UNIT NO. 4

PHARMACOLOGICAL MANAGEMENT OF OSTEOPOROSIS

Dr Linsey Utami Gani

ABSTRACT

Osteoporosis is a common problem encountered in primary care. Mortality and long-term morbidity is associated with almost all types of symptomatic osteoporotic fractures. Local data suggests that osteoporosis remains undiagnosed and undertreated. Primary care physicians play a central role in closing the gap for osteoporosis treatment with the opportunity to diagnose, investigate, and treat these patients effectively. In this article, we explore different pharmacological options in the treatment of osteoporosis, including the role of calcium and vitamin D, antiresorptive agents, hormonal therapy, and anabolic treatment options.

Keywords: Osteoporosis; Fragility Fracture; Calcium and Vitamin D; Antiresorptive Treatment; Hormonal Therapy; Anabolic Treatment;

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INTRODUCTION

Osteoporosis is a common problem encountered in primary care. It is characterised by both low bone mineral density (BMD) and micro-architectural deterioration of bone tissue, leading to decreased bone strength, increased bone fragility and a consequent increase in fracture risk. Osteoporotic fractures usually result from falls from a standing height or less in individuals with decreased bone strength. BMD can be measured by dual energy X-ray adsorptiometry (DXA). BMD is usually reported as a T-score, the number of standard deviations (SDs) of the BMD measurement above or below that of young healthy adults of the same sex. Table 1 shows the WHO definitions of osteoporosis and osteopenia. It is important to note that ***BMD is only one of several factors that contribute to an individual's risk of fracture. Approximately 50 percent of first or subsequent minimal trauma fractures occur in people who have T-scores in the normal or osteopenic range.***[1]

Table 1: WHO definitions of osteoporosis and osteopenia

Normal BMD	T-score of -1.0 or above	BMD not more than 1.0 SD below young adult mean
Osteopenia	T-score between -1.0 and -2.5	BMD between 1.0 and 2.5 SDs below young adult mean
Osteoporosis	T-score -2.5 or below	BMD 2.5 or more SDs below young adult mean

LINSEY UTAMI GANI
Endocrinology, Changi General Hospital

A. MORBIDITY AND MORTALITY

Fractures give rise to pain, reduced mobility, and loss of quality of life. Long-term morbidity is associated with almost all types of symptomatic osteoporotic fractures with many patients losing the ability to live independently following a hip fracture. Mortality in the first year after a major osteoporotic fracture has been shown to increase up to three times compared to the age-matched non-fracture population.[2] The risk of death is greatest in the first year after hip fracture: approximately 20 percent of women die within a year of fracturing a hip, with 10 percent dying during hospitalisation.[3] Excess mortality occurs mainly in the first five years after a minimal trauma fracture, but may continue up to 10 years following the fracture.

Treatment Gap in Osteoporosis Care in Singapore

It is estimated that 1 in 3 women and 1 in 5 men over 50 years old will experience a fragility fracture in their lifetime. In Singapore, the incidence of hip fractures in 1998 had increased 5 times in women and 1.5 times in men compared to those observed in the 1960s.[4] There remains a treatment gap for patients with osteoporosis, with evidence suggesting that up to 80 percent of individuals with at least one fragility fracture are neither identified or treated.[5] Local data suggests that 1 year post a fragility hip fracture, only 10–30 percent had been initiated on antiresorptive treatment.[6]

Studies have shown that 50 percent of patients with a hip fracture have presented with a prior minimal trauma fracture and that the risk of future fracture can be reduced up to 80 percent if the root causes (osteoporosis and falls) are appropriately addressed.[7]

The central role of primary care physicians

A number of patients with minimal trauma fracture may not present to a hospital, whereas almost all patients with a minimal trauma fracture will eventually see their primary care physician (although not usually just for the purpose of the minimal trauma fracture). Therefore, the primary care physician is key to ensuring patients are appropriately managed after a minimal trauma fracture. Supporting primary care physicians to manage osteoporosis in patients who do not have access to these programmes is critical to ensuring that all patients with a minimal trauma fracture are evaluated and managed appropriately.

B. RISK FACTOR ASSESSMENT, DIAGNOSIS, AND REFERRAL

International guidelines recommend fracture risk assessment in postmenopausal women and men older than 50 years of age. See Figure 1 (Osteoporosis treatment algorithm).

