UNIT NO. 2

SECONDARY CAUSES OF OSTEOPOROSIS

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ABSTRACT

Osteoporosis is primarily caused by menopause and ageing. However, secondary causes of bone loss can be found in up to 64 percent of patients with osteoporosis. Common medical causes identified have included Vitamin D deficiency, glucocorticoid excess, hyperthyroidism, hyperparathyroidism, malabsorption, hypercalciuria, rheumatoid arthritis, and myeloma, while other lifestyle related causes, such as smoking and excessive alcohol consumption can also result in bone loss. Addressing all of these factors are required to optimise the management of osteoporosis.

Keywords: Secondary causes; Contributary causes; Osteoporosis;

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INTRODUCTION

Osteoporosis is primarily caused by menopause and ageing. However, **secondary causes of bone loss can be found in up to 64 percent of patients with osteoporosis**. Common medical causes identified have included Vitamin D deficiency, glucocorticoid excess, hyperthyroidism, hyperparathyroidism, malabsorption, hypercalciuria, rheumatoid arthritis, and myeloma, while other lifestyle related causes, such as smoking and excessive alcohol consumption can also result in bone loss. Addressing all of these factors are required to optimise the management of osteoporosis.

SECONDARY CAUSES OF OSTEOPOROSIS: PREVALENCE AND IMPORTANCE

One of the largest studies on causes of secondary bone loss was from the 2002 analysis of the Canadian Database of Osteoporosis and Osteopenia (CANDOO).[1] In 5,604 women and 561 men over the age of 50, secondary causes of osteoporosis were found in 41.4 percent of the women and 51.3 percent of the men. They were present in 45.9 percent of the patients with fracture and 40.1 percent of the patients without fracture. The most common cause was the **use of glucocorticoids**.

In a 1999 US study by Haden et al,[2] a retrospective chart review resulted in a finding of a secondary cause of low BMD in 237 community-dwelling women with median age of 56 years, median Dual X-ray Absorptometry (DXA) T-score of spine of -2.35 and median T-score of hip of -3.25. Table 1 shows the prevalence of these causes in this study.

Table 1: Secondary Causes in Haden's Study

Diagnosis	% of 237 community-dwelling women in Haden study
Glucocorticoid use at Prednisolone ≥7.5 mg /day	16.5
Vitamin D deficiency <15 ng/ml	16
Thyroid disease	12.7
Premature ovarian failure without oestrogen therapy	11
Myeloma	6
Malabsorption, e.g. sprue and inflammatory bowel disease	4.6
Subclinical Hyperthyroidism with low TSH	4
Rheumatoid arthritis	3
Organ transplant	2.5
Hyperparathyroidism	1.7

In another US study by Tannebaum et al,[3] 54 percent of the 664 postmenopausal women who were of age 45 years and older, and with T-score <-2.5, already had known medical disorders that can cause bone loss, such as glucocorticoid use, just based on history alone. Of the remaining apparently otherwise healthy 309 women, 173 women with mean age 65.6 years had comprehensive laboratory testing. Forty-four percent of these 173 women were found to have previously unrecognised disorders that affected bone metabolism. These disorders are listed in Table 2 and included Vitamin D deficiency, defined as 25(OH)D <20 ng/ml, hypercalciuria, malabsorption, hyperparathyroidism, exogenous hyperthyroidism, and Cushing's disease.

Table 2: Secondary Contributors to Osteoporosis in Tannebaum's Study

Diagnosis	% of 173 otherwise healthy women with Osteoporosis in Tannebaum study
Vitamin D deficiency <20 ng/ml	20
Hypercalciuria	10
Malabsorption	7
Hyperparathyroidism	3
Exogenous Hyperthyroidism	2
Cushing's Disease	~1
Others	1

Freitag et al[4] also studied 258 women and 14 men, who were community-dwelling Americans, with mean age 71.8 years and central DXA T-scores -2 or worse. Of these, 24.7 percent were found to have a secondary cause of bone loss, with 17.9 percent with Vitamin D deficiency, defined as 25(OH)D of <16 ng/ml. Hypercalciuria, defined as >250 mg/24 hours, was present in 6.3 percent and hyperparathyroidism in 0.8 percent.

