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OSTEOPOROSIS: RISK ASSESSMENT AND TREATMENT

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INTRODUCTION

Osteoporosis is a common musculoskeletal disease in older people characterised by a progressive loss in bone mineral density and microarchitectural deterioration. Fractures cause pain, disability and a reduced quality of life, and are associated with an increased re-fracture rate. Fractures lead to a five-year mortality rate of 25%, which increases to up to 50% in the event of a re-fracture.[1] The clinical diagnosis of osteoporosis is based mainly on bone mineral density (BMD), measured using dual-energy X-ray absorptiometry (DEXA), and/or the occurrence of fragility fractures[2]

Osteoporosis risk assessment

There are a number of non-modifiable and modifiable risk factors, diseases and drugs associated with osteoporosis and minimal trauma fractures.[3]

Age, a family history of hip fractures and previous fractures are key risk factors. All men and women over the age of 50 years who have sustained a fracture have a higher risk of subsequent fractures and should be assessed and considered for treatment. Bone mineral density testing is also recommended and subsidised for all men and women over 70 years of age. Along with falls-risk screening, it is recommended as part of general health checks for all individuals, yet medical record audits indicate that this prevention strategy is currently underused.[4]

Bone consists of dense outer cortical bone and spongy inner cancellous bone, both having distinct properties that work together to maintain bone strength. They are made up of cells, including osteocytes, osteoclasts, osteoblasts and stem cells, and bone matrix, which is composed of calcium, phosphorus, inorganic salts and bone collagen. Osteoclasts resorb bone, whereas osteoblasts form new bone. The antagonistic actions of these two cell types occur constantly in the body in order to maintain bone health and structural integrity of the skeleton. This process is termed bone remodeling or bone turnover.[5] Any factors that decrease the activity of osteoblasts and/or increase the activity of osteoclasts will result in greater bone resorption than bone formation. This imbalance in bone remodeling also induces the destruction of bone microstructure, especially the structural destruction of cancellous bone, which leads to a decrease in bone strength and subsequent fragility fractures.[6]

The regulation of bone remodeling in Health and Osteoporosis

Osteoporosis results from an imbalance of normal bone remodeling, such that bone resorption is favored over bone formation. Human bones are stimulated by body weight, muscle traction, and high-intensity exercise. Over time, bones are damaged and degraded. Bone remodeling starts with bone resorption and ends with bone formation (Fig. 1). It is an essential process for maintaining mechanical strength, structural integrity, and mineralization by replacing old and damaged bone with new bone. However, the exact initial mechanisms underlying remodeling are yet to be fully elucidated. It is known that the process occurs in response to a number of factors, including hormone signals, paracrine and autocrine factors, and the physical pressure of mechanical loading.[7] Additionally, a range of systems —endocrine, immune, nervous, and more—are involved in the regulation of bone remodeling.[8] Environmental and genetic factors further influence this process; menopause, low BMI, white or Asian background, lack of sunshine, low exercise, malnutrition, disease, and certain drugs lead to bone microstructure damage and osteoporosis.[9] Although the exact mechanisms that initiate osteoporosis are yet to be fully elucidated, the signaling pathways that regulate bone resorption and formation have been extensively described. These are briefly outlined below. This is significant to note as most of the existing medications under development have focused on targeting such pathways, which mainly comprise mechanisms to control osteoclast and osteoblast action.[10]