Major risk factors include:
- History of minimal trauma fracture
- Height loss of ≥3 cm and/or back pain suggestive of vertebral fracture
- Female
- Age >70 years of age
- History of falls
- Parental history of hip fracture
- Premature menopause or hypogonadism
- Prolonged use of glucocorticoids (>3 months ≥7.5 mg/d)
- Use of medications that cause bone loss
- Conditions or diseases that lead to bone loss
- Low body weight
- Low muscle strength and mass

Other risk factors:
- Smoking
- High alcohol intake
- Energy, protein, or calcium undernutrition
- Vitamin D insufficiency

History of Minimal Trauma Fractures

Numerous studies have reported increased risks of hip, spine, and other fractures among people who had previously clinically diagnosed fractures, or have radiographic evidence of vertebral fractures. The strongest association was observed between prior and subsequent vertebral fractures—women with pre-existing vertebral fractures had approximately 4 times greater risk of subsequent vertebral fractures. This risk increases with the number of prior fractures. Most studies reported a risk of 2 to 2.2 times for prior and future fracture sites (hip, spine, wrist, or any site).[8]

Absolute Fracture Risk Assessment

In addition to bone mineral density, there are other clinical factors associated with minimal trauma fracture risk. Absolute fracture risk is most commonly expressed as an individual's percentage chance of suffering a minimal trauma fracture over a given period of time, generally 10 years. Absolute fracture risk is currently used internationally as a basis for treatment decisions. Countries differ globally as to the treatment threshold that they have adopted based on their cost-effectiveness calculation.

- Fracture Risk Assessment Tool (FRAX). FRAX is the most commonly used absolute risk calculation tool. It predicts the 10-year risk of hip fracture and the combined group of "major osteoporotic" fractures.
- Limitations of FRAX
  - o Falls as a risk factor is not included in the FRAX calculator. Falls risk is recognised as an independent risk factor for fracture
  - o The FRAX questionnaire provides risk factor assessment as a yes/no variable and does not allow for assessment of extent of exposure, e.g., in smoking, alcohol, and glucocorticoid use.

Fracture Risk Intervention Threshold

Health economic modelling in the UK and USA has demonstrated that treatment is cost-effective when FRAX is used to identify at-risk patients.[9,10] Based on a drug cost of US$600 per year for 5 years (with 35% fracture reduction) and an average cost per quality-adjusted life year (QALY) designated at US$60,000 or less, the US National Osteoporosis Foundation guidelines recommend treatment when the 10-year risk of hip fracture is 3 percent or higher, or the 10-year risk of major osteoporotic fracture is 20 percent or higher.[10]

MOH is releasing it's ACG (Appropriate Care Guideline) for Osteoporosis in October 2018 with the new published threshold for treatment in the local Singapore population. Please keep a lookout for the new local intervention threshold guideline.

C. THE ROLE OF CALCIUM AND VITAMIN D IN THE TREATMENT OF OSTEOPOROSIS

Calcium and vitamin D support bone growth in children and adolescents and lower rates of bone loss in adults and the elderly. Calcium and vitamin D play an important role in the maintenance of bone health. However, evidence indicates that the absolute benefit of these treatments in terms of fracture prevention in non-institutionalised individuals is low and considerably less than conventional osteoporosis treatments. There could be benefit for those who may be deficient and, in particular, institutionalised individuals. The US preventive services has found inadequate benefit of routine supplementation of calcium and vitamin D for primary fracture prevention in community-dwelling, asymptomatic men and postmenopausal women.[11] However, this recommendation does not apply to persons with a history of osteoporotic fractures, increased falls risk, or a diagnosis of osteoporosis or vitamin D deficiency.[11]

The target calcium intake from dietary sources and supplements should be 1000 mg per day for adults and 1300 mg per day for women older than 50 years of age and men older than 70 years of age. Vitamin D from sunlight exposure and supplements should ensure 25-hydroxyvitamin D (25-OH-D) levels of 20 ug/L or more in the general population and a level of 30 ug/L or more in elderly at risk of falls or people diagnosed with osteoporosis. If vitamin D supplements are required, a dose of 800–1000 IU/day is usually sufficient, although higher doses may be needed initially to achieve target levels.

