UNIT NO. 5

TREATMENT OF OSTEOPOROSIS

Dr Lydia Au Shu Yi, Mr Chang Wei Terk

ABSTRACT

Non-pharmacological recommendations for osteoporosis prevention are based on lifestyle measures to reduce bone loss and modify factors that can influence fracture risk. Lifestyle measures include smoking cessation, avoidance of heavy alcohol, adequate intake of calcium and vitamin D, exercise, and counselling on fall prevention. Calcium from dietary intake if adequate will not need supplementation; however vitamin D supplementation is usually required. The target of calcium 1000mg and 800iu of vitamin D daily are advised.

Key words: Smoking; Alcohol Calcium; Vitamin D; Falls; Exercises;

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INTRODUCTION

Worldwide, osteoporosis causes more than 8.9 million fractures annually, resulting in an osteoporotic fracture every 3 seconds.[1] Likewise, 1 in 3 women over age 50 will experience osteoporotic fractures, as will 1 in 5 men aged over 50.[2,3,4] An IOF survey, conducted in 11 countries, showed that **denial of personal risk** by postmenopausal women, lack of dialogue about osteoporosis with their doctor, and restricted access to diagnosis and treatment before the first fracture, result in under-diagnosis and under-treatment of the disease.[5]

Fixed risk factors determine whether an individual is at heightened risk of osteoporosis. Also, unlike modifiable risks, they are factors which we can't change, including **age, gender and family history**.

Secondary causes of osteoporosis are extensive, and some of them are represented in the table below (reproduced from American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis — 2016).

LYDIA AU SHU YI
Director & Senior Consultant, Geriatric Medicine
Ng Teng Fong General Hospital

CHANG WEI TERK
Principal Pharmacist
Ng Teng Fong Hospital

Table 1: Causes of Secondary Osteoporosis in Adults

Endocrine or metabolic causes	Nutritional/GI conditions	Drugs	Disorders of collagen metabolism	Other
Acromegaly	Alcoholism	Antiepileptic drugs[a]	Ehlers-Danlos syndrome	AIDS/HIV[a]
Diabetes mellitus Type 1	Anorexia nervosa	Aromatase inhibitors	Homocystinuria due to cystathionine deficiency	Ankylosing spondylitis
Type 2	Calcium deficiency	Chemotherapy/ immunosuppressants	Marfan syndrome	Chronic obstructive pulmonary disease
Growth hormone deficiency	Chronic liver disease	Depo-Provera	Osteogenesis imperfect	Gaucher disease
Hypercortisolism	Malabsorption syndromes/ malnutrition (including celiac disease, cystic fibrosis, Crohn's disease, and gastric resection or bypass)	Glucocorticoids		Hemophilia
Hyperparathyroidism		Gonadotropin-releasing hormone agents		Hypercalciuria
Hyperthyroidism		Heparin		Immobilization
Hypogonadism		Lithium		Major depression
Hypophosphatasia		Proton pump inhibitors		Myeloma and some cancers
Porphyria		Selective serotonin reuptake inhibitors		Organ transplantation
Pregnancy	Total parenteral nutrition	Thiazolidinediones		Renal insufficiency/ failure
	Vitamin D deficiency	Thyroid hormone (in supraphysiologic doses)		Renal tubular acidosis
				Rheumatoid arthritis
				Systemic mastocytosis
				Thalassemia

Abbreviations: AIDS = acquired immunodeficiency syndrome; GI = gastrointestinal; HIV = human immunodeficiency virus; GI = gastrointestinal.
[a] Phenobarbital, phenytoin, primidone, valproate, and carbamazepine have been associated with low bone mass.

This article sets out the non-pharmacological strategies in osteoporosis management that should be **universally adopted** and also includes the algorithm for assessing falls risk in elderly patients who are at high risk of fracturing after a fall.

NON-PHARMACOLOGICAL STRATEGIES

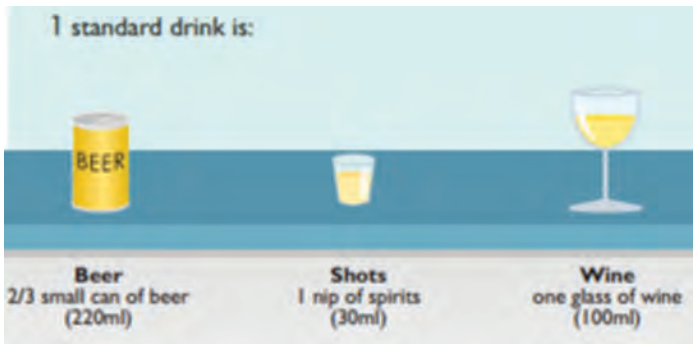
Cessation of Smoking

Data strongly persuades women to cease smoking to aid bone health because smoking cigarettes accelerates bone loss. Smoking one pack per day throughout adult life was associated with a 5 to 10 percent reduction in bone density.[1] Smoking may also negate the beneficial effect of oestrogen therapy in postmenopausal women.[6,7] This may be mediated in part by acceleration of the metabolism of oestrogen, thereby lowering serum oestrogen concentrations.

