracycline labelling on bone biopsy).[21]

Antiresorptive agents

Antiresorptive agents reduce vertebral fracture rates by 30 to 50%, increase spinal BMD by 4 to 8% and inhibit bone resorption by 60 to 80%, as confirmed by biochemical bone markers (Table 4).[22] These agents include bisphosphonates such as alendronate, risedronate, ibandronate and zoledronic acid , in addition to other drug classes such as hormone replacement therapy and selective oestrogen receptor agonists (e.g. raloxifene).



Figures 3a and b. a (left). Bone biopsy demonstrating only scant single tetracycline label (arrow) in keeping with oversuppression of bone turnover, taken from a patient with atypical fractures and receiving chronic alendronate therapy. b (right). Bone biopsy demonstrating normal double tetracycline labelling indicative of normal bone turnover (arrows), taken from a normal individual.

The bisphosphonates have differential effects on hip, vertebral and nonvertebral fracture reduction, according to their potency (Table 5). An annual infusion of zoledronic acid (5 mg), which is the most potent of the bisphosphonates, has recently been shown in a three-year randomised, placebo-controlled trial (n = 7736) to reduce vertebral fracture by 70% and hip fracture by 41% compared with controls.[23] The high potency of these agents also allows for simpler dosing regimens so that alendronate and risedronate can be administered as a single weekly oral dose and zoledronic acid as a single annual intravenous infusion. In a recent study of 2127 elderly patients, an annual infusion of zoledronic acid administered within three months of a hip fracture repair was associated with a 35% reduction in the rate of new clinical fractures and a 28% reduction in mortality compared with placebo.[26]

Bisphosphonates differ from other antiresorptive agents by their avid binding affinity to hydroxyapatite crystals in bone, resulting in long-term skeletal retention.[27] When given for protracted periods, large stores of the bisphosphonates are recycled in bone and result in marked suppression of bone turnover. Adynamic bone disease has recently been described in patients who receive alendronate for many years (Figure 3).[28] These patients present with paradoxical increases in bone fragility and atypical fractures (e.g. sacroiliac, femoral shaft and proximal femur fractures). Although this may present a possible long-term complication of chronic bisphosphonate therapies, more detailed studies are required.

Jaw osteonecrosis is another complication that may occur (incidence of 1 to 10%) in patients with malignant bone diseases who receive monthly intravenous infusions of pamidronate and zoledronic acid (see the box on page 12). It is rarely seen in osteoporotic patients treated with either alendronate or risedronate (incidence of 0.01 to 0.001%).[29]

The data on alendronate from the Fracture Intervention Trial Long-term Extension (FLEX) trial has made it possible to rationalise the duration of 'safe' therapies. In this study, patients who had been taking alendronate for a mean of five years were randomised to five more years of alendronate or five years of placebo. In patients who switched to placebo, mean BMD levels remained at or above pretreatment values, suggesting that this drug could be discontinued after five years of continuous therapy.[30a] This would allow patients a one- to two-year drug-free holiday (depending on their fracture risk)

continued

Jaw osteonecrosis and bisphosphonate therapy

- Patients with jaw osteonecrosis (Figure 4) have:
  - exposed bone in the maxilla and mandible
  - suppression of the bone remodelling cycle and inhibition of endothelial cell proliferation
  - poor healing and secondary infection that can lead to loss of teeth and segments of jaw bone.
- Risk factors for jaw osteonecrosis are systemic (e.g. myeloma, cancer, chemotherapy and comorbidities) and local disease (e.g. infection, trauma, tooth extraction).
- Jaw osteonecrosis is more common with intravenous than oral bisphosphonates. The withdrawal of these drugs has no effect on healing.

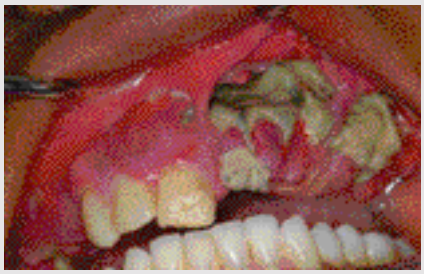


Figure 4. Jaw osteonecrosis.

before reassessment of their BMD, providing that they understand their osteoporosis is not cured and they are not lost to follow up. These data apply only to alendronate since other bisphosphonates have variable bone binding affinities. Lifestyle intervention should be maintained lifelong.

Denosumab, a monoclonal antibody directed against RANK ligand, is a new antiresorptive agent that has recently been approved by the TGA for the treatment of osteoporosis in postmenopausal women. It is administered as a twice-yearly subcutaneous injection. The Freedom Study, published in 2009, has shown that compared with placebo denosumab reduced the risk of new radiographic vertebral fracture, with a cumulative incidence of 2.3% in the denosumab group versus 7.2% in the placebo group (risk ratio, 0.32; 95% confidence interval [CI], 0.26 to 0.41; $p < 0.001$) – a relative decrease of 68%. It also showed that denosumab reduced the risk of hip fracture, with a cumulative incidence of 0.7% in the denosumab group versus 1.2% in the placebo group (hazard ration, 0.60; 95% CI, 0.37 to 0.97; $p = 0.04$ – a relative decrease of 40%.[30b] Atypical fractures have been reported after treatment with denosumab, and this drug also has the potential for contributing to the occurrence of osteonecrosis of the jaw.[30c]

Other new antiresorptive agents aimed at various receptors are under development. Theses include enzymes (cathepsin K inhibitor) and integral parts of the osteoclast ($\alpha v\beta 3$ integrin inhibitor). It is anticipated that these will have similar clinical efficacies with various side effects.

Anabolic agents

Anabolic agents stimulate bone formation at the cellular, biochemical and molecular level leading to a net gain in bone. Their main action is to increase the number of osteoblast precursors, stimulating the differentiation into mature osteoblasts and enhancing function and survival.[31] The agents that have been studied include bone morphogenetic proteins, agonists of the Wnt-signalling pathway, insulin growth factor-1, parathyroid hormone (PTH) and PTH-related peptide. The most extensively studied form of PTH in osteoporosis is the PTH (1-34) fragment, teriparatide.

In a study of postmenopausal women with osteoporosis (n=1637), 20 or 40 μg daily of PTH (1-34) by subcutaneous injection reduced spinal fractures by 65% and nonvertebral fractures by 54% over 21 months.[32] Teriparatide is listed on the PBS (authority required) for patients with severe osteoporosis (BMD T-score -3.0 or less and two or more fractures due to minimal trauma) who continue to have a fracture despite optimal antiresorptive therapies. PTH therapy is prescribed for a total of 12 to 18 months only and is followed by antiresorptive therapies to prevent rapid loss of the bone accrued (evidence from clinical trials suggests sequential and not concurrent therapy with antiresorptive agents).

Strontium ranelate is a novel agent with a dual mechanism of action and is given orally at a recommended dose of 2 g at bedtime. It has been shown to stimulate new bone formation, probably by recruiting osteoblast precursors, as well as decrease bone resorption. The Spinal Osteoporosis Therapeutic Intervention study (SOTI; n=1649) and the Treatment of Peripheral Osteoporosis Study (TROPOS; n=5091) demonstrated a 41% reduction in vertebral and 16% reduction in nonvertebral fractures over three years compared with controls.[33,34] Moreover, strontium ranelate reduced hip fractures by 36% in a high-risk subgroup (BMD T-score of -3.0 or less and age over 74 years).[33] Strontium ranelate is listed on the PBS (authority required) for the primary prevention of fractures in women aged 70 years and older and for the treatment of osteoporosis in postmenopausal women with a fracture due to minimal trauma.

Therapeutic adherence

Adherence to treatment among individuals with osteoporosis is currently suboptimal, with at least 50% of women discontinuing their antiosteoporotic medications within the first year.[35] Dosing frequency and therapy preferences are important factors for patient adherence. Numerous studies have shown that reducing bisphosphonate dosing frequency from daily to weekly results in improved adherence rates. Unfortunately, the level

of adherence in clinical practice still remains low, resulting in suboptimal clinical benefit, increased fracture-related endpoints and increased healthcare costs.

In a recent study (n=38,000) over a 24-month period, postmenopausal women who complied with therapy (defined as a medication possession ratio of more than 80%) demonstrated 26% lower fractures rates than noncompliant patients.[36] Improving drug tolerability, establishing patient compliance programs and offering a more convenient and simpler regimen that complements a patient's lifestyle might encourage women to continue therapies for longer periods of time and enhance therapy outcomes.

Fracture risk algorithm – the future

In a collaborative project, the WHO has developed a model for estimating the 10-year absolute fracture risk for an individual. This utilises multiple risk factors for hip fracture that have been validated in 12 international cohorts (60,000 men and women). The risk factors include age, gender, hip BMD, prior fragility fracture after the age of 50 years, low BMI, use of corticosteroids, secondary osteoporosis, parental history of hip fracture, current cigarette smoking and an alcohol intake of more than two drinks per day. The FRAX calculator is now available on the internet and is used in some centres (www. sheffield.ac.uk/FRAX).

Although not routinely used in clinical practice, risk-factor stratification will eventually predominate and affect treatment thresholds. Recommendations for therapy will shift from young postmenopausal women at low risk (primarily healthy women with osteopenia) towards older women without osteoporosis who are at moderate or high risk for osteoporosis on the basis of non-BMD risk factors.

The GP's perspective

GPs often address issues regarding menopause and ageing in women. A simple handout questionnaire (see the International Osteoporosis Foundation one-minute osteoporosis risk test, available at www.iofbonehealth.org) enquiring about risk factors for osteofragility fractures may identify women at high risk of osteoporosis and who may be candidates for BMD testing. Pharmacological agents such as alendronate, risedronate, raloxifene, strontium ranelate and zoledronic acid should be offered to women aged 70 years or over with a BMD T-score of -3.0 or less and to postmenopausal women with a BMD T-score of -2.5 or less and a prior osteofragility fracture. Adherence to long-term therapy in these patients is usually poor, and support groups and patient compliance programs should be encouraged. A progress BMD test is advisable two years after commencing therapy to assess drug efficacy.

Women with secondary causes of osteoporosis, those who continue to sustain fractures, cannot tolerate or do not respond to antiresorptive agents or those aged 70 years or less with severe osteoporosis (BMD T-score of -3.0 or less) may require specialist referral for further evaluation and treatment. All women should be encouraged to follow a 'healthy bone lifestyle'. Some of these women may be candidates for treatment with PTH according to PBS criteria. Pharmacological agents for osteoporosis should not be prescribed indefinitely in view of the lack of long-term safety data. Clinical reassessment is usually indicated after about five years of continuous therapy.

The patient handout that accompanies this article outlines risk factors for osteoporosis in postmenopausal women and describes how patients can follow a 'healthy bone lifestyle' to decrease their risk of fracture (see pages 15 and 16). Patients may also be interested in handout sheets on exercising to help prevent osteoporotic fractures that were published in the February and March 2007 issues of *Medicine Today*. MT

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DECLARATION OF INTEREST: Associate Professor Diamond is a scientific advisor to Eli Lilly, Merck Sharp & Dohme, Novartis, Roche, Sanofi Aventis and Servier, but does not receive financial remuneration. Honoraria for GP lectures and travel grants to attend local and international bone meetings have been received from all the above companies.

Osteoporosis and bone fragility fractures in women

This handout provides information on the different factors that increase fracture risk in postmenopausal women and how this risk can be reduced.

Prepared by Professor Terry Diamond, Associate Professor in Endocrinology at the University of New South Wales and Senior Endocrinologist at St George Hospital, and Dr Terry Golombik, Research Fellow at St George Hospital, Sydney, NSW.

What is a bone fragility fracture?

A bone fragility fracture is a fracture that results from the combination of reduced bone strength and a fall or minimal trauma. Bone strength becomes reduced when the density of bone (known as the bone mineral density or BMD) is low and the bone quality is altered.

The bones affected by these fractures are usually those of the hip, spine and wrist. Fractures usually occur as a result of a fall but can be caused by a simple movement or even a sneeze or a cough.

How can I assess my fracture risk?

Your risk of having a bone fragility fracture can be assessed by your doctor who will carry out a risk-factor assessment and refer you for further testing, if necessary.

What is bone mineral density and how is it measured?

BMD is a measure of the amount of bone at a particular site, such as the hip or spine. The recorded value is compared with that of a healthy young woman without osteoporosis. The difference in BMD as it deviates from normal is expressed in T-score values. We rely on BMD to quantitate bone strength because BMD is a good predictor of fracture risk in the elderly.

The machine used to measure BMD is called a dual energy x-ray absorptiometer or DXA. It is similar to an x-ray machine and there is minimal radiation exposure.

What is an abnormal BMD reading?

As fracture risk increases, BMD declines. We define osteoporosis as a BMD T-score of -2.5 or less. However, fractures can also occur in women with higher T-scores (i.e. between -1 and -2.5) and when a number of other risk factors are present.

What other risk factors increase the likelihood of bone fragility fractures?

Other risk factors that can increase fracture risk are listed in the Table on the next page. Some of these factors are fixed (such as age) and others can be modified (such as poor nutrition, smoking, a history of falls). The more risk factors a woman has, the higher is her risk of fracture.

IMAGE ZOO/IMAGES.COM/GETTY IMAGES

A healthy bone lifestyle includes an adequate calcium intake (through diet or supplements), an adequate vitamin D intake (through diet, supplements and/or sun exposure), weight-bearing exercise, and avoidance of alcohol and tobacco.

COPY FOR YOUR PATIENTS

Table. Examples of risk factors for bone fragility fractures in postmenopausal women*

Modifiable risk factors	Fixed risk factors
Alcohol consumption	Age
Smoking	Female gender
Low body mass index	Previous fracture
Poor nutrition	Family history of fracture
Eating disorders	Race/ethnicity
Low dietary calcium intake	Long term use of corticosteroid therapy
Vitamin D deficiency	Menopause/hysterectomy
Frequent falls	Rheumatoid arthritis
Insufficient exercise	

* Based on data from the International Osteoporosis Foundation (http://www.iofbonehealth.org/patients-public/about-osteoporosis/symptoms-risk-factors.html).

How can I reduce my risk of bone fragility fractures?

You can reduce your risk of having a bone fragility fracture by adopting a 'healthy bone lifestyle'. You should also consult with your doctor to determine whether other simple lifestyle interventions or pharmacological agents are required.

A healthy bone lifestyle includes:

- taking a calcium supplement or increasing dietary calcium intake by drinking a glass of milk and eating a tub of yogurt or block of cheese every day. A total of 1500 to 2000 mg of calcium is required each day
- taking a vitamin D_3 supplement (more than 800 IU daily) or having 10 to 15 minutes of sun exposure on the legs, arms and face, four to five times per week (avoiding the midday heat)
- performing weight-bearing exercise (e.g. brisk walking, hiking, stair climbing, jogging and weight lifting)
- avoiding tobacco and alcohol
- taking part in a falls prevention program if you are at an increased risk of falling.

What happens if I don't take treatment?

Hip fracture is the most catastrophic outcome of a bone fragility fracture, and can result in chronic pain, disability and increased mortality. Women who suffer spinal fractures may develop chronic spinal pain, recurrent chest infections and premature death.

The best course of action is to prevent bone fragility fractures by good medicine and a healthy bone lifestyle. However, it is never too late to treat. MT

Osteoporosis support services

Osteoporosis Australia
www.osteoporosis.org.au
Tel: (02) 9518 8140

Osteoporosis Sydney Support Group
www.osteoporosis.com.au
Tel: (02) 9113 2649

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MedicineToday PEER REVIEWED ARTICLE

MedicineToday 2008; 9(5): 48-62
Updated June 2010

Secondary causes of osteoporosis in women

diagnoses not to be missed

Underlying secondary causes of osteoporosis should be sought and treated before specific antiosteoporotic therapies are initiated.

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Postmenopausal osteoporosis is common, occurring in half of all women aged above 60 years. However, 20 to 40% of these women will also have some osteoporosis secondary to a condition other than oestrogen deficiency due to ovarian failure at menopause or to a medication they are taking.[1,2] Actively seeking out and treating these other causes may not only prevent or partially reverse the osteoporosis, but may also reduce fracture risk.

Disorders in addition to ovarian failure at menopause may not only cause premature or accelerated bone loss and a decrease in bone mineral density (BMD) and quality, but may also be accompanied by muscle weakness and wasting (sarcopenia).[3] The reduction in bone strength in secondary osteoporosis is often more marked than that seen in primary postmenopausal osteoporosis.[4]

Osteoporotic fractures result in pain, loss of height, deformity and loss of independence (with premature admission of patients to aged care facilities), and predispose patients to serious complications such as pulmonary embolus and pneumonia. Following a single fracture, the risk of further fracture is increased, resulting in the 'fracture cascade'. Mortality after osteoporotic fracture is increased two- to threefold compared with that of the normal population, and may be as high as eight- to 10-fold if the fracture is due to osteoporosis secondary to underlying disease.[5]

Osteoporosis affects some 300,000 Australian women, costing the community $1.6 billion. The number of these women who have untreated secondary causes, some of which would be partly or completely reversible, is unknown. Appropriate management of these women could, therefore, potentially reduce this cost burden.

IN SUMMARY

- **Secondary osteoporosis is characterised by increased skeletal fragility and fracture risk over and above that seen with menopause.**
- **The qualitative changes seen in osteoporosis associated with secondary disorders result in fragility fractures occurring at higher bone mineral density (BMD) T-scores (-1.5 or less) than expected.**
- **Poor bone accrual during puberty, bone loss at menopause and changes seen with advanced ageing are compounded by secondary osteoporosis.**
- **Specific medications (aromatase inhibitors, corticosteroids, antiepileptic drugs, selective serotonin reuptake inhibitors, glitazones) used in medical conditions may interfere with normal bone remodelling and have detrimental effects on the skeleton.**
- **The treating physician should consider, seek out and treat any underlying secondary cause of osteoporosis before recommending specific antiosteoporotic pharmacological agents.**

continued

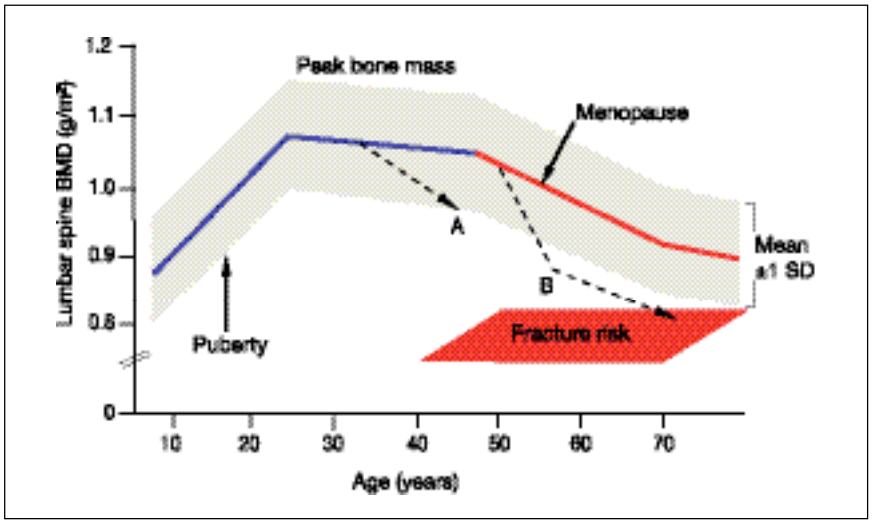


Figure 1. Bone density changes in puberty and menopause and with ageing. Peak bone mass is acquired through puberty and reaches a maximum at about 25 to 30 years of age (solid blue line). Rapid bone loss occurs at the menopause and then slows (solid red line). Fracture risk is increased with BMD T-score -2.5 or less (represented by the red-shaded rhomboid). The broken black lines represent rapid bone loss occurring with secondary medical disorders such as premature menopause (A) and high-dose corticosteroid therapy (B).