Calcium and vitamin D supplements work by reducing secondary hyperparathyroidism and reducing bone turnover. Bone mineral density is also increased by calcium and vitamin D, but this effect appears to be modest. Calcium supplements are available in two common forms: calcium carbonate and calcium citrate. Calcium tablets contain between 250–600 mg of elemental calcium.

Side Effects and Potential Harms

MOH will be releasing it's ACG on osteoporosis with guidelines on osteoporosis screening in October 2018. Please keep a lookout for this for local guideline use.

Calcium supplements modestly increase the risk of renal calculi, and also abdominal bloating and constipation.[11] Some studies have reported an increased risk of myocardial infarction,[12] but not all studies support this conclusion.[13] Clinical toxicity is uncommon with vitamin D and single doses of up to 500,000 IU are tolerated without causing hypercalcemia or hypercalciuria[14].

Summary of the Role of Calcium and Vitamin D

In otherwise healthy non-institutionalised individuals, the relative risk reduction in fracture risk with calcium and/or vitamin D supplementation alone is small and may be associated with some adverse events. As such, these should not be considered routinely in healthy people or as first-line treatments for people with osteoporosis.

Recommended calcium intake should be 1000 mg per day in adults and 1300 mg per day in postmenopausal women and older men, ideally from dietary sources. Where this cannot be achieved, a supplement of 500–600 mg of elemental calcium is appropriate. Target vitamin D levels should be 20 ug/L in the general population and a level of 30 ug/L or more in elderly at risk of falls or those diagnosed with osteoporosis.

Calcium and vitamin D supplements are more likely to be effective in reducing fracture risk when given in combination to individuals who are deficient. Vitamin D is recommended by several organisations to lower the risk of falling.

In conclusion, adequate intakes of calcium and vitamin D are essential preventative measures and components of any therapeutic regimen for osteoporosis. The majority of studies in osteoporosis treatments have been conducted in the setting of concurrent calcium and vitamin D supplementation.

D. ANTIRESORPTIVE AGENTS

Bisphosphonates

Bisphosphonates (BP) are synthetic analogues of inorganic pyrophosphate in which the oxygen atom that connects the two phosphates is replaced by a carbon (Figure 2). The two phosphonic acids cause bisphosphonates to be avidly absorbed to bone surfaces. The central carbon renders the compound impervious to enzymatic degradation. Side chains R1 and R2 affect the avidity of adsorption to bone and antiresorptive potency.[15,16] The R1 side chain determines bone-binding affinity, and the R2 side chain determines antiresorption potency. Bisphosphonates that have been approved for use in osteoporosis (Alendronate, Ibandronate, Risedronate and Zoledronate) have nitrogen containing R2 side chains that enhances antiresorptive and antifracture potency.[17]

Pharmacology

The intestinal absorption of BPs is poor (less than 1 %) and decreases further in the presence of food, calcium, or other minerals that bind to them. Oral BPs should be given in the fasting state 30 to 60 minutes before meals, with water. Skeletal uptake depends on the rate of bone turnover, renal function, as well as on the structure of BPs.[18]

The decrease of bone resorption by BPs is followed by a slower decrease in the rate of bone formation, due to the coupling of the two processes, so that a new steady state at a lower rate of bone turnover is reached 3 to 6 months later. In addition to decreasing the rate of bone turnover, BPs maintain or may improve trabecular or cortical architecture, improve the hypomineralisation of osteoporotic bone, increase areal mineral density, and may reduce the rate of osteocyte apoptosis. These actions reduce the overall clinical risk of fractures.[19]

Current routinely available preparations are oral weekly (alendronate 70 mg, risedronate 35 mg). Intravenous BPs (once-yearly 5 mg zoledronic acid) can be used as a first-line osteoporosis treatment but are often used in patients intolerant to oral formulations or who are likely to be non-adherent to oral medications.