Alcohol

Avoid excessive amounts of alcohol (defined as >3 drinks/day for men and >2 drinks/day for women) as it may adversely affect bone health and increase risk of falls.[8]

Figure 1: Examples of a standard drink excerpted from the brochure on Osteoporosis for Patients (Jan 2009)



Source: Ministry of Health Singapore. Available from https://www.moh.gov.sg/content/dam/moh_web/HPP/Doctors/cpg_medical/current/2009/CPG_Osteoporosis_PatientVersion.pdf

Calcium Supplements

Rules of thumb

Determination of the dietary calcium intake is important because:

- Total daily elemental calcium intake (supplement and diet combined) should be 1000mg/day (max=2000mg)
  - UpToDate recommends that the maximal total calcium intake (diet plus supplement) be kept at 1200mg/day, with 500mg/day or less of this amount contributed to by calcium supplements, in patients with creatinine clearance of <30ml/min. This is in keeping with KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) recommendations on restricting the use of calcium-based phosphate binders. Numerous studies have shown that calcium-free phosphate binders have no harm or more beneficial effects when compared to calcium-based phosphate binders in terms of such benefits as survival, calcium deposition, etc.[9,10]

- The information in Figure 2 can help with the estimation of dietary calcium intake.

Figure 2: Calcium content of some common food. Extracted from from the brochure on Osteoporosis for Patients (Jan 2009).

Calcium Content of Some Common Food

SOURCE	SERVING SIZE	CALCIUM (mg) per Serving
Milk & Milk Products		
Low-fat yoghurt	1 carton (200g)	420
Low-fat milk	1 glass (250ml)	300
Cheese	1 slice (20g)	130
Fish/ Meat/ Beans/ Nuts		
Dried ikan bilis (with bones)	2 tablespoons (40g)	240
Soya beans (cooked)	1 mug (180g)	190
Canned sardines (with bones)	1 fish (50g)	190
Beancurd, firm (tau kwa)	1 small cake (90g)	150
Almonds	1/4 mug (40g)	100
Dhal (raw)	1/4 mug (50g)	85
Soya beancurd with syrup (tau huay)	1 bowl (620g)	380
Beancurd, silken (tofu)	2 squares (170g)	50
Roasted peanuts, without shell	1/4 mug (60g)	30
Egg	1 (50g)	30
Soya bean drink	1 glass (250ml)	25
Fruit/Vegetables		
Dried figs	5 whole (95g)	240
Kailan, cooked	3/4 mug (100g)	195
Spinach (bayam), cooked	3/4 mug (100g)	140
Chye Sim, cooked	3/4 mug (100g)	135
Beans (long, french), cooked	3/4 mug (100g)	50
Broccoli, cooked	3/4 mug (100g)	50
Apricot, dried	1/4 mug (60g)	40
Papaya	1 wedge (130g)	40
Raisins	1/4 mug (60g)	30
Green peas, cooked	3/4 mug (100g)	30
Calcium-Fortified Products		
High-calcium milk powder	4 scoops (25g)	450
High-calcium soya bean milk	1 glass (250ml)	450
Egg noodles	1 portion (100g)	210
Wholemeal bread	2 slices (60g)	120

Source: Ministry of Health Singapore. Available from https://www.moh.gov.sg/content/dam/moh_web/HPP/Doctors/cpg_medical/current/2009/CPG_Osteoporosis_PatientVersion.pdf

Adverse reactions

In susceptible individuals, calcium supplements can increase risk of kidney stones. If at all, they should be used with caution and given after meals so that the absorption of dietary oxalate can be reduced through chelation by the calcium. It is believed that the reason a low-calcium diet is associated with higher risk of kidney stone formation than a normal-calcium diet is the reduced availability of calcium leading to higher dietary oxalate absorption.

The association of calcium supplements with the adverse cardiovascular events such as myocardial infarction is debatable.

The common side effects associated with calcium supplements are dyspepsia and constipation.