This review discusses the pathogenesis and management of secondary osteoporosis in women. Management of primary postmenopausal osteoporosis has been discussed in a previous review (published in the January 2008 issue of *Medicine Today;* pages 4 to 14 of this supplement).[6] Men also suffer from secondary osteoporosis, and the discussion of secondary osteoporosis here generally applies also to men.

Differential patterns of bone loss

In women, peak bone mass is achieved at about 25 to 30 years of age (at age 30 to 35 years for cortical bone, and earlier for trabecular bone). From age 40 years onwards, bone loss is continuous, at a baseline rate of 0.3 to 0.5% per year. This increases to 4 to 6% per year in the perimenopausal period, and then decreases to 1 to 2% after the age of 70 years (Figure 1). Osteoporosis results from any combination of failure to achieve maximal peak bone mass, age-related changes (postmenopausal osteoporosis and senile osteoporosis) and secondary causes.[7]

The restricted accrual of bone through puberty and adolescence may result in a low peak bone mass. This can occur with primary genetic disorders (familial syndromes, osteogenesis imperfecta and collagen disorders), chronic protein and calorie malnutrition (eating disorders), calcium and vitamin D deficiency (coeliac disease and malabsorption syndromes) and hypo-oestrogenaemia (primary or secondary premature ovarian failure).[8] Premature menopause causes rapid bone loss similar in magnitude to natural menopause but as it occurs earlier it results in longer lifetime exposure to fracture risk.[9] Management of premenopausal osteoporosis due to low peak bone mass is beyond the scope of this review.

Histomorphometry

Bone formation and resorption is normally a coupled process. However, the process becomes disrupted by oestrogen withdrawal at the menopause or by some secondary disorders and medications,[10] leading to high or low bone turnover states and net loss of bone (Figure 2).

High bone turnover occurs when increased osteoclastic activity causes bone resorption to exceed bone formation. Low bone turnover occurs when osteoblast suppression causes decreased bone formation but bone resorption continues at the normal rate.

The histological characteristics of osteoporosis include decreased cortical thickness and decreased number and size of trabeculae with preservation of osteoid seams. Oestrogen withdrawal causes high bone turnover with increased remodelling units and increased bone resorption and formation, leading to net endocortical and trabecular bone loss: 40 to 50% of the bone mass is cumulatively lost, predominantly from the spine, hip and distal radius.[9]

Some medications and some disorders other than oestrogen deficiency can result in high or low bone turnover states and affect cortical and trabecular bone disproportionately (Table 1).[11,12] Osteoclast activation and differentiation occurs with elevated levels of hormones such as thyroxine (hyperthyroidism) and parathyroid hormone (hyperparathyroidism), and with elevated levels of cytokines such as RANK-ligand (elevated in cancers and inflammatory arthropathies).[13] This leads to uncoupling of bone turnover with accelerated bone resorption and formation but the resorption exceeding the formation, eroding medullary cavities and perforating trabecular plates (i.e. high bone turnover). When chronic, this results in profound osteoporosis. Osteoblast suppression occurs with coeliac disease, hepatobiliary disorders and chronic corticosteroid excess, resulting in low bone turnover, trabecular plate thinning and osteofragility.

In myeloma there is a very high rate of resorption and the osteoblasts are directly inhibited, leading to a more dramatic uncoupling of bone turnover than in other conditions.

Thyroxine excess directly stimulates high bone turnover, aromatase inhibitors cause profound oestrogen deficiency with high bone turnover, high dose corticosteroids excess causes predominantly high bone turnover, while chronic low dose corticosteroid excess causes predominantly low bone turnover (Table 1).

Differentiating primary postmenopausal osteoporosis from secondary causes

Secondary causes for osteoporosis should be suspected in women aged over 40 years who suffer a low trauma osteofragility fracture (clinical or asymptomatic morphometric vertebral fracture) and those with a BMD Z-score of less than -2.0.[6,14] (The Z-score is the number of standard deviations below the average BMD of age-matched healthy women.) The fracture site, severity of osteoporosis and presence of risk factors (certain endocrine and other diseases, nutritional disorders and medications) may help differentiate these women from those with primary postmenopausal osteoporosis. The characteristic features of secondary osteoporosis due to various causes are given in Table 1.

Age, however, remains the major BMD-independent risk factor for fracture, and many women with secondary osteoporosis may also have an element of primary osteoporosis, especially with life expectancy now exceeding 80 years. Also, some of the newer therapies that prolong survival also accelerate bone loss, for instance, aromatase inhibitors in breast cancer.

A thorough clinical examination supported by detailed laboratory investigations is required prior to recommending treatment for all patients with osteoporosis.

Fracture type

Vertebral fractures make up approximately 46% of postmenopausal osteoporotic fractures. Other common fracture sites are the hip (16%), wrist (distal radius or Colles fracture; 16%), and proximal humerus, distal tibia and pelvis (22%).[14]

Women with secondary causes of osteoporosis tend to have fractures in specific sites: for instance, peripheral and vertebral fractures in primary hyperparathyroidism,[15,16] hip fractures in hyperthyroidism,[17-19] recurrent vertebral fractures in hypercortisolism[20,21] and myeloma,[22] and hip and peripheral fractures in vitamin D deficiency.[23]

The relative risk of refracture in postmenopausal women is 3.3 for Colles fractures, 2.3 for hip fractures and 4.4 for vertebral fractures.[6] These figures may be increased by four- to sixfold or more in women with hypercortisolism

Bone turnover states

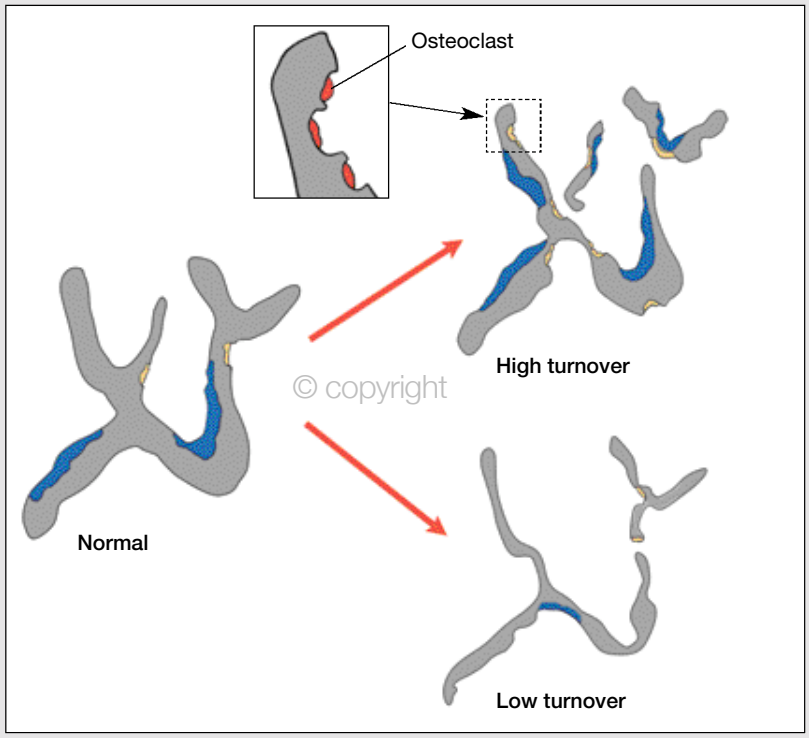


Figure 2. Schematic representation of normal, high and low bone turnover. Trabecular bone is shaded grey, areas of active bone formation blue and areas of active bone resorption beige.

In a high bone turnover state, osteoclastogenesis occurs with an increase in osteoclast numbers and increased resorption surfaces. There is also increased osteoid formation by osteoblasts, which on mineralisation will become new bone. The number of remodelling bone units is increased, but formation cannot keep up with resorption and hence a net bone deficit occurs. Trabecular plates are often perforated, leading to disruption of the bone architecture.

In a low bone turnover state, normal to low bone resorption occurs, but there is marked suppression of bone formation and reduction in the numbers of bone remodelling units, leading to net bone loss. This results in very few, narrow and scant osteoid seams, trabecular plate thinning rather than perforation and, if administered, reduced tetracycline double labelling (which in indicative of very low bone formation).

continued

Table 1. Characteristics of secondary osteoporosis due to various causes

Disorder	Bone mineral density	Bone turnover	Fracture risk	Most common fracture site
Oestrogen deficiency				
Oestrogen deficiency other than primary ovarian failure	↓↓	↑↑	↑	Distal radius (Colles), vertebrae
Endocrine disorders				
Cushing's syndrome	↓↓↓	↓↓	↑↑↑	Vertebrae
Primary hyperparathyroidism	↓↓	↑↑	↑	Peripheral sites, vertebrae
Hyperthyroidism	↓	↑	↑	Hip
Gastrointestinal and hepatobiliary disorders				
Coeliac disease	↓	↓	↑	Probably Colles
Gastrectomy	↓↓	↑↑↑	↑↑	Vertebrae
Inflammatory bowel syndromes	↓	↑/↓	↑	Vertebrae
Chronic liver disease	↓	↓	↑	Vertebrae
Pernicious anaemia				Vertebrae
Toxins and drugs				
Alcohol excess	↓	↓	↑	Peripheral sites
Glitazones	↓↓	↓	↑	Peripheral sites
Antiepileptic agents	↓	↓	↑	Peripheral sites
Selective serotonin reuptake inhibitors	↓ ↓	↑/↓ ↓	↑ ↑	Hip
Corticosteroid excess				Vertebrae
Aromatase inhibitors	↓↓↓	↓↓	↑↑	Peripheral sites
Thyroxine excess	↓↓		↑↑	Hip
Haematological and bone marrow disorders				
Myeloma and monoclonal gammopathy of undetermined significance	↓ ↓↓	↑↑ ↑	↑ ↑↑	Vertebrae
Systemic mastocytosis		↓		Vertebrae
Other conditions				
Post-transplantation				Vertebrae, peripheral sites

or myeloma.[21] The increased absolute refracture risk remains elevated for up to 10 years, unless secondary disorders are reversed or specific antiosteoporotic therapies are initiated.

BMD, bone quality and fracture risk

Fracture risk is related to BMD and bone quality.[14] In women with secondary osteoporosis, changes in bone quality are often impressive due to dramatic alterations in micro- and macrotrabecular bone patterns that are reflected in changes in markers of bone turnover. These women are more likely to sustain fractures at higher BMD thresholds (T-score of -1.5 or less) than

Table 2. Investigations to identify secondary causes of osteoporosis

Full blood count, erythrocyte sedimentation rate and protein electrophoresis

- Required to exclude myeloma and haematological disorders. Bone marrow aspirate and trephine biopsy required for definitive diagnosis.

Serum chemistry (calcium, phosphate, creatinine, liver functions)

- Deranged liver enzyme levels ('transaminitis') suggest alcohol excess, while a cholestatic pattern may indicate primary biliary cirrhosis.

Serum 25-hydroxyvitamin D and parathyroid hormone (PTH)

- A low serum 25-hydroxyvitamin D level (< 50 nmol/L) indicates vitamin D deficiency (a common cause of secondary hyperparathyroidism). An elevated serum calcium level in the presence of a nonsuppressed serum PTH (a normal or high level) suggests primary hyperparathyroidism or familial hypocalciuric hypercalcaemia.

Urinary calcium excretion (24-hour)

- Required to differentiate between familial hypocalciuric hypercalcaemia (FHH) and primary hyperparathyroidism (PHPT) (is reduced in FHH and elevated in PHPT).

Serum vitamin B_{12}

- A reduced serum vitamin B_{12} level suggests pernicious anaemia and/or small bowel disorders.

Thyroid stimulating hormone (TSH)

- A reduced serum TSH level suggests hyperthyroidism; may be associated with normal or elevated serum free thyroxine (T4).

Follicle stimulating hormone (FSH) and oestradiol

- In the setting of a low serum oestradiol level, an elevated serum FSH level suggests primary gonadal failure (menopause) and a low serum FSH level suggests secondary gonadal failure (hypothalamic-pituitary disorder). Causes of secondary gonadal failure may be functional (eating disorder, over-exercise) or structural (pituitary tumours).

Urinary free cortisol (24-hour)

- An elevated urinary cortisol level suggests ACTH-dependent disease (Cushing's disease – pituitary tumour) or ACTH-independent disease (Cushing's syndrome – adrenal or other tumour). Dexamethasone suppression testing required for differentiating between these disorders.

Anti-tissue transglutaminase and antiendomyseal antibodies

- Elevated levels suggest coeliac disease; a small bowel biopsy may be required for definitive diagnosis.

Bone turnover markers (C-terminal and N-terminal telopeptides of type 1 collagen)

- Elevated levels indicate osteoporosis with high bone turnover. Levels normalise with effective treatment of causes of secondary osteoporosis. Also used to measure responses to treatment with antiresorptive agents (reduced levels indicating response).

Bone imaging with technetium-99 radionucleide scanning, computed tomography and magnetic resonance imaging

- Required to distinguish between acute and chronic fractures and between simple osteoporotic and infiltrative or malignant fractures.

Bone marrow trephine biopsy or bone biopsy with double tetracycline labelling

- The former test is the gold standard for excluding malignancy or infiltrative bone disorders; the latter may be used to quantitate bone mass, turnover and mineralisation rates.

women with only postmenopausal osteoporosis (T-score of -2.5 or less).[24] (The T-score is the number of standard deviations below the average BMD of a young, healthy adult of the same sex.) Fracture rates in corticosteroid users are about sixfold higher than in nonusers.[24]

Changes in BMD correlate with disease activity and affect different bone sites disproportionately.[25] For instance, thyroxine levels in thyrotoxicosis correlate with lumbar spine bone loss, parathyroid hormone levels in primary hyperparathyroidism correlate with forearm bone loss, and C-reactive protein level and erythrocyte sedimentation rate in inflammatory bowel and joint diseases correlate with femoral neck bone loss. Treatment of the underlying primary disorder may prevent or partly reverse the negative trends in BMD.

Investigations

Not all women will manifest classic clinical signs of a medical disorder that may cause secondary osteoporosis. Many instead have silent or subclinical disease and present with either a fracture or densitometric evidence of osteoporosis. Women presenting this way may have primary or secondary osteoporosis and require detailed laboratory investigations to exclude secondary causes before treatment of the osteoporosis is considered.[1,2,9]

Decisions to perform any of the tests listed in Table 2 should be based on an increased likelihood of individual patients having these disorders as determined from the history and examination.

Management of secondary osteoporosis

The pharmacological therapies for osteoporosis are classified as antiresorptive (those agents that inhibit or slow the bone resorption phase of the bone remodelling cycle) and anabolic (those agents that stimulate new bone formation as demonstrated by increased double-tetracycline labelling on bone biopsy). Antiresorptive agents include the bisphosphonates, hormone replacement therapy and raloxifene (a selective oestrogen receptor agonist). Anabolic agents include teriparatide (a recombinant human parathyroid hormone) and strontium ranelate.

Specific treatment of the underlying disorder causing osteoporosis in a woman presenting with secondary osteoporosis may result in bone recovery without the need for additional antiosteoporotic therapies. However, antiresorptive agents such as the bisphosphonates may be beneficial in women with a variety of endocrine disorders (hyperthyroidism, primary hyperparathyroidism and hypercortisolism),[26-28] oncological disorders (breast cancer and myeloma)[22,29,30] and inflammatory disorders (rheumatoid arthritis and inflammatory bowel disease),[31a] as well as in those with drug-induced bone loss (corticosteroids and aromatase inhibitors).[28-30]

Denosumab, a monoclonal antibody directed against RANK ligand, is a new antiresorptive agent that has recently been approved by the TGA for the treatment of osteoporosis in postmenopausal women. Trials in progress on the use of denosumab for the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma have shown that subcutaneous denosumab 120 mg every four weeks is very similar to that of intravenous zoledronic acid 4 g every four weeks in terms of delaying the time to first skeletal-related event.[31b,31c]

These antiresorptive agents act by supressing bone turnover (through the inhibition of osteoclasts, thereby reducing bone resorption) and increasing BMD. Possible long-term complications of marked suppression of bone turnover by bisphosphonates and denosumab include atypical fractures and, rarely, osteonecrosis of the jaw.[31c]

The mechanism by which bisphosphonates are effective in preventing corticosteroid-induced bone loss remains poorly understood. These agents are beneficial in high bone turnover, yet corticosteroid-induced disease is predominantly a low bone turnover state. In clinical practice, antiresorptive agents are used for all osteoporosis disorders irrespective of bone turnover, and appear to be more beneficial in high turnover states.

Anabolic agents like recombinant human parathyroid hormone (PTH) have only recently become available; PTH is superior to alendronate in corticosteroid excess.

The suggested BMD T-score for recommending bisphosphonates in women who have secondary osteoporosis may be higher than that for primary postmenopausal osteoporosis (T-score -1.5 or less, as compared with -2.5 or less), and is based on fracture risk and BMD threshold values.

TGA-approved indications and PBS reimbursement of therapies

Bisphosphonates

The oral bisphosphonates alendronate and risedronate and the intravenous bisphosphonate zoledronic acid (5 mg once-yearly) are PBS listed for the treatment of osteoporosis in:[32]

- women and men aged 70 years or older with BMD T-score of -3.0 or less (primary prevention)
- women and men with a prior osteofragility fracture (secondary prevention).

