

Review article

A practical approach to secondary osteoporosis – Case studies in Asia

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Abstract

Osteoporosis is a major health disease that is increasing in Asia especially given the rapidly aging population in many of the countries. A major aim of the management of osteoporosis is to prevent the next fracture from happening and its attendant morbidity and possible mortality. A failure to identify a possible secondary cause of osteoporosis might lead to suboptimal benefits of treatment or possibly treatment failure. This article aims to use a series of cases in order to best illustrate the approach to the screening of secondary causes of osteoporosis and highlight learning points from each case with a slant towards the management of patients in Asia, focusing on the East and South East Asia (SEA). © 2016 The Korean Society of Osteoporosis. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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1. Introduction

Osteoporosis is a major health disease that is increasing especially given the rapidly aging population in many parts of the world. An integral goal of the management of osteoporosis is to prevent the next fracture from happening and its attendant morbidity and possible mortality. A failure to identify a possible secondary cause of osteoporosis might lead to suboptimal benefits of treatment or possibly treatment failure, not to mention the non-bone consequences of the condition.

There are unfortunately many causes of secondary osteoporosis. When we should screen for them and how extensive the workup should be is still a matter of debate. To date there is a paucity of cost-analysis studies with regards to the screening of secondary causes or even which tests should be included in the initial assessment, especially in Asia. Various studies include different cohorts of patients and different selection of investigations. Clinicians have to decide then when to embark on a search for these causes and which tests to use for initial screening.

This article aims to use a series of cases in order to best illustrate the approach to the screening of secondary causes of osteoporosis and highlight learning points from each case with a slant towards the management of patients in Asia, focusing on the East and South East Asia (SEA).

1.1. Case 1

A 65-year-old woman is referred to an endocrine clinic for management of her osteoporosis. She had bent down to pick up a cup that she had dropped and felt a sudden pain in her back. An x-ray showed that she had sustained a T12 compression fracture. Her bone mineral density (BMD) is as shown:

	Spine (L1-L4)	Total hip (TH)	Neck of femur (NOF)
T-score	−1.3	−2.6	−2.7

The questions to ask for this patient in order to appropriately treat her are these:

- 1) Does the patient have osteoporosis?

The answer is yes both clinically and by bone mineral density criteria as set out by the WHO. She had suffered a

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fragility or low trauma fracture from less than a standing height. This means a fracture from a force that does not justify a fracture. This satisfies the clinical definition of osteoporosis – a condition where the bones are brittle and susceptible to fracture. By BMD criteria osteoporosis can also be diagnosed via a T-score ≤ -2.5 in any of the 3 regions of interest (ROI) as denoted above.

Note that the spine for this patient showed a relatively dense BMD as compared to the other regions. This might be due to osteosclerosis and/or osteophytes present in an elderly patient, inaccurately increasing the BMD in that region. Indeed, it was found that about 46% of females between the ages of 40–84 years of age had osteophytes and this increased with increasing age [1].

2) Now that you have ascertained that the patient indeed has osteoporosis, do you screen for secondary causes of osteoporosis and if so, which ones?

To answer this question, several factors should be taken note of:

- The list of possible secondary causes of osteoporosis are many and shown in Table 1.
- It is estimated that there are about 200 million patients worldwide with osteoporosis and this number is estimated to increase [2].
- Globally and in Asia, the elderly population is rapidly increasing. Indeed, in Singapore, the proportion of the population aged 65 years and above was 7.3% in 2000 and this is projected to increase to 18.7% in 2030 [3].
- About 30% of patients with postmenopausal osteoporosis will have secondary causes of osteoporosis [4].

Taking into account the figures above and hence the sheer volume of cases, it would certainly not be cost-effective to screen for all secondary causes of osteoporosis for all postmenopausal patients. Yung et al. showed that in the patients referred to an osteoporosis clinic in a tertiary hospital in

Table 1
Secondary causes of osteoporosis.

<ul style="list-style-type: none"> • Endocrine disorders such as hyperthyroidism, hyperparathyroidism, Cushing's syndrome whether exogenous or endogenous, hypogonadism, acromegaly, diabetes mellitus, idiopathic hypercalciuria, early menopause. • Gastrointestinal diseases – inflammatory bowel disease, severe liver diseases, malsorption syndromes • Hematologic diseases eg multiple myeloma, mastocytosis • Rheumatological diseases eg rheumatoid arthritis • Drug induced osteoporosis <ul style="list-style-type: none"> – Steroids, anti-epileptic drugs, anti-depressants, glitazones, proton pump inhibitors (PPIs), thyroxine, aromatase inhibitors, GnRH agonists • Genetic disorders such as osteogenesis imperfect, hypophosphatasia • Others: Immobilization, smoking, low BMI, HIV infection, heavy alcohol use, organ transplantation, poor accrual of bone health from deprivation in early years from either systemic illnesses

