Betty's bones

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The case of an elderly woman concerned that she may be at risk of sustaining a fragility fracture is used to review osteoporosis in older women.

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Osteoporosis, like several other endocrinological conditions, is common and often goes unrecognised in older women. This article reviews the identification of women with the condition and their management.

CASE SCENARIO

Betty is 69 years old and is concerned that her bones might be 'too thin'. Her neighbour recently had a fall and fractured her hip, and is now in a nursing home after having had a stroke in hospital. Betty remembers that her mother had a 'widow's hump' and lost a lot of height in the last 15 years of her life.

How typical is Betty's neighbour's post-fracture outcome?

The sequence of events that happened to Betty's neighbour after she fractured her hip is fairly typical. After a hip fracture, about one in four patients die, one in eight are no longer able to live independently and a further one in eight do not regain their previous functional level; fewer than half make a full recovery.

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The outcome after a Colles' fracture is less lethal but again fewer than half of patients regain full and painless use of that hand. Vertebral fractures also take their toll, both through the discomfort of the fracture itself and the subsequent deformity and through the loss of self-image and function because of height loss and kyphosis.

How likely is Betty to have a fracture in the future?

The lifetime risk of an osteoporotic fracture in a woman aged 60 years is one in two (for men, it is one in three). The annual risk of a femoral fracture for a woman aged 60 years is one in 1000. Betty is more likely to have any osteoporotic fracture because of her family history of osteoporosis and the fact that she is already 69 years old. She has two of the three osteoporosis risk factors beginning with 'F': Fracture, Family and Fifty. Family history and each 10 years over the age of 50 years each roughly double the risk. Her absolute femoral fracture risk would at present be approximately four in 1000 each year. This risk is increased further if she has low bone mineral density (BMD). Figure 1 shows the relation at various ages between hip fracture risk and BMD (as the T-score; see later for more discussion of T-score).

Other factors might be protective, such as a high level of fitness and regular weight-bearing exercise, while still others may further increase her risk, such as multiple previous falls.

What are the eligibility criteria for Medicare rebate for bone densitometry by dual x-ray absorptiometry?

Medicare rebates are available for dual x-ray absorptiometry measurements in patients with conditions associated with an increased risk of osteoporosis, in those who have suffered a fracture due to minimal trauma and in those aged 70 years or over (see the box on page 58).

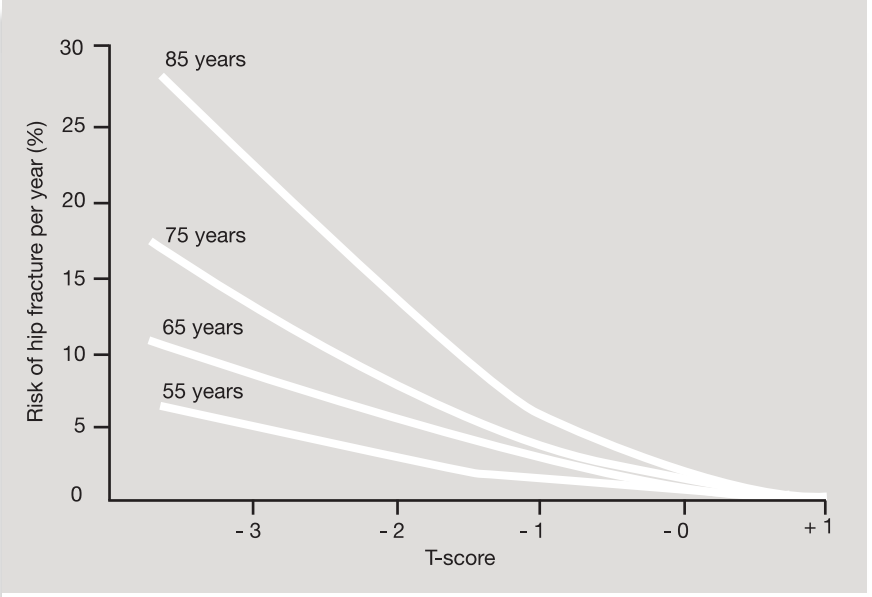


Figure 1. Hip fracture risk.