Antifracture Efficacy

All BPs given daily in adequate doses significantly reduce the risk of vertebral fractures by 35–65 percent. To overcome reduced adherence to daily treatment and potential GI s/e, once-weekly formulations, the sum of 7 daily doses, have been developed for alendronate and risedronate, and have been shown to significantly improve patient adherence to treatment while sustaining the same pharmacodynamics response as daily treatment.[20,21] The overall efficacy and consistency of BPs in reducing vertebral fracture risk has been demonstrated by meta analyses of RCTs for alendronate and risedronate. In studies in which radiographs were taken annually (e.g., the Vertebral Efficacy with Risedronate Therapy VERT study), the effect of the BPs in reducing the risk of vertebral fractures was already evident after 1 year, demonstrating rapid protection of skeletal integrity. This was also shown for clinical vertebral fractures with alendronate.[22]

The efficacy of BPs in reducing the risk of non-vertebral fractures has also been confirmed in a number of RCTs. A meta-analysis of the Cochrane Collaboration reported an overall reduction of the risk of non-vertebral fractures in women with osteoporosis of 23 percent (RR 0.77, 95% CI 0.74–0.94) with alendronate and 20 percent (RR 0.80, 95% CI 0.72–0.90) with risedronate. The corresponding risk reductions for hip fractures were 53 percent (RR 0.47, 95% CI 0.26–0.85) with alendronate and 26 percent (RR 0.74, 95% CI 0.59–0.94) with risedronate.

Side Effects and Potential Harms

Bisphosphonates used in the management of osteoporosis are

usually well tolerated. In two separate systematic reviews of oral bisphosphonate therapy, there was no statistically significant difference in adverse events in the active versus placebo arm.[23] The most commonly reported adverse effects from observational data are gastrointestinal (gastric irritation, oesophageal erosions, gastric ulcers, perforations and strictures). This has been postulated to be related to incorrect administration.[24]

Medication-related osteonecrosis of the jaw (MRONJ) is a rare adverse effect. Its incidence ranges between <1 case per 10,000 patients to 10 cases per 10,000 patients treated with oral bisphosphonates[25] and 1.7 cases per 10,000 patients treated with zoledronic acid.[26] Potential risk factors for MRONJ includes poor oral hygiene, smoking, diabetes mellitus, concomitant glucocorticoids and/or chemotherapy, and invasive dental procedures such as dental extractions or implants.

Atypical fracture of the femur (AFF) also appears to be a rare adverse event, occurring at 3.2 to 50 cases per 100,000 person years of BP treatment. Importantly documented AFFs have also occurred in individuals without any history of antiresorptive therapy. Updated diagnostic criteria were published in 2014. Some, but not all, studies suggest a duration response relationship, with a rise in age-adjusted incidence rates from 1.8/100,000 per year with a 2-year exposure to 113/100,000 per year with exposure from 9–9.9 years. Such results suggest that, although rare, AFF risk increases with prolonged BP treatment duration and this should be taken into consideration when continuing BPs beyond 5 years.

However, it is important to note that for most patients treated for osteoporosis, the BP-associated benefit of reduced fracture risk beyond 5 years is greater than the risk of developing either MRONJ or AFF.

Long term effects on bone fragility

Skeletal fragility on long-term BP therapy has been examined in extensions of 4 clinical trials for 6–10 years. In all 4 studies, the incidence of non-vertebral fractures was constant with time. In the extension of the FIT (Fracture Intervention Trial) (FLEX) continuation of alendronate treatment led to further increases in BMD of the spine and stabilisation of that of the hip, whereas there was a slow progressive decrease of the total hip BMD in patients who received a placebo during the extension. In a post hoc analysis, women who entered the extension with a femoral neck BMD T-score below -2.5, without history of previous vertebral fractures continued treatment with alendronate, showed a significant reduction in the risk of non-vertebral fractures during the 5-year extension. These results suggest that alendronate should be continued in patients at high risk, whereas discontinuation of treatment after 5 years may be considered in patients with lower risk. Similar BMD and fracture data were also reported in the extension of the HORIZON trial in which patients treated with zoledronate for 3 years were randomised to 3 additional years of zoledronate or placebo.

The Task Force of the American Society for Bone and Mineral Research has published a recommendation on managing osteoporosis in patients on long-term BP treatment. In the recommendation the Task Force suggests that after 5 years of oral BP or 3 years of intravenous BP, reassessment of risk should be considered. In women at high risk, for example, older women, those with a low hip T-score or high fracture risk score, those with previous major osteoporotic fracture, or who fracture on therapy, continuation of treatment for up to 10 years (oral) or 6 years (intravenous), with periodic evaluation, should be considered (see Figure 3).