Risedronate and zoledronic acid are also PBS listed for corticosteroid-induced osteoporosis.

Ibandronate injection and tablets are PBS listed for metastatic bone disease in patients with breast cancer but are not TGA approved for osteoporosis. (Oral ibandronate 150 mg once-monthly is, however, registered overseas for osteoporosis treatment and prevention of postmenopausal women.)

The oral bisphosphonate clodronate and the intravenous bisphosphonate pamidronate are not TGA approved for osteoporosis treatment or prevention. Pamidronate and the injection concentrate formulation of zoledronic acid are restricted on the PBS for hypercalcaemia of malignancy or skeletal related events. Use of agents outside the TGA-approved indications is based on individual doctor and patient decisions.

Raloxifene

Raloxifene is listed on the PBS for the treatment of osteoporosis in postmenopausal women with a prior osteofragility fracture (secondary prevention).[32]

Teriparatide

Teriparatide is listed on the PBS (authority required) for patients with severe osteoporosis (BMD T-score -3.0 or less and two or more fractures due to minimal trauma) who continue to have a fracture despite optimal antiresorptive therapies. It is also TGA approved for use in patients with established osteoporosis who are at high risk of fractures.

Strontium ranelate

Strontium ranelate is listed on the PBS for the treatment of osteoporosis in:[32]

- women aged 70 years or older with BMD T-score of -3.0 or less (primary prevention)
- postmenopausal women with a prior osteofragility fracture (secondary prevention).

Strontium ranelate is not indicated for the treatment of secondary causes of osteoporosis, including premenopausal osteoporosis, as there are no published data in this cohort.

Breast cancer

Breast cancer is a common disorder affecting 10 to 15% of postmenopausal women. Advances in treatment have resulted in mean 10-year survival rates of more than 80%. Adjuvant treatment with the aromatase inhibitors anastrozole, letrozole and exemestane significantly improves survival and reduces disease recurrence rates.

Osteoporosis and fragility fractures commonly occur in women with breast cancer, because of longer survival rates (increasing age) and the use of aromatase inhibitor therapies.[29,30] Results from the Women's Health Initiative Observational Study (WHI-OS) demonstrated the risk of vertebral fracture was 4.7-fold higher in postmenopausal women with newly diagnosed breast cancer and 1.31 times higher in breast cancer survivors than in age-matched healthy women.[33]

Aromatase inhibitors act by suppressing normal endogenous conversion of androgens to oestrogen in peripheral tissues. The resultant hypo-oestrogenaemia causes increased osteoclast activity and high bone turnover, with a 40 to 60% rise in bone turnover markers. In the Arimidex, Tamoxifen, Alone or in Combination (ATAC) study (n=9366) anastrozole administered to postmenopausal women with breast cancer resulted in 6 to 8% absolute decreases in BMD over two years and an 11% increase in absolute fracture rates (48% increase in relative risk) over five years.[34] Similar increases in fracture rates have been reported in studies using letrozole and examestane.[29]

Recent data have shown the beneficial effects of bisphosphonates in postmenopausal women with breast cancer with and without metastatic disease. In the former, intravenous bisphosphonates potentially reduce the risk of aromatase inhibitor-induced bone loss and onset of osteoporosis, skeletal-related events (hypercalcaemia, pathological fractures, need for radiation therapy or orthopaedic surgery, and spinal fractures) and death.[35] In three parallel studies (Zometa, Femara and Adjuvant Synergy Trials, n=2194) zoledronic acid 4 mg intravenous infusion every six months over three years normalised bone turnover markers in all women, prevented aromatase-induced bone loss and increased BMD (by 5 to 7% in the lumbar spine and 3 to 5% in the hip) compared with placebo.[36] Currently, there are no studies demonstrating significant antifracture efficacy in this cohort, predominantly due to the low fracture ascertainment and short follow up. Although there are no studies demonstrating the benefits of oral bisphosphonates (alendronate or risedronate) in this setting, there is no reason to believe they will be ineffective. In the adjuvant setting, oral clodronate and intravenous ibandronate, pamidronate and zoledronic acid have been shown to be very effective in reducing the risk of developing skeletal-related events (by approximately 20 to 40%) and death (by 15 to 40%).[35a]

Denosumab has been shown to reduce the risk of skeletal-related events in women with breast cancer and bone metastases.[35b]

The detrimental skeletal effects in postmenopausal women with breast cancer receiving aromatase inhibitor therapies has led to the development of guidelines by the American Society of Clinical Oncology to identify high risk women.[37] Included in these guidelines are:

- the recommending of baseline BMD and supplementation with optimal oral calcium and vitamin D for all women, and
- the need to consider bisphosphonate therapies for women with established osteoporosis and BMD T-scores of -2.0 or less and, as 82% of women who suffered fractures were not osteoporotic on BMD criteria (National Osteoporosis Risk Assessment[38]), those with BMD T-scores of -1.5 or less and an additional risk factor. Risk factors include age 65 years and older, BMI 20 kg/m^2 or less, family history of hip fracture, personal history of fragility fracture after age 50 years, oral corticosteroid use for more than six months and a history of smoking.

In Australia, BMD measurements are reimbursable on Medicare for women with breast cancer receiving aromatase inhibitors unless they have premature menopause.

Corticosteroid excess (exogenous and endogenous)

Chronic corticosteroid therapy and Cushing's syndrome (ACTH-dependent or independent disease) are common causes of osteoporosis, especially in postmenopausal women.[20,21,39] Loss of collagen tissue with thinning of skin, ecchymoses, abdominal striae and buffalo hump are the classic signs of chronic corticosteroid exposure that may be associated with osteoporotic fractures, most commonly of the vertebrae.

Rapid loss of 5 to 20% of trabecular bone occurs within the first six to 12 months of exposure to corticosteroids. The loss then decreases but is ongoing, even with chronic low dose therapies. A strong inverse relation is seen between cumulative corticosteroid dose and BMD.[21]

Corticosteroid use almost completely suppresses bone formation through inhibition of osteoblastogenesis and the causing of premature osteoblast cell death (apoptosis). Corticosteroids also cause malabsorption of calcium in both the gut and renal tubule, and directly or indirectly activate osteoclastic bone resorption (indirectly by causing secondary hyperparathyroidism and hypogonadism). The resultant microarchitectural deterioration increases bone fragility, with the earliest changes seen in sites of high trabecular bone content such as the lumbar spine and ribs; bone loss and fractures can, however, occur at any site.[21] Fracture risk is significantly increased as, in addition to a dramatic decline in BMD and

alteration in bone quality, proximal muscle weakness also occurs. In one study, vertebral fractures occurred in more than 20% of patients in the first year of commencing corticosteroid therapies.[21] The relative risk (RR) of hip and vertebral fracture after corticosteroid therapy in this study was 1.9 and 2.9, respectively. With prolonged corticosteroid exposure of greater than 20 months, this study showed that hip fracture risk may increase by five-fold and vertebral fracture risk by 5.9-fold.

The bone loss associated with hypercortisolism may be partly reversible. Patients with successfully treated Cushing's syndrome show dramatic improvement in skeletal pain and BMD, as well as reduction in fracture rates. Similar improvements are seen after withdrawal of corticosteroid therapy. The large UK General Practice Research Database study involved more than 240,000 corticosteroid users and age- and sex-matched controls and found that the excess risk in fracture in oral corticosteroid users almost disappeared within one year of stopping therapy, particularly for vertebral fractures.[40] Other studies have shown similar reductions in hip fracture rates.[21,39]

Several large randomised controlled trials have been performed in women at risk of corticosteroid-induced osteoporosis, measuring both BMD and fractures as the primary endpoint. In a meta-analysis, bisphosphonates were shown to have the most consistent efficacy when compared with calcium, vitamin D, calcitonin and fluoride.[28] Lumbar spine and femoral neck BMD increased by 2 to 3% in women treated with alendronate and risedronate compared with those receiving calcium and vitamin D. In post hoc analyses, vertebral fracture risk was reduced by 38 to 60%. Subjects were treated with doses equivalent to prednisone 7.5 mg/day or more.

As mentioned before, the mechanism by which bisphosphonates are effective in preventing corticosteroid-induced bone loss, a predominantly low bone turnover state, remains poorly understood.

Teriparatide (parathyroid hormone), an anabolic agent that acts by direct stimulation of osteoblastogenesis and inhibition of osteoblast apoptosis, counteracts two of the key inhibitory effects of corticosteroid on bone formation. A recent study compared teriparatide with alendronate in patients with low BMD (T-score -2.5 or less) or a prevalent fracture and receiving long-term corticosteroid therapy – i.e. secondary prevention.[41] Teriparatide was significantly better than alendronate in terms of increase in lumbar spine BMD (7.2% *v.* 3.4%) and fewer new vertebral fracture reduction (0.6% *v.* 6.1%).

Important lifestyle measures such as resistance (strength) training and minimising the corticosteroid dose should be considered. In this cohort, fractures occur at higher BMD thresholds (T-scores -1.5 or less), suggesting that therapies should be considered earlier. The optimal approach is primary prevention (i.e. at the time when bone loss is maximal). Given the evidence, the first line therapy should be an oral bisphosphonate such as alendronate or risedronate, with calcium and vitamin D adjunctive therapy. For young patients with low BMD who are receiving long-term low-dose corticosteroid, teriparatide should be considered as a potential first-line therapy.

UK guidelines advise primary prevention of corticosteroid-induced osteoporosis in women at high risk, such as those aged 65 years or over or those with a prior fragility fracture.[42] The guidelines recommend that BMD measurement be considered in other women receiving corticosteroids with an expected duration of treatment of three months or longer, and that a T-score of -1.5 or less may indicate a need for intervention, depending on age.

A case study of a woman with Cushing's syndrome and stress fractures is presented in Figures 3a to d.

Primary hyperparathyroidism

Primary hyperparathyroidism is a common endocrine disorder that frequently presents in postmenopausal women as osteoporosis and fragility fractures.[15,16] Osteitis fibrosa cystica is a rare complication due to chronic untreated hyperparathyroidism. An increased risk of vertebral, distal forearm and pelvic fractures has been shown to occur in hyperparathyroidism, related to its severity and chronicity.[16]

Bone resorption marker levels are elevated and BMD is reduced (forearm more than lumbar spine) in women with hyperparathyroidism; both may be partly or completely reversed with curative parathyroidectomy. In one study conducted over four years, lumbar spine, femoral neck and, to a lesser degree, forearm BMD increased progressively after parathyroid surgery (+12.8%, +12.7% and +4%, respectively, by year 4), with most change seen in the first year.[43] While lumbar spine BMD was restored, a deficit in forearm BMD persisted, evident even 17 years after surgery. Vitamin D deficiency frequently co-exists in hyperparathyroidism and may be responsible for the attenuated BMD responses after surgery. An important unresolved question is whether these improvements in BMD translate to fracture reduction, with some data suggesting that fracture risk decreases with time following successful parathyroid surgery.[44]

The finding of osteoporosis (defined as BMD T-score of -2.5 or less) in hyperparathyroidism is considered in the US National Institutes of Health Consensus Statement on primary hyperparathyroidism as an indication for parathyroidectomy.[45] Today, minimally invasive parathyroid surgery is considered safe and cost effective treatment in women with hyperparathyroidism and 'MIBI positive' disease (i.e. a single adenoma demonstrated on parathyroid sestamibi scan). For women with hyperparathyroidism and multiple gland disease, parathyroid

neck exploration is still required. Oestrogen therapy and alendronate have been shown in randomised trials to prevent parathyroid-induced bone loss in women with hyperparathyroidism who are unfit or unwilling to undergo parathyroid surgery.[27]

Women with hyperparathyroidism and osteoporosis who have undergone curative parathyroidectomy should be managed with active lifestyle intervention for at least two to three years before pharmacological therapies are considered. This allows optimal time for skeletal calcium reaccumulation and increases in BMD.

Hyperthyroidism and thyroxine excess

Hyperthyroidism is the most common endocrine disorder in women. Whether endogenous (Graves' disease or toxic multinodular goitre) or exogenous (overzealous thyroxine supplementation for hypothyroidism or thyroxine-suppression for thyroid cancer), it causes high bone turnover, bone loss and increased fracture risk.[17-19,46] In a US population-based study of women aged 65 years and over (n=9516), hyperthyroidism was an independent risk factor for hip fracture (RR=1.8).[18] In a UK population-based study (n=7209), an excess mortality due to hip fracture (standardised mortality ratio, 2.9) was noted in hyperthyroid patients treated with radioiodine.[19] The negative impact of thyroxine therapy on the skeleton is not so clear. While suppressive doses of thyroxine used in thyroid cancer or multinodular goitre have been shown to increase noninvasive markers of bone resorption and decrease BMD, the data relating to fracture risk are controversial. In one study (n= 23,183), 1.6% of patients prescribed thyroid hormone had a history of hip fracture compared with 1.4% of 92,732 controls.[17]

Reversibility in bone loss has been seen with successful treatment of both Graves' disease and toxic goitres. Restoring normal thyroid function with antithyroid medications, radioactive iodine or thyroidectomy results in normalisation in bone turnover and a 4 to 6% increase in BMD.[47] Similar positive increases in BMD have been seen in a select group of hyperthyroid women treated with bisphosphonates.[26]

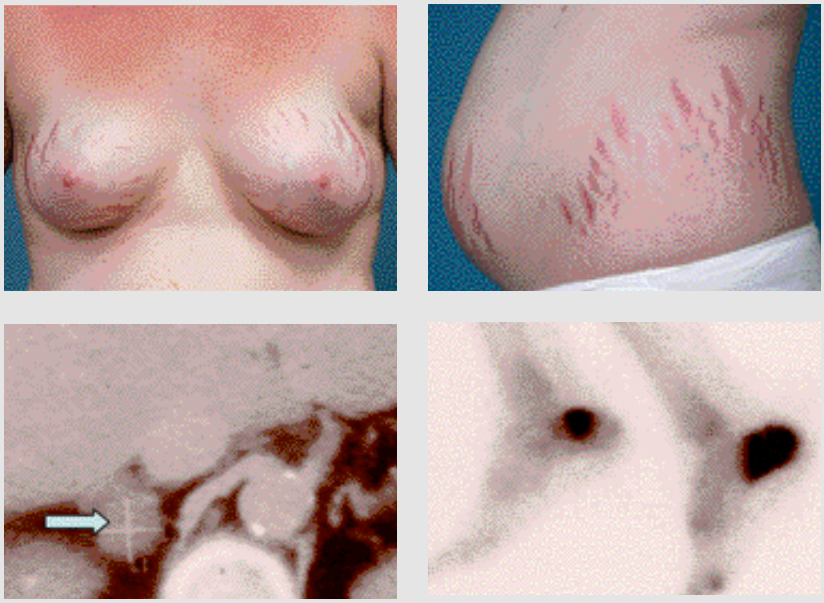
It is thus recommended that women presenting with osteoporosis and hyperthyroidism be treated for their thyroid disorder before considering specific antiosteoporotic therapies.

Coeliac disease

Osteoporosis may be a sign of subclinical coeliac disease and is a frequent long-term complication of untreated coeliac disease.[48-50] Likewise, low serum 25-hydroxyvitamin D or iron levels should alert the physician to the diagnosis of coeliac disease, although osteomalacia is now rare.

Osteoporosis affects the lumbar spine in 30 to 50% and femoral neck in 20 to 30% of patients with newly diagnosed coeliac disease.[49] Data relating to fragility fractures are conflicting, which probably reflects the prolonged time to diagnosis. In one study (n=165 patients), coeliac disease-affected patients had a higher prevalence of fractures in the peripheral skeleton (25% had one to five fractures) compared with age- and sex-matched controls (7%).[51] In another study (n=75), 21.3% of patients with coeliac disease had past fractures compared with 2.7% of matched controls.[52] However, two other studies failed to show an increased fracture rate.[49] Patients with bowel diseases (coeliac disease n=1021, Crohn's disease n=7072, and ulcerative colitis n=8323) were each compared with three

Cushing's syndrome and osteoporosis



Figures 3a to d. A 52-year-old woman presented with pain in both heels thought to be due to osteofragility fractures. a and b (upper left and right). Centripetal adiposity and prominent abdominal striae (purple tinge), important clinical signs suggestive of Cushing's syndrome. c (lower left). CT image demonstrating a corticosteroid-producing right adrenal adenoma, 18 mm in diameter. d (lower right). Radionuclide technetium bone scan demonstrating tracer uptake in both calcanei indicative of stress fractures.

age- and gender-matched controls randomly drawn from the background population over 14 years.[50] No increase in fracture risk was demonstrated before or after diagnosis, irrespective of the type of their bowel disease.

Bone disease in coeliac disease is partly due to chronic hypovitaminosis D and calcium malabsorption (caused by atrophy of the intestinal villi), leading to secondary hyperparathyroidism, bone loss and mineralisation defects. Inflammatory cytokines may also contribute to bone loss by inhibiting osteoblast activity.[49]

The treatment of coeliac disease is a gluten-free diet. Adults who adhere to this diet demonstrate a 5 to 10% increase in BMD during the first year or two, which then plateaus.[49] Responses may vary with disease state. In one prospective study, BMD normalised after three years of gluten-free diet in adults without secondary hyperparathyroidism.[53] In this study, elderly women with a relatively late diagnosis, gluten-free diet alone had minimal effect on BMD. These women predominantly had severe osteoporosis.

Calcium supplements are important in patients with coeliac disease, and are required even in women who have a good response to a gluten-free diet. Oral vitamin D supplementation may be required if serum 25-hydroxyvitamin D levels are low, while parenteral formulations are required in those with poor gut absorption. Adequate sunlight exposure (10 to 15 minutes, five days per week)is advised as a means of acquiring more vitamin D.

Oestrogen replacement therapy should be considered in perimenopausal women with coeliac disease. Bisphosphonates and teriparatide have not been evaluated in coeliac disease. If they are to be considered for secondary prevention, osteomalacia and secondary hyperparathyroidism need to be effectively treated in order to avoid the risk of hypocalcaemic tetany.

Conclusion

By seeking and managing causes of osteoporosis other than oestrogen deficiency, it may be possible to avoid the need for antiosteoporotic therapies.