Once low bone density has been diagnosed, further bone density measurements are subsidised one year after a change in therapy and each two years to monitor stable therapy.

What height loss suggests crush fractures of vertebrae?

Even if vertebral height were maintained, some decrease in height is expected with age because of desiccation of the intervertebral discs. The commonly accepted height loss attributable to disc compression is 5 cm. Height loss exceeding 5 cm is strongly suggestive of vertebral fracture.

Height loss with ageing occurs due to asymptomatic vertebral wedging as a result of vertebral compression (crushing) from osteoporosis and the progressive kyphosis from the resultant loss in vertebral height. It is usually the anterior part of the vertebral body that crushes, forming an anterior wedge fracture; in these fractures there is loss of anterior height of the vertebra while the posterior height remains unchanged, as shown in Figure 2a.

Less commonly the anterior, middle and posterior parts of the vertebral body collapse such that vertebral height is decreased across the whole vertebral body (a crush fracture), or the anterior and posterior heights are maintained but there is loss of height in the mid portion of the vertebral body (a body, or central, fracture), as shown in Figures 2b and 2c respectively.

If kyphosis is present or the previous height is not known, a rough rule to determine previous height is that a person's standing height approximates his or her arm span (i.e. the distance between the laterally outstretched distal fingers). This measurement is less reliable for very tall or short people as most of the variation in height in an ethnically similar population relates to variation in limb length (rather than in the length of the spine).

CASE SCENARIO CONTINUED

Betty has a bone density scan, which shows a T score of -2.7 and a Z-score of -1.9 at the hip.

How should Betty's T-score be interpreted?

The T-score compares a person's BMD measurement to the mean BMD measurement of a normal young (aged 20 to 40 years) adult of the same sex. The T-score is given in standard deviations (SDs) from this mean and each unit (one SD) decrease in T-score is associated with an approximately 10% loss of BMD.

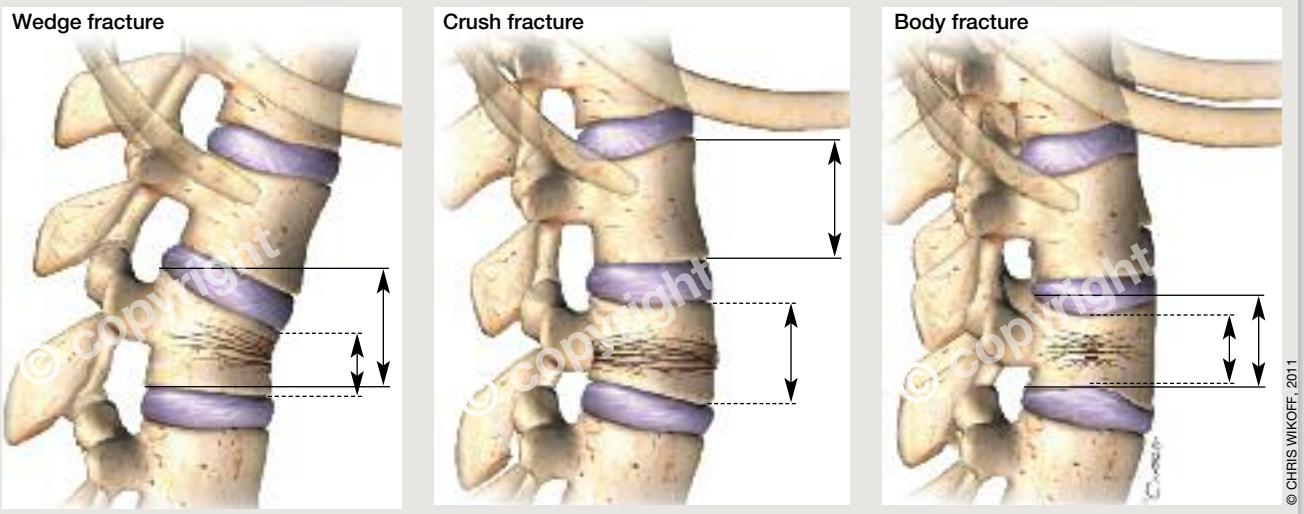
T-scores above -1 are considered normal, and between -1 and above -2.5 are defined as 'osteopenic' and should trigger action to prevent future bone loss. 'Osteoporosis' is defined as a T-score of -2.5 or below, and generally should prompt further assessment and consideration of intervention.

