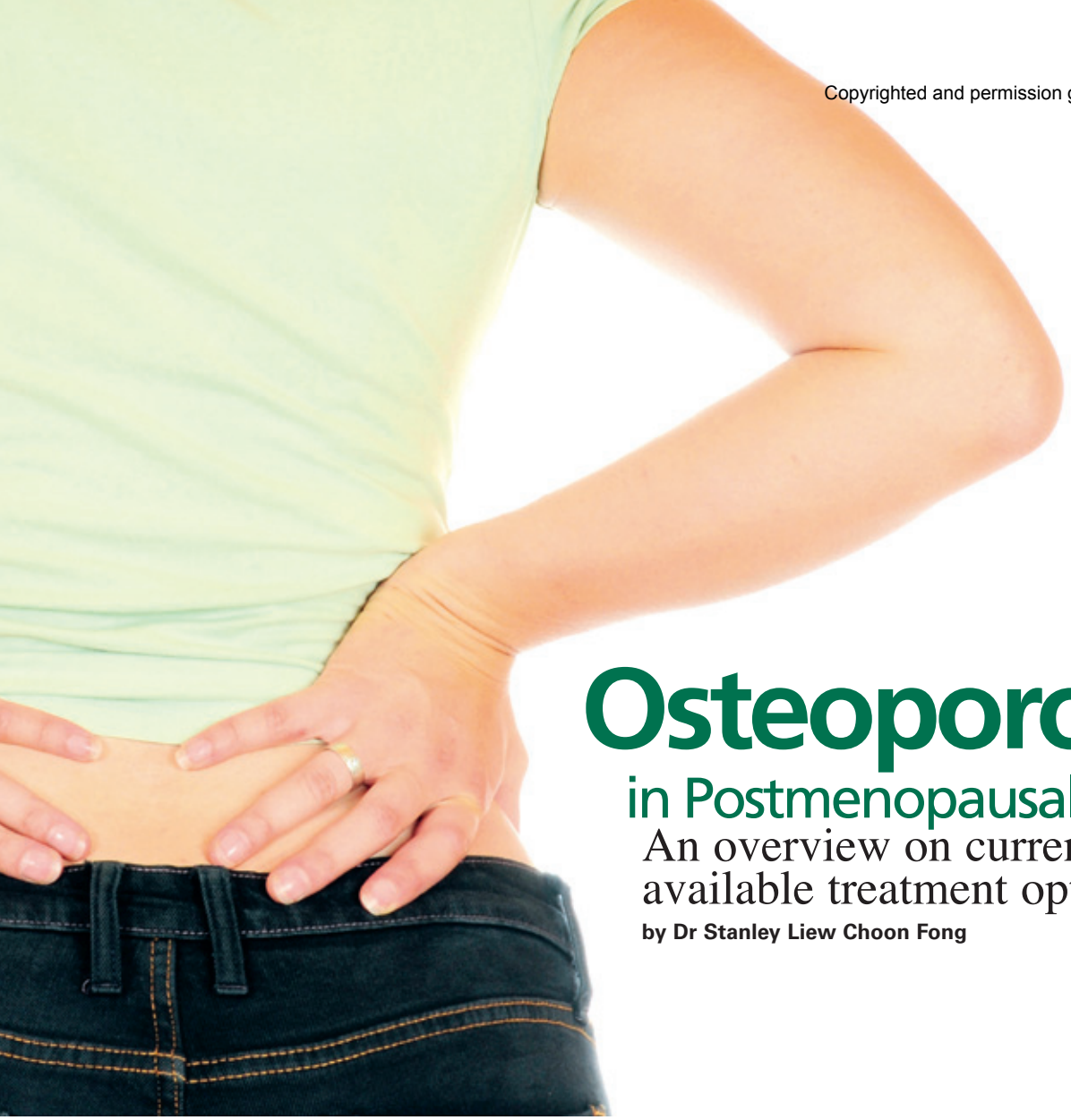

Osteoporosis
in Postmenopausal Women
An overview on currently available treatment options

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Osteoporosis is a growing public health issue as our population ages. It is a systemic skeletal disease characterised by low bone density and microarchitectural deterioration of the bone tissue with a consequent increase in bone fragility, leading to an increased risk of fractures.

The lifetime risk for hip, vertebral and forearm fractures has been estimated to be approximately 40%. Osteoporosis does not only cause fractures, it also causes people to become bed-ridden with secondary complications that may be life threatening in the elderly. Since osteoporosis also causes back pain and loss of height, prevention of the disease and its associated fractures is essential for maintaining health, quality of life, and independence among the elderly.[1]

Risk Assessment

It is not recommended to screen the general population at normal risk for low bone mineral density (BMD). BMD screening should be performed selectively through a case-finding approach based on an individual's risk for low bone mass and bone-mass-independent risk.[2] Different risk factors for osteoporosis and fractures are listed in **[Table 1]**.