Denosumab

Denosumab is a fully human, high-specificity and high-affinity monoclonal antibody against receptor activator of nuclear factor k-B ligand (RANKL) available for the treatment of osteoporosis and other bone diseases. The binding of RANKL to its receptor RANK on preosteoclasts is required for the proliferation, maturation, activation, and survival of osteoclasts. As a consequence, osteoclast formation, function, and survival are disrupted, resulting in decreased bone resorption and increased mass and strength of both cortical and trabecular bone. Denosumab is given as a subcutaneous injection of 60 mg every 6 months.

Antifracture Efficacy

Denosumab significantly reduces the risk of vertebral, non-vertebral, and hip fractures in postmenopausal women. In the pivotal FREEDOM[27] trial, denosumab decreased the incidence of new morphometric vertebral fractures from 7.2 percent to 2.3 percent (68% relative reduction, CI 59–74%). The relative risk reduction of hip fracture was 40 percent (CI 3–63%). Denosumab was effective in increasing bone density and decreasing the incidence of vertebral fracture in women of the FREEDOM trial across the spectrum of baseline renal function. This included 2,817 women with estimated GFR between 30–59 cc per minute and 73 women with estimated GFR of 15–29 cc per minute. The efficacy and safety of denosumab therapy in patients with renal failure on dialysis has not been studied.

Side Effects and Potential Harms

Denosumab is generally well tolerated. There was no significant increase in adverse events and frequency of infection, malignancies, cardiovascular disease, peripheral vascular disease, or medication-related osteonecrosis of the jaw (MRONJ), while atypical fractures of femur (AFF) was similar between the denosumab and placebo groups. Injection site reactions and post-dose symptoms were not observed. Cellulitis has been more frequently reported with denosumab compared with placebo, although the incidence remains low (less than 0.2 events per 100 subject-years for long-term denosumab).[28] Hypocalcaemia following denosumab administration is a significant risk in patients with severe renal impairment and vitamin D deficiency.

Long-term Responses

In an extension of FREEDOM, about 4,500 women on denosumab 60 mg every 6 months for up to 10 years were studied. In women who received denosumab during the first 3 years of the study, treatment during years 4 and 5 resulted in continued increase in BMD, resulting in 5-year gains of 13.7 percent and 7.0 percent in the lumbar spine and total hip, respectively.[28] Unlike BPs which are sequestered in bone, the effects of denosumab on bone resorption do not persist after treatment has stopped. Therefore regular six-monthly administration is required for continued fracture risk reduction.

E. HORMONE THERAPY (HT)

Oestrogen

Oestrogen replacement therapy is effective in preventing loss of BMD and reducing risk of fractures when given at, or near, menopause (and is also useful for controlling menopausal symptoms) and has a role in reducing the risk of fractures in postmenopausal women with osteoporosis.[29,30] Adjuvant progestogens are necessary in women who still have a uterus, to protect against endometrial cancer. They may be given cyclically for 10–14 days each month in perimenopausal women or a continuous therapy combined with oestrogen in postmenopausal women. The minimum effective dose of oestrogen therapy on bone loss has yet to be clearly established, but the beneficial effects of oestrogen therapy can be achieved through different administration routes including oral and transdermal. Patients who demonstrate ongoing bone loss with low-dose oestrogen replacement therapy may be considered for higher doses, with attention paid to calcium intake and vitamin D status, provided that the risk associated with oestrogen replacement therapy is not increased (e.g., clotting, CV disease, or breast cancer).

Tibolone

Tibolone has oestrogenic, progestogenic and androgenic effects and does not need to be given with a progestogen. It has similar efficacy to traditional hormone therapy in reducing fracture risk.

Raloxifene

Raloxifene is a selective oestrogen receptor modulator (SERM) and is used for treatment of postmenopausal osteoporosis. SERMs have evidence of breast cancer prevention, so their use can be tailored to suit an individual's unique risk factor profile and may be particularly useful in the younger postmenopausal female with low spine BMD and a prior or family history of breast cancer.

While there is excellent evidence for raloxifene in reduction of vertebral risk,[31] there is minimal evidence for reduction in non-vertebral fractures. Therapy should be continuous and there is no need for concomitant progestogens.

Potential Adverse Effects

The role of long-term postmenopausal HT in the prevention and management of osteoporosis remains controversial, following publication of the results of the Women's Health Initiative (WHI) study of combined oestrogen and progestin therapy[32] and its study of oestrogen-alone therapy. In the oestrogen-alone group, there was no increased risk of invasive breast cancer or CV disease, although the other outcomes were similar to the combined group.[33] For the combined oestrogen/progesterone group, increased risk of invasive breast cancer has been reported, although the initial report of increased coronary heart disease was no longer significant in subsequent analyses of the post-intervention follow up.[34] The side-effect profile is more favourable in women starting HT within 10 years of the menopause (50–59 years) with low absolute risks of thromboembolic events and stroke.

