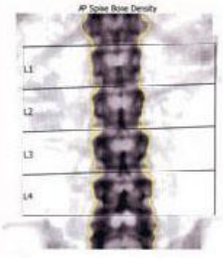
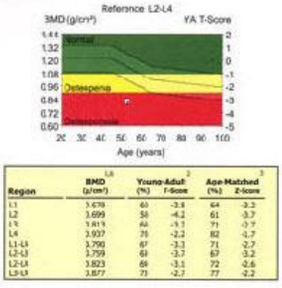
# CASE FIVE

**Short case number: 3_26_5**
**Category: Musculoskeletal System & Skin**
**Discipline: Medicine**
**Setting: General Practice**
**Topic: Osteoporosis**

## Case



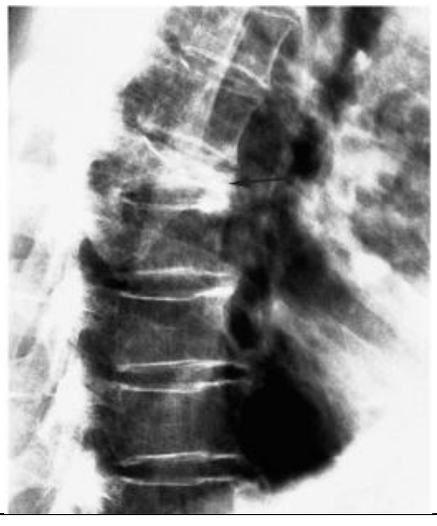

| Region | BMD (g/cm²) | Young-Adult (%) | Young-Adult T-Score | Age-Matched (%) | Age-Matched Z-Score |
|---|---|---|---|---|---|
| L1 | 1.678 | 60 | -3.8 | 64 | -3.3 |
| L2 | 1.699 | 58 | -4.2 | 61 | -3.7 |
| L3 | 1.815 | 66 | -3.1 | 71 | -2.7 |
| L4 | 1.937 | 75 | -2.2 | 82 | -1.7 |
| L1-L3 | 1.790 | 67 | -3.3 | 71 | -2.7 |
| L2-L3 | 1.759 | 63 | -3.7 | 67 | -3.2 |
| L2-L4 | 1.823 | 69 | -3.1 | 72 | -2.6 |
| L3-L4 | 1.877 | 73 | -2.7 | 77 | -2.2 |

**Lady Margaret Hooper, is 56 years old she presents for her 'women's health check-up.' At her last visit you recommended that she have her bone density measured because she has been menopausal since age 48. She has not had any problems and did not use menopausal hormone therapy. She takes no regular medications.**

**The report for her lumbar spine is seen here; the comments indicate that she has an increased risk of fracture.**

## Questions

1. Explain to Margaret why she has an increased risk of fracture and correlate this with the changes that occur in bone histology with osteoporosis.
2. To what does a T-score and a Z-score on a bone density report refer? What are the definitions for normal, osteopenia and osteoporosis?
3. Margaret explains that she did a lot of sport as an adolescent and is surprised that she has developed osteoporosis. Explain the changes that occur in bone mass across a lifetime and outline the risk factors for osteoporosis.



4. Margaret asks if her early menopause has contributed to her bone problems. Explain the role of oestrogen, progesterone and testosterone in bone density and the changes that occur after menopause.
5. You discuss the management of osteoporosis with Margaret and decide to x-ray her lumbar spine for fractures. How does the presence of a vertebral crush fracture influence your management of Joan? How does the presence of a fracture alter the costs of medication for Margaret?
6. Identify the features seen on the x-ray, what types of vertebral fracture can occur in osteoporosis?

| Questions |
| --- |
| 7. You discuss commencing Margaret on medication outline the different classes of medication that can be used in the management of osteoporosis outlining the mechanism of action, efficacy, side effects and contraindications.<br>8. Justify an evidence-based management plan for Margaret's osteoporosis. |

**Suggested reading:**


- Kumar P, Clark ML, editors. Kumar & Clark's Clinical Medicine. 8th edition. Edinburgh: Saunders Elsevier; 2012.
- Colledge NR, Walker BR, Ralston SH, Penman ID, editors. Davidson's Principles and Practice of Medicine. 22nd edition. Edinburgh: Churchill Livingstone; 2014.
- **Osteoporosis Australia: Osteoporosis prevention, diagnosis and management in postmenopausal women and men over 50 years of age https://www.osteoporosis.org.au/clinical-guidelines**

## ANSWERS

1. Explain to Margaret why she has an increased risk of fracture and correlate this with the changes that occur in bone histology with osteoporosis.
   Osteoporosis is the most common bone disease. It is characterised by reduced bone mineral density (BMD), micro-architectural deterioration of bone tissue and an increased risk of fracture.