Singapore, secondary causes included the following- Vitamin D deficiency in 18.5%, hyperthyroidism in 10.1%, primary hyperparathyroidism in 1%, secondary hyperparathyroidism in 6%, hypercalciuria in 21.6% and glucocorticoid use in 8.4% of the patients. The mean calcium intake was 660 mg per day [5]. Bour et al. reported that about a quarter of patients presenting with an osteoporotic fracture to an emergency department in the Netherlands had a known secondary cause of osteoporosis on presentation and a quarter of the patients had a newly discovered secondary cause after investigations. More than 90% of the study participants were found to have an inadequate calcium (recognized as 1200 mg in the study) and about two thirds had vitamin D deficiency (recognized as < 50 nmol/L in the study) [6].

A universally agreed upon list of screening tests to be carried out in the pursuit of secondary causes of osteoporosis has not been settled on and varies with differing studies and practices. Table 2 gives some of the more common tests that are routinely performed. The first segment would be more commonly performed as opposed to the second. In an ideal situation, it might be prudent to screen all patients and to screen for the commonest causes. A thorough history and physical examination might contain clues to help pinpoint a secondary cause and focus the investigations. The list of possible causes in Table 1 would be helpful in tailoring the questions and also physical examination.

However, the approach depends on the individual circumstances of the patients. For instance, if the patient in case 1 was in a primary medical facility with no resources other than a bisphosphonate at hand and no financial ability or technical capability of further managing the secondary cause, screening for secondary causes of osteoporosis becomes a moot point. Even should a secondary cause exist and there was a further drop in the bone mineral density upon follow-up consultation,

Table 2
Investigations for secondary osteoporosis.

More routinely done:

- Full blood count
 - The hemoglobin levels are of especial interest as both a marker of chronic disease and also the triad of anemia, hypercalcemia and increased creatinine may signify multiple myeloma
- Urea, electrolytes and creatinine – in order not to miss renal bone disease
- Thyroid function screen
- 25-OH Vitamin D
- Ca with or without PTH
- Testosterone – for males
- 24 hours urine calcium
- Liver function test

Other tests to consider:

- Screening for endogenous Cushing's syndrome when suspected – such as the overnight dexamethasone suppression test or the 24 hours urine free cortisol
- Screening for coeliac's disease - this is a rare condition in East and South East Asia and as such rarely is a first line test to be carried out.
- Protein electrophoresis for multiple myeloma – given that this is relatively rare and also relatively more expensive to carry out requiring specialised laboratories, it is generally not first line of choice for investigations.

PTH, parathyroid hormone.

it had been shown that adding on a bisphosphonate still worked in decreasing the fracture risk when compared to placebo. For those where the drop was more than 4% per year there was a trend towards benefit however the numbers were small in this group and this did not reach statistical significance [7].

For our patient in case 1, gathering a history from her gave one of lactose and dairy intolerance since childhood. Physical examination was unremarkable except to note that she was lean with a BMI of 19.6 kg/m². Given the patient had been referred to an endocrinology clinic, routine tests in the first category in Table 1 were carried out. All were normal except for a low vitamin D level at 32 nmol/L. Calcium was normal and so was the intact parathyroid hormone (iPTH).

As such this lady's postmenopausal osteoporosis was contributed by a combination of poor bone accrual, lean body mass, vitamin D deficiency and a low calcium intake.

Vitamin D deficiency is common in Asia, even in tropical countries. Using 30 ng/mL or 75 nmol/L as cut-off this would give a prevalence of 45.2% in Thailand [8] to 90.5% in Korea [9]. Of note in these studies was the fact that younger generations seemed to have a higher prevalence than the older generation and this might be attributed to the lack of sun-exposure for various reasons in the younger group including indoor jobs [10]. Generally, with age though, the ability of the skin to produce vitamin D decreases and the elderly also tend to stay indoors hence exacerbating the vitamin D adequacy issue.

To compound the problem, many Asians, especially East and SEA elderly patients are averse to dairy products from their youths and are lactose intolerant. The average calcium intake in Singapore has been increasing and in the most recent National Nutrition Survey in 2010 [11], a mean of 794 mg of calcium per day was noted for Singaporeans. However, for

6.4% were underweight. The oldest age group in the survey was between 60 and 69 years and the obesity statistics was the lowest of all the age ranges at 7.2%.

Learning points:

- This case illustrates a typical case of postmenopausal osteoporosis with several factors that may contribute to the osteoporosis in a typical Asian elderly lady.

The next few cases will illustrate instances where one might be alerted to a possible underlying secondary cause.