Tibolone has a different side effect profile from traditional HT. There's no RCT evidence for an increase in breast cancer, however it does appear to increase breast cancer recurrence in those previously treated for breast cancer. There's no evidence for increased heart disease or thromboembolic events in younger women, but in older women there was an increased risk of stroke.[35]

Raloxifene may increase hot flushes and is likely to aggravate vasomotor symptoms. While it did not significantly affect CHD risk, studies have shown increased risk of venous thromboembolic events. The increase in these events is similar to that for oestrogen and is highest during the initial months of treatment. The occurrence of stroke was not different between the raloxifene and placebo groups, but there were more fatal strokes in the raloxifene group.[36]

F. ANABOLIC AGENT

Parathyroid Hormone

Parathyroid hormone (PTH) is the only approved anabolic therapy for bone, producing larger increments in bone mass (especially the spine), than those seen with antiresorptive therapies. hPTH (1-34), also known as teriparatide is currently the form of PTH available in Singapore for administration. Teriparatide works predominantly on osteoblasts to increase new bone formation, and subsequently increases both bone resorption and formation although the balance remains positive for formation even in the latter phase of PTH activity. The growth of new bone with PTH permits restoration of bone microarchitecture, including improving trabecular connectivity and enhanced cortical thickness.[37,38] Bone formation may also be induced on the outer periosteal surface, possibly affecting bone size and geometry, with additional effects on bone strength.

Teriparatide is given as a daily subcutaneous injection via a multi-dose pen device. Because of its high cost, it is generally considered more cost-effective in patients who are at very high risk of fracture.

Candidates for Anabolic Therapy

Good candidates for PTH therapy are women and men who are at high risk of future osteoporosis-related fractures, including those with vertebral compression fractures, other osteoporosis-related fractures or those very low BMD (T score below -3.0). PTH is also recommended for those who have been on antiresorptive treatment and had a suboptimal response to treatment, defined as incident fractures or active bone loss during therapy.

Individuals who might be at elevated risk for osteosarcoma, such as those with a history of Paget's disease, bone irradiation, unexplained elevation in alkaline phosphatase, adults with open epiphyses and children should not receive PTH treatment. Those with metastatic bone cancer, primary bone cancer, myeloma, hyperparathyroidism, and hypercalcemia should also not receive PTH. Treatment duration course is between 18–24 months, a function of the pivotal trial duration and the finding that effect of medication appears to wane after this time.

Glucocorticoid Treated Patients

PTH has been studied as the preferred treatment for glucocorticoid osteoporosis, as some of the major physiologic skeletal problems with glucocorticoid administration are reduced osteoblast function and lifespan which are counteracted by PTH. Trials in this population comparing alendronate and PTH found a more significant increase in BMD at the spine and total hip with fewer new vertebral fractures. There were no differences in non-vertebral fractures between the groups.[39,40]

Persistence of Effect

A series of observational studies suggests that BMD is lost in individuals who do not take antiresorptive agents after cessation of teriparatide, whereas antiresorptive agents after cessation of teriparatide can maintain PTH-induced BMD gains or even provide further increments in BMD after a course of PTH.[41,42]

Potential Adverse Effects

Dizziness, leg cramps, nausea, injection reactions, and headaches are the most commonly described side effects occurring in less than 5 percent of cases. These are generally mild and do not require treatment discontinuation. Mild transient hypercalcemia has been noted, but monitoring serum calcium is not a requirement of therapy.[43] Oncogenicity studies in rats treated with high doses of teriparatide of near-lifetime duration resulted in an increased risk of osteogenic sarcoma. Surveillance of human osteosarcoma cases has found no relationship with teriparatide.[44]

