Investigation of postmenopausal women with low bone density

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The investigations in endocrinology section uses case scenarios to educate doctors on the best approach to the diagnosis and management of patients with different endocrine problems. The appropriate selection of tests and correct interpretation of test results are discussed.

Osteoporosis imposes a significant burden on the quality of life of people in Australia. There are 20,000 hip fractures per year in Australia (increasing by 40% each decade), with approximately 25% of people who sustain a hip fracture dying within 12 months postfracture.[1] Furthermore, of those who do not die following their hip fracture, 50% will experience some level of dependence in their activities of daily living,[2] representing a direct cost of 1.9 billion dollars per year in Australia.[1]

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The risk of fractures can be determined through previous episodes of falls and the identification of common risk factors for osteoporosis, including age, gender (most common in postmenopausal women), use of corticosteroids, high alcohol intake, tobacco use, family history of hip fracture, coeliac disease and rheumatoid arthritis. Although fracture risk can be determined using one of the online fracture assessment tools (e.g. FRAX [www.shef.ac.uk/FRAX/] and Garvan [www.garvan.org.au/bone-fracture-risk/] online calculators), bone mineral density (BMD) quantified by dual energy x-ray absorptiometry (DXA) is still considered the 'gold standard' for the diagnosis of osteopenia and osteoporosis.[3,4] General indications to order a BMD scan include: patients with more than two risk factors for osteoporosis, all women older than 65 years and men over 70 years, history of previous minimal trauma fracture, rheumatoid arthritis, chronic use of oral corticosteroids (more than three months), primary hyperparathyroidism, tobacco use, high alcohol intake (three or more units/day) or a history of eating disorders.[3]

According to the World Health Organization criteria, a BMD T-score (defined as the comparison between the patient's BMD versus the mean value in a young adult) between -1 standard deviation (SD) and -2.5 SD is considered diagnostic of osteopenia and a BMD T-score of less than -2.5 SD is considered diagnostic of osteoporosis.[5] Although new, more precise techniques are being developed to quantify bone density and structure, most of these techniques remain in the experimental phases. BMD by DXA, therefore, remains the most useful method to diagnose osteoporosis and to predict fracture in the clinical setting.[4] Despite its usefulness, interpreting DXA reports and making therapeutic decisions based on the results remain challenging.

The following two cases illustrate common clinical situations in postmenopausal women in which a decision to order further assessments or initiate/continue osteoporosis treatment is needed.

Case 1

An 82-year-old woman, who is a retired accountant and spends most of her time indoors, attends her annual clinical assessment. Her previous medical history includes hypertension, hyperlipidaemia, and a history of bilateral oophorectomy at

age 45 years. She drinks two glasses of wine every day and has no history of smoking. Her mother experienced a hip fracture at the age of 75 years. Medications include metoprolol and pravastatin. The patient is asymptomatic and her physical examination is unremarkable apart from osteoarthritis in her arms and knees. Her full blood count, electrolyte levels, liver function tests and inflammatory markers are all normal. Her cholesterol level has improved since her last visit and is now borderline high.

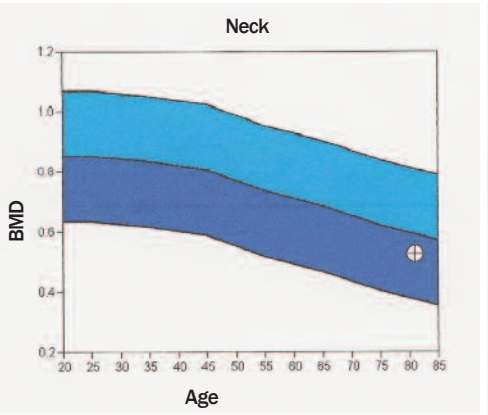

Figure 1. Case 1: BMD at the femoral neck.