In a study of 285 women and 92 men in Austria, Deutschmann et al[5] found that 63.9 percent had one or more secondary causes. Table 3 lists the common secondary causes found in this study.

Table 3: Secondary Causes Found in Deutschmann's Study

Diagnosis	% of Austrian men and women in the Deutschmann study
Lactose intolerance	18.6
History of hyperthyroidism	13.3
Hypercalciuria	7.7
Hyperparathyroidism	4.9

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A local study at the Singapore General Hospital[6] confirmed that secondary causes are commonly found in osteoporosis patients. **Vitamin D deficiency** was present in 18.5 percent of the patients, **hyperthyroidism** in 10.11 percent, **primary hyperparathyroidism** in 1 percent, **secondary hyperparathyroidism** in 6 percent, **hypercalciuria** in 21.63 percent, **glucocorticoid use** in 8.43 percent, and **hypogonadism** in 9.4 percent of males.

A list of many, but not all, of the medical conditions and medications that can cause bone loss and osteoporosis can be seen in Table 4. FRAX™ is an algorithm that calculates an individual's risk of a fragility fracture based on risk factors. These risk factors include race, age (incorporating most of the risk represented by falls), sex, weight (incorporating the risk of thinness and frailty), several of the secondary medical causes with high individual impact, such as the excessive use of glucocorticoids and presence of rheumatoid arthritis, as well as the significant lifestyle factors of smoking and excessive alcohol consumption. The rest of the secondary causes with less individual impact have been put under a common risk factor called "Secondary Causes" in the calculation of fracture risk.

EVALUATION OF PATIENTS WITH OSTEOPOROSIS

A **careful history and physical examination** will exclude many overt medical conditions that lead to bone loss and osteoporosis. Thus, enquiring about the **personal and parental history of fractures, alcohol intake, smoking, dietary history for calcium and protein intake, exercise regimen, propensity for falls, menstrual history, and past medical problems** is necessary. One should always do a thorough review of systems, including asking about **weight loss**, which may occur with the sarcopaenia of ageing, or when there is myeloma or other haematological malignancy. Other important symptoms to enquire about are **bloating or diarrhoea**, which may occur with lactose intolerance or malabsorption; and the presence of **significant oesophageal reflux** or **chronic kidney disease** may influence the choice of medications in treating osteoporosis.

Laboratory Assessments

Based on Tannebaum's study, the authors initially suggested that a cost-effective approach would be to test with serum calcium, PTH, 24-hour urine calcium, and TSH in women on thyroxine. This would cost US$75 per woman tested, or US$272 per secondary diagnosis detected, while identifying 85 percent of secondary causes. A later analysis showed that checking 25(OH)D instead of PTH would result in identification of 92 percent of secondary causes, at a lower cost of US$56-79 or US$134 per diagnosis.

The International Society for Bone Densitometry (ISCD)[7], American Association of Clinical Endocrinologists (AACE)[8] and the National Osteoporosis Foundation (NOF)[9] have issued guidelines recommending that the initial evaluation of a patient with osteoporosis should include **FBC, serum chemistry, 25(OH)D and urinary calcium excretion**. Depending on clinical findings, further tests may be considered as laid out in Table 5. Extensive testing for secondary causes should be considered in **premenopausal women**, in **men especially below the age of 50–65 years**, when the patient's **DXA Z-scores are <-2.0** or if there is **apparent treatment failure, with recurrent fragility fractures despite medication compliance**.

