UNIT NO. 5

DIAGNOSIS AND EXCLUSION OF SECONDARY CAUSES OF OSTEOPOROSIS

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#### ABSTRACT

Osteoporosis is a major health concern and treatment of primary osteoporosis with anti-osteoporosis medications is needed to reduce fracture risk and burden. Before initiating anti-osteoporosis medications, secondary causes of osteoporosis should be considered and satisfactorily excluded. However, it can be challenging to differentiate primary osteoporosis from secondary osteoporosis, especially in patients with paucity of symptoms or who have less common clinical presentation. Hence, practical tips like Appropriate Care Guide on Osteoporosis forms the basis of initial secondary osteoporosis workup for primary care physicians. Snapshots of secondary osteoporosis are briefly discussed to facilitate "pattern recognition".

Keywords: Pattern recognition; primary hyperparathyroidism; vitamin D deficiency; osteomalacia; Fanconi syndrome; tenofovir

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## INTRODUCTION

In Singapore, osteoporotic fractures in women above the age of 50, is among the highest in Asia and these figures are expected to increase several-fold as the population ages. The population aged over 50 years is projected to increase by three-fold to 3.9 million in 2050, or 46 percent of the total population.<sup>1</sup>

Osteoporosis can be divided into Primary Osteoporosis and Secondary Osteoporosis.<sup>2</sup> The former occurs in post-menopausal women or is age-related. In secondary osteoporosis, bone loss is enhanced or driven by specific contributors, e.g. vitamin D deficiency, glucocorticoids exposure, and rheumatoid arthritis.

## DIAGNOSIS OF SECONDARY OSTEOPOROSIS

## History and physical examination

Careful history taking and physical examination are critical to the diagnosis of Secondary Osteoporosis. A high index of clinical suspicion, coupled with logical ordering of specific

MATTHEW TAN ZHEN-WEI Consultant Endocrinologist Dr Matthew Tan Diabetes and Endocrine Care investigations to confirm the diagnosis is the most elegant and cost-saving approach to clinching the diagnosis. For example, performing thyroid function assay in a person with anxiety and palpitations; checking calcium and parathyroid hormone levels in a patient with elements of "bones, moans, groans, thrones and psychiatric overtones".

However, many cases presenting to primary care are largely asymptomatic. A typical scenario is that of a well patient who underwent health screening, whose bone mineral density testing picked up osteoporosis with T-score -2.5 and lower. It is challenging to define what would constitute adequate screening tests at the primary care level, balancing between thoroughness and health care spending, especially if the full cost of such testing is borne by the patient.

## **Routine investigations**

There are numerous review papers<sup>2-6</sup> that seek to address this subject, and the Ministry of Health Clinical Practice Guidelines on Osteoporosis<sup>7</sup> 3/2008 had suggested the following routine investigations including relevant radiographs to document fractures, blood tests including full blood count, erythrocyte sedimentation rate (ESR), creatinine, calcium, phosphate, albumin, AST and alkaline phosphatase, and urine test including urinalysis to look for haematuria and proteinuria. Additional investigations that can be considered include bone turnover markers like osteocalcin and C-telopeptide cross-links (CTX), urinary calcium/creatinine ratio or 24-hour urinary calcium, thyroid function free T4 and TSH, 25 hydroxyvitamin D, FSH, LH, prolactin, tumour markers, myeloma screen amongst others.

## Appropriate Care Guide on Osteoporosis

## It also emphasised that "Before initiating therapy, secondary causes of osteoporosis should be considered and satisfactorily excluded". <sup>7</sup>

This guidance relies heavily on the practising Primary Care physician's clinical acumen and experience to make the right decision to investigate the patient himself or refer the patient with osteoporosis to specialist care for a full diagnostic workup to avoid missing the less common causes of secondary osteoporosis.

To provide further guidance and practical tips to Primary Care, the Ministry of Health Agency for Care Effectiveness released an Appropriate Care Guide on Osteoporosis<sup>8</sup> in November 2018. In the section devoted to excluding secondary contributors of osteoporosis, there is a table of common tests to order like serum creatinine, full blood count, corrected serum calcium and 25 hydroxyvitamin D, and a curated shortlist of other investigations namely thyroid-stimulating hormone, erythrocyte sedimentation rate, alkaline phosphatase, serum phosphate, spot urine calcium/creatinine ratio and serum total testosterone with accompanying notes and explanation to justify the use of the tests. It is a good starting point for most cases, and additional tests should be performed depending on the outcome of the initial screen and with the evolution of symptoms/signs of the patient and clinical progress or lack thereof.