Calcium is a divalent cation that can chelate a number of drugs when administered simultaneously via the oral route and reduce the oral bioavailability of these drugs in the intestines. Examples of such drugs are **levothyroxine, iron, ciprofloxacin, tetracycline**.[11]

Vitamin D

Benefits

Vitamin D promotes intestinal absorption of calcium and phosphate. It is also important for the proper mineralisation of the bones as well as the optimisation of muscle functions and balance.[19] Vitamin D insufficiency/deficiency has also been shown to be associated with higher fall risks.[13]

Sources and mechanism of actions

Obtaining vitamin D from dietary sources such as salmon, liver, eggs, cod liver oil and fortified foods such as margarine and some low-fat milk is ***normally insufficient***. The best natural way to get enough vitamin D is to be exposed to sunlight for 15 mins/day, provided it is not contraindicated (e.g. SLE patients).[27]

For those with limited sun exposure, oral supplementation with vitamin D is advisable. The Osteoporosis Society of Singapore recommends daily vitamin D intake of 600iu for healthy adults and 800–1000iu for at-risk patients as recommended by the International Osteoporosis Foundation (IOF), which defines these patients as seniors aged 60 years and above.[11,12,14]

When exposed to ultraviolet light, the 7-dehydrocholesterol in the skin is converted to pre-vitamin D3, which then converts to vitamin D3 by a temperature-dependent process. However, prolonged sunlight exposure does not lead to vitamin D overload as the elimination of pre-vitamin D3 and vitamin D3 is also increased with UV exposure.

Vitamin D2 and D3 need to be hydroxylated first to 25(OH) vitamin D2 and D3, respectively, then to 1, 25-dihydroxyvitamin D (calcitriol) before they become

biologically active. The active vitamin D metabolite, 1, 25-dihydroxyvitamin D, binds to the intracellular nuclear receptors to exert its physiological effects. The first hydroxylation at position 25 of vitamin D takes place in the liver, followed by a similar process at position 1 in the kidney. The enzyme involved in the latter process, 1-α-hydroxylase, is also present in **extrarenal sites**. This is the basis on which the vitamin D2 and D3 are still used to correct low serum vitamin D levels in patients with advanced chronic kidney disease and secondary hyperparathyroidism, including those already on dialysis.[15,16,17]

Dosing and monitoring

Serum 25(OH) vitamin D levels can be measured for patients with:

- Limited effective sun exposure due to consistent use of sunscreen, sun-protective clothing, or institutionalisation;
- Intake of medications that increase metabolism of vitamin D (e.g. phenytoin);
- Malabsorption (e.g. coeliac disease);
- Osteoporosis;
- Dark skin;
- Obesity; and
- Hospitalisation on general medical service.

Most labs do not report serum 25(OH) vitamin D2 and D3 separately but give only the total serum 25(OH) vitamin D level. As the former is of shorter half-life than the latter, it is not surprising that vitamin D3 is found to be more efficient in raising the serum 25(OH) vitamin D levels. That said, the clinical significance of the difference is unknown at the moment.

The 25(OH) vitamin D has a half-life of 2–3 weeks.

Optimal serum 25(OH) vitamin D level is still uncertain. Institute of Medicine (USA) recommends that achieving a level of ≥20ng/ml is adequate for optimal overall health for 97.5 percent of the population. However, Endocrine Society (USA) and several other professional organisations advocate for a higher level of ≥30ng/ml.

Even though vitamin D is generally safe, it is not innocuous. There is evidence showing that serum levels as low as 30–48ng/ml are associated with increases in all-cause mortality, greater risk of cancer at some sites like the pancreas, greater risk of cardiovascular events, and more falls and fractures among the elderly. As a result, the Food and Nutrition Board (USA) recommends that serum levels above 50–60ng/ml should be avoided.[11,15,18,19]

For patients with severe vitamin D deficiency, defined as serum 25(OH)D level <10ng/ml, load with 50,000iu of vitamin D2 or D3 once per week for 6–8 weeks followed by 800iu of vitamin D3 daily for maintenance (can substitute with 1000iu if commercial preparation containing 800iu not available).

For patients with serum 25(OH)D levels of 10–20ng/ml, initial supplementation with 800–1000iu daily may be sufficient.

For patients with serum 25(OH)D levels of 20–30ng/ml, 600–800iu daily of vitamin D3 may be sufficient (maintenance dose of 1000iu daily is also acceptable per OSS recommendation).

Patients taking medications that bind vitamin D (e.g. cholestyramine) in the gut or induce cytochrome P450 enzymes (e.g. carbamazepine, phenytoin) may also need higher daily maintenance doses of vitamin D because of reduced absorption and increased clearance, respectively.

Every 100iu (2.5mcg) of vitamin D3 is expected to increase the serum 25(OH)D levels by 0.7–1.0ng/ml. The magnitude of increase is inversely proportionate to the baseline. it is recommended to recheck the serum 25(OH)D levels 3–4 months (≈5 half-life) after initiating therapy.