Betty's T-score of -2.7 indicates she has osteoporosis, with a decrease of approximately 27% of the normal bone density at the hip.

OSTEOPOROSIS AND BMD TESTING

Patients (men and women) eligible for Medicare Benefits Schedule subsidy for bone mineral density (BMD) testing by dual x-ray absorptiometry include:

- Those with a fracture due to minimal trauma
- Those aged 70 years and over
- Those with a condition associated with an increased risk of osteoporosis:
  - prolonged glucocorticoid therapy
  - conditions associated with excess glucocorticoid secretion
  - male hypogonadism
  - Turner's syndrome
  - amenorrhoea lasting more than six months before the age of 45 years
  - primary hyperparathyroidism
  - chronic liver disease
  - chronic renal disease
  - proven malabsorptive disorders (e.g. coeliac disease)
  - rheumatoid disorders
  - conditions associated with thyroxine excess.
- Those who have had a change in osteoporotic therapy
- Those whose low BMD requires monitoring



Figures 2a to c. Vertebral fractures. a (left). Wedge fracture: the height of the anterior portion of the vertebral body is less than that of the posterior part of the same vertebra or an adjacent vertebra. b (centre). Crush fracture: the heights of all portions of the vertebral body are less than those of an adjacent vertebra. c (right). Body (or central) fracture: the height of the mid portion of the vertebral body is less than that of the posterior part of the same vertebra or an adjacent vertebra.

How should Betty's Z-score be interpreted?

The Z-score compares a person's BMD measurement to the mean BMD measurement of age-matched healthy adults of the same sex and, like the T-score, is given in SDs from the mean. The Z-score indicates whether a person's bone density is as expected for his or her age, within the 95% population range (i.e. between +2 and -2). As for the T-score, each unit (one SD) decrease in Z-score approximately doubles the fracture risk. Z-scores below -2 suggest a pathological cause contributing to bone loss (e.g. one of the condition listed in the box on page 58, as well as vitamin D deficiency or myeloma in Betty's age group) and should prompt further investigation.[1]

Although Betty's Z-score is within the normal range, further investigation may be worthwhile as it is only just within the range.

Do T- and Z-scores help to predict future fracture risk?

The combination of age and BMD predicts a person's future fracture risk (Figure 1). Increasing age becomes the dominant contributor to risk in people with low bone densities (e.g. T-scores around -3). As Betty has osteoporosis, she has a high risk of future fractures (approximately 10% per year, from Figure 1).

The risk of fracture is increased more in those individuals who also have a fracture, and even more so in those with more than one fracture. In one meta-analysis, fracture risk increased eight times in association with osteoporosis and a further eight times in those with one or more vertebral fractures.[2] The use of spinal x-rays to detect previous asymptomatic vertebral fractures can be helpful in predicting future fracture risk.

An individual's absolute fracture risk can be evaluated through the use of a fracture risk calculator such as the Australian-derived Garvan Fracture Risk Calculator (www.garvan.org.au/bone-fracture-risk) and the WHO-developed FRAX calculator from Sheffield, UK (www.sheffield.ac.uk/FRAX). These calculators take into consideration age, BMD and other potential contributors and indicators of bone fragility and fracture risk.

What would happen to Betty's bone density if she were left untreated?

After the menopause and without oestrogen replacement, a woman's bone density decreases by about 15% over the next five years (i.e. the T-score decreases by 1.5 over the five years, as one unit T-score equals approximately 10% of bone density). This decrease is according to the '5, 4, 3, 2, 1 rule' – roughly 5% in the first year, 4% in the second, 3% in the third, 2% in the fourth and 1% in the fifth year. Thereafter, decreases are age-related and are about 0.5 to 1% per year.