Table 5: Recommendations for Laboratory Assessment Based on ISCD, AACE and NOF Guidelines

Initial Laboratory Tests
FBC
Serum chemistries: calcium, phosphate, ALP, albumin, liver enzymes, creatinine and electrolytes
25(OH)D
24-hour urine for calcium, sodium and creatinine
Further Tests as Clinically Indicated
PTH
TSH +/- fT4, especially if on thyroxine
Test for hypercortisolism (e.g. UFC, ONDST; OR 8 am cortisol if suspected to be on steroids)
Testosterone in men
Serum and urine protein electrophoresis
24-hour urine phosphate
Anti-tissue transglutaminase antibodies
Serum tryptase, urine N-methylhistidine
Bone marrow aspiration and biopsy
Bone biopsy
Genetic testing for rare metabolic bone disease

Table 6: Patients with Osteoporosis in Whom More Comprehensive Testing May be Required

Men, especially if younger than age 50
Premenopausal women
People with extremely low DXA BMD T-scores
People with low Z-scores <-2.0
People with treatment failure and recurrent fragility fractures despite medication adherence

Radiological Imaging

An **X-ray of the thoracolumbar spine** should be done at baseline to exclude asymptomatic fractures of the spine, which are common in osteoporosis. Such fractures will play a role in the decision to treat pharmacologically, even if BMD shows "osteopaenia". Other imaging, such as CT or MRI spine, may be necessary to confirm subtle fragility fractures or to exclude pathological fractures.

Vitamin D Deficiency

The International Osteoporosis Foundation (IOF)[10] recommends a **Vitamin D intake of 800–1,000iu/day for people age 60 years and above**, and to maintain a level **25(OH)D level of at least 20ng/ml (50nmol/L)** for good bone and muscle function. The Institute of Medicine, USA (IOM),[11] recommends a vitamin D intake of 600iu/day for healthy people aged 51 years and above, and 800iu/day for healthy people aged 71 and above, while the Health Promotion Board of Singapore (HPB) has kept its recommended daily intake of vitamin D at 1000iu/day. However, the Endocrine Society (USA)12 considers >30 ng/ml (75 nmol/L) an optimal level of 25(OH)D, but it must be noted that while the IOM recommendations are for the normal healthy population, the Endocrine Society's recommendations are more for patients. A low vitamin D level results in osteomalacia, with inadequate bone crystallization, as well as proximal muscle pain and weakness, contributing to falls. Both bone and muscle weakness

lead to an increased risk of fracture. My personal approach to patients with low bone mass and fragility fractures would be to aim for the higher standards recommended by the Endocrine Society.

Table 7: Summary of Recommended Daily Intakes of Calcium and Vitamin D and Recommended 25(OH)D Levels in People Aged ≥51 years

	HPB	IOM, USA	IOF	Endocrine Society, USA
Elemental Calcium (mg/day)	1,000	1,000 for males 51–70 years 1,200 for females ≥51 years and males ≥71 years	Country-dependent	
Vitamin D (IU/day)	1000	600 for age ≥51 years 800 for age ≥71 years	800–1,000 for age ≥60 years	600 for age 19–70 years 800 for age ≥71 years
Vitamin D Insufficiency: 25(OH)D Level (ng/ml) (nmol/L)		<20 <50	< 20 < 50	<30 <75
Vitamin D Deficiency: 25(OH)D level (ng/ml) (nmol/L)		<10 <25		<20 <50

Many conditions are associated with vitamin D deficiency,[13] and the most common are listed in Table 8.

Table 8: Common Conditions Associated with Vitamin D Deficiency

Lack of sun exposure and dietary vitamin D (oily fish, eggs, liver)
Age-related decline in cutaneous vitamin D production
Ethnicity-related reduction in cutaneous vitamin D production
Gastrointestinal disease
Liver disease
Renal disease
Drugs such as Phenytoin

Despite Singapore being in the tropics, the prevalence of Vitamin D deficiency is high. This is not surprising, considering that we are an urban population with largely indoor professions and activities. Hawkins R[14] measured 25(OH)D levels of 240 apparently healthy Singaporeans, with median age of 36 years (range 19–71) who underwent multiphasic health screening at a local hospital clinic. He found that 21 percent of Chinese females, 12 percent of Chinese males, 35 percent of Malay females, 19 percent of Malay males, 34 percent of Indian females and 30 percent of Indian males had suboptimal 25(OH)D levels below the IOF recommendation of ≥ 20 ng/ml (50 nmol/L). Using the more stringent Endocrine Society recommendations, 34 percent of Chinese females, 31 percent of Chinese males, 40 percent of Malay females, 34 percent of Malay males, 39 percent of Indian females and 39 percent of Indian males had suboptimal 25(OH)D levels of <30 ng/ml (75nmol/L).