Secondary osteoporosis should be suspected in women aged over 40 years who suffer a low trauma osteofragility fracture and those with a BMD Z-score of less than -2.0. Women with secondary osteoporosis can be differentiated from those with primary postmenopausal osteoporosis by the fracture site, the severity of osteoporosis and presence of risk factors (certain disorders and the use of certain medications). However, age remains the major BMD-independent risk factor for fracture, and many women with secondary osteoporosis may also have an element of primary osteoporosis. MT

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DECLARATION OF INTEREST: Associate Professor Diamond is a scientific advisor to Eli Lilly, Merck Sharp & Dohme, Novartis, Roche, Sanofi-Aventis and Servier, but does not receive financial remuneration. Honoraria for GP lectures and travel grants to attend local and international bone meetings have been received from all the above companies.

MedicineToday PEER REVIEWED ARTICLE
MedicineToday 2009; 10(10): 44-56
Updated June 2010

Treatment options for men with osteoporosis

Adequate treatment of the under-recognised common condition of osteoporosis in men can almost halve the risk of future low trauma fractures.

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Osteoporosis in men is largely ignored by both health professionals and patients, with one in three men in Australia aged over 60 years suffering an osteoporotic fracture yet fewer than 20% receiving appropriate care.[1] With men expected to live longer, it has been predicted that the number of hip fractures in men will double by 2026. Morbidity increases significantly in men who have had osteoporotic fractures, and those who suffer major fragility fractures often lose their independence and many will die prematurely (Figures 1a and b). Importantly, at least 60% of men with osteoporosis have an underlying secondary cause.

Treatments for men with osteoporosis include preventative therapies for those at high risk of fracture and pharmacotherapies for those who sustain fractures.[2-5] This article reviews the causes and diagnosis of osteoporosis in men and then discusses the treatment options and the evidence supporting these options.

Pathogenesis of osteofragility fractures in men

Although much has been learnt about bone mineral density (BMD) in men, little is known about the components of bone quality.[6] Increases in sex-hormone binding globulin levels in ageing men result in significant reductions in the amounts of serum bioavailable sex hormones.[7] The consequential lowering in serum oestradiol leads to increased bone resorption on both endocortical and trabecular surfaces, and the lowering in serum testosterone causes decreased bone formation but increased bone remodelling.[8,9] Low testosterone levels and low oestrogen levels have both been associated with increases in fracture risk.[10] In addition, a polymorphism of the gene coding

IN SUMMARY

- **About one in three men in Australia aged over 60 years will suffer an osteoporotic fracture, yet about 80% of those admitted to hospital with major fractures will be discharged without appropriate or osteoporosis-relevant investigation or treatment.**
- **The gold standard of care for men with osteoporosis includes preventative therapies for those at high risk of fracture and pharmacotherapies for those who sustain fractures.**
- **Oral alendronate and risedronate are effective antiosteoporotic agents in men.**
- **Intravenous zoledronic acid is also an effective antiosteoporotic agent in men and may have the additional benefits of improving drug compliance and reducing mortality in the elderly after hip fractures.**
- **Subcutaneous injections of teriparatide are reserved for men with severe osteoporosis (T-score, -3.0 or less) who continue to sustain fractures despite adequate antifracture therapies.**
- **Therapy with testosterone is likely to be beneficial in hypogonadal men presenting with osteoporosis.**

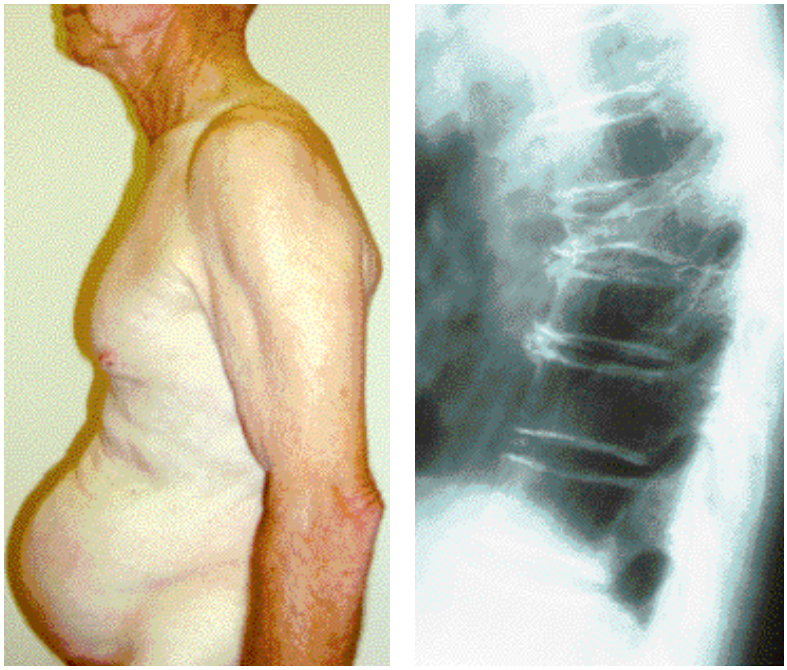
aromatase (which converts testosterone to oestrogen) has been associated with increased rates of bone loss and increased fracture risk.[11]

With ageing, there is uncoupling of bone formation and resorption (decreased formation but normal resorption – i.e. a low bone turnover state) and a net bone loss averaging approximately 5 to 10% per decade in men.[12] Physical immobility, poor nutrition, calcium and vitamin D deficiencies and reduced cytokines and growth factors may all contribute to the decline apparent in the ageing human skeleton.[6] (Calcium deficiency is related to low dietary intake and diminished intestinal absorption of calcium. Vitamin D deficiency is mainly due to inadequate sunlight exposure although there may also be low dietary intake and reduced absorption.) In men, cortical and trabecular thinning secondary to reduced bone formation lead to a reduction in volumetric vertebral body BMD, femoral areal BMD and femoral neck diameter.[6,7] These structural changes result in bone fragility and predispose to an increased fracture risk, and are in contrast to the trabecular loss that is seen in women with postmenopausal osteoporosis, a high bone turnover state due to oestrogen deficiency.

Osteoporotic risk factors

Osteoporosis results from a failure to achieve an adequate peak bone mass or secondary causes of bone loss, or a combination of these.[2-6] Timing of puberty is an important determinant of peak bone density in both sexes, and in boys at least 40% of peak bone mass is acquired between the ages of 9 and 13 years. Men with a history of constitutional delay in puberty have significantly reduced spinal and forearm BMD. Bone loss in men begins soon after puberty, and this early bone loss is characterised by trabecular thinning and may be related to alterations in the insulin-like growth factor I (IGF- I) regulating system.

At least 60% of men presenting with osteoporosis have a secondary cause for the condition. The four most common causes are, in order of frequency, excessive use of corticosteroids, excessive alcohol intake, smoking and hypogonadism (Table 1). The remainder have no identifiable medical conditions or risk factors associated with bone loss and are referred to as having primary or idiopathic osteoporosis.



Figures 1a and b. Spine fracture in an elderly man. a (left). Marked thoracic kyphosis or 'Dowager's hump' and exaggerated lumbar lordosis, causing a protruding abdomen and upper thoracic back pain. b (right). X-ray showing a T7 osteoporotic spinal compression fracture.

Bone histomorphometry in men with idiopathic osteoporosis (who have normal levels of oestrogen and testosterone) shows thin trabecular rods, reduced osteoid parameters and low bone turnover.[13] This is in contrast to the high bone turnover seen in men presenting with hypogonadism (who have low oestrogen and testosterone levels).[8] The patterns of bone turnover in idiopathic, age-related and secondary osteoporosis have previously been reviewed in *Medicine Today* (January and May 2008 issues; pages 4 to 14 and 17 to 27, respectively, of this supplement).[14,15]

Men with secondary causes of osteoporosis have been shown to have a twofold increase in the risk of hip fractures (odds ratio [OR], 2.3; 95% confidence interval [CI], 1.3–4.3), whereas men with an increased risk of falling have an even greater increase in risk of hip fracture (OR, 6.9; 95% CI, 3.3–4.8).[16]

Measuring absolute fracture risk

FRAX is a mathematical tool that has been developed by the WHO to calculate the absolute fracture risk of an individual based on his or her clinical risk factors and hip BMD in g/cm^2.[17] The risk factors used are age, weight, height, previous fracture history, familial history of hip fracture, current smoking, corticosteroid therapy,

continued

Table 1. Secondary causes of osteoporosis in men

Most common (in order of frequency)

- Corticosteroid excess
  - prolonged corticosteroid therapy
  - conditions associated with excess corticosteroid secretion (Cushing's syndrome)
- Alcohol excess
- Smoking
- Hypogonadism or androgen deficiency
  - primary testicular failure/orchiectomy
  - secondary hypogonadism (hypothalamic–pituitary disorders)
  - androgen deprivation therapy (combined GnRH agonists and antiandrogens for prostate cancer)

Others

- Chronic comorbidities
  - cardiac, pulmonary, neuromuscular and rheumatological disorders
  - hepatobiliary and inflammatory bowel diseases
  - chronic depression
  - chronic kidney disease
  - thyroxine excess
  - primary hyperparathyroidism
- Malabsorption
  - gastrectomy or small bowel resection
  - coeliac disease or infiltrative small bowel disorders
- Haematological malignancies (myeloma, lymphoma, mastocytosis)
- Vitamin D and calcium deficiencies
- Vitamin B_{12} deficiency
- Others – HIV disease or its treatment, post-organ transplantation, certain antiepileptic drugs, diabetes mellitus

rheumatoid arthritis, secondary osteoporosis and an alcohol intake of three or more drinks per day. Among the FRAX algorithms available are those giving the 10-year probabilities of suffering a major fracture (spine, forearm, hip or shoulder fracture) or a hip fracture in men aged 40 to 90 years (www.shef.ac.uk/FRAX).

One of the major drawbacks of FRAX is that it does not account for other important variables contributing to hip fracture in men, such as sleep disturbance, impaired mental status, poor appetite, falls, stroke with hemiplegia, senile dementia and gastrectomy. In addition, the datasets from which absolute fracture risk is calculated in men are less extensive than those for women.

Other fracture risk calculators are available that incorporate a history of falls. An example is the Fracture Risk Calculator, which was developed using data collected in the Dubbo Osteoporosis Epidemiology Study conducted by the Bone and Mineral Research Program of Sydney's Garvan Institute of Medical Research (www.fracturerisk calculator.com). This calculator applies to men and women aged 60 years and over. A recent study comparing FRAX and the Fracture Risk Calculator suggested that FRAX discriminated fracture risk poorly in men, supporting the concept that all algorithms need external validation before clinical implementation.[18]

Fracture outcomes in men

Osteoporotic fractures have become a major healthcare problem in the ageing community.[3-5] Some figures on fracture outcomes in men are given below.

- In 2007, the estimated cost of osteoporotic fractures to the Australian community was $1.9 billion annually, with 23% attributable to men.
- Mortality and morbidity have been shown to increase significantly in men who have had osteoporotic fractures.[19,20] In men living in Australia, the risk of dying has been shown to increase by 3.2-fold after a hip fracture, 2.4-fold after a spinal fracture and 2.2-fold after any major fracture.[21] Men who suffer a hip fracture have been shown to have a 30-day case fatality of 16% and fatality rate of up to 37.5% in the first year, with more than half of the remainder discharged to nursing homes.[16,19,20] Only 40% of hip fracture survivors recover to their level of functioning before the fracture and nearly 60% limp or require a cane or walker.[16,21]
- A previous osteoporotic fracture at one site increases the risk of fracture at any other site. The risk has been shown to be greatest for subsequent spinal fractures (RR, 12.6; 95% CI, 11–14) and lower for subsequent hip (RR, 2.3; 95% CI, 1.8–2.9) and forearm fractures (RR, 1.6; 95% CI, 1.1–2.4); these figures are for men and women, but the risk was greater in men.[22]

Compared with elderly women, elderly men presenting with a hip or vertebral fracture have a higher mortality at 12 months.[20]

Diagnosis of osteoporosis in men

The occurrence of minimal trauma fractures or the radiological finding of a spinal fracture is highly suggestive of underlying osteoporosis in men, as it is in women. Chronic spinal deformities (due to degenerative spinal disease, spondylosis or Scheuermann's disease or to a normal variant, short vertebral height) are common in men and often misdiagnosed as osteoporotic fractures (Figures 2a and b).

Men with secondary causes of osteoporosis tend to have fractures in specific sites. These sites are the same as for women, as previously reviewed in the May 2008 issue of *Medicine Today* (pages 17 to 27 of this supplement).[14] Considering the more common secondary causes for the condition in men, the most common fracture types associated with excessive use of corticosteroids are vertebral fractures, with excessive alcohol intake, peripheral

fractures, and with hypogonadism, vertebral and hip fractures.

Role of bone densitometry

Dual energy x-ray absorptiometry (DXA) is an important tool in diagnosing osteoporosis, predicting future fracture risk, selecting patients for antiosteoporotic therapies and monitoring responses.[23,24] In a recent study, the relative risk of hip fracture in men was 3.2 (95% CI, 2.4–4.1) for each standard deviation decrease in hip BMD.[25] An example of a DXA BMD report is given in Figure 3.

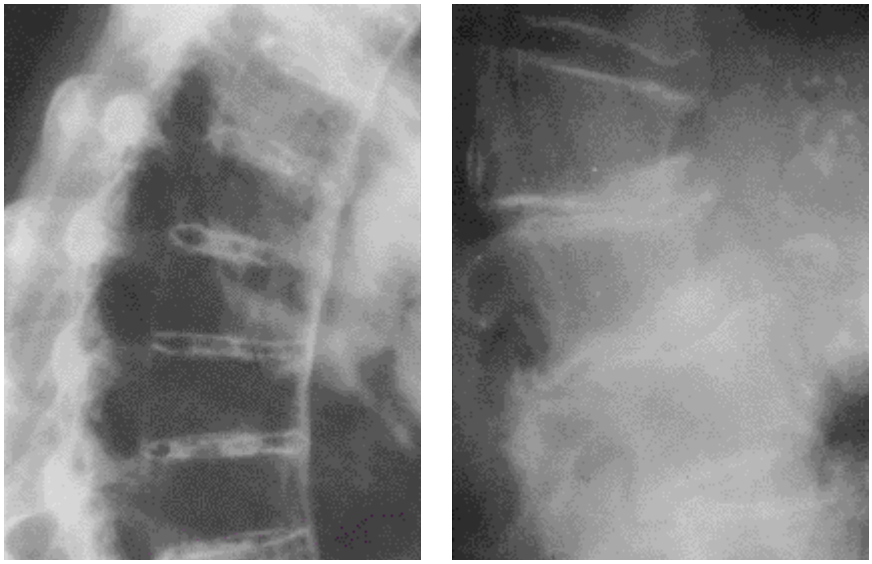
Although DXA is the usual method for assessing BMD at the hip and spine, several other techniques, including quantitated computed tomography, are also used. However, the use of these other methods for monitoring of BMD is limited because their reproducibilities are poor.

In Australia, Medicare rebates are available for measuring BMD in patients who have radiological evidence of bone demineralisation, significant risk factors, a history of an atraumatic fracture, are aged 70 years or older or are receiving prolonged corticosteroid therapy.

BMD criteria

The BMD criteria for diagnosing osteoporosis in men are noted below.

- In men aged 50 years and older, osteoporosis is defined as a BMD (at the proximal femur, spine or distal forearm) of 2.5 standard deviations or more below the mean for young normal adult Caucasian men aged 20 to 40 years using a male reference database (i.e. a T-score value of -2.5 or less).[23]
- In men aged less than 50 years, osteoporosis is defined as a BMD Z-score value of -2.0 or less (i.e. a BMD of 2.0 standard deviations or more below the average BMD of age-matched men) in the presence of other clinical indicators such as previous fracture or secondary causes of osteoporosis.[23]



Figures 2a and b. Spinal x-rays showing spinal deformities that are not considered osteoporotic spinal fractures. These changes are responsible for pseudoelevations in spinal BMD measurements. a (left). Severe intervertebral disc degeneration and calcification with spondylosis. b (right). Marked degenerative changes of the lumbar spine, with disc degeneration, retrolisthesis and osteochondrosis.

BMD scan artefacts

Advanced spondyloarthropathy, facet joint disease and aortic calcification have been shown to be responsible for falsely elevated BMD values in elderly men. Most centres report a mean spinal BMD value of three or four vertebrae, such as L2 to L4 or L1 to L4. If an artefact is noted (e.g. pseudoelevation of a single vertebral body BMD) then the affected vertebra should be excluded from the BMD scan analysis (Figure 3).

Monitoring BMD

When monitoring progressive changes with age or responses to therapy, absolute BMD measurements should be compared, not T-scores.[24,26] Both spinal and total hip BMD are the preferred sites for monitoring changes.[27]

Repeated measurements should be performed on the same densitometer to enhance reproducibility.

Laboratory investigations

Men with a BMD Z-score of -2.0 or less require further investigations to exclude underlying secondary causes. The choice of investigations should be guided by the clinical presentation.

The common and important secondary cause of osteoporosis of hypogonadism is defined by an early morning serum testosterone concentration of 6.9 nmol/L or below on three occasions.[7,8] Measurement of levels of serum gonadotrophins (follicle stimulating hormone and luteinising hormone) is required to differentiate between primary testicular failure and secondary hypothalamic–pituitary disorders.