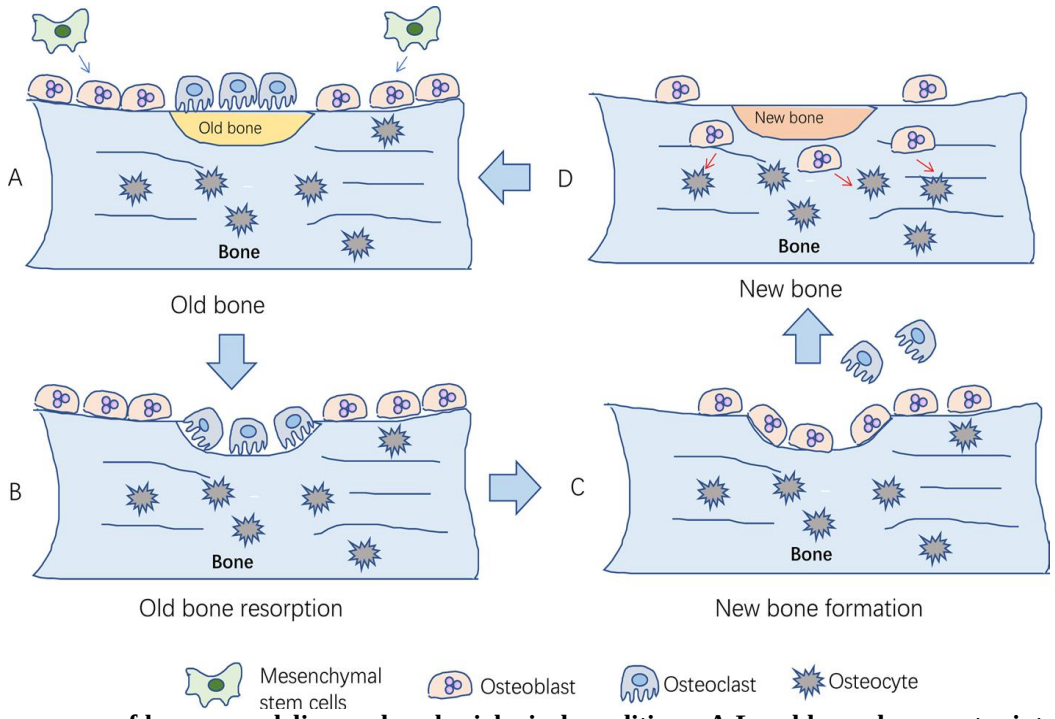

Fig. 1: The process of bone remodeling under physiological conditions. A Local bone degenerates into old bone. Mesenchymal stem cells differentiate into osteoblasts; B osteoclasts migrate to the surface of old bone for bone resorption; C osteoclasts leave the surface after the old bone is absorbed, and then osteoblasts migrate to the surface for bone formation; D new bone replaces old bone to maintain bone quality, strength, and mass. After bone formation, osteoblasts differentiate into osteocytes.

Role of Calcium and Vitamin D

Ninety-nine percent of the body's calcium is stored in the bones. Sufficient calcium intake is essential for maintaining bone mass and strength. This is also dependent on sufficient intake and activation of vitamin D, which promotes effective absorption of intestinal calcium. Active vitamin D [1, 25 (OH)2D3] also directly promotes bone health by binding to vitamin D receptors (VDRs) in bone cells to regulate bone remodeling.[11] To be converted into its active form,[12] it is hydroxylated twice, first in the liver and then in the kidneys. 1,25(OH)2D3 can promote both osteoclast activity, by influencing RANKL and NFATc1 signaling[13], and osteogenic activity, through BMP-2, Smad, Runx2, and the Wnt pathway.[14] In addition to its essential role in bone health, calcium, in the form of ionized calcium, is critical in a number of physiological functions, including neuronal function, muscle contraction, clotting, and intracellular signaling. Organisms cannot survive when such functions are compromised. As such, in conditions of low circulating calcium, bone undergoes increased resorption in order to supply circulating calcium ions for these life-sustaining functions. This is achieved predominantly via PTH, which stimulates bone resorption and increases the renal formation of active vitamin D to increase.[15]

Drugs for osteoporosis

Pharmacotherapy is indicated for individuals with a significantly increased risk of fractures. First-line treatment is available under the Pharmaceutical Benefits Scheme (PBS) for:

1) Those 50 years of age and over who have sustained a minimal trauma fracture.
2) Those 70 years of age and over with established osteoporosis.
3) Those who require long-term corticosteroids (Minimum three months) on at least 7.5 mg of prednisolone or equivalent per day.

Antiresorptive therapy can reduce the risk of fractures by up to 50%. There is a consensus to treat individuals who have a hip fracture risk of more than 3% or any fracture risk of more than 20% over 10 years.[16]

1) Bisphosphonates

Bisphosphonates inhibit osteoclast activation and prevent bone resorption. They slow the rate of bone loss, improve bone mineral density and reduce both hip and vertebral fractures. Alendronate, risedronate and zoledronic acid are currently available. Oral and intravenous bisphosphonates can be extended up to 10 and six years, respectively, without an increase in adverse events compared to placebo.

Oral bisphosphonates

Alendronate and risedronate are inexpensive and have once-weekly or once-monthly oral dosing. It is important to counsel patients to take oral bisphosphonates in the morning on an empty stomach with a full glass of water and to remain upright for 30 minutes after ingestion to

ensure adequate drug absorption and prevent erosive oesophagitis.

Intravenous bisphosphonates

Zoledronic acid is an intravenous bisphosphonate given as an annual infusion. It can help overcome the gastrointestinal limitations of oral formulations, but it has other potential adverse effects, most notably the risk of flu-like reactions following infusions.

2) Denosumab

Denosumab is a monoclonal antibody that reversibly inhibits bone resorption by reducing osteoclast formation and differentiation while increasing osteoclast apoptosis. It increases bone mineral density at the lumbar spine and hip and reduces the risk of fractures. Denosumab is administered as a six-monthly subcutaneous injection. In contrast to bisphosphonates, denosumab can be used in patients with chronic kidney disease. However, these patients are particularly at risk of hypocalcaemia, so baseline concentrations of calcium and vitamin D should be assessed before starting therapy.