The recommendations listed above are for healthy populations. Patients with osteoporosis who have insufficient vitamin D levels should take cholecalciferol 1,000–2,000 units daily together with adequate calcium intake. Very low 25(OH)D levels may first be treated with high-strength oral cholecalciferol (D3) 25,000 units/week or ergocalciferol (D2) 50,000 units/week for 8 -10 weeks, before going on to maintenance cholecalciferol doses.

Poor Calcium Intake

HPB[15] recommends that men and women age **51 years and over**, and breastfeeding or pregnant women, should take **1,000 mg of elemental calcium daily**, while those age **19-50 years** should take **800 mg daily**.

Poor calcium intake may occur in many Singaporeans because of the high prevalence of **lactose intolerance**. Such individuals should be encouraged to take fortified, high-calcium soya milk, bean curd products, and oats. The calcium content of various foods may be found on apps such as the ones provided by the IOF or on its website at: https://www.iofbonehealth.org/osteoporosis-musculoskeletal-disorders/osteoporosis/prevention/calcium/calcium-content-common-foods

If adequate calcium intake in the diet is not possible, calcium supplements may be taken, preferably with food, so that absorption can be smoothened with no sudden spikes in venous calcium levels. It is important to know how much elemental calcium is available from the calcium supplements. Calcium carbonate, for example, yields 40 percent elemental calcium. Hence, the commonly available CaCO3 450mg and Vitamin D 200iu tablet yields 180 mg of elemental calcium per tablet.

Sedentary Lifestyle

Essentially, 3 forms of exercise are recommended to prevent fractures:

1. **Weight-bearing aerobic or "cardio" exercises** such as walking, jogging, dancing, climbing stairs and jumping help to improve bone density and strengthen muscles. Swimming and cycling, although good for the heart, do not increase BMD.
2. **Resistance exercises**, which can be performed with an exercise band, gym weights, or pilates equipment, help to improve muscle mass and muscle strength.
3. **Balance exercises**, such as tai chi or the Otago exercises, help to improve balance and reduce the propensity to fall.

Ethanol Excess

Consumption of more than 3 alcoholic drinks a day results in bone loss. The HPB has recommended that Singaporean **women should consume fewer than 2 drinks daily**, and **men fewer than 3 drinks daily.**

Smoking

Cessation of smoking will help alleviate bone loss, in addition to a whole host of non-osteoporosis related benefits, such as avoidance of chronic asthma and COPD.

Hypercalciuria

In a routine dipstick test, the **urine calcium/creatinine ratio can exceed the normal value of <0.6.** Such hypercalciuria can be found in 3 conditions:

1. **Hypercalcaemia**, such as in primary hyperparathyroidism.

However, an early-stage normocalcaemic primary hyperparathyroidism can occur, where PTH is elevated while serum calcium remains normal. It is important to test for PTH in a fasting state as food depresses its values.

2. A diet **high in calcium/calcium supplementation** and/or **"gut hyper-absorbers"**. Putting patients on 2 weeks of a low-calcium diet and checking 24-hour urinary calcium will find that the hypercalciuria resolves in such patients.
3. **Idiopathic hypercalciuria.** In such patients, a low-calcium diet does not eliminate the renal calcium wasting, and 24-hour urinary calcium remains >250mg (62.6mmol)/24 hours. Such patients can be treated with hydrochlorothiazide twice daily.

Premature Menopause, Accentuated Menopause and Androgen Deprivation Therapy

Women may have **premature menopause** at age 40 years or younger, due to a familial or autoimmune syndrome. It may also be due to iatrogenic medications such as GnRH analogues, used to treat breast cancer in premenopausal women. Postmenopausal women with breast cancer treated with **aromatase inhibitors** such as Letrozole will have more severe hypogonadism, as will men with prostate cancer treated with **GnRH analogues** or castration.