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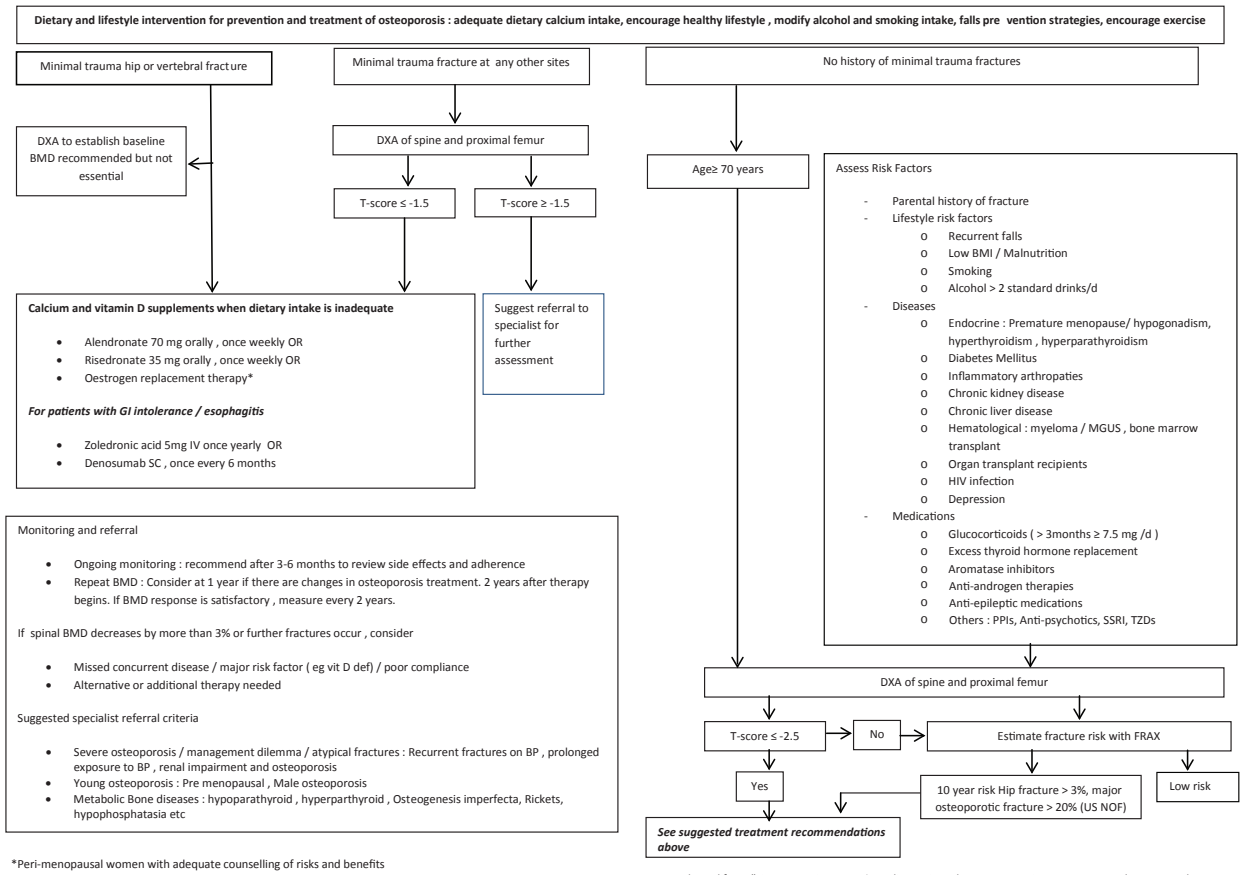
LEARNING POINTS

- **Primary care physicians play a central role in closing the gap for osteoporosis treatment with opportunities to diagnose, investigate and treat these patients effectively**
- **BMD is only one of several factors that contribute to an individual's risk of fracture. Absolute fracture risk assessment with tools such as FRAX is essential in determining the fracture risk intervention threshold.**
- **In otherwise healthy non-institutionalised individuals, the relative risk reduction in fracture risk with calcium and/or vitamin D supplementation alone is small and may be associated with some adverse events. As such, these should not be considered routinely in healthy people or as first-line treatments for those with osteoporosis.**
- **Calcium and vitamin D supplements are more likely to be effective in reducing fracture risk when given in combination to individuals who are deficient. Most studies in osteoporosis treatments have been done with concurrent adequate calcium and vitamin D supplementation.**
- **All bisphosphonates given in recommended therapeutic doses have been proved to reduce fracture risk. Bisphosphonates are generally well tolerated and have not shown increased adverse effects compared to placebo. For high-risk patients treated for osteoporosis, the BP-associated benefit of reduced fracture risk beyond 5 years is greater than the risk of developing either MRONJ or AFF.**
- **Denosumab is a fully human, high-specificity, and high-affinity monoclonal antibody against receptor activator of nuclear factor k-B ligand (RANKL) available for the treatment of osteoporosis. The effects of denosumab on bone resorption do not persist after treatment has stopped. Therefore regular six-monthly administration is required for continued fracture risk reduction.**
- **Hormonal therapy may be appropriate in women at the peri-menopausal stage and requires adequate counselling of its benefits and risks.**
- **Parathyroid hormone is an anabolic agent available for treatment of osteoporosis in patients at very high risk of fracture.**