1.2. Case 2

The patient is an 81-year-old female weighing only 34.2 kg. She was hunched over with a prominent dowager's hump suggesting multiple compression fractures in her vertebrae and came to the clinic in a wheelchair. She was first seen in 2012 with T-scores in the three ROIs. The spine BMD could not be interpreted since at least 2 vertebrae between the levels of L1-4 are needed in order to compute the BMD and T-score. There were compression fractures in 3 of the relevant lumbar vertebrae. The initial attending physician started her on an oral bisphosphonate. The only secondary workups done then was calcium, a full blood count and vitamin D. They were all normal. She was already on vitamin D supplementation which had been provided by another doctor several years back. No other secondary workup was initiated. Her menopause occurred in her 50s.

The following year she came back with worsening BMD. There was a 36% decrease in the TH and 35% decrease in the NOF as seen below. The primary physician referred her to an endocrinologist then.

	Spine (L1-L4)	Total hip (TH)		Neck of femur (NOF)	
		BMD (g/cm ²)	T-score	BMD (g/cm ²)	T-score
2012	Not admissible	0.410	-4.4	0.340	-4.3
2013	Not done	0.260	-5.7	0.220	-5.5

participants in the 5th percentile, this could be as low as 361 mg per day of calcium intake.

In addition, many elderly patients might have undergone dietary deprivation in their younger days affecting their ability to achieve maximum bone potential. Take Singapore for instance – though we are currently a developed country, a generation ago we were not and our elderly might have grown up in circumstances very different from the current level of food security that we know now.

Indeed, in our patient, a quick calculation of the dietary calcium intake yielded only 300 mg of calcium daily. She was also lean with a BMI of 19.6 kg/m². This is not at all uncommon in East or SEA for their elderly to stay so lean. The Singapore National Health Survey in 2010 [12] showed that a majority of Singaporeans were within normal BMI range and

This patient's osteoporosis is severe and she certainly has a very high risk of future fractures. Given that she has had multiple fractures, her low BMD scores and the significant drop in her BMD within a year, there was a high suspicion for a secondary cause of the disorder. As such, the search for secondary causes was of necessity more extensive than in case 1 and involved most of the investigations in Table 2.

Further investigations were as follows:

Calcium 2.4 mmol/L (2.1–2.6)

iPTH 4 pmol/L (1.3–6.8)

25-OH vitamin D 50.4 ug/L.

Liver tests and creatinine were normal

Multiple myeloma panel was negative

24 hours urine calcium 12.8 mg (inadequate sample)

C-telopeptide 0.46 ug/L (premenopausal upper limit of normal is 0.67 ug/L)
 free thyroxine (fT4) 39.6 pmol/L (10–23)
 Thyroid stimulating hormone (TSH) < 0.005 mIU/L.
 Thyroid hormone receptor antibody (TRAb) was positive.

Hence this lady had osteoporosis secondary to hyperthyroidism from Graves' disease. She was relatively asymptomatic though in retrospect upon questioning, she did admit to losing a few kilograms of weight that she could ill-afford to lose and her family noticed that she seemed more lethargic and less mobile. This compounded her problem as well – both the decreased mobility and her being underweight. It was discussed with her and her family regarding further management of osteoporosis with a possibility of switching to either an anabolic agent or an injectable. However, owing to cost issues, the patient decided to continue with a bisphosphonate. In addition, she was prescribed carbimazole for her Graves' disease. In a year's time, her BMD had increased by about 27% in the TH and 29% in the NOF.

Learning points:

- Risk of fracture increases exponentially with age. Hence for a patient who is in the oldest old category, presenting with one fracture might not raise alarm bells, but multiple fractures to the point of being severely kyphotic does. In addition, the scores of the BMD were very low as well even right at the first visit. Hence a more extensive secondary workup should have been considered.
- The loss in BMD at the follow-up scan a mere year apart strongly suggests that a secondary cause might have been missed out. Hence a follow-up bone mineral density scan might be helpful in monitoring treatment progress especially in the cases where only rudimentary if any secondary workup is done. A deterioration beyond the least significant change should prompt further investigation.
- Hyperthyroidism is often overlooked in the elderly as they might not have typical presenting features [13]. A strong suspicion is required in this group of patients. Given that treatment will improve the BMD and its relatively common presence – up to about 10% in osteoporotic patients referred to an osteoporosis clinic [5] – this should be considered for testing in elderly patients with osteoporosis, especially if they are lean or underweight.