Patients should either continue denosumab indefinitely or be transitioned to an alternative treatment drug (e.g. bisphosphonates) for at least 12 months on discontinuation. Unlike bisphosphonates, the effect of denosumab is not durable and is rapidly reversible after cessation.[17]

3) Raloxifene

Raloxifene is a selective oestrogen receptor modulator that reduces postmenopausal bone loss. It reduces the risk of vertebral fractures, but it does not reduce the risk of non-vertebral fractures. It is taken as a daily tablet, which patients may find inconvenient. Raloxifene is an alternative to bisphosphonates or denosumab (if they cannot be tolerated) for women with postmenopausal osteoporosis and may be appropriate for younger women with spinal osteoporosis soon after menopause. It increases the incidence of hot flushes, which can be a significant problem in young postmenopausal women. Raloxifene reduces the risk of breast cancer, so it can be considered in women with a high risk of breast cancer. However, it increases the risk of deep venous thrombosis, and other evidence suggests slightly increased mortality after stroke.[18]

4) Menopausal hormone therapy

Menopausal hormone therapy can consist of combined oral or transdermal oestrogen with oral progesterone therapy, or tibolone alone as a daily tablet. It is an effective option for women who require treatment for osteoporosis and have either premature menopause or significant postmenopausal symptoms requiring pharmacotherapy. Menopausal hormone therapy reduces the risk of all fractures, while tibolone has not been shown to reduce the risk of hip fractures.41 While menopausal hormone therapy may be useful when osteoporosis and fracture prevention therapy is required in women younger than 50 years of age, the risks of this therapy must be considered with long-term use.[19]

5) Teriparatide

Teriparatide is a synthetic form of parathyroid hormone that stimulates bone formation. It is given as a once-daily subcutaneous injection. Teriparatide is used to treat severe osteoporosis and is subsidised for an 18-month treatment course in Australia when patients continue to sustain fractures and remain severely osteoporotic (T-score less than –2.5) despite receiving at least 12 months of first-line treatment. The rate of vertebral fractures may be reduced by up to 65%. Teriparatide has been shown to reduce non-vertebral and hip fractures by up to 55%.[20]

6) Romosozumab

Romosozumab is an antisclerostin monoclonal antibody that decreases bone resorption and increases bone formation. Similar to teriparatide, it is only subsidised in patients with severe osteoporosis who continue to sustain fractures despite receiving at least 12 months of first-line treatment. It is administered as two subcutaneous injections once a month for 12 months.

Romosozumab is superior to both alendronate and teriparatide in improving bone density at the spine and hip. It has been shown to reduce the relative risk of vertebral fractures by 73% compared to placebo, and by 48% compared to weekly alendronate. It has also been shown to reduce the risk of non-vertebral fractures by 19% and hip fractures by 38%.[21]

7) Stem cell therapy

Stem cell therapy is an emerging new treatment approach that harnesses stem cells' great potential to differentiate and regulate intercellular communication. The stem cells used for research can come from different sources, including embryonic stem cells (ESCs), adult stem cells (ASCs), and induced pluripotent stem cells (iPSCs).[22] So far, stem cell therapy has provided a great opportunity for degenerative disease and diseases that require tissue regeneration, such as stroke, premature ovarian failure, and spinal cord injury.[23] The main aim of stem cell therapy in osteoporosis treatment is to promote bone formation, rather than reducing resorption.[24]

Monitoring osteoporosis

Repeat bone mineral density testing with dual-energy X-ray absorptiometry is useful to monitor a patient's response to therapy. It is recommended to test patients one year after starting or changing therapy, which can be spaced out to every 2–3 years if the bone density remains stable.[25]

Adverse effects of osteoporosis drugs[16]

Drug	Common adverse events	Notable rare adverse events
1) Oral bisphosphonates	Hypocalcaemia Upper gastrointestinal effects (gastro-oesophageal reflux, erosive oesophagitis)	Osteonecrosis of the jaw Atypical femoral fractures
2) Intravenous bisphosphonates	Hypocalcaemia Flu-like illness following infusion	Osteonecrosis of the jaw Atypical femoral fractures
3) Denosumab	Hypocalcaemia Injection-site reactions Atraumatic vertebral fractures following discontinuation	Osteonecrosis of the jaw Atypical femoral fractures
4) Raloxifene	Hot flushes Venous thromboembolism	Stroke
5) Teriparatide	Hypercalcaemia Injection-site reactions	Theoretical risk of osteosarcoma

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