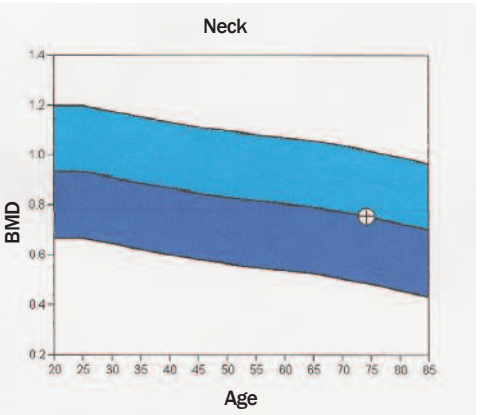

Figure 2. Case 2: BMD at the femoral neck.

What investigations are indicated in this patient?

This woman's age and the presence of two risk factors for osteoporosis (family history and early menopause) justify testing her BMD by DXA. Her BMD T-score at her femoral neck is -3.0 SD, consistent with a diagnosis of osteoporosis (Figure 1).

What further investigations should be ordered?

Osteoporosis treatment is indicated in this case. However, before initiation of treatment, secondary causes of osteoporosis should be ruled out. The suggested screening for osteoporosis includes:[3]

- measurement of serum calcium and phosphate levels
- thyroid function tests
- measurement of creatinine levels and glomerular filtration rate (GFR)
- protein electrophoresis.

Serum vitamin D levels should be ideally 75 nmol/L to assure antifall and antifracture efficacy.[6] Measurement of parathyroid hormone (PTH) levels in patients with osteoporosis is controversial. Nevertheless, recent evidence suggests that PTH measurements should be included in the assessment of patients with osteoporosis due to the high prevalence of hyperparathyroidism in response to vitamin D deficiency in the context of normal GFR.[7]

What do the tests show?

This patient's osteoporosis screening is normal. Her serum vitamin D level is 35 nmol/L, PTH level is borderline high (6.8 pmol/L, normal range: 1.6–6.9 pmol/L), and her calcium and phosphate levels are normal.

How should this patient be managed?

Osteoporosis treatment should be initiated in this patient. Considering that she has not experienced any previous minimal trauma fracture and her renal function is normal, treatment with any of the current therapeutic choices could be started according to her preference, potential compliance and history of gastrointestinal symptoms. If an intravenous bisphosphonate is selected for therapy, her vitamin D levels should be increased to above 50 nmol/L before starting the intravenous infusion to prevent hypocalcaemia. This correction should be obtained either after a load dose of vitamin D (50,000 IU) followed by supplementation with 1000 IU/day, or after starting her on a relatively high dose of vitamin D (2000 to 3000 IU/day) with new measurement of serum concentrations three weeks later to adjust the dose.[8] In either case, vitamin D supplementation should be part of the osteoporosis treatment and should be continued indefinitely independently of the treatment choice. Recommended calcium levels should be ideally achieved through dietary intake. Low-dose calcium supplementation should only be considered if dietary intake is inadequate.

Should treatment be monitored in this case?

A new DXA scan should be ordered at least two years after starting osteoporosis treatment. According to major clinical trials, this patient's BMD should improve by at least 5 to 7% in two years, which assures a fracture risk reduction of at least 50%.[3] Regular monitoring of serum vitamin D levels is only indicated in patients with potentially poor compliance or a diagnosis of malabsorption. In this case, regular supplementation of vitamin D at a dose of 1000 IU/day should be sufficient to maintain appropriate serum concentrations in the long term.

Case 2

A 75-year-old woman presented to the emergency department of her local hospital after experiencing a fall at the residential aged care facility where she lives. She was unable to walk after the fall due to severe pain in her right hip. The patient's previous medical history includes a vertebral fracture (L3) four years ago, mild dementia, hypertension, coronary artery disease and diabetes. She has a previous history of heavy smoking (she quit 10 years ago). She reports two falls within the past year. Her medications include metformin, aspirin, pindolol, alendronate (weekly; indicated after her vertebral fracture four years ago), and vitamin D supplements (1000 IU/day).

The patient is in severe pain and her physical examination shows shortening and external rotation of her right leg. Her full blood count, electrolyte levels, liver function tests and inflammatory markers are all normal. Her x-ray revealed a complete, comminuted, intertrochanteric fracture of the right hip.