Toxicity manifesting as hypercalcemia and hypercalciuria is only observed at serum 25(OH)D levels above 88ng/ml. The risk of hypercalcemia increases as the creatinine clearance falls below 60ml/min because the efficiency of the homeostatic adaptation by the kidney in response to changes in calcium metabolism declines. Monitoring of serum calcium becomes more important in such patients.

Vitamin D metabolites such as alfacalcidol and calcitriol are not routinely used for treatment and prevention of osteoporosis. There is a lack of studies using fracture risk as endpoints to guide proper dosing. In addition, serum 25(OH)D levels cannot be used to monitor treatment with these agents. Hence, they are not recommended for use in patients without liver or kidney impairments.[9, 11, 18, 20, 21]

Exercise

Overall, the beneficial effect of exercise on bone density is small. Consistency is more important compared to intensity.

Fracture reduction

In general, the recommendation is for at least 30 minutes of exercise three times per week. Meta-analysis data indicated that exercise reduced the occurrence of overall fractures in older adults (4.8 versus 10.9 percent in the control group; relative risk [RR] 0.49, 95% CI 0.31-0.76)[22] with reduction in vertebral fractures being not statistically significant (three trials, 18 versus 30 percent; RR 0.56, 95% CI 0.30-1.04).[22] This was attributed to the small number of patients included in the vertebral fracture trials. In prospective cohort studies, exercise was associated with a reduced risk of hip fracture in older women.[23,24]

BMD effects

Exercise improves BMD in premenopausal and postmenopausal women.[25,26] Postmenopausal women showed a significant positive effect of exercise on BMD at the lumbar

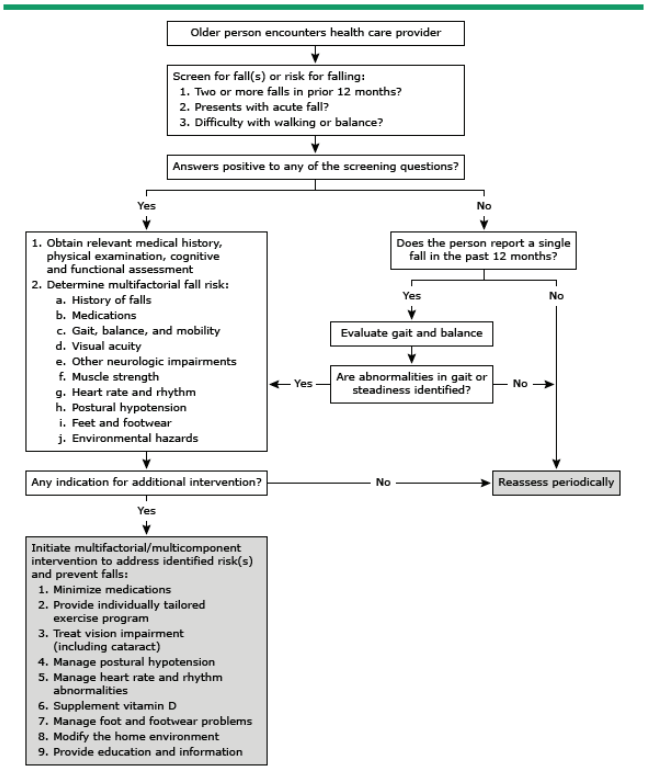
spine (LS) (mean difference 0.85, 95% CI 0.62-1.07) and trochanter (mean difference 1.03, 95% CI 0.56-1.49) compared with controls.[26] Resistance training, jogging, jumping, and walking, were effective. Non-weight-bearing, high-force exercise (e.g. progressive resistance strength training) improved femoral neck BMD best whereas a combined program (mixture of more than one exercise type) was most effective for LS BMD.[26] The meta-analysis was limited by loss to follow-up and the poor quality of allocation concealment and blinding.

Fall Prevention

Regardless of patient populations, the ultimate goal of treatment of osteoporosis is to prevent fracture. Most osteoporotic fractures result from falls. Hence, fall prevention is important in patients with or at risk of osteoporosis.[8]

- Every patient aged 65 years and older who is being treated for osteoporosis should be screened for risk of fall according to the American Geriatric Society 2010 Prevention of Falls in Older Persons Guidelines. At-risk patients should be comprehensively evaluated and treated in order to reduce fall risks.[9]
- Of note: medication "de-prescribing", vision, and footwear share emphasis with the rest of the areas of falls assessment. The algorithm is attached for easy reference (URL: http://www.medcats.com/FALLS/frameset.htm).

Figure 3: Fall Prevention Algorithm



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LEARNING POINTS

- **Exercises have a significant impact on falls risk reduction and a small effect in BMD increase.**
- **Dietary calcium should form the greater portion of calcium intake and calcium supplements can interfere with medication absorption.**
- **Smoking one pack per day throughout adult life was associated with a 5 to 10 percent reduction in bone density.**