2. To what does a T-score and a Z-score on a bone density report refer? What are the definitions for normal, osteopenia and osteoporosis?

   Osteoporosis is diagnosed by Bone Mineral Density (BMD) scans. The preferred technology is dual energy X-ray absorptiometry (DXA) and the preferred measurement sites are the lumbar spine and hip. Bone mineral densitometers work on the principle that the calcium in bone attenuates passage of X-ray beams in proportion to the amount of mineral present. By comparing the degree of attenuation with known standards, BMD values can be estimated for various skeletal sites and the values are expressed in grams of hydroxyapatite per $cm^2$ of the area scanned. In addition to giving absolute BMD values, DXA machines give results as 'T-scores' and 'Z-scores'. The T-score measures by how many standard deviations the patient's BMD value differs from that of a young healthy control, whereas the Z-score measures by how many standard deviations the BMD deviates from that of an aged-matched control of the same sex. Osteoporosis is diagnosed when the T-score value is -2.5 or lower, whereas T-score values that lie between -1.0 and -2.5 are defined as being in the osteopenic range. Values of BMD above -1.0 are regarded as normal

3. Margaret explains that she did a lot of sport as an adolescent and is surprised that she has developed osteoporosis. Explain the changes that occur in bone mass across a lifetime and outline the risk factors for osteoporosis.

   In normal individuals, bone mass increases during skeletal growth to reach a peak between age 20-40 but falls thereafter. There is an accelerated phase of bone loss in women after the menopause as a result of oestrogen deficiency which causes uncoupling of bone resorption and bone formation, such that the amount of bone removed during the bone remodelling cycle slightly exceeds that which is replaced. Similar changes occur with age in both men and women and is also accelerated in hypogonadal men.
   Bone mass and bone loss are regulated by a combination of genetic and environmental factors. Genetic factors play an important role, accounting for up to 80% of the population variance in peak bone mass and other determinants of fracture risk such as bone turnover and bone size. Polymorphisms have been identified in several genes that contribute to the pathogenesis of osteoporosis, including the oestrogen receptor, vitamin D receptor and collagen type I, though most of the genes responsible remain unidentified. Environmental factors such as exercise and calcium intake during growth and adolescence are important in maximising peak bone mass and in regulating rates of post-menopausal bone loss. Smoking has a detrimental effect on BMD and is also associated with modestly increased fracture risk, partly because female smokers have an earlier menopause than non-smokers. Moderate amounts of alcohol do not appreciably influence the risk of osteoporosis, although alcoholism is a recognised cause of secondary osteoporosis.

4. Margaret asks if her early menopause has contributed to her bone problems. Explain the role of oestrogen, progesterone and testosterone in bone density and the changes that occur after menopause.

   Bone remodelling is also regulated by several circulating hormones, including oestrogens, androgens, vitamin D and parathyroid hormone (PTH), as well as locally produced growth factors such as IGF-I and -II, transforming growth factor (TGF), parathyroid hormone–related peptide (PTHrP), ILs, prostaglandins, and members of the tumour necrosis factor (TNF) superfamily. These factors primarily modulate the rate at which new remodelling sites are activated, a process that results initially in bone resorption by osteoclasts, followed by a period of repair during which new bone tissue is synthesized by osteoblasts. The cytokine responsible for communication between the osteoblasts, other marrow cells, and osteoclasts has been identified as RANK ligand (receptor activator of NF-kappa-B; RANKL). RANKL, a member of the TNF family, is secreted by osteoblasts and certain cells of the immune system. The osteoclast receptor for this protein is referred to as *RANK*. Activation of RANK by RANKL is a final common path in osteoclast development and activation. A humoral decoy for RANKL, also secreted by osteoblasts, is referred to as osteoprotegerin. Modulation of osteoclast recruitment and activity appears to be related to the interplay among these three factors. Additional influences include nutrition (particularly calcium intake) and physical activity level.

5. You discuss the management of osteoporosis with Margaret and decide to x-ray her lumbar spine for fractures. How does the presence of a vertebral fracture influence your management of Margaret? How does the presence of a fracture alter the costs of medication for Margaret?

   Margaret has presented with a vertebral fracture on X-ray. Interestingly the majority of women and men with evidence of vertebral deformity fractures on X-ray do not know that they had had such a fracture nor can they recollect when it might have occurred.
   Given the presence of a vertebral fracture, it is appropriate that she be commenced on a specific anti-osteoporosis drug. As Margaret has suffered this fracture, she will automatically be able to receive a bisphosphonate, alendronate, risedronate or zoledronic acid, under the PBS scheme. She is also eligible for denosumab that blocks the action of RANKL.