Table 2 lists investigations for secondary causes of osteoporosis in men.[14]

Osteoporotic treatments in men

Treatments for osteoporosis are classified as either preventative or therapeutic. Recent reviews indicate an evidence-treatment gap and suggest that very few men (fewer than 20%) receive any form of antiosteoporotic treatments. Many men who sustain hip or spinal fractures are discharged from hospital without

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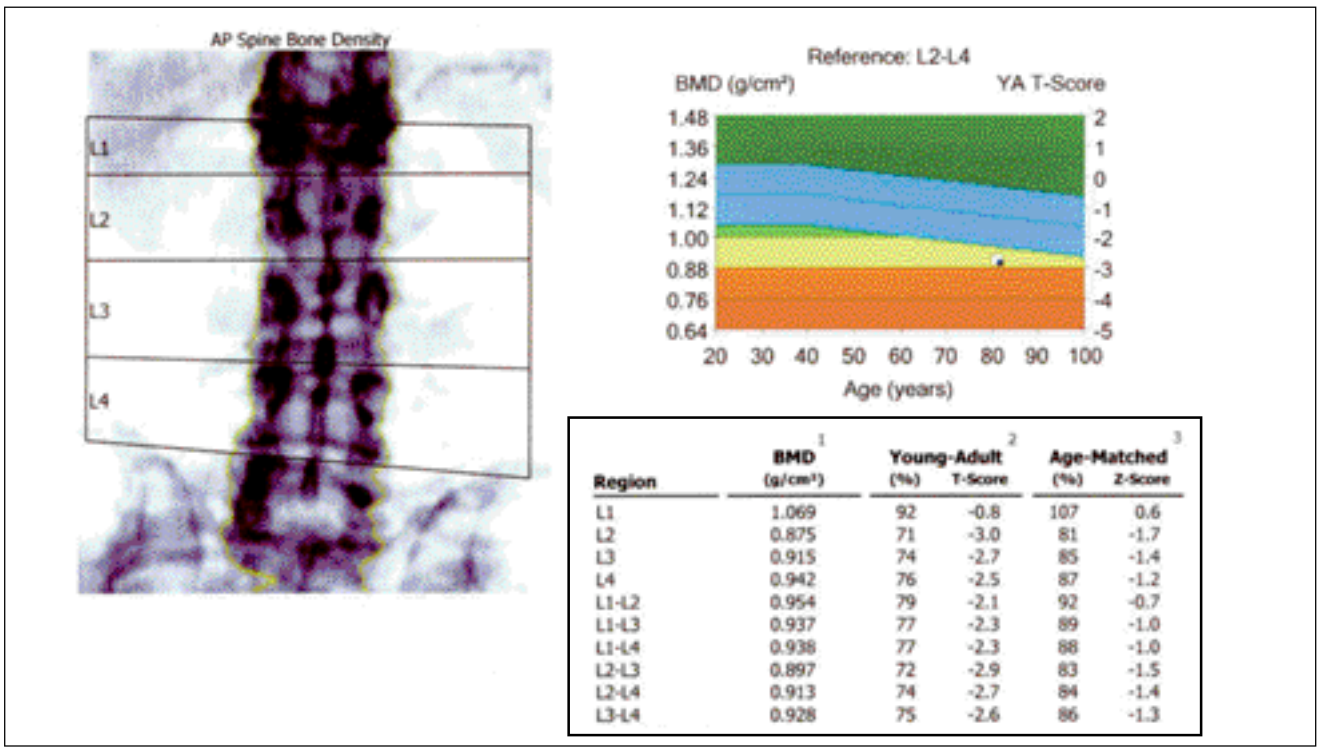

Region	1 BMD (g/cm²)	2 Young-Adult (%)	2 Young-Adult T-Score	3 Age-Matched (%)	3 Age-Matched Z-Score
L1	1.069	92	-0.8	107	0.6
L2	0.875	71	-3.0	81	-1.7
L3	0.915	74	-2.7	85	-1.4
L4	0.942	76	-2.5	87	-1.2
L1-L2	0.954	79	-2.1	92	-0.7
L1-L3	0.937	77	-2.3	89	-1.0
L1-L4	0.938	77	-2.3	88	-1.0
L2-L3	0.897	72	-2.9	83	-1.5
L2-L4	0.913	74	-2.7	84	-1.4
L3-L4	0.928	75	-2.6	86	-1.3

Figure 3. An example of a dual-energy x-ray absorptiometry BMD report for the lumbar spine, anteroposterior (AP) projection. In this case, the mean L1-4 absolute BMD value is 0.938 g/cm^2 (T-score value, -2.3). This value is pseudoelevated by the presence of the L1 spinal fracture (BMD of L1 vertebra, 1.069 g/cm^2). More accurate spinal BMD can be estimated by ignoring the L1 vertebral body and calculating the mean BMD value for the L2-4 vertebrae only, which gives a value of 0.913 g/cm^2; T-score, -2.7 (defined as osteoporosis).

any follow up or management of their osteoporosis.[28]

The decision regarding whether to use preventive or therapeutic treatment in patients with densitometric evidence of osteoporosis is based on the following:

- preventative nonpharmacological measures are usually considered in 'high risk' men – that is, those aged 50 years or older presenting with densitometric evidence of osteoporosis (BMD T-score values, -2.5 or less) who have not sustained a fracture
- specific antiosteoporotic therapy is indicated in men with low BMD (T-score values, -1.0 or less) who have a history of osteoporotic fractures, or in men aged 70 years or older with a T-score of -3 or less.

Preventative measures

A 'healthy lifestyle' is recommended for all men with osteoporosis.[2-5] Advice should be given about:

- adequate dietary calcium intake – recommended daily intakes are 1000 mg a day for men aged 19 to 70 years and 1300 mg a day for men aged over 70 years
- optimal sunlight exposure to maintain adequate vitamin D levels (at least 10 to 15 minutes of sun exposure a day, five days a week), with vitamin D_3 supplementation in individuals at risk of vitamin D deficiency
- safe and regular participation in weight-bearing exercise programs
- cessation of smoking
- restriction of alcohol intake – to fewer than four standard drinks a day.

Pharmacotherapies

Antiosteoporotic therapies can be considered as either antiresorptive (inhibiting osteoclastic bone resorption) or anabolic (stimulating osteoblastic bone formation). Sex steroid replacement therapy has a role in men with osteoporosis and androgen deficiency. Antiosteoporotic agents have a similar action in men and women and have previously been reviewed in *Medicine Today* (January and May 2008 issues; pages 4 to 14 and 17 to 27, respectively of this supplement).[14,15]

Although there are many randomised controlled trials (RCTs) demonstrating the antifracture efficacy of antiosteoporotic agents in women, studies in men have been fewer in number and much smaller in size (and, consequently, often have insufficient statistical power to measure differences in fracture rates).The efficacies of treatments in men have been based predominantly on their positive effects on BMD and the inferred similarities to the antifracture effects in women of agents such as alendronate and teriparatide.

Antiresorptive agents

Bisphosphonates

Bisphosphonates inhibit bone resorption by causing osteoclast apoptosis. These agents have been studied in men with osteoporosis, those with low serum levels of free testosterone, those with prostate cancer and who are receiving androgen deprivation therapy and those who are being treated with corticosteroids. (The last three of these groups of men are discussed in greater detail later in this article.)

- *Alendronate.* Alendronate 10 mg daily increased spinal and hip BMD by 7.1% and 2.0%, respectively, and reduced morphometric spinal fractures by greater than 80% (p=0.02) over two years.[29] Alendronate 70 mg weekly increases BMD as effectively as alendronate 10 mg daily in postmenopausal women with osteoporosis; the same effect is assumed in men.

  Alendronate (70 mg once weekly) is reimbursed on the Pharmaceutical Benefits Scheme (PBS) for the treatment of osteoporosis in men and women aged 70 years and older with a BMD T-score of -3.0 or less and in patients with a prior osteofragility fracture.
- *Risedronate.* Risedronate 5 mg daily increased spinal and hip BMD by 6.5% and 3.2%, respectively, and reduced spinal fractures by 61% (p=0.0026) over two years in an uncontrolled study.[30] Risedronate 35 mg once weekly and 150 mg once monthly have been shown to be as effective as risedronate 5 mg daily in postmenopausal women with osteoporosis.

  Risedronate 5 mg daily, 35 mg once weekly and 150 mg once monthly are reimbursed on the PBS for the treatment of osteoporosis with the same criteria as for alendronate. These dosages of risedronate are also listed on the PBS for the treatment for corticosteroid-induced osteoporosis in patients with a BMD T-score of -1.5 or less who are currently on long-term high-dose corticosteroid therapy (prednisolone equivalent dose of at least 7.5 mg/day for at least three months' duration). Risedronate 35 mg once weekly and 5 mg daily are also listed on the Repatriation Pharmaceuticals Benefit Scheme (RPBS) for the preservation of BMD in osteopenic patients (BMD T-score of less than -1.0) on long-term high-dose corticosteroid therapy.
- *Zoledronic acid.* Zoledronic acid 5 mg annual intravenous infusions given to elderly men and women after hip fractures increased hip BMD by 3.6% and reduced the risk of all clinical fractures by 35% (p=0.001) and all-cause mortality by 28% (p=0.01) over a mean follow up period of 1.9 years.[31]

  Zoledronic acid 5 mg once yearly is reimbursed on the PBS for the treatment of osteoporosis with the same criteria as risedronate.

Calcium and vitamin D

Calcium and vitamin D have weakly antiresorptive effects. Their importance for bone health has previously been reviewed in *Medicine Today* (January 2009 issue; pages 38 to 44 of this supplement).[32]

Table 2. Investigations in men with osteoporosis

For secondary causes of osteoporosis

- Full blood count, erythrocyte sedimentation rate and protein electrophoresis – to exclude myeloma and haematological disorders
- Serum chemistry (calcium, phosphate, creatinine, liver functions) – to identify possible alcohol excess
- Serum 25-hydroxyvitamin D and parathyroid hormone (PTH) – to identify possible vitamin D deficiency (a common cause of secondary hyperparathyroidism) or possible primary hyperparathyroidism
- Urinary calcium excretion (24-hour) – to differentiate between familial hypocalciuric hypercalcaemia (FHH) and primary hyperparathyroidism (PHPT)
- Serum vitamin B_{12} – to identify possible pernicious anaemia and/or small bowel disorders
- Thyroid stimulating hormone (TSH) – to identify possible hyperthyroidism
- Testosterone – to identify possible hypogonadism
- Serum gonadotrophins (follicle stimulating hormone [FSH] and luteinising hormone [LH]) – to identify and differentiate between possible primary gonadal failure (testicular failure) and secondary gonadal failure (hypothalamic–pituitary disorder)
- Urinary free cortisol (24-hour) – to identify possible Cushing's syndrome
- Anti-tissue transglutaminase and antiendomyseal antibodies – to identify possible coeliac disease

Other investigations

- Bone turnover markers (C-terminal and N-terminal telopeptides of type 1 collagen) – to identify high bone turnover and to measure responses to treatment with antiresorptive agents
- Bone imaging with technetium-99 radionucleide scanning, computed tomography and magnetic resonance imaging – to distinguish between acute and chronic fractures and between simple osteoporotic and infiltrative or malignant fractures
- Bone marrow trephine biopsy or bone biopsy with double tetracycline labelling – the former test is the gold standard for excluding malignancy or infiltrative bone disorders; the latter may be used to quantitate bone mass, turnover and mineralisation rates

There are no RCTs specifically assessing the antifracture efficacy of calcium and vitamin D_3 in men with osteoporosis. Fracture prevention studies in 'healthy' elderly men have demonstrated mixed results. In a study in which 75% of the participants were men, oral cholecalciferol 100,000 IU administered four-monthly for five years reduced the risk of major osteoporotic fractures by 33%.[33] A recent meta-analysis showed calcium or the combination of calcium and vitamin D reduced fracture risk by 11% in men and woman aged 50 years and older, and by 24% in those with at least an 80% compliance rate.[34]

Daily dietary supplementation with calcium (1200 to 1500 mg) and vitamin D_3 (800 to 2000 IU [20 to 50 µg] if serum 25-hydroxyvitamin D levels are below 75 nmol/L) must be considered an important adjunct to other therapeutic interventions such as bisphosphonates or testosterone.

Calcitriol

There are no data supporting the use of calcitriol in idiopathic osteoporosis in men.[35]

Anabolic agents

Parathyroid hormone (1-34) – teriparatide

The 34-amino acid fragment of parathyroid hormone known as PTH (1-34) or teriparatide at low dose prevents osteoblast apoptosis and increases bone formation and bone volume.[36] Teriparatide increased lumbar spine and hip BMD by 9% and 2.9% respectively over 11 months in a study of osteoporosis in men.[37] Too few clinical fractures occurred during the study to have a meaningful result. However, in an 18-month extension study, the occurrence of moderate to severe spinal fractures was significantly reduced.[38]

Teriparatide therapy is recommended for a lifetime total of 18 months only, with three-monthly monitoring of serum calcium levels, as there is evidence that this drug has caused bone sarcomas in rats, although the relevance of these findings to humans has not yet been established. To prevent the loss of BMD accrued during teriparatide therapy, antiresorptive therapy with bisphosphonates should be considered once teriparatide therapy has been completed; antiresorptive agents should not be coadministered with teriparatide.

Teriparatide can be of use in the treatment of osteoporosis when other drugs have failed or are not tolerated and there is a high risk of fractures. It is reimbursed on the PBS for men and women with severe osteoporosis (BMD T-score of -3 or less and the radiological presence of two or more fractures) who have had at least one new fracture despite 12 months of continuous adequate antiresorptive therapy.

Other agents

Testosterone

Testosterone replacement is appropriate for men who have osteoporosis secondary to testosterone deficiency as a result of either delayed puberty (idiopathic hypogonadotrophic hypogonadism) or hypogonadism.[39-41] Its anabolic effects on bone are less certain in eugonadal men, so it should only be given to men with significantly reduced serum testosterone concentrations.

Testosterone is listed on the PBS for the treatment of androgen deficiency in men with established pituitary or testicular disorders and in men aged 40 years and older without such disorders.

Newer agents under evaluation

A number of drugs are currently undergoing phase III clinical trials for men with osteoporosis. These include denosumab, strontium ranelate and a selective androgen receptor modulating agent (SARM).

Denosumab is a human monoclonal antibody that binds and neutralises receptor activator for nuclear factor kappa B ligand (RANKL), a molecule necessary for osteoclast activation.[42] Strontium ranelate is already TGA approved (and PBS listed, with restrictions) for the primary prevention of fractures in women with postmenopausal osteoporosis.

Specific conditions related to osteoporosis in men

Osteoporosis associated with hypogonadism

Although serum testosterone levels decline with age, this hormone accounts for only 5% of the age- and weight-adjusted variance in bone loss.[39] Hypogonadism *per se*, with serum testosterone levels in the 'castrate' range, is a major risk factor for osteoporosis. In patients with hypogonadism, lumbar spine BMD decreases by approximately 4 to 8% over 12 months, while markers of bone resorption such as the pyridinoline cross-links may increase by up to 200%.[4,5] About 16% of men with spinal fractures have evidence of hypogonadism.[8]

There are no RCTs assessing the antifracture efficacy of testosterone. Testosterone therapy has been shown to increase lumbar spine BMD (by as much as 5 to 14%) but not hip BMD in men with established hypogonadism.[5] The biological significance of testosterone replacement in men with subclinical hypogonadism or with testosterone levels just below or in the low-to-normal reference range remains controversial.

Testosterone replacement can be adequately achieved by the transdermal route (patch 5 mg/day or gel 50 mg/day), by intramuscular injections (depot testosterone either 250 mg every two to three weeks or 1000 mg every three months) or by subcutaneous implants (600 mg every four to six months). The dose frequency of therapy may have a significant impact on BMD changes.

A safe approach to testosterone therapy is recommended, such as the following:

- treat men with established hypogonadism, as defined by early morning serum testosterone concentrations on three occasions of 6.9 nmol/L or below

- adjust testosterone dosing to achieve serum testosterone levels in the mid-normal range (10.4 to 15.6 nmol/L)
- monitor for possible testosterone-dependent diseases by full blood examination, digital rectal examination of the prostate and measurement of serum prostate specific antigen levels before treatment is commenced and then every 12 months.

Osteoporosis in men with prostate cancer

Androgen deprivation therapy (ADT) by either bilateral orchidectomies or chronic treatment with a gonadotrophin releasing hormone (GnRH) agonist is the mainstay of treatment for men with metastatic prostate cancer. ADT is now commonly used as sole therapy for men with high-grade prostate cancer, for elderly men who are frail and unfit for radical prostatectomy and as adjuvant therapy combined with either brachy- or localised radiotherapy. More than one-third of the estimated 2 million prostate cancer survivors in the USA are currently treated with a GnRH agonist.

The intended therapeutic effect of ADT is severe hypogonadism. ADT increases bone turnover, decreases BMD and is associated with greater fracture risk.[43] Longer treatment duration confers greater fracture risk. Age, vitamin D deficiency, alcohol excess and comorbidities are also associated with higher fracture incidence.

ADT decreased lumbar spine (measured using quantitated computed tomography) by 5.7 to 8.5% and hip BMD (measured using DXA) by 1.8 to 2.3% after 12 months of therapy.[43] Osteoporosis has been reported in 27% and osteopenia in 51% of men receiving long-term ADT, and a two-fold increase in fracture rates has been noted.[44] In a review of 50,613 men with prostate cancer, 20% of those treated with ADT had fractures, as compared with 13% who had not received ADT ($p<0.001$).[45] The number of doses of GnRH agonist had a significant impact on fracture rates.

Several therapies with antiosteoporotic effects have been shown to prevent bone loss in men with nonmetastatic prostate cancer receiving ADT. These include alendronate 10 mg/day, intravenous disodium pamidronate 90 mg every three months and zoledronic acid 4 mg every three to four weeks. (It should be noted that disodium pamidronate 90 mg and zoledronic acid 4 mg are not TGA approved for osteoporosis treatment or prevention. They are restricted on the PBS for hypercalcaemia of malignancy, private hospital authority required.)

More recently, both oral toremifene and subcutaneous denosumab have been shown not only to increase BMD but also to decrease spinal fracture risk in men.[40,46] (Toremifene, a selective oestrogen receptor-modulating agent, is reimbursed on the PBS for the treatment of hormone-dependent metastatic breast cancer in postmenopausal women.)

Men with prostate cancer are living longer but with a greater burden of treatment. The results of the antifracture trials in men with prostate cancer and receiving ADT now provide critical evidence to guide new standards of care. Close liaison with urologists is critical.

Osteoporosis in men receiving corticosteroids

Corticosteroids are a common cause of osteoporosis and spinal fractures in both men and women.[2-5,47] These drugs are commonly used to treat asthma, autoimmune diseases and inflammatory bowel disease and after organ transplantation. Their detrimental effect on bone is similar in men and women and has previously been discussed (*Medicine Today*, May 2008 issue; pages 17 to 27 of this supplement).[14]

In men, corticosteroid use causes an acute fall in plasma testosterone level as a result of either a direct action on the testes or an effect on the hypothalamic–pituitary–testicular axis.[47] The reduction in testosterone level is dose-dependent. Rapid loss of trabecular bone (ranging from 5 to 20%) may occur within the first six to 12 months of commencing therapy. The rate of loss then decreases but is

Consultant's comment

Osteoporosis in men is important for a number of reasons:

- the frequency of osteoporotic fractures in men is widely under-recognised
- 25 to 30% of older Australian men will suffer an osteoporotic fracture
- a single fragility fracture quadruples a man's subsequent risk, which then is comparable to that of a woman of the same age who has also already had a fragility fracture; this risk is comparable to 20 years of ageing
- osteoporotic fractures are associated with increased risk of mortality in both women and men but the increase in risk is greater in men
- women are relatively unlikely (less than 30%) to get specific treatment to reduce their further fracture risk; however, the situation is worse for men, probably less than 10% of men getting appropriate treatment.

