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.**

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*).[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.

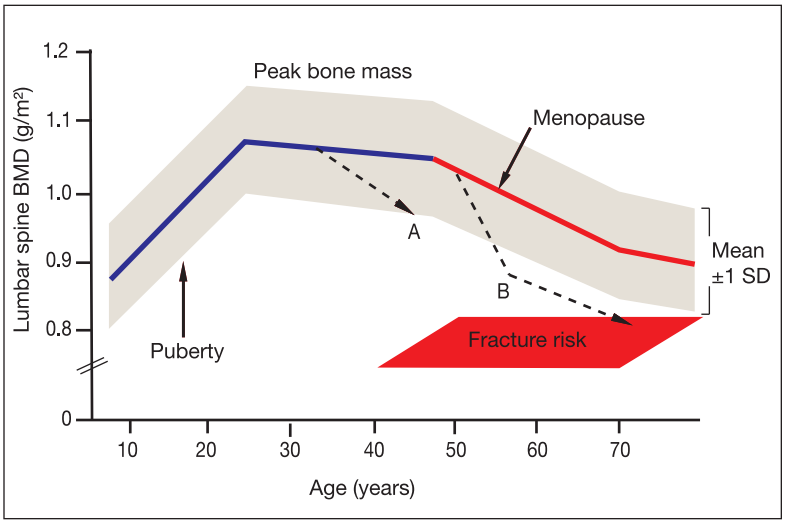


Figure 1. Bone density changes in puberty and menopause and with ageing. Peak bone mass is acquired through puberty and reaches a maximum at about 25 to 30 years of age (solid blue line). Rapid bone loss occurs at the menopause and then slows (solid red line). Fracture risk is increased with BMD T-score -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).

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

Bone turnover states

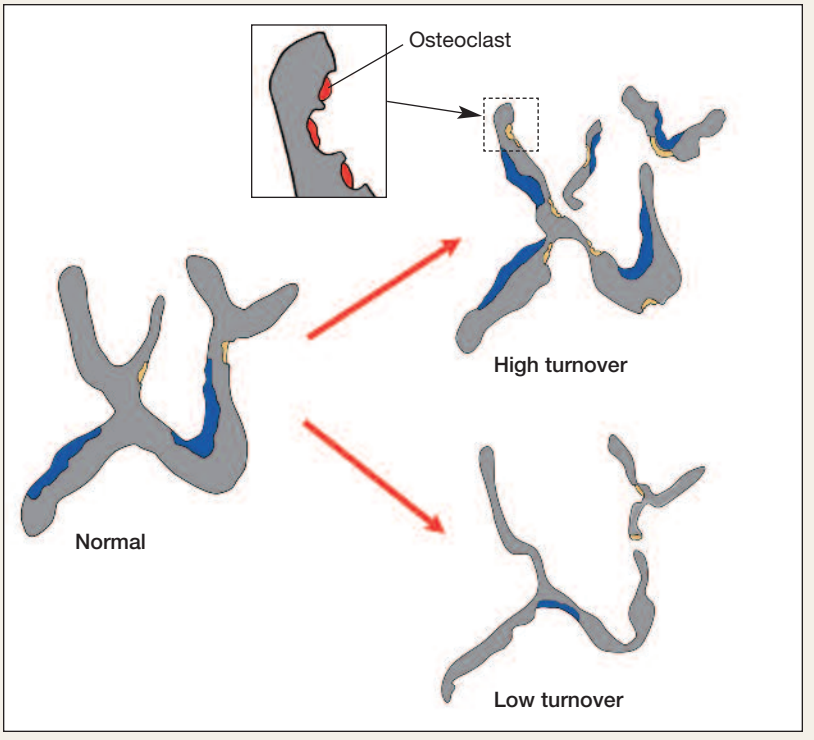


Figure 2. Schematic representation of normal, high and low bone turnover. Trabecular bone is shaded grey, areas of active bone formation blue and areas of active bone resorption beige.

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).

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 corti - costeroids 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

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
Gastointestinal 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

hyperparathyroidism,[15,16] hip fractures in hyperthyroidism,[17-19] recurrent vertebral factures 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 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.