The patient is admitted to the orthopaedics service and undergoes surgery with excellent postsurgical progress. She is then transferred to an orthogeriatrics rehabilitation bed where physiotherapy is started. The question of

osteoporosis treatment is discussed at the case conference.

What considerations should be made before selecting this patient's osteoporosis treatment?

Fractures can still happen in patients receiving treatment for osteoporosis, especially in those who fall frequently and who have a low BMD. In the patient described, the following questions should be asked.

- Was her compliance with her medications appropriate? Considering her cognitive impairment, compliance could be an issue. Patients with a history of cognitive impairment could either forget to take their weekly osteoporosis medication or have difficulties to follow the instructions related to the administration of oral bisphosphonates. This includes taking the drug first thing in the morning after awakening with a full glass of plain water. In addition, the patient should not lie down or eat or drink anything for at least 30 to 60 minutes after taking any oral bisphosphonate drug.
- Were serum levels of vitamin D appropriately corrected? Appropriate serum concentrations of vitamin D are essential to optimise antifracture efficacy of osteoporosis treatments. In an institutionalised patient with very low sun exposure and at potential risk of undernutrition, the required dosing of vitamin D is higher than in ambulatory populations.

Is measurement of BMD by DXA indicated in this case?

BMD by DXA is indicated in this patient and could suggest poor treatment compliance or lack of therapeutic response. The patient's new BMD score is -1.3 SD in her left femoral neck (Figure 2), which is slightly higher than her previous BMD four years ago (-1.5 SD) when her osteoporosis treatment was started. (Note that her BMD was never within the diagnostic range for osteoporosis although patients with osteopenia, especially those who have frequent falls, are also at risk of fractures.) Nevertheless, the presence of a minimal trauma fracture was enough indication to start osteoporosis treatment four years ago.

What additional investigations should be ordered and what do the results show?

Bone biomarkers are indicated in this case.[9] The most commonly used bone biomarkers are C-telopeptide for determination of bone resorption and type 1 procollagen for determination of bone formation. Considering that this patient is taking an oral bisphosphonate, her serum concentrations of both C-telopeptide and type 1 procollagen should be below postmenopausal levels. However, her serum concentrations are above postmenopausal levels (baseline levels were unknown), which may indicate either poor compliance or treatment failure. Finally, despite her regular vitamin D supplementation, her serum vitamin D level is low (42 nmol/L).

How should this patient be managed?

A higher dose of vitamin D (2000 IU/day) should be started in this patient. In terms of her osteoporosis treatment, the patient could be started on medications that assure better compliance and have shown effectiveness for the prevention of hip fracture. These medications include either intravenous bisphosphonates once a year or subcutaneous denosumab every six months.

Is a new BMD measurement by DXA indicated in the future for this patient?

The patient is clearly osteoporotic based on the occurrence of two minimal trauma fractures. Now that her compliance is assured by the new parenteral therapeutic choices, a new BMD measurement by DXA in two years would be useful to assess the effectiveness of her new osteoporosis treatment. However, the performance of a new BMD by DXA in two years, although useful, could be limited by the cognitive and functional status of the patient at that time.

Summary

Although measurement of BMD by DXA is considered the gold standard in the diagnosis of osteoporosis, patients can still be at high risk of fracture despite normal reports in their BMD. Every case should be individualised taking into consideration the presence of risk factors for osteoporosis, previous history of falls, low vitamin D level and risk of poor nutrition.

BMD is a useful tool to monitor osteoporosis treatment although bone biomarkers could be required to determine treatment effectiveness and compliance, especially in patients who experience a new fracture while taking osteoporosis medication. Finally, vitamin D supplementation is essential to assure an optimal response to osteoporosis treatment and also to obtain additional falls prevention efficacy. **ET**

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COMPETING INTERESTS: Professor Duque has received honoraria as speaker and funding for clinical studies from Amgen, Novartis, Eli Lilly, LEO Pharma and Procter & Gamble Pharmaceuticals.