Considering that treatment appears effective in men and that there is a substantial risk of osteoporotic fractures in men, who in general do worse than woman, the need for greater recognition and focus on osteoporosis in men is obvious.

Associate Professor Diamond and Professor Ebeling's timely review puts this concern forward clearly and presents the evidence base for intervening actively in men.

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COMPETING INTERESTS: Professor Eisman has served as a scientific consultant to and/or received research support from Amgen, deCode, Eli Lilly, Merck Sharp and Dohme, Novartis, Roche-GlaxoSmithKline, Sanofi-Aventis, Servier and Wyeth.

ongoing, even with chronic low-dose corticosteroid therapies. Spinal fractures occur in more than 20% of patients in the first year of commencing therapy, with more than one-third of patients experiencing fractures after five to 10 years of therapy. The risk of hip fracture is tripled with chronic therapy.[48]

As the most rapid bone loss often occurs within the first 12 months of commencing corticosteroid therapy, from a clinical point of view the optimal approach is primary prevention in men commencing such therapy because they will not yet have lost bone. However, treating men already taking prolonged corticosteroid therapy (secondary prevention) will also reduce fracture risk.

Recommendations for the management of men receiving corticosteroids are given below.

- Use the lowest corticosteroid dose possible. Generally, doses below 2.5 mg prednisone equivalent/day result in minimal bone loss whereas doses above 10 mg/day will result in significant bone loss in most patients; doses between 2.5 and 10 mg/day result in some but not all patients losing bone, and monitoring BMD may be useful in these patients.
- Use an agent to prevent or reverse corticosteroid-induced bone loss. Alendronate 70 mg once-weekly is TGA approved for the prevention of corticosteroid-induced osteoporosis in patients on long-term corticosteroid therapy; risedronate 5 mg daily, 35 mg once-weekly and 150 mg once-monthly are TGA approved for the preservation of BMD in patients on long-term corticosteroid therapy; and zoledronic acid 5 mg once-yearly is TGA approved for the prevention of corticosteroid-induced bone loss in patients with osteoporosis associated with long-term corticosteroid use. Only risedronate has any Government subsidy relating to use in preventing corticosteroid-induced bone loss: risedronate 5 mg daily and 35 mg once-weekly are RPBS-listed for the preservation of BMD in osteopenic patients on long-term, high-dose corticosteroid therapy (prednisolone equivalent dose of greater than 7.5 mg daily for three months or more).
- Use an agent to treat corticosteroid-induced osteoporosis. Alendronate, risedronate and zoledronic acid are effective in men with corticosteroid-induced osteoporosis, and risedronate reduces vertebral fractures in men with corticosteroid-induced osteoporosis.[31] Both risedronate and zoledronic acid are listed on the PBS for the treatment of corticosteroid-induced osteoporosis, whereas alendronate is TGA approved for this indication. Teriparatide is also TGA approved for the treatment of osteoporosis associated with prolonged corticosteroid therapy, and may have superior effects to the bisphosphonates, but is usually reserved for patients with severe osteoporosis who continue to sustain fractures.
- Use calcium and vitamin D supplements as an adjunctive therapy. Although calcium supplementation alone does not prevent rapid bone loss in patients commencing corticosteroid therapy, dietary supplementation with both calcium and vitamin D is an appropriate adjunctive therapy
- Use testosterone in men with coexisting hypogonadism.

Conclusion

Osteofragility fractures occur more commonly in elderly men than diseases such as prostate or bowel cancer. Men who suffer fractures and have osteoporosis are four to five times more likely to suffer another spontaneous fracture, often with an adverse outcome. Use of antiosteoporotic therapies can reduce fracture risk by at least 40 to 50%. Despite this, the diagnosis of osteoporosis is largely ignored in most elderly men who are admitted to hospital with major fractures, and they are discharged without appropriate or osteoporosis-relevant investigation or treatment. Increasing the awareness of osteoporosis may lead to its better management and improved health outcomes in men. MT

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COMPETING INTERESTS: Associate Professor Diamond is a scientific advisor to Eli Lilly, Merck Sharp and Dohme, Novartis, Roche, Sanofi-Aventis and Servier, but does not receive financial remuneration. He has received honoraria for GP lectures and travel grants to attend local and international bone meetings from all the above companies. Professor Ebeling has received research or other funding from Eli Lilly, Merck Sharp and Dohme, Novartis, Roche-GlaxoSmithKline, Sanofi-Aventis, Amgen and Servier.

MedicineToday PEER REVIEWED ARTICLE
MedicineToday 2009; 10(1): 18-25
Updated June 2010

Understanding the importance of vitamin D for bone and systemic health

Vitamin D deficiency can result in disorders such as abnormal bone metabolism (osteoporosis and osteomalacia) and reduced muscle function (leading to increased falls). There is increasing evidence that inadequate levels of vitamin D can also contribute to, or exacerbate, cardiovascular disease, type 2 diabetes, cellular dedifferentiation (oncogenesis) and immune derangement.

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Vitamin D is an essential regulator of calcium homeostasis, cellular division and immune function. The active vitamin D metabolite, 1α,25-dihydroxyvitamin D (calcitriol), through its ligand the vitamin D receptor, directly regulates gene expression in a wide variety of vitamin D target cells, and is central to the regulation of vitamin D physiology.[1] Circulating as a hormone, it regulates calcium and phosphate homeostasis. At the cellular level, it acts by suppressing or upregulating gene transcription and altering cell signalling and cellular differentiation.[1]

Vitamin D deficiency can result in disorders such as abnormal bone metabolism (osteoporosis and osteomalacia) and reduced muscle function (leading to increased falls).[2] There is increasing evidence that inadequate levels of vitamin D can also lead to, or exacerbate, cardiovascular disease,

IN SUMMARY

- **Vitamin D is an essential regulator of calcium homeostasis, cellular division and immune function.**
- **Vitamin D deficiency can result in disorders such as abnormal bone metabolism and reduced muscle function. There is increasing evidence that inadequate levels of vitamin D can also contribute to, or exacerbate, cardiovascular disease, type 2 diabetes, cellular dedifferentiation and immune derangement.**
- **Levels of serum 25-hydroxyvitamin D of 50 to 75 nmol/L and above are considered optimal for maintaining good 'overall health'.**
- **Adequate sunlight exposure remains the simplest effective way to maintain vitamin D levels. Exposure of around 15% of the body surface (that is, the hands, face and arms or legs) to around one-third of a minimal erythemal dose of sunlight (the amount that causes faint redness), most days is recommended for adequate endogenous vitamin D synthesis.**
- **In patients with a mild to moderate vitamin D deficiency, supplementation with 3000 to 5000 IU (75 to 125 µg) oral cholecalciferol per day for at least six weeks is recommended.**
- **In patients with severe vitamin D deficiency, higher dosages of vitamin D supplementation (above 5000 IU per day) are usually required.**

type 2 diabetes, cellular dedifferentiation (oncogenesis) and immune derangement (autoimmune disorders such as lupus, type 1 diabetes, rheumatoid arthritis and multiple sclerosis).[1-3] The most compelling evidence for the pleiotropic actions of vitamin D, however, comes from reports linking vitamin D deficiency to higher risks of death from all causes, by mechanisms as yet unknown.[4]

One of the major uncertainties in vitamin D research is the optimal level of serum 25-hydroxyvitamin D (25-OHD) that is required for 'good health'.[5-7] The definitions of vitamin D deficiency as a serum 25-OHD level of below 25 nmol/L and insufficiency as a serum 25-OHD level of between 25 and 50 nmol/L have largely been derived from metabolic bone studies.[8] Optimal levels may be higher, around 75 nmol/L. Healthy individuals who receive adequate sunlight exposure usually have serum 25-OHD levels above 90 nmol/L.[1] This review will focus on some of the clinical evidence linking low levels of serum 25-OHD to a number of diseases that are sensitive to vitamin D, and outlines the importance of maintaining high levels of serum 25-OHD for disease prevention.

Vitamin D metabolism

The main source of vitamin D is its formation endogenously in the skin through exposure to ultraviolet B light (Figure 1).[9,10] Vitamin D can be ingested orally as either plant-derived vitamin D_2 (ergocalciferol) or animal-derived vitamin D_3 (cholecalciferol), which is the type made in the skin. Circulating vitamin D is transported to the liver and converted to 25-OHD. This is the major circulating metabolite, with a half-life of 12 to 19 days. It is converted intracellularly to the highly active metabolite 1α,25-dihydroxyvitamin D, which has a half-life of only a few hours. The enzyme 1α-hydroxylase, which is found in the kidney and a number of other cell types, is crucial to the activation of this pathway and serves as the regulator of calcitriol production.[1,2] Most circulating vitamin D compounds are bound to vitamin D carrier proteins, principally vitamin D binding protein. The affinity of vitamin D binding protein for calcitriol is high, so only a small fraction of the calcitriol circulates in a 'free' form.[1]

Vitamin D metabolites decrease by approximately 40 to 50% in patients after they reach the age of 65 years, resulting in approximately a 40% reduction in calcium absorption. This may occur as a result of age-related factors (such as low dietary intake, diminished sunlight exposure, low previtamin D concentrations in the skin and a decline in renal function) and secondary causes (Table 1).[1,2,10] Serum 25-OHD is the key metabolite reflecting vitamin D stores in the body.

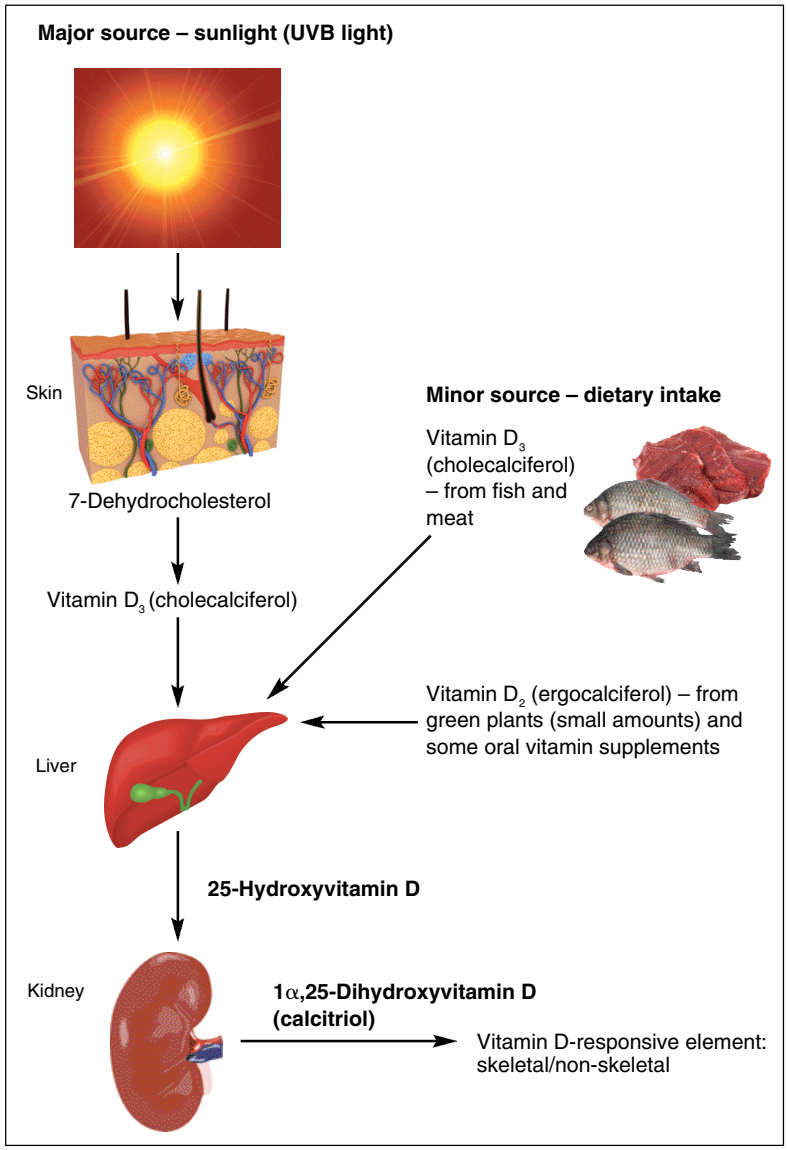

Figure 1. The pathway for vitamin D synthesis and its modes of action.

Bone and muscle

Vitamin D deficiency and fracture risk

Calcitriol facilitates the absorption of calcium, phosphate and magnesium (which together constitute about 90% of the skeleton) from the

Table 1. Causes of vitamin D deficiency

Reduced production or intake of vitamin D

- Low sunlight exposure or availability of ultraviolet B (due to dark skin pigmentation, ageing, veiling, excessive use of sunscreens, chronic illness, avoidance of sun due to chronic skin disorders or cancers)
- Low dietary intake

Reduced absorption of vitamin D from the gut

- Pancreatic and bile duct disorders
- Small bowel disorders – coeliac disease, inflammatory bowel disorders and small bowel resection

Reduced synthesis or enhanced degradation of 25-hydroxyvitamin D

- Chronic liver diseases – hepatitis, cirrhosis
- Chronic anticonvulsant therapies (epilepsy)

Reduced synthesis of 1α,25-dihydroxyvitamin D

- Chronic renal disease

small intestine, maintains calcium homeostasis through this and its interaction with parathyroid hormone, and promotes skeletal mineralisation and bone formation by regulating specific osteoblast gene transcription.[11] It also controls bone turnover and bone remodelling through the receptor activator of nuclear factor-kappaB ligand (RANKL) and osteoprotegerin cytokine system.[11]

A mild deficiency in vitamin D (defined as a serum 25-OHD level of between 25 and 50 nmol/L) is usually associated with secondary hyperparathyroidism and an increase in age-related bone loss.[12] Severe vitamin D deficiency (defined as a serum 25-OHD level of below 12.5 nmol/L) is usually associated with a mineralisation defect.[11] Figures 2a to c show examples of fragility fractures occurring with vitamin D deficiency).[11] A decrease in bone mineral density and an increase in fracture rates have been reported in several cross-sectional studies in individuals with the lowest quartile of serum 25-OHD (in one study this was defined as below 47.5 nmol/L).[13,14]

Vitamin D is also responsible for regulation of muscle function.[2,3] Severe vitamin D deficiency results in a metabolic myopathy.[1] Increases in body sway and quadriceps muscle weakness have been reported in patients with levels of serum 25-OHD below 30 nmol/L.[15] A dose–response relationship between vitamin D status and muscle health has been reported in the National Health and Nutrition Examination Survey (NHANES), with increasing muscle strength continuing through the reference range of 25 to 90 nmol/L of 25-OHD.[15] These findings suggest a link between vitamin D deficiency, falls and an increased risk for hip fracture.

Vitamin D therapy and fracture reduction

Vitamin D and its analogues correct vitamin D deficiency by normalising gut calcium absorption and parathyroid function, establishing normal bone turnover, increasing bone mass and reducing falls and fracture risk.[12-14] The greatest therapeutic effect of vitamin D supplementation has been seen in high-risk individuals with low levels of serum 25-OHD. These individuals demonstrated increases in bone densities ranging from between 0 and 4% in patients who were vitamin D insufficient to between 10 and 40% in those who were vitamin D deficient.[16,17]

Vitamin D therapy has also been shown to improve reflexes and reduce the risk of body sway and falls.[18] In a meta-analysis (three randomised trials, n = 5572), vitamin D supplementation (700 to 800 IU per day) with or without calcium supplementation was associated with a 26% reduction in the risk of sustaining a hip fracture versus calcium supplementation alone or placebo.[19] The musculoskeletal benefits of vitamin D demonstrated in clinical trials may partly be attributed to the combined effect of additional oral calcium supplementation.

Cardiovascular system

Observational studies in humans have demonstrated an inverse relationship between calcitriol and blood pressure or plasma renin levels in normotensive and hypertensive individuals.[20] Two randomised controlled trials have shown that levels of serum 25-OHD of 75 nmol/L or above were associated with the lowest incidence of hypertension over a four-year follow-up period.[21,22] In a recent prospective study of 3258 patients scheduled for coronary angiography, individuals with levels of serum 25-OHD in the lower two quartiles (14 to 42 nmol/L) had an almost doubling in cardiovascular mortality compared with those in the highest quartile.[4]

Reports have also shown that vitamin D therapy not only reduced blood pressure in hypertensive individuals, but also resulted in a 50% lower risk of heart attack and an 80% lower risk of peripheral vascular disease.[23]

Oncogenesis

Vitamin D deficiency and cancer risk

There are a number of cancers that are vitamin D-sensitive, where there is some evidence of an association between low vitamin D and increased risk of, or mortality from the disease. These include cancers of the gastrointestinal tract (colon, oesophageal, gall bladder, gastric, pancreatic and rectal) and urogenital tract (bladder, kidney and prostate), and breast, endometrial and ovarian cancer, as well as lymphoma.[24] Vitamin D inhibits tumour growth by its tumour suppressor action on more than 400 tumour-related genes.[3]

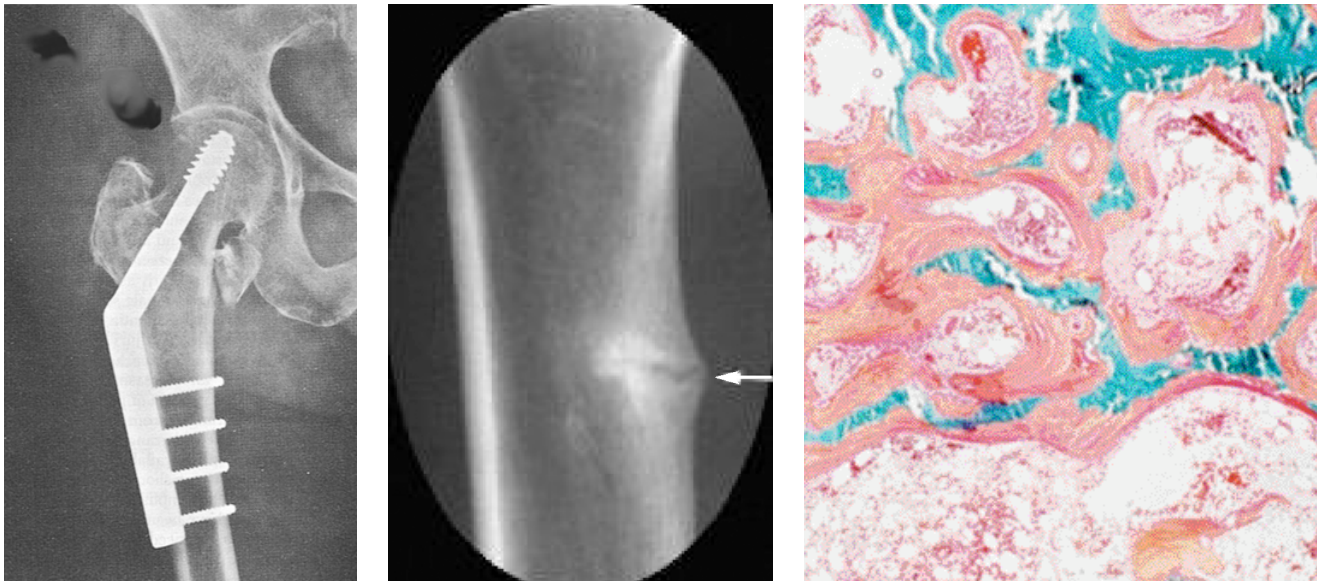

Figure 2. Examples of fragility fractures occurring in patients with vitamin D deficiency. a (left). X-ray of osteoporotic hip fracture treated by surgical stabilisation. b (centre). X-ray of pseudofracture of femoral shaft (also known as Looser zone). c (right) Bone biopsy of classic osteomalacia showing decreased bone volume (blue) and increased osteoid or unmineralised bone (orange).