Betty, at the age of 69 years, is well past the menopause and would have lost 15% of her bone density over the first five years after the menopause (corresponding to a T-score decrease of 1.5 units) plus a further 0.5 to 1% per year since then (corresponding to a T-score decrease of 0.5 to 1.0 units after 10 years). If she had comorbidities increasing bone loss, her T-score would have decreased by more.

This estimation of Betty's long-term bone loss should be considered with her likely longevity when intervention

is being determined. If Betty were unlikely to reach the age of 75 years, the call for action might be less than if she were expected to live into her 80s and 90s.

CASE SCENARIO CONTINUED

At 161 cm tall and weighing 50 kg, Betty is on the verge of being underweight (her body mass index is 19.3 kg/m^2; the healthy range is 18.5 to 25 kg/m^2).

What investigations are indicated regarding osteoporosis in a person such as Betty?

Serum calcium levels

Serum calcium measurement is recommended to exclude primary and secondary hyperparathyroidism. A raised serum calcium level or one in the upper reference range might prompt further investigation for hyperparathyroidism. Primary hyperparathyroidism often presents after the menopause, when the protective effects of oestrogen are lost and the osteolytic effect of parathyroid hormone is no longer restrained. Asymptomatic hyperparathyroidism can be present for many years without detection.

Parathyroid hormone levels

A raised parathyroid hormone level may indicate a tendency to high or low serum calcium level and should therefore always be interpreted in the light of the serum calcium level. As noted above, a raised or high-normal serum calcium level might suggest primary hyperparathyroidism. A parathyroid hormone level that is raised or not suppressed by hypercalcaemia suggests primary hyperparathyroidism.

A raised parathyroid hormone level could also be secondary to a condition adversely affecting calcium absorption (often vitamin D deficiency or renal disease reducing activation of vitamin D). If the dietary calcium intake were low or the calcium absorption abnormal, the parathyroid hormone level would rise to increase activation of renal vitamin D-1-hydroxylase and thereby increase serum 1,25-dihydroxyvitamin D levels and calcium absorption from the gut.[3] If this were not possible because of renal impairment, the parathyroid hormone secretion would continue to rise, resulting in increased bone calcium resorption that would counteract the decrease in serum calcium levels.

A suppressed parathyroid hormone level would suggest an alternative cause of hypercalcaemia. These causes include the presence of a malignancy that is eroding bone, and increased concentrations of 1,25-dihydroxyvitamin D from the taking of calcitriol or endogenous production of 1,25-dihydroxyvitamin D in granulomatous tissue.

Vitamin D levels

Serum 25-hydroxyvitamin D measurement is recommended to exclude vitamin D deficiency, which is surprisingly common in Australia. Even at the currently accepted lower limit of serum 25-hydroxyvitamin D level of 50 nmol/L, community surveys suggest a prevalence of vitamin D deficiency of 37 to 67% in winter/spring in this country.[3-5] Many experts believe that ill effects attributable to vitamin D deficiency still occur at higher levels.

Endomysial antibody levels

Coeliac disease is an underrecognised condition, and endomysial tissue trans - glutaminase antibodies are reasonably sensitive and specific indicators for it. Although endomysial antibody testing is not a routine investigation in osteoporosis, it may be an appropriate investigation in patients with borderline Z-score and low body weight, such as Betty. Certainly, if a patient has a history of previous auto - immune endocrine disease, testing for coeliac disease would be indicated.

Liver function tests and serum creatinine

Vitamin D is activated in the liver and kidney and hence assessments of liver and renal functions by liver function tests and measurement of serum creatinine levels are important.

Vitamin D is converted in the liver to the major circulating vitamin D metabolite 25-hydroxyvitamin D, by vitamin D-25-hydroxylase. This metabolism may be affected by liver damage and by some medications that decrease the hepatic activation of vitamin D (particularly anticonvulsants such as phenytoin). Abnormal liver enzyme induction, biliary obstruction and associated fat malabsorption may all be associated with abnormal hepatic vitamin D metabolism.