Table 1. ***Risk Factors for Osteoporosis and Fractures****

Non-modifiable
Personal history of previous fragility fracture as an adult Height loss of more than 2cm over three years History of fracture in a first-degree relative Low body weight Elderly age group Poor health or frailty
Potentially-modifiable
Current cigarette smoking Alcohol abuse Low calcium intake (<500mg/day among Asians) Lack of regular physical activity Prolonged immobilisation
Secondary osteoporosis
Drugs, e.g. corticosteroids, excessive thyroxine, etc. Ongoing disease conditions, e.g. hypogonadism, hyperthyroidism, etc. Early menopause before age 45

**Modified from Ministry of Health, Singapore. Clinical Practice Guidelines: Osteoporosis; 2009*

Diagnosis

Osteoporosis can be diagnosed clinically or radiographically. Osteoporosis may present with low-impact fractures (e.g. occurring from a fall at or below standing height) or fragility fractures (e.g. occurring spontaneously).[3] The World Health Organisation (WHO) defines osteoporosis as a spinal or hip BMD of 2.5 standard deviations or more below the mean for healthy, young women (T-score of –2.5 or below), as measured by dual energy x-ray absorptiometry (DEXA) **[Table 2]**. Osteopenia is defined as a spinal or hip BMD between 1.0 and 2.5 standard deviations below the mean. DEXA currently is the test of choice for measuring BMD.

Table 2. ***WHO Definitions of Osteoporosis***

Classification	DEXA T-score
Normal	≥-1.0
Osteopenia	>-2.5 and <-1.0
Osteoporosis	≤-2.5

Who Should Be Considered for Treatment?

Patients at high risk for fracture are most likely to benefit from therapy. The US National Osteoporosis Foundation (NOF) recommends treating postmenopausal Caucasian women, age 50 years or older, presenting with the following[4]:

- A hip or vertebral fracture;
- T-score ≤-2.5 at the femoral neck or spine after appropriate evaluation to exclude secondary causes; or
- Low bone mass (T-score between -1.0 and -2.5 at the femoral neck or spine) and a 10-year probability of a hip fracture ≥3% or a 10-year probability of a major osteoporosis-related fracture ≥20%, based on the US-adapted WHO algorithm.

Pharmacotherapy

Several pharmacological agents have been approved for the treatment of osteoporosis. The beneficial effects of these agents on bone turnover and BMD in postmenopausal women with or without prevalent fractures have been reported. All patients undergoing pharmacological treatment for osteoporosis should be calcium and vitamin D replete.

Bisphosphonates

Bisphosphonates are analogues of pyrophosphate. They bind to hydroxyapatite crystals in bone, and inhibit bone resorption by their effects on osteoclasts. Bisphosphonates have vast amount of data for reduction of fracture risk, including postmenopausal women, men, and in the setting of glucocorticoid use.

Bisphosphonates are available in oral (alendronate, risedronate, and ibandronate) and intravenous (zoledronic acid) forms. Oral bisphosphonates should be taken with a full glass of water. A 30- to 60-minute wait is required before reclining or consuming other medications, beverages, or food to lower the risk of upper gastrointestinal adverse effects.

The optimal duration of bisphosphonate therapy for osteoporosis is not known. The long half-life of the bisphosphonates suggests that their effects may persist after discontinuing therapy. A randomised study found that women who took alendronate for five years, followed by five years of placebo, have no increase in the incidence of non-vertebral or hip fractures compared with women who took alendronate for 10 years. There is, however, an increase in vertebral fractures.[5] This suggests that relatively low-risk women (i.e. no personal history of vertebral fractures and only modestly reduced T-score) may consider an

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interruption in bisphosphonate treatment after five years of therapy, with appropriate monitoring of BMD.

Safety concerns have been raised about the association of bisphosphonates with osteonecrosis of the jaw. To date, this rare complication is most often associated with the frequent infusion of intravenous bisphosphonates in patients with cancer undergoing dental procedures.

Atypical, low-energy, or low-trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare, and are transverse or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.

Raloxifene

Raloxifene is a non-steroidal selective oestrogen receptor modulator. It binds to oestrogen receptors and inhibits bone resorption without significantly stimulating the endometrium. Raloxifene is effective for reducing the incidence of vertebral fractures.

Its use is associated with increased vasomotor symptoms. Although raloxifene increases the risk of venous thromboembolism, it decreases the risk of invasive breast cancer in postmenopausal women with osteoporosis. Perhaps it may be best used in postmenopausal women with osteoporosis who have no vasomotor symptoms or history of venous thromboembolism, and have a high breast cancer risk score.