1.3. Case 3

71 years old lady with weight 42.2 kg, height 1.5 m and BMI of 18 kg/m². She presented with back pain to the orthopedics department, who subsequently referred her when osteoporosis was diagnosed on the BMD and they saw how low the T-scores were as shown below:

	Spine (L1-L4)	Total hip (TH)	Neck of femur (NOF)
T-score	-2.4	-4.2	-3.9

Similar investigations to case 2 were carried out and they were all negative. However, the history yielded a decades' long history of smoking starting from her teenage years and she was still smoking about 10 sticks per day. She often does not have appetite to eat and her family reports that her meal portions are small and she dislikes dairy products.

Learning points:

- The low T-scores alert us to the possibility that there might be a secondary cause at play.
- Smoking is a major risk factor of osteoporosis especially with such a long history as in this case. Cessation of smoking after a year increased femoral trochanter and total hip BMD [14].

1.4. Case 4

A 30 years old female was referred for renal stones and a right adrenal tumor incidentally discovered when imaging the kidneys as part of the investigation of renal stones. A simple history taking proved to be remarkably important as she gave a history of a left neck of femur fracture a year prior when she slipped and fell. This was certainly a low trauma fracture and the clinical diagnosis of osteoporosis was confirmed and also borne out in her Z-scores which were < -2.0. She had been started on a bisphosphonate by her original physician.

On further questioning, she did admit to a weight gain of about 10 kg gradually over 2 years. She was not typically Cushingoid with a BMI which was only 23 kg/m² – barely considered overweight even in Asian society, with no purplish striae or hypertension or skin thinness. However, she did have proximal myopathy.

The common underlying diagnosis for all of the three conditions above could be explained by Cushing's syndrome and since she denied any extraneous sources of steroids, she underwent screening with both an overnight dexamethasone suppression test as well as 24 hours urine free cortisol, both of which turned out positive. Her ACTH was also suppressed. She had also concurrently undergone all the other secondary workups. They were negative.

She underwent a resection of the right adrenal tumor with resolution of her Cushing's syndrome. Given that she was still pre-menopausal, married and yet to start a family and the secondary cause has been eliminated, it was chosen to hold off anti-osteoporosis treatment and monitor the bone mineral density.

Learning points:

- A secondary cause of osteoporosis occurs in more than half of pre-menopausal females [4]. As such a more extensive approach to searching for secondary causes should be adopted.
- Endogenous Cushing's syndrome as a secondary cause of osteoporosis is rare. A high index of suspicion should be present.

1.5. Case 5

A 50-year-old man presented with a Colles' fracture after just a minor fall onto the ground where he used his outstretched hand to break his fall. He was referred for management. The BMD was as shown below:

	Spine (L1-L4)	Total hip (TH)	Neck of femur (NOF)
T-score	1.0	-0.6	-0.9

However, the BMD in the wrist was -3.2 . Most of the investigations in table two were carried out and the abnormal findings were the following:

- Calcium 2.7 mmol/L (2.1–2.6)
- iPTH 14.7 pmol/L (1.3–6.8)

Idiopathic hypercalciuria was ruled out as well. Hence the patient had primary hyperparathyroidism. Indeed, on retrospect, a clue to the diagnosis was the fact that the spine was preserved and yet the wrist T-score was rather low for a relatively young man. An ultrasound of the kidney showed bilateral stones, he had documented osteoporotic fracture and given his relatively young age, this would satisfy the criteria for surgery [15]. The patient decided to pursue a surgical cure of the disease.

Learning points:

- Secondary causes occur in two-thirds of males [4] and hence a more vigilant approach to detecting secondary causes of osteoporosis would be justified. Evaluation of men referred for osteoporosis yielded 75% with secondary causes [16].

1.6. On Z-scores

There is an inverse relationship between Z-scores and the presence of causes of secondary osteoporosis. However only a small difference in mean Z-scores of 0.3 between those with and without secondary causes of osteoporosis was detected [17]. Indeed, a study done in Singapore found that the traditional Z-score value of ≤ -2 as an indicator of patients with secondary cause of osteoporosis performed abysmally with a sensitivity of less than or below 20.7% for both males and females. Using a Z-score of ≤ -1 gives a sensitivity of 71.7% in females and 59.1% in males. The specificity was 37.8% and 35.3% respectively [5]. Moreover, the Z-score is obtained from comparison of the patient's BMD to the mean BMD of a cohort consisting of people in the same age range as the patient. This is as opposed to the T-score where the comparison is against the peak BMD of the cohort. In the oldest old, this might at times not be possible as there were insufficient volunteers in the age range to calculate the mean BMD in that age range.

2. Conclusion

The approach to the screening for secondary causes of osteoporosis is individualized depending on the patient's circumstances. History and physical examination might help to focus the search while patient characteristics such as presence of a fracture and multiple fractures, pre-menopausal female or males, or a drop in the BMD despite treatment might heighten the index of suspicion.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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