In the kidney, 25-hydroxyvitamin D is converted to the active metabolite 1,25-dihydroxyvitamin D, by vitamin D-1-hydroxylase. The presence of renal disease decreases this activation, and the reduced level of 1,25-dihydroxyvitamin D causes gut calcium absorption to be decreased.

Spinal x-ray

As previously mentioned, spinal x-rays to detect vertebral fractures can be helpful in predicting future fracture risk because fracture risk in people with osteoporosis is increased in those with a fracture and even more so in those with multiple fractures. Many vertebral fractures are not noticed by the person or are dismissed as 'a bit of back pain'; the minority present with local severe back pain. Many people, and particularly those over the age of 65 years, have evidence of previous asymptomatic vertebral fractures on a lateral thoracolumbar spinal x-ray. Hence a spinal x-ray would be of use in Betty.

Spinal x-ray is also useful for determining a patient's eligibility for subsidy on the PBS for osteoprotective medications.

CASE SCENARIO CONTINUED

Betty does not smoke or drink alcohol and has started attending an exercise program for seniors at the local community centre. She would like to consider other active measures to reduce her risk of future fracture.

Should Betty have a spinal x-ray before medication is considered?

Many of the osteoprotective medications are subsidised on the PBS for patients who have already had a fracture due to minimal trauma.

For PBS purposes, a vertebral fracture is defined as at least a 20% decrease in the height of a vertebra in comparison to an adjacent vertebra or to another part of the same vertebra (see Figures 2a to c). With a wedge fracture or a body (or central) fracture, the anterior or mid portion, respectively, of the vertebral body should be compared with the posterior part of the same vertebra or with the respective parts of adjacent vertebrae. With a crush fracture, the height of any part of the vertebral body should be compared with the same part of adjacent vertebrae.

Sometimes in radiology reports only a limited definition of a wedge fracture is used and crush and body fractures are not included. GPs may find it worthwhile requesting and examining such x-rays themselves.

Which osteoprotective medications would be appropriate for Betty if she had a fracture?

Each class of osteoprotective agents has its pros and cons, as summarised in the Table. Unfortunately, there are no direct comparisons of the various classes of osteoprotective medications (individually or by class) in terms of effectiveness and safety.

For Betty, a bisphosphonate is probably the most appropriate choice of antiosteoporotic agent as long as she is able to take it as recommended and has had no problems with oesophageal motility or patency. If she has had oesophageal problems or has significant side effects from taking an oral bisphosphonate, the intravenous bisphosphonate zoledronic acid (yearly for three years) could be used. Strontium ranelate would be another alternative, as would also raloxifene. The various osteoprotective agents are discussed briefly below.

Bisphosphonates

The most often used class of osteoprotective agents is the bisphosphonates, which are antiresorptive agents and have been shown to reduce both vertebral and nonvertebral fracture risk. There are differences between the individual bisphosphonates.

The major concerns with oral bisphosphonates are oesophagitis and gastritis. The risk is increased in patients not following the administration procedure (oral bisphosphonates should be taken when fasting, with 300 mL of water and the patient should remain upright for at least 30 minutes after administration) and in those with compromised oesophageal motility or patency. Both these factors become more relevant as people age.

The use of intravenous zoledronic acid avoids these side effects but may be associated with an acute phase reaction.

Bisphosphonate use in patients with osteoporosis is also rarely associated with osteonecrosis of the jaw.