Individuals who live in regions of the world where sunlight exposure is low (e.g. some countries in the Northern hemisphere)[25] or who have low vitamin D intakes or low levels of serum 25-OHD are at higher risk of developing breast, colon and prostate cancer.[26] Moreover, women with high levels of serum 25-OHD have been shown to have lower mortality rates from breast cancer than those with low levels.[27] In the laboratory setting, animals implanted with tumours have been shown to have lower rates of tumour growth and size when treated with vitamin D.[28]

Vitamin D therapy and cancer risk

There is only one randomised control trial to date relating to vitamin D therapy and cancer risk. In this trial, postmenopausal women (n = 1179) aged over 55 years were randomised to supplemental calcium alone (1400 to 1500 mg daily), supplemental calcium plus vitamin D_3 (1100 IU [27.5 µg] daily) or placebo for four years. During this period, levels of serum 25-OHD increased from 71.8 (+/- 20.0) to 96.0 (+/- 21.4) nmol/L in the calcium plus vitamin D_3 group. All-cancer incidence was reduced by 77%.[29]

Autoimmunity

Cells of the immune system, have receptors for calcitriol as do other nucleated cells.[2] Adequate vitamin D levels appear to be important in immune regulation, in particular in relation to the development of autoimmune diseases such as type 1 diabetes, multiple sclerosis, inflammatory bowel disease and rheumatoid arthritis.[30-32] There is epidemiological evidence for a latitude gradient for multiple sclerosis.[30] The incidence of multiple sclerosis is low in the tropics and increases with distance from the equator in both hemispheres. A lower risk of multiple sclerosis with higher intakes of vitamin D was also reported in studies of over 95,000 nurses.[33]

A Finnish study that examined neonatal records of over 10,000 children found that those who took recommended vitamin D supplements of 2000 IU (50 µg) per day during infancy had one-fifth the risk of developing type 1 diabetes over the next 30 years. Conversely, those infants with suspected rickets had a threefold increase in risk of developing type 1 diabetes over the next 30 years.[32,34]

Although these sorts of studies show association, rather than causation, vitamin D status or supplementation with vitamin D compounds is clearly implicated in modulating the severity and time course of several animal models of autoimmune disease, including type 1 diabetes, inflammatory bowel disease, arthritis and systemic lupus erythematosis.[1-3] Adequate vitamin D status appears to help maintain an appropriate balance between effector cells that destroy target cells and the regulatory immune cells that dampen down the response.[3]

Innate immunity

It has long been suspected that low levels of vitamin D predispose individuals to infections, but this has been difficult to disentangle from other socioeconomic factors and, until recently, was poorly

Ten important facts relating to vitamin D

- Vitamin D is important for the normal functioning of most cells.
- Vitamin D deficiency results in calcium malabsorption from the gut.
- Chronic vitamin D deficiency results in increased parathyroid hormone activity, liberation of calcium from skeletal bone stores, osteoporosis and increased risk of falls and fragility fractures.
- Patients with serum 25-hydroxyvitamin D levels of less than 50 nmol/L are at risk for fragility fractures.
- People at high risk of vitamin D deficiency include:
  - elderly people
  - people who avoid sunlight due to medical reasons
  - people who are institutionalised or chronically ill
  - people who are modestly clothed (veiled) for religious reasons
  - people who use overzealous amounts of block-out sunscreens (even when there is little or no sun exposure or in winter)
  - people who have dark skin, such as individuals from the Horn of Africa, Middle East and Asia
  - people with secondary medical disorders such as chronic hepatobiliary, coeliac and renal disease
  - obese individuals undergoing bariatric surgery for their metabolic disorder.
- Correcting vitamin D deficiency with optimal therapy reduces risk of fracture by increasing bone strength and reducing risk of falls.
- Serum 25-hydroxyvitamin D levels above 75 nmol/L are considered optimal for maintaining good 'overall health'.
- The principal source of vitamin D is from the action of sunlight (ultraviolet B radiation) on a vitamin D precursor in the skin.
- To be most effective, vitamin D supplements should always be administered with adequate calcium supplements because of a likely combined deficiency.
- The recommended daily vitamin D requirement is controversial, but an intake of 1000 to 2000 IU (25 to 50 µg) per day is considered optimal for all body functions. In patients with a mild to moderate vitamin D deficiency, supplementation with 3000 to 5000 IU (75 to 125 µg) oral cholecalciferol per day for at least six weeks is recommended. Dosages above 5000 IU per day may be required to correct a severe vitamin D deficiency.

understood.[35] In 1903, Niels Finsen won the Nobel prize for showing that sun exposure ameliorated cutaneous tuberculosis.[36] It took more than 100 years for the mechanism to be elucidated. *Mycobacterium tuberculosis* activates Toll-like receptors on macrophages, which are part of the innate immune system.[36] This triggers upregulation of the vitamin D receptor and the 1α-hydroxylase enzyme that converts 25-OHD into calcitriol. Provided that there is an adequate level of 25-OHD, it is converted locally into calcitriol. This then acts on the vitamin D receptor to promote the production of antimicrobial peptides (defensins), which kill bacteria.[37] It is unclear at this stage whether this mechanism is important for a broad range of pathogens or only applicable to limited infective agents.

Skin conditions

Calcitriol has an antiproliferative effect on cells, which may partly contribute to anticancer activity. This effect also applies to skin keratinocytes.[38] Calcitriol and, more recently, less calcaemic vitamin D analogues have been used with some success in the hyperproliferative disorder of psoriasis. The observed usefulness of sun exposure in the management of psoriasis may be explained by vitamin D being produced by ultraviolet B radiation and then being converted to the active calcitriol in the skin.[39] There is some evidence, mainly from cell and animal studies, showing that increased levels of calcitriol in the skin may contribute to protection from ultraviolet radiation, particularly by reducing the DNA damage that occurs as a result of sun exposure.[38]

What is a normal serum 25-OHD level?

Adults with an abundant skin surface to sun exposure (e.g. sea rescue life savers) have mostly been shown to have levels of serum 25-OHD above 90 nmol/L. This is very similar to the levels that were likely to be seen in our ancestors who ploughed the fields or hunted in the wild. In contrast, individuals who live in cities and work all day in offices may have serum 25-OHD levels below 50 nmol/L,[40] particularly at the end of winter.

Other individuals at risk of vitamin D deficiency include those with limited sunlight exposure (due to old age and limited mobility), those who live at high latitudes and those who avoid the sun because of chronic skin disorders or cancers. Individuals with a reduced availability of ultraviolet B due to dark skin, pigmentation, veiling or sunscreens, a low dietary intake (although foods provide less than 10% of requirements), malabsorption (due to pancreatic, bile and small bowel disorders, especially coeliac disease) or

other chronic illnesses that impair the synthesis of active metabolites (chronic liver and renal disease) are also at risk of vitamin D deficiency.[2,3,8]

Vitamin D therapy

Adequate sunlight exposure remains the simplest effective way to maintain levels of vitamin D. Exposure of around 15% of body surface (that is, the hands, face and arms or legs) to around one-third of a minimal erythemal dose of sunlight (the amount that causes faint redness), most days, is recommended for adequate endogenous vitamin D synthesis. For people with fair skin, six to eight minutes of sun exposure just before 11 a.m or just after 3 p.m most days in summer, or around 20 minutes at noon most days in the winter (eight to 40 minutes, depending on latitude) should be adequate. Although sun exposure can be used to treat vitamin D deficiency, this has to be balanced against the risk of skin damage.[8-11]

Oral cholecalciferol may be the most appropriate agent to treat vitamin D deficiency. To be most effective, vitamin D supplements should be administered with adequate amounts of calcium supplements because of a likely combined deficiency (combined vitamin D and calcium supplements are available).

Calcitriol is not considered ideal for treating patients with simple vitamin D deficiency, in part because of the potential risk of hypercalcaemia. Vitamin D_2 – ergocalciferol – is less effective at raising serum 25-OHD levels, and is therefore generally not used for dietary supplementation.[41]

The daily requirement for vitamin D is probably between 1000 and 2000 IU (25 to 50 µg) per day.[42] A larger dose is probably required for cancer prevention, aiming to maintain levels of serum 25-OHD above 75 nmol/L. Vitamin D enters fat, but whether it can be released from there is unclear.

In patients with a mild to moderate vitamin D deficiency, supplementation with 3000 to 5000 IU (75 to 125 µg) per day oral cholecalciferol is recommended (three to five capsules of oral cholecalciferol 1000 IU per day). At least six weeks of therapy is required to achieve levels of serum 25-OHD above 75 nmol/L. In patients with a moderate to severe vitamin D deficiency, higher dosages of vitamin D supplementation (above 5000 IU per day) are usually required. Higher oral dose formulations (10,000 to 25,000 IU capsules) can be used and are available through local compounding chemists.

Vitamin D (cholecalciferol) can be administered by intramuscular injection to facilitate compliance in elderly patients. Intramuscular injections can be monthly (50,000 IU), four-monthly (100,000 IU), six-monthly (300,000 IU) or 12-monthly (600,000 IU) doses. Although these dosage regimens have been considered safe provided patients do not have underlying conditions associated with hypercalcaemia, there is recent evidence of a potential increase in falls and fracture rates when administered chronically for five years to elderly individuals.[43] Intramuscular megadose formulations are most beneficial for patients with malabsorption or those with persistent vitamin D deficiency, but are only available through tertiary care hospitals.

Summary

There is now level 1 evidence demonstrating fracture risk reduction in vitamin D-deficient individuals supplemented with optimal vitamin D. Although an association between vitamin D deficiency and numerous medical disorders has been described, there remains a question about its role in direct causality. The box on page 42 lists some important facts relating to vitamin D.

A large-scale, placebo-controlled clinical trial conducted over several years with mortality rates as a primary outcome, in addition to several substudies investigating effects of vitamin D supplementation on other secondary outcomes (including infection, autoimmune diseases, progression of type 2 diabetes mellitus and cancer) is undoubtedly needed. MT

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COMPETING INTERESTS: Associate Professor Diamond is a scientific advisor to Eli Lilly, Merck Sharp & Dohme, Novartis, Roche, Sanofi-Aventis and Servier, but does not receive financial remuneration. Honoraria for GP lectures and travel grants to attend local and international bone meetings have been received from all the above companies. Professor Mason has received research funding from Servier (France) and Nycomed (Germany) and honoraria from Abbott Pharmaceuticals and Blackmores (Australia).

MedicineToday PEER REVIEWED ARTICLE

MedicineToday 2010; 11(5): 56-66
Updated June 2010

The fracture cascade

managing individuals who continue to fracture on antiosteoporotic therapies

The effective management of individuals with osteoporosis should include not only the prescribing of an antiosteoporotic agent but also regular encouragement to ensure drug persistence and adherence.

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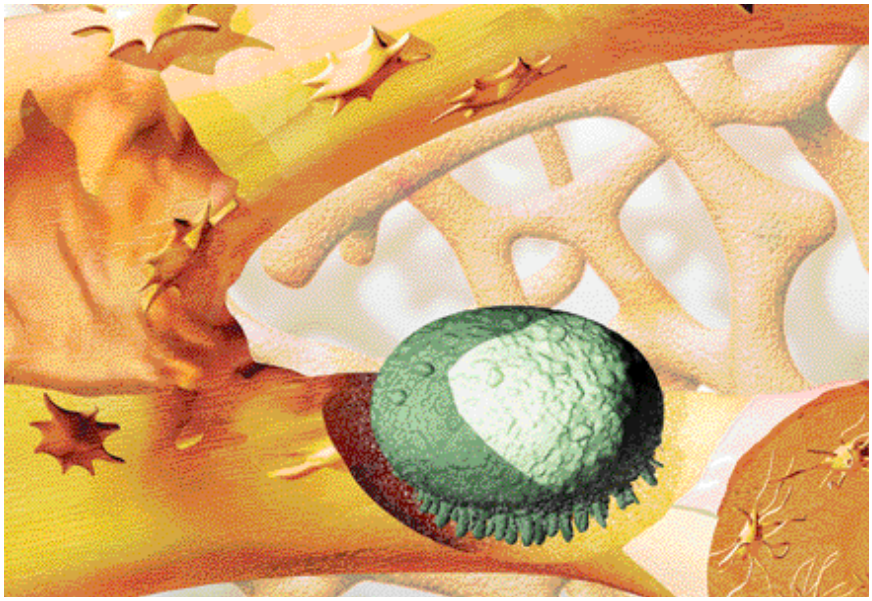
Fractures in people with osteoporosis can occur with minimal trauma such as falls or even spontaneously while coughing, sneezing or just turning in bed. The less the force involved in the injury, the greater the 'brittleness' of the individual's bone, reflecting the severity of his or her osteoporosis. Following a single fracture, the risk of further fracture is increased, resulting in the 'fracture cascade'. Recurrent fractures can be devastating, leading to loss of confidence, despair and physical, psychological and social decline.[1,2]

In women, fractures of the wrist (Colles fracture) and ankle occur within five to 10 years after the onset of menopause. Spinal, hip and pelvic fractures increase in incidence in men and women into their eighties and beyond.[3] The number of individuals suffering from the consequences of osteoporotic fractures in the year 2000 was

IN SUMMARY

- **Following a single fracture in an individual with osteoporosis, the risk of further fracture is increased, resulting in the 'fracture cascade'.**
- **The effective management of individuals with osteoporosis should include not only the prescribing of an antiosteoporotic agent but also regular encouragement to ensure persistence and adherence with taking their medications.**
- **Antiosteoporotic agents reduce the risk of subsequent fractures rather than prevent them. Unfortunately, this means that there will be a number of individuals who comply with therapy and continue to fracture.**
- **Factors influencing recurrent fracturing while on antiosteoporotic therapy include the antiosteoporotic agent being used and compliance with taking it, calcium and vitamin D status, smoking, alcohol consumption, secondary causes of osteoporosis, trauma due to falls and abnormal bone remodelling due to long-term (more than five years) use of antiresorptive osteoporotic agents.**
- **People who fracture recurrently usually require detailed evaluation and appropriate treatment, and specialist referral is recommended.**
- **Resistance and balance training exercise programs improve reflexes and muscle strength and reduce the risk of falls.**
- **The atypical peripheral fractures reported to be associated with long-term bisphosphonate therapy should not detract from prescribing bisphosphonates. However, caution and avoidance of indefinite long-term exposure to these medications must be considered in all patients.**



PHOTOLIBRARY

Figure 1. An osteoclast destroying bone trabeculae. Antiresorptive agents act by inhibiting osteoclast bone resorption.

Table 1. Potential reasons for refracturing on antiosteoporotic agents

- Severity of osteoporosis
- Limited antifracture efficacy of antiosteoporotic agent being used
- Poor drug adherence or persistence
- Suboptimal calcium and/or vitamin D serum levels
- Lifestyle factors (smoking and alcohol excess)
- Undiagnosed secondary causes of osteoporosis
- Recurrent falls
- Antiosteoporotic agent-related abnormalities in bone remodelling

conservatively estimated to be 50 million worldwide.

There are many reasons why individuals sustain fractures. As patients generally believe that treatment with effective antiosteoporotic agents will stop recurrent fractures, it is no wonder that many start panicking when they continue to fracture while they are taking these drugs.

Reasons for recurrent fracture on treatment

Some of the reasons why individuals continue to fracture while on antiosteoporotic therapy are discussed below and summarised in Table 1.

Efficacy of antiosteoporotic agents

All individuals who sustain a minimal trauma or osteoporotic fracture should receive antiosteoporotic therapies. The risk of suffering a further fracture is at least doubled, irrespective of the type of fracture, and may even be higher if the individual is older than 70 years or has an underlying medical illness that predisposes to osteoporosis.[4,5]

Antiosteoporotic therapies can be classified as antiresorptive or anticatabolic (those agents that inhibit or slow the bone resorption phase of the bone remodelling cycle – Figure 1) and anabolic (those agents that stimulate new bone formation). The antiresorptive agents include the bisphosphonates, oestrogens and progestogens used as hormone therapies and the selective oestrogen receptor modulator raloxifene.

The bisphosphonates have differential effects on hip and other nonvertebral fracture reduction according to their potency (Table 2). Strontium ranelate is an antiosteoporotic agent with a dual mechanism of action: it has been shown to stimulate new bone formation, probably by recruiting osteoblast precursors, as well as to decrease bone resorption.

All antiosteoporotic agents are effective. In randomised clinical trials, they have been shown to reduce the risk of subsequent fractures by 25 to 70%, rather than by 100%.[6] Unfortunately, this means that there will be a number of individuals who comply with therapy and continue to fracture.

Optimal calcium and vitamin D supplementation

The efficacy of antiosteoporotic agents is dependent on individuals having optimal levels of calcium and vitamin D and optimal lifestyles.