Multiple Myeloma

Patients with concerning clinical features such as **weight loss, multiple vertebral fractures, anaemia, high ESR, and hypercalcaemia with normal PTH levels** should have screening for multiple myeloma and for bone metastases.

CONCLUSION

Secondary contributors of bone loss are common and must be looked for. Many, such as vitamin D deficiency, poor calcium intake, lack of physical activity, smoking, excessive alcohol consumption, and primary hyperthyroidism, are easily manageable by the primary care physician and generalist physician, while others such as primary hyperparathyroidism, Cushing's syndrome, malabsorption and myelo- and lympho-proliferative disorders, will need to be referred for specialist management.

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LEARNING POINTS

- **Secondary causes of bone loss are common. They include medical conditions such as glucocorticoid excess, hyperthyroidism, hyperparathyroidism, premature hypogonadism, hypercalciuria, use of PPIs, as well as lifestyle choices such as smoking, excessive alcohol consumption, poor calcium intake, low sun exposure, low Vitamin D intake and a sedentary lifestyle.**
- **Basic laboratory tests for all osteoporosis patients recommended in most international guidelines include FBC, serum calcium, phosphate, ALP, albumin, liver enzymes, creatinine and electrolytes, 25(OH)D, and urine for calcium and creatinine**
- **It is important to consider more extensive tests in premenopausal women, men below age 50 years, patients with DXA Z-scores less than -2.0 and patients with deteriorating BMD and/or recurrent fragility fractures despite adherence to osteoporosis medications.**

Table 4: Medical Conditions That Cause or Contribute to Osteoporosis and Fractures

Lifestyle Factors	
Smoking	Thinness / sarcopaenia
Alcohol ≥3 drinks/day	Frailty, deconditioning, Falls
Low calcium intake (< 400 mg/day)	Immobilisation
Inadequate physical activity	(Past history of fracture)
Endocrine Disorders	
Premature ovarian failure	Male hypogonadism
Anorectic and Athletic amenorrhoea	Turner's and Klinefelter's syndromes
Hyperthyroidism / Excessive thyroid hormone	Androgen insensitivity
Pregnancy	Panhypopituitarism
Hyperparathyroidism	Prolactinoma
Cushing's syndrome	Acromegaly
Diabetes mellitus Types 1 & 2	Adrenal insufficiency
Gastrointestinal Disorders	
Lactose intolerance	Chronic liver disease
Malabsorption	Primary biliary cirrhosis
Pancreatic disease	Bariatric surgery / Gastrectomy
Inflammatory bowel disease	Intestinal surgery
Coeliac disease	
Rheumatological and Autoimmune Diseases	
Rheumatoid arthritis	SLE
Ankylosis spondylosis	
Haematological Disorders	
Multiple myeloma	Thalassaemia
Lymphoma and leukemia	Haemophilia
Systemic mastocytosis	Sickle cell anaemia
Skeletal metastases	
Genetic/Familial Causes	
Parental history of fracture	Idiopathic hypercalciuria
Osteogenesis imperfecta	Marfan syndrome
Hypophosphatasia	Haemochromatosis
Homocystinuria	Ehlers-Danlos
Miscellaneous Disorders	
COPD	Epilepsy
CCF	Parkinson's disease
ESRD	Stroke
Sarcoidosis	Neuropathy / autonomic dysfunction
Renal tubular acidosis	Proximal myopathy
AIDS / HIV	Dementia
Post-transplant	Poor vision
Medications	
Glucocorticoids at Prednisolone ≥ 5 mg/day and ≥ 3 months	Anticonvulsants
PPIs	SSRIs
Glitazones	Lithium
Aromatase inhibitors	Tamoxifen or Depo-progesterone (premenopausal women)
GnRH agonists / Androgen deprivation therapy	Immunosuppressants Cyclosporine A, Tacrolimus, Methotrexate
Chemotherapy	Heparin
Sedatives	Narcotics