There is also some concern about the

TABLE. OSTEOPROTECTIVE MEDICATIONS

Osteoprotective agent	Pros	Cons
Most commonly used		
Bisphosphonates*	Weekly, monthly or yearly dose	Complex administration
HRT	Other benefits	Women: prothrombosis Men: prostatism Both men and women: cancer risk
Raloxifene	Cancer protection	Prothrombosis
Less commonly used		
Strontium ranelate	Dual action	Prothrombosis
Calcitriol	–	Associated with hypercalcaemia, hypercalciuria and renal impairment
Tibolone	Possible benefits of combined oestrogenic, progestogenic and androgenic effects	Prothrombosis Limited PBS indication
Teriparatide (parathyroid hormone 1–34 fragment)	Increases BMD	Too expensive for many patients
Denosumab	–	Limited PBS indication
Complementary therapies	–	Unknown side effects No evidence for fracture prevention

* There are differences between the individual bisphosphonates.

long-term use of bisphosphonates, particularly whether they allow accumulation of microfractures and thereby predispose patients to future bone fragility. There is safety data for alendronate use for 15 years, but there might still be some concern about its use for 20 to 30 years if such medication were necessary for a young woman.

Alendronate, risedronate and zoledronic acid 5 mg once yearly are PBS listed for the treatment of osteoporosis in women and men with a prior osteofragility fracture. These three bisphosphonates are also PBS listed for primary prevention of osteoporosis in those over the age of 70 years with a T-score of -3.0 or less and for those taking prednisolone at a dose of at least 7.5 mg/day for at least three months and who have a T-score of -1.5 or less.

Calcitriol

The evidence that calcitriol is osteoprotective is less convincing than for other osteoprotective medications and it can cause hypercalcaemia and hypercalciuria. Although it is recommended that plasma and urine calcium levels and renal function be monitored, these precautions are not commonly practiced. Although it is listed on the PBS for the treatment for established osteoporosis in patients with fracture due to minimal trauma among other indications, it is rarely used to treat osteoporosis.

Denosumab

Denosumab is another antiresorptive agent for osteoporosis in postmenopausal women. As it is only listed on the PBS for osteoporosis in a woman aged 70 years of age or older with a T-score of -3.0 or less, Betty would not qualify for the PBS subsidy if it were prescribed for her.

Hormone therapy

Hormone therapy is indicated for the short-term relief of menopausal symptoms and has the additional benefit of preventing bone loss.

The major disadvantage of hormone preparations in women (oestrogenic preparations, raloxifene and tibolone) is that they increase thromboembolic risk roughly three-fold. (Strontium ranelate also has a prothrombotic effect.)

Betty's baseline risk of thromboembolism will be much higher than that of a younger woman even if she does not have the additional risk factors of a past event or limited mobility.

Raloxifene

Raloxifene, a selective oestrogen receptor modulator, is TGA approved for the prevention and treatment of osteoporosis in postmenopausal women. This antiresorptive agent is listed on the PBS for the treatment of postmenopausal osteoporosis in women with a previous osteofragility fracture.

It is effective for reducing vertebral fractures but there is only limited evidence for its reducing nonvertebral fractures. Also, it has prothrombotic effects.

Strontium ranelate

Strontium ranelate is a recently developed medication that has both antiresorptive and anabolic effects. It is TGA approved for fracture risk reduction in postmenopausal osteoporosis and is listed on the PBS for the treatment of osteoporosis in women with a prior osteofragility fracture and for osteoporosis in women aged 70 years or older with a BMD T-score of -3.0 or less. Side effects include skin rashes, diarrhoea and an increased thromboembolic risk.

Teriparatide

The parathyroid hormone (1–34) fragment known as teriparatide is an anabolic agent approved by the TGA for the treatment of osteoporosis in postmenopausal women and the treatment of primary osteoporosis in men when other agents are considered unsuitable and there is a high risk of fractures. It is listed on the PBS (authority required) for severe, established osteoporosis in patients with a very high risk of fracture.

It would not be considered an appropriate treatment for Betty.

Tibolone

Tibolone, a selective tissue oestrogenic activity regulator, is TGA approved but not PBS listed as a second-line therapy for the prevention of BMD loss in postmenopausal women who are intolerant of, or contraindicated for, other medications approved for BMD loss. It would not be appropriate for Betty.

By how much do osteoprotective medications reduce fracture risk?