Figure 1 : Recommended Osteoporosis Investigation and Treatment Algorithm

MOH will be releasing it's ACG on osteoporosis with guidelines on osteoporosis screening in October 2018. Please keep a lookout for this for local guideline use.



*Peri-menopausal women with adequate counselling of risks and benefits

Adapted from " Osteoporosis prevention , diagnosis and management in postmenopausal women and men over 50 years" . 2nd edition RACGP Australia & Osteoporosis Australia 2017

Figure 2 : Structure of pyrophosphate and bisphosphonates

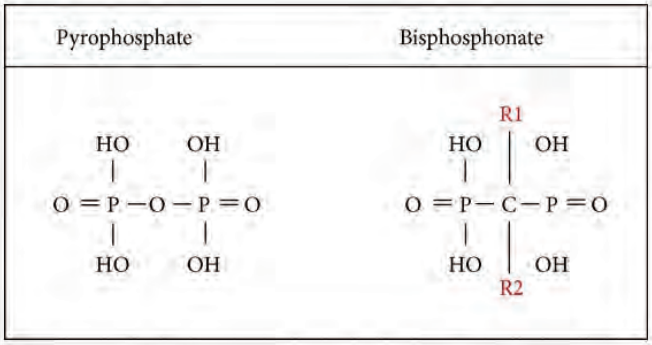
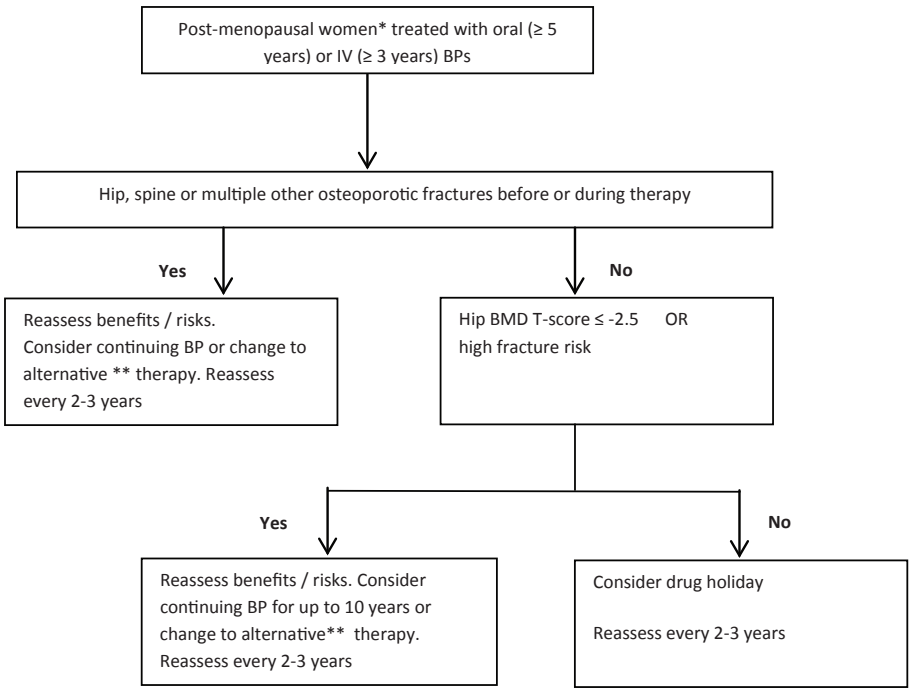


Figure 3 : ASBMR Task Force Recommendation for Patients on Long Term Bisphosphonates



*The approach developed by the ASBMR Task Force on Long - term bisphosphonates can be generally applicable to older men

**Alternative therapy includes teriparatide and denosumab