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 anticatabolic 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.

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 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 anticatabolic (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). Anticatabolic 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, 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),[31] as well as in those with drug-induced bone loss (cortico - steroids and aromatase inhibitors).[28-30] These anticatabolic agents act by reducing bone turnover (through the inhibition of osteoclasts, thereby reducing bone resorption) and increasing BMD.

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 disease is predominantly a low bone turnover state. In clinical practice, anticatabolics 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 (Adronat, Alendro, Alendrobell, Fosamax, Ossmax) and risedronate (Actonel) are reimbursed by the PBS for the treatment of osteoporosis (including corticosteroid-induced 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).

The intravenous bisphosphonate zoledronic acid (Zometa) has recently (April 2008) received a positive recommendation for use in osteoporosis from the Australian Drug Evaluation Committee (ADEC), a step in its approval by the TGA for this use. The intravenous bisphosphonate ibandronate (Bonviva) is approved by the TGA for osteoporosis but is not available in Australia. The oral bisphosphonate clodronate (Bonefos) and the intravenous bisphosphonate pamidronate (Aredia, Pamisol) are not TGA-approved for osteoporosis treatment or prevention. Pamidronate and 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 (Evista) is reimbursed by the PBS for the treatment of osteoporosis in:[32]

- postmenopausal women with a prior osteofragility fracture (secondary prevention).

Teriparatide

Although teriparatide (Forteo) is available in Australia and is indicated for women with severe osteoporosis (BMD T-score -3.0 or less), those who continue to sustain fractures despite optimal anticatabolic therapies and those with established corticosteroid-induced osteoporosis, it is not listed on the PBS.

Strontium ranelate

Strontium ranelate (Protos) is reimbursed by 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 (Arimidex),

letrozole (Femara) and exemestane (Aromasin) 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%).[35]

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 not reimbursable on the PBS 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.

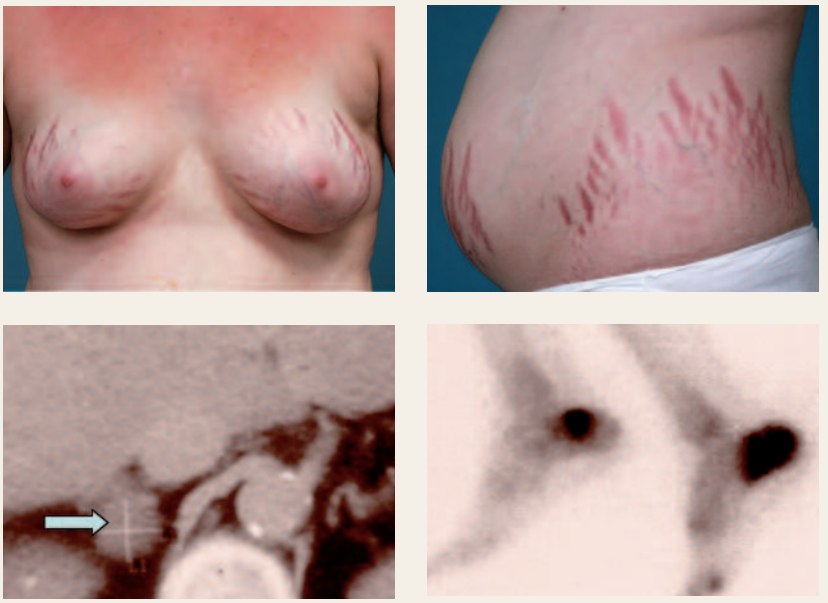
Teriparatide (parathyroid hormone), an anabolic agent that acts by direct stimulation of osteoblastogenesis and inhibition of osteoblast apoptosis, counteracts two of the key inhibitory effects of corticosteroid on bone formation. A recent study compared teriparatide with alendronate in patients with low BMD (T-score -2.5 or less) or a prevalent fracture and receiving long-term cortico - steroid 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.

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.

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 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

A list of references is available on request to the editorial office.

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Secondary causes of osteoporosis in women

diagnoses not to be missed

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