   The bisphosphonates, alendronate and risedronate are administered orally. They are usually taken once a week or once a month. As they are very poorly absorbed, they are taken fasting, i.e. on an empty stomach, and food is withheld for ½ to 1 hour afterwards. A new formulation of risedronate is enteric-coated and this can and should be taken with a light breakfast. Zoledronic acid is administered annually as an intravenous infusion, over 15-30 minutes.

6. Identify the features seen on the x-ray, what types of vertebral fracture can occur in osteoporosis?

   The lateral radiograph of the thoracic spine shows a compression fracture. The other types of fractures that can occur include biconcave and wedge fractures. Individuals with such fractures may recognise that they have lost height from their peak height in their 20's and 30's, but most often do not know when such a fracture may have occurred

7. You discuss commencing Margaret on medication outline the different classes of medication that can be used in the management of osteoporosis detailing the mechanism of action, efficacy, side effects and contraindications.

Bisphosphonates

Bisphosphonates are synthetic analogues of pyrophosphate that adsorb on to bone surfaces and become incorporated within bone matrix. When osteoclasts resorb bone that contains bisphosphonate, the drug is released within the cell, where it inhibits signalling pathways that are essential for osteoclast function. Bisphosphonate therapy results in a decrease in bone resorption, but bone formation is also suppressed because of coupling between these processes in the bone remodelling cycle. The suppression of bone resorption acts to prevent bone loss, however, and allows mineralisation of existing bone to increase. Patients who are treated with bisphosphonates usually experience a gradual increase in BMD of about 5-8% with a plateau about 2-3 years after commencing therapy.

Nitrogen-containing (amino) bisphosphonates such as alendronate (10 mg daily, or 70 mg once weekly) and risedronate (5 mg daily, or 35 mg once weekly) have similar therapeutic profiles and have both been shown to prevent post-menopausal bone loss and reduce the risk of vertebral and non-vertebral fractures. They are also effective in the prevention and treatment of corticosteroid-induced osteoporosis and alendronate has been found to be of benefit in male osteoporosis.

Bisphosphonates are very poorly absorbed from the gastrointestinal tract and should be taken on an empty stomach with plain water only, avoiding food for 45-60 minutes after administration. Upper gastrointestinal upset can occur, so these drugs should be used with caution in patients with gastro-oesophageal reflux disease, and avoided in patients with oesophageal stricture or achalasia.

The enteric coated form of risedronate (only available as Actonel EC) seems less likely to cause any GE upset and can and should be taken with a light breakfast.

Denosumab

Denosumab is a fully humanised antibody to the osteoclast-activating signalling molecule, RANK ligand. It blocks RANKL activity so osteoclasts do not form and even those that are present do not actively resorb bone. The antibody is administered as a subcutaneous injection every 6 months. It has been shown to increase bone density to a similar or greater extent than the bisphosphonates. It also reduces the risk of most types of fragility fractures by about 50%. However, there are no direct head-to-head comparisons of denosumab and bisphosphonates as regards fracture risk reduction. This is an excellent agent. However, its efficacy wanes rapidly after 6 months and bone loss is rapid in individuals, who miss a dose. It is important to apply a diary reminder and this agent may not be ideal in any person with a history of or behavioural characteristics related to non-adherence to therapy.

Menopausal Hormone Therapy (MHT)

MHT with oestrogen (and progestogens) prevents post-menopausal bone loss and reduces the risk of osteoporotic fractures. The use of MHT as a treatment for osteoporosis has diminished in recent years following publication of the large Women's Health Initiative study which showed that long-term MHT increased the risk of breast cancer, thromboembolic disease, stroke and cardiovascular disease. These risks are lower with oestrogen-only HRT in women who have had

a hysterectomy, but even in this group MHT is regarded as second-line treatment because safer alternatives are available. It is not clear that such a negative view is appropriate in women with an early menopause and perhaps for the first 5-10 years after a natural menopause.

Similarly, testosterone is indicated for men with osteoporosis who have hypogonadism. However there may be adverse effects of testosterone therapy as well.

Calcium and Vitamin D supplements

These are generally used as an adjunct to other treatments. Calcium is typically given in doses of 500-1000 mg daily, and vitamin D supplements in doses of 400-800 U daily. When given as monotherapy, calcium and vitamin D supplements have been shown to prevent fragility fractures in elderly institutionalised patients with vitamin D deficiency, but they do not seem to be effective at preventing fractures in other patient groups.