Strontium Ranelate

Strontium ranelate is a divalent strontium salt of ranelic acid. Strontium is an element with properties similar to calcium. It is thought to have a dual effect on bone metabolism, increasing bone formation and decreasing bone resorption. It is approved for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures.

The recommended dose is a 2g sachet taken daily as a suspension in water. The absorption of strontium ranelate is reduced by food, milk and products derived from milk. It should therefore be administered at bedtime and preferably at least two hours after eating.

In general, strontium ranelate was not associated with an increased risk of adverse effects, and for the most part, side effects were mild and transient; nausea, diarrhoea and creatinine kinase elevations were the most commonly reported. A serious adverse event associated with strontium ranelate treatment was an increased incidence of venous thromboembolism and pulmonary embolism.

In 2007, the European Medicines Agency (EMEA) was alerted to a number of reports of drug rash with eosinophilia and systemic

symptoms (DRESS) associated with the use of strontium ranelate. The latency period between the first ingestion and the display of symptoms of DRESS is about three to six weeks. In most cases, the symptoms resolved upon discontinuation of strontium ranelate and with the initiation of corticosteroid therapy. Our Health Science Authority (HSA) has also received reports of serious skin reactions associated with it. These reports include a few cases of DRESS, exfoliative dermatitis, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

Teriparatide

Teriparatide is approved for the treatment of osteoporosis in postmenopausal women and men at high risk for fracture. It is also used for treatment in those at high risk of fracture with osteoporosis associated with sustained systemic glucocorticoid therapy. Teriparatide is also indicated to increase bone mass in men with primary or hypogonadal osteoporosis who are at high risk of fracture. It is an anabolic (bone-building) agent administered by daily subcutaneous injection. Teriparatide in a dose of 20mcg daily was shown to decrease the risk of vertebral fractures by 65% and non-vertebral fractures by 53% in patients with osteoporosis, after an average of 18 months of therapy.

Teriparatide is well tolerated, although some patients experience leg cramps and dizziness. Because it was associated with an increased incidence of osteosarcoma in rats, patients with an increased risk of osteosarcoma (e.g. patients with Paget's disease of bone) and those having prior radiation therapy of the skeleton, bone metastases, hypercalcaemia or a history of skeletal malignancy, should not receive teriparatide therapy.

The safety and efficacy of teriparatide has not been demonstrated beyond two years of treatment. Teriparatide is used for a maximum of two years. It is common practice to follow teriparatide treatment with an antiresorptive agent, usually a bisphosphonate, to maintain or further increase BMD.

Denosumab

Denosumab is a human monoclonal antibody that targets the receptor activator of the nuclear factor-kappa-B ligand (RANKL) protein, which acts as the primary signal to promote bone removal. By inhibiting the development and activity of osteoclasts, denosumab decreases bone resorption and increases bone density. It is administered as a single subcutaneous injection of 60mg once every six months.

It is indicated for the treatment of postmenopausal women who have a high risk for osteoporotic fractures, including those with a history of fracture or multiple risk factors for fracture, or those who have failed or are intolerant to other osteoporosis therapy.

A large three-year randomised, placebo-controlled trial of postmenopausal women showed that denosumab reduced the incidence of vertebral, non-vertebral, and hip fractures in postmenopausal women with osteoporosis.[6]

Some common side effects reported with denosumab include back pain, pain in the extremities, musculoskeletal pain, hypercholesterolaemia and cystitis. Serious adverse reactions include hypocalcaemia, non-fatal serious infections, including infections of the skin, and dermatological reactions such as dermatitis, rashes and eczema. Denosumab is known to cause significant suppression of bone turnover and this has raised concerns that it may potentially contribute to the occurrence of osteonecrosis of the jaw.

Conclusion

Osteoporosis is a preventable condition, not an inescapable sequela of ageing. Management of skeletal health should be directed towards maximising peak bone mass and minimising bone loss that occurs with ageing. The cornerstone of prevention at population level is healthy lifestyle: calcium and vitamin D supplementation as needed, regular weight-bearing exercise, and avoidance of smoking and excess alcohol. Patients at high risk for osteoporotic fracture should be identified and considered for pharmacotherapy. MG

References

[1] Prevention and management of osteoporosis: report of a WHO Scientific Group. Geneva, Switzerland; 2003.

[2] Ministry of Health, Singapore. Clinical Practice Guidelines: Osteoporosis;2009.

[3] Mauck KF, Clarke BL. Diagnosis, screening, prevention, and treatment of osteoporosis. Mayo Clin Proc 2006;81(5):662-72.

[4] National Osteoporosis Foundation. Clinician's Guide to Prevention and Treatment of Osteoporosis 2010.

[5] Black DM et al., for the FLEX Research Group. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. JAMA 2006;296(24):2927-38.

[6] Cummings SR et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 2009;361(8):756-65.