In general, osteoprotective medications reduce fracture rate by about half and do this within one year. The most data available are for alendronate and risedronate.

Does Betty need a calcium supplement?

Patients likely to be at risk of calcium deficiency are those with low dietary calcium intake, the elderly, the socially disadvantaged, those with calcium malabsorption or hypogonadism and those taking corticosteroids. Betty, being 69 years old and, like most elderly people, probably not achieving an adequate daily intake of calcium, is likely to need to take a calcium supplement.

Betty's recommended intake of calcium is at least 1000 mg/day.[6] About 400 mg/day is available from a normal intake of nondairy food, leaving the balance, about 600 mg/day – the equivalent of about 600 mL of unfortified milk, to come from dairy products. However, the intake of this amount of dairy products is not often achieved.

Generally it is recommended that all postmenopausal women and men over the age of 60 years take a calcium supplement to boost their intake. Moreover, most studies assessing the benefits of antiosteoporotic therapies have been performed in patients taking calcium and vitamin D supplements, and a case

USEFUL RESOURCES

Fracture risk calculators

- Garvan Fracture Risk Calculator – www.garvan.org.au/bone-fracture-risk
- FRAX calculator from Sheffield, UK – www.sheffield.ac.uk/FRAX

Patient resources and websites

- Australian and New Zealand Bone and Mineral Society – www.anzbms.org.au
- Australian Menopause Society – www.menopause.org.au
- Osteoporosis Australia – www.osteoporosis.org.au
- International Osteoporosis Foundation – www.osteofound.org

can be made that patients taking an osteoprotective medication should consider also taking calcium and vitamin D supplements.

The debate rages about when best to take calcium supplements. The morning advocates argue that taking calcium at breakfast ensures the acid flow needed to dissolve the commonly used calcium carbonate supplement. Moreover, calcium at breakfast reduces bone turnover during the day.

The evening advocates argue that taking calcium at bedtime will protect bone during the night because bone resorption is increased during the night as there is no input of calcium from the gut to suppress parathyroid hormone. One simple solution is to take two calcium tablets each day, one in the morning and the other at night.

There is also debate about which calcium supplement is best. In general, the bioavailability of the different forms is the same and similar to that of dairy products.

Calcium carbonate requires acid to dissolve and become bioavailable. This can be a problem in those with achlorhydria. Although proton pump inhibitors and H2-receptor antagonists may reduce acid secretion and thus calcium absorption, in many cases gastric contents remain acidic enough to dissolve calcium carbonate.

The soluble forms of calcium supplements, calcium citrate and calcium glucolactonate, do not have this disadvantage and the effervescent preparations can be more palatable. However, these soluble calcium supplements may be more expensive than calcium carbonate and unavailable in supermarkets.

It is important to ensure that adequate elemental calcium is available in calcium supplements (e.g. of 1000 mg calcium carbonate, only 400 mg is elemental calcium). Usually at least 600 mg of elemental calcium is required per day.

Calcium supplements are often taken in combination with a vitamin D supplement (cholecalciferol). Calcium is also included, along with cholecalciferol, in some formulations of alendronate and risedronate.

USEFUL RESOURCES

The website addresses for the fracture risk calculators and some sources of information for patients are listed in the box on this page.

SUMMARY

- Osteoporosis is common in older women and is associated with a significant risk of fragility fracture, leading to increased morbidity, loss of independence and premature mortality.
- In BMD measurements, T-scores quantify absolute levels of bone mass and Z-scores identify those persons likely to have an underlying potentially treatable medical condition.
- Routine investigations before starting osteoprotective treatment include measurement of serum calcium, parathyroid hormone and 25-hydroxyvitamin D levels, liver and renal function tests and lateral thoracolumbar spinal x-ray. Additional investigations may also be indicated.
- Several osteoprotective medications halve the fracture risk in one year and are subsidised by the PBS for patients suffering a fracture due to minimal trauma.
- It is appropriate to consider recommending that patients take calcium and vitamin D supplements. Patients should also be advised to participate in regular weight-bearing exercise. MT

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