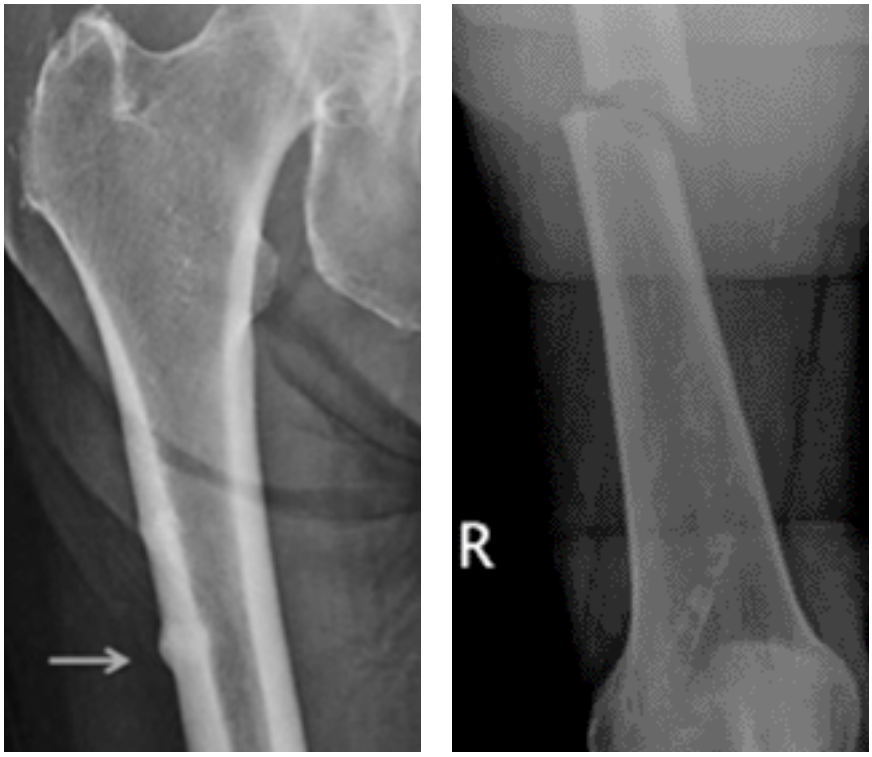
Most randomised trials have been performed with calcium and vitamin D as additives to antiosteoporotic agents. A daily intake of 1500 to 2000 mg of calcium (dietary and/or supplemental) is recommended when prescribing antiosteoporotic agents to optimise skeletal efficacy.[6,7] This may need to be balanced against gastrointestinal side effects (e.g. constipation) and possible cardiovascular risks, which are still debated. Vitamin D deficiency is common in patients with osteoporosis and contributes to the fracture risk. Cholecalciferol should be added if individuals have a serum 25-hydroxyvitamin D (25-OHD) level of less than 75 nmol/L.[8,9]

Individuals should be encouraged to modify lifestyle factors such as smoking and excessive alcohol intake because stopping smoking and reducing alcohol consumption may add to fracture risk reduction.

Table 2. Bisphosphonates: potencies and osteoporosis treatment regimens*

Bisphosphonate	Relative potency	Route	Regimen for osteoporosis and cancer-induced bone disease	PBS listing and availability†
Etidronate	1x	Oral	Osteoporosis: 400 mg daily for two weeks of every three-month cycle; calcium carbonate 1.25 g daily for other 76 days	Listed on PBS for established osteoporosis in patients with fracture due to minimal trauma
Clodronate	10x	Oral	Osteolytic lesions (breast cancer metastases, multiple myeloma): 800 mg twice daily	Listed on PBS for bone metastases from breast cancer. Not TGA approved for osteoporosis
Pamidronate	100x	Intravenous	Osteolytic lesions (breast cancer metastases, advanced multiple myeloma): 90 mg infusion every three to four weeks, administered over two hours Osteoporosis (off-label use): 30 to 90 mg infusion every four to six months, administered over two to three hours	Listed on PBS for bone metastases from breast cancer. Not TGA approved for osteoporosis
Alendronate	1000x	Oral	Osteoporosis: 70 mg once weekly	Listed on PBS for osteoporosis in patients aged 70 years and older with confirmed osteoporosis and in patients with fracture due to minimal trauma
Ibandronic acid	5000x	Oral	Metastatic bone disease from breast cancer: 50 mg daily (also 6 mg intravenous infusion every four weeks, but private hospital authority required) Osteoporosis (off-label use): 150 mg once monthly	Listed on PBS for bone metastases from breast cancer. Not TGA approved for osteoporosis Once-monthly 150 mg oral dose is registered overseas for osteoporosis treatment and prevention in postmenopausal women. Infusion 3 mg/3 mL every three months is TGA approved for use in the treatment of postmenopausal osteoporosis but is not available
Risedronate	5000x	Oral	Osteoporosis: 35 mg once weekly or 150 mg once monthly (also 5 mg daily)	Listed on PBS for osteoporosis in patients aged 70 years and older with confirmed osteoporosis and in patients with fracture due to minimal trauma, and for corticosteroid-induced osteoporosis
Zoledronic acid	10,000x	Intravenous	Osteoporosis: 5 mg infusion once yearly, administered over 15 to 30 minutes, maximum of three doses	Listed on PBS for osteoporosis in patients aged 70 years and older with confirmed osteoporosis and in patients with fracture due to minimal trauma, and for corticosteroid-induced osteoporosis

ABBREVIATIONS: PBS = Pharmaceutical Benefits Schedule; TGA = Therapeutic Goods Administration.
* As of 1 June 2010. † Various authorities are required for the prescription of bisphosphonates on the PBS.



Figures 2a and b. Atypical femoral diaphyseal fractures in two individuals treated with long-term alendronate. a (left). Stress fracture with callus formation on the outer cortex of the femoral shaft. b (right). Complete transverse fracture through a previous stress fracture.

Drug persistence and adherence

Less than 40% of women persevere with long-term therapy with bisphosphonates for osteoporosis. Published studies demonstrate that the antifracture efficacies of bisphosphonates are reduced by at least 50% in women who comply poorly with their medications.[10,11] Men have been poorly researched in this respect, and data are not available.

Bisphosphonate side effects such as heartburn, gastrointestinal upset, bone pains and skin rashes often lead to poor compliance and reduced long-term adherence.[12] Many of the oral bisphosphonates are very poorly absorbed from the gut; alendronate and risedronate, for example, need to be taken on an empty stomach, in an erect position and at least 30 minutes prior to ingestion of a meal so as to allow for adequate gut absorption. Incorrect dosing may lead to suboptimal drug absorption and lack of efficacy.[12] Individuals must comply with the 'how to take' pharmaceutical instructions when administering their antiosteoporotic medications. Ingestion of any foods or liquids other than water may result in suboptimal absorption and reduced efficacy.

Changing to newer drug regimens – once-weekly (alendronate and risedronate) and once-monthly (risedronate) oral preparations or the once-yearly parenteral infusion (zoledronic acid) – have been shown to improve drug compliance.[13] Strict dosing instructions may lessen drug-related side effects, improve persistence and adherence and result in reduced risk of recurrent fractures.[12,14] The use of formulations of alendronate and risedronate combined with cholecalciferol may enhance compliance by obviating the need for additional oral vitamin D supplementation.

Secondary causes of osteoporosis

Recurrent fractures may occur in individuals with secondary causes of osteoporosis who receive antiosteoporotic agents and in whom their underlying disorder has been overlooked. Secondary causes of osteoporosis should be suspected in women aged over 40 years who suffer low trauma osteofragility fractures and those with a bone mineral density (BMD) Z-score of less than -2.0. Medical illnesses such as coeliac disease, blood dyscrasias (e.g. myeloma), hyperthyroidism, hyperparathyroidism, anorexia and vitamin D deficiency and medications such as corticosteroids may result in accelerated bone loss and an increased fracture risk.[15] Some of these disorders may not only cause a dramatic decline in BMD and alteration in bone quality but may also result in proximal muscle weakness and propensity to falling.

The premature onset of menopause, whether spontaneous or following chemotherapy, results in an increased lifetime fracture risk because these women live longer with a decreased bone density than do women who have natural menopause. Women with breast cancer treated with aromatase inhibitors can experience rapid rates of bone loss (since these medications cause profound oestrogen deficiency and resultant high bone turnover and net bone loss).[16] Similarly, men receiving androgen deprivation therapy for prostate cancer and those with 'silent' male testosterone deficiency are at increased risk (through the low sex steroid levels of hypogonadism resulting in high bone turnover).[17]

Investigating for and treating the underlying cause may significantly reduce the risk of recurrent fractures. Detailed discussion relating to secondary causes of osteoporosis in women and men have previously been published in *Medicine Today*.[15,18]

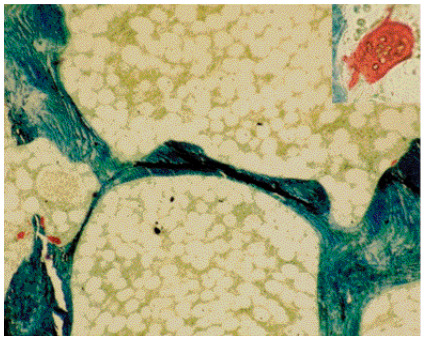
Table 3. Managing recurrent osteoporotic fracturing

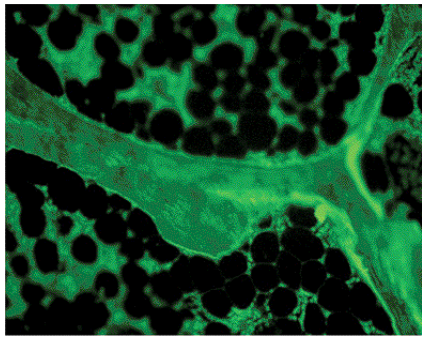
- Investigate for causes of recurrent falls and severity of osteoporosis
- Check compliance with antiosteoporotic medication
- Check intake of calcium and vitamin D
- Encourage stopping smoking and limiting excessive alcohol intake
- Evaluate and treat possible secondary causes of osteoporosis
- Encourage participation in resistance and balance training exercise programs
- Optimise testosterone replacement in men with hypogonadism
- Assess bone turnover by measuring markers of bone resorption
- Treat severe osteoporosis more aggressively with an anabolic agent

Recurrent falls and repetitive trauma

Trauma remains the most common cause of recurrent fractures. Individuals who fall because of balance disorders due to oversedation, overtreatment with antihypertensive drugs or middle ear disease (vertigo), or because of poor vision (cataracts and age-related macular degeneration) or recurrent mini-strokes (microvascular cerebral disease) are susceptible to recurrent fractures.[19,20] Antiosteoporotic agents will not reduce their risk of falling and hence it is important to investigate and manage the specific causes of falling.

General practitioners have a critical role in assessing and managing the contributions of balance, vision and medications associated with falling. Although many patients fall, it is those who need assistance to regain their feet who are most at risk of fracture. Review by a geriatrician and an occupational therapist, enrolment in falls prevention and balance programs and the use of hip protectors are important strategies to minimise the risk of fracture.[21]





Figures 3a and b. Histomorphometric changes of bone turnover suppression in a bone biopsy specimen taken from an individual with adynamic bone disease treated with long-term alendronate. a (left). Static bone histomorphometry showing minimal osteoid matrix synthesis on the surfaces of cancellous bone due to reduced osteoblast activity and large inactive osteoclasts with multiple nuclei lying dormant on the bone surface (see insert of a magnified view of an osteoclast) due to suppression of osteoclast activity by bisphosphonates. b (right). Low bone turnover demonstrated by the absence of tetracycline labels.

Abnormal bone remodelling and adynamic bone disease

Approximately 10% of the human skeleton is remodelled each year. Osteoblast activity (bone formation) and osteoclast activity (bone resorption) coupling and microdamage repair is crucial to maintaining a healthy skeleton.[22] Bone coupling is a mechanism whereby old bone is removed and replaced with new viable bone and stress risers (microfractures occurring along trabecular plates) are repaired. Normal bone turnover allows for microfracture repair and maintains optimal bone elasticity.

Antiresorptive agents act by inhibiting the bone remodelling cycle, inhibiting osteoclast bone resorption and allowing osteoblast bone formation to continue, with adequate bone formation to fill in the resorption pits. The antifracture efficacies of bisphosphonates relate to their avid binding affinity to hydroxyapatite crystals in bone, resulting in long-term skeletal retention. When given for protracted periods, large stores of the bisphosphonates are recycled in bone and may result in marked suppression of bone turnover. This can lead to adynamic bone disease in which the bone is homogenously hypermineralised, brittle and more susceptible to minimal trauma or spontaneous fracture (atypical fractures).[23] Also, suppression of bone turnover may contribute to the occurrence of osteonecrosis of the jaw, although this is rare.

Atypical peripheral fractures were reported in the late 1980s when etidronate (a first-generation bisphosphonate) was used for treating various metabolic bone disorders.[24,25] It was administered as an oral continuous daily dosage and often for a protracted time. This regimen was shown to cause bone mineralisation defects and focal osteomalacia. Later developments led to the use of a cyclical regimen (a 400 mg daily dose administered for two weeks of a three-monthly cycle) designed to mimic the normal bone remodelling cycle without causing prolonged suppression of bone turnover. This regimen resulted in effective fracture risk reduction without untoward effects onbone.

More recently, isolated reports have emerged in the literature of atypical femoral diaphyseal and sacroiliac fractures occurring in individuals receiving long-term aminobisphosphonates (Figures 2a and b).[26-30a] These newer agents – alendronate, risedronate and zoledronic acid

– are many times more potent than etidronate because of their avid uptake, low desorption, higher reattachment and less diffusion in bone (high bone affinity). Bone biopsies taken from individuals receiving these agents have shown severe suppression of bone turnover (Figures 3a and b).[26]

Atypical fractures have also been reported after treatment with the RANKL neutralising antibody denosumab.[30b] This drug also has the potential for contributing to the occurrence of osteonecrosis of the jaw.

Although the number of reports in the literature is growing, the incidence density (the person–time incidence rate) for a patient on a bisphosphonate sustaining atypical fractures is calculated to be as low as 1/1000 per year (95% confidence interval, 0.3–2).[29] Moreover, a review of 284 records for hip or femur fractures among 14,195 women in three trials – the Fracture Intervention Trial (FIT), the FIT Long-Term Extension (FLEX) trial and the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly Pivotal Fracture Trial (HORIZON-PFT) – found a total of only 12 fractures in 10 patients that were classified as occurring in the subtrochanteric or diaphyseal femur, a combined rate of 2.3 per 10,000 patient-years.[30]

Antiosteoporotic agents that significantly suppress bone turnover as part of their mechanistic effect to treat osteoporosis may, therefore, potentially cause harm with long-term use.[12,26-30] A fine balance is required to allow for 'optimal' inhibition of bone resorption yet allow sufficient turnover to repair microdamage. Individuals who sustain recurrent or atypical fractures and who have been treated with antiresorptive agents for more than five years require specialist referral and evaluation. However, it is often difficult to elucidate the cause for their recurrent fractures. Many have coexisting severe osteoporosis with BMD T-scores of less than -3.5 and remain at high risk of osteoporotic fractures. The decision to continue, suspend or change the treatment is a significant challenge that may warrant expert opinion.

Managing individuals with recurrent fractures

People who fracture recurrently usually require detailed evaluation and appropriate treatment, as described below and summarised in Table 3. Specialist referral is recommended.

Reducing falls

Patients should be investigated for the causes of recurrent falls and the severity of osteoporosis. GPs have a critical role in identifying individuals at risk of falling and sustaining recurrent fractures. Resistance and balance training exercise programs have been shown to improve reflexes and muscle strength and reduce falls risk.[31]

Improving medication compliance and calcium/vitamin D status

Compliance with antiosteoporotic medication should be checked, as should also intake of calcium and vitamin D.

Repeat BMD monitoring and regular patient review may enhance patient compliance with antiosteoporotic medications. If there are problems with compliance, then an annual intravenous infusion of a potent bisphosphonate such as zoledronic acid may be preferred to daily, weekly or monthly tablets.

High-dose vitamin D supplements (3000 to 5000 IU daily) are required to correct severe vitamin D deficiency.[9]

Modifying smoking and alcohol consumption

Lifestyle modification regarding stopping smoking and limiting excessive alcohol consumption should be encouraged.

Treating secondary osteoporosis

Any secondary causes of osteoporosis should be evaluated and treated.[15]

Optimising testosterone replacement

Testosterone replacement therapy in men with hypogonadism in whom testosterone is not contraindicated should be optimised. There is no role for anabolic steroids in women who continue to fracture.

Assessing bone turnover

Bone turnover can be assessed by measuring the markers of bone resorption. These include the degradation products of type 1 collagen such as amino or C-terminal ends of carboxytelopeptides (NTX or CTX) or urinary deoxypyridinoline excretion rates.[32]

Elevated resorption markers in an individual treated with an antiresorptive agent such as a bisphosphonate may suggest poor compliance, suboptimal drug absorption or an underlying secondary cause.[33] In contrast, individuals treated with long-term bisphosphonates who are found to have suppression in bone resorption markers may be at risk for adynamic bone disease.

Treating severe osteoporosis

Severe osteoporosis may be treated more aggressively with an anabolic antiosteoporotic agent. There is no role for combining different classes of antiresorptive agents (e.g. a bisphosphonate with raloxifene or strontium ranelate).

Individuals with multiple spinal fractures (two or more) who continue to fracture despite 12 months of therapy with antiresorptive agents such as alendronate, risedronate, raloxifene and strontium ranelate may be considered for daily subcutaneous injections of the parathyroid hormone (1–34) fragment, teriparatide. This potent anabolic agent has been shown to reduce fracture risk by up to 70%.[34] Antiresorptive agents are ceased during the 18-month course of teriparatide therapy, but calcium and vitamin D supplements must be continued. Antiresorptive agents should be recommenced after the course is completed. Treatment with teriparatide requires

specialist supervision and monitoring of serum calcium levels.

Summary

The effective management of individuals with osteoporosis should include not only the prescribing of an antiosteoporotic agent but also regular encouragement to ensure persistence and adherence with medication. Repeat bone densitometry and the use of bone resorption markers may be useful for confirming both compliance and efficacy. Resistance and balance training exercise programs improve reflexes and muscle strength and reduce the risk of a patient falling. Reports of atypical femoral fractures should not detract from prescribing appropriate therapies. However, caution and avoidance of indefinite long-term exposure to bisphosphonates must be considered in all patients.

General practitioners are well placed to identify individuals at risk for falling and sustaining recurrent fractures and a recently released NHMRC-approved guideline from the Royal Australian College of General Practitioners provides evidence-based recommendations to help them manage postmenopausal women and older men (over 60 years of age) with osteoporosis.[35] MT

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COMPETING INTERESTS: Associate Professor Diamond is a scientific advisor to Eli Lilly, Merck Sharp and Dohme, Novartis, Roche, Sanofi-Aventis and Servier, but does not receive financial remuneration. Honoraria for GP lectures and travel grants to attend local and international bone meetings have been received from all the above companies.
Dr White: None.