Raloxifene

Raloxifene binds to the oestrogen receptor and inhibits osteoclastic bone resorption in patients with post-menopausal osteoporosis. Raloxifene has differential effects on the oestrogen receptor in different tissues, acting as an agonist in some tissues such as bone and liver, but as an antagonist in the breast and endometrium. Therefore, it is classified as a selective oestrogen receptor modulator (SERM). Administration of raloxifene (60 mg daily) to women with post-menopausal osteoporosis results in a modest increase in BMD (2%) and a reduction in the risk of vertebral fractures. It can provoke muscle cramps and hot flushes and increases the risk of venous thromboembolism to a similar extent to HRT, but reduces the risk of breast cancer and does not have the adverse cardiovascular or cerebrovascular side-effects of HRT. Raloxifene is not generally considered as first-line treatment for osteoporosis because it does not reduce the risk of non-vertebral fractures, but it can be useful in patients with predominantly vertebral osteoporosis.

Parathyroid Hormone

PTH is an effective treatment for osteoporosis and works by stimulating bone formation. The beneficial effects of PTH on the skeleton are thought to depend on its intermittent mode of administration which results in peaks and troughs of circulating hormone. This contrasts with the situation in primary hyperparathyroidism where there is a sustained elevation in PTH which causes bone loss and can result in an increased risk of osteoporosis.

The formulation currently available is the 1-34 fragment peptide (teriparatide), given by single daily subcutaneous injection of 20 µg over a 12-18-month period. Teriparatide increases BMD by 10% or more in osteoporotic subjects and reduces the risk of both vertebral and non-vertebral fractures. It is also effective in male osteoporosis and corticosteroid-induced osteoporosis. Teriparatide has been successfully combined with HRT but administration of bisphosphonate therapy prior to or during teriparatide treatment has been shown to blunt the anabolic effect. Because of its high cost, teriparatide is currently reserved for patients with severe osteoporosis or those who have not responded adequately to other therapies.

Other agents

Tibolone is a steroid hormone receptor modulator that acts as a partial agonist at oestrogen, progestogen and androgen receptors. It increases BMD in post-menopausal and has been shown to decrease fracture risk, including hip fracture risk. There may be an increase in stroke but this was not shown in all studies. Interestingly, it also reduced the diagnoses of breast cancer. However, it did not decrease recurrence risk in women who prior breast cancer and may have increased that risk.

Calcitriol ($1,25(OH)_2D$), the active metabolite of vitamin D, is licensed for treatment of osteoporosis, but the data on fracture prevention are less robust than for other agents.

The anabolic steroids stanozolol and nandrolone decanoate have been used to treat osteoporosis but there are no data on fracture prevention, and adherence is poor due to side-effects such as hirsutism, weight gain, fluid retention and disturbance of liver function.

8. Justify an evidence-based management plan for Margaret's osteoporosis.

Margaret's management needs to include non-pharmacological and pharmacological interventions.

Non-pharmacological
-Exercise
Observational data and clinical trials indicate that weight-bearing activities, such as aerobics, walking, and resistance training, all are modestly effective at increasing spine bone mineral density. The studies are of limited quality (primarily because of difficulty of blinding patients), however, and exercise does not seem to reduce the risk for osteoporotic fractures.

-Fall Prevention
Prevention of falls requires attention to risk factors including medications, gait, vision, and environmental hazards (e.g., poor lighting, area rugs, and lack of handrails in bathrooms). Additionally, medical causes of falls need to be considered in particular medications which remain the most common causes of falls in the elderly.
Falls risk prevention can reduce the risk of falls but there few data on fracture risk reduction.

-Hip Protectors
Hip protectors are anatomically designed plastic shields or pads worn in side pockets of special underwear. In spite of multiple randomized trials, the benefit of hip protectors remains unclear. Hip protectors often are difficult to put on and uncomfortable to wear; therefore, compliance may play a role in reducing their potential effectiveness.

Pharmacologic therapy
When assessing the effectiveness of different pharmacologic therapies for osteoporosis, clinical events such as fractures and radiologic changes in bone mineral density as endpoints have been used. Although clinical endpoints are preferable, they are not always practical. For example, the studies that demonstrated the effectiveness of bisphosphonates and estrogen over placebo in

reducing hip fractures required more than 10,000 patients. Thus, many studies rely on changes in bone mineral density as a surrogate marker. Although low bone mineral density is an excellent predictor of fracture risk in postmenopausal women, increases in bone mineral density show an inconsistent relationship to fracture. Each of the available classes of bisphosphonates, selective estrogen receptor modulators, estrogens and tibolone reduce vertebral fracture rates in postmenopausal women. Most of these medications also show reduced fracture risk at combined non-vertebral sites. Although this term includes hip fractures, it also includes other sites, such as ribs and wrist.

Currently, the medications with clinical data supporting reduction of hip fractures are alendronate, risedronate, zoledronic acid, oestrogen, tibolone and denosumab.