For post-menopausal women, majority of osteoporosis cases would be Primary Osteoporosis with some cases having concomitant vitamin D insufficiency or deficiency.<sup>6</sup> This is a prevalent problem in the elderly population in Singapore.<sup>9,10</sup>

## MANAGEMENT AFTER INITIAL SCREEN

If the initial screen is largely unremarkable, and there are no suspicious symptoms or signs to suggest secondary causes, a practical approach is to help the patient with the following areas:

- 1) Adequate calcium intake through dietary means and judicious use of supplementation
  - Aiming for a total daily intake of 800 to 1000 mg of elemental calcium
- 2) Optimise vitamin D intake or sunlight exposure
  Aiming for a vitamin D level of at least 20 mcg/L, and preferably above 30 mcg/L<sup>11,12</sup>
- 3) Regular weight-bearing exercises
- 4) Fall prevention
- 5) Smoking cessation and limiting alcohol intake
- Regular medication review reduce or eliminate unnecessary drugs that can worsen bone health or increase fall risks
- 7) Initiate effective anti-osteoporosis medications as clinically indicated

## **HIGHER INDEX OF SUSPICION**

A higher index of suspicion to perform a more comprehensive evaluation and refer to specialist care would include cases that have advanced Chronic Kidney Disease (CKD stage 4 and 5), multiple fragility fractures and very low BMD T-score -3, continued significant bone loss of more than four to five percent decrease in DXA BMD after a year of treatment (assuming adherence to treatment was assured, which may include switching from oral options to parenteral or subcutaneous options) or cases that complex secondary causes is confirmed or strongly suspected which should include premenopausal women and younger men.

# SNAPSHOTS OF SECONDARY OSTEOPOROSIS – TO FACILITATE "PATTERN RECOGNITION"

# Case I

A 55-year-old woman, with a background history of Schizophrenia on risperidone, is admitted with a fall and hip fracture which required surgical intervention. Initial labs showed normal creatinine, free T4/TSH and ALP. Her serum calcium was normal on initial glance 2.47 mmol/L (reference range 2.10 to 2.60 mmol/L). However, with a low albumin of 31 g/L, her corrected calcium is calculated to be 2.65 mmol/L which is elevated. In addition, her serum phosphate was low 0.69 mmol/L (reference range 0.77 to 1.38 mmol/L). Intact parathyroid hormone level (iPTH) was performed, and it was elevated 28.1 pmol/L (reference range 0.9 to 6.2 pmol/L). Diagnosis: Primary hyperparathyroidism. Further work-up was done localizing it to a single hyperfunctioning parathyroid adenoma which was excised successfully. She was discharged to primary care with calcium and vitamin D replacement post-parathyroidectomy.

Tip: Remember to look at both serum calcium and serum phosphate as a pair, and to correct serum calcium with paired albumin result (some labs do auto-calculate and report corrected calcium as well).

#### Case 2

A 48-year-old woman, with aches and pain for months, and in recent weeks suffering from debilitating pain over the thigh. An X-ray showed Looser's zone which looked like insufficiency fracture over the left proximal femur shaft. Initial labs showed low-normal calcium 2.10 mmol/L and low phosphate 0.65 mmol/L, and severely low 25 hydroxyvitamin D level of 4.4 mcg/L and raised ALP 157 U/L and iPTH was elevated 20.4 pmol/L. Initial diagnosis: severe vitamin D deficiency and osteomalacia with secondary hyperparathyroidism which responded to vitamin D replacement. Intriguingly, as the vitamin D was corrected to a safer level, close to 20 mcg/L, her serum calcium became elevated 2.70 mmol/L, and on re-evaluation, she also has primary hyperparathyroidism which was masked by the initial severe vitamin D deficiency. diagnosis: Concomitant Overall Primary Hyperparathyroidism with severe vitamin D deficiency initial presentation more of osteomalacia. She was treated surgically for the Primary Hyperparathyroidism, and required high dose of calcium and vitamin D to treat the post-operative bone hunger, and is doing well thereafter with healing of the Looser's zone/femur insufficiency fracture.

Tip: Re-evaluate your patients regularly and ascertain if the initial clinical diagnosis was correct or complete. Occam's razor sometimes fails, and patients do present with multiple concurrent pathologies.

#### Case 3

A 55-year-old man was treated overseas for Osteoporosis with Prolia and with Forteo. He had become progressively weaker over one to two years, from ADL independent to wheelchair bound, and had multiple stress fractures over the hips. Labs done overseas were perused, and intriguingly the following prominent biochemistry was found including hypokalaemia, hypophosphatemia, hypouricemia and elevated ALP. There was urine glucose 4+ with normal serum glucose. We re-ran the labs locally and had similar biochemical findings except that his potassium has normalized. Detailed history taking revealed that he has chronic Hepatitis B and two years ago, his hepatitis B treatment was changed to tenofovir. Diagnosis: Hypophosphatemic Osteomalacia and Fanconi Syndrome likely secondary to tenofovir. We stopped Prolia and Forteo. He was referred to a Hepatologist who stopped the tenofovir and switched him to entecavir for the Hepatitis B treatment. He was supported with phosphate replacement while awaiting recovery of the renal tubules with the cessation of the offending drug. His fractures healed spontaneously without surgical intervention.

Tip: *Re-visit history and especially drug history, which may give us a clue to the diagnosis.* 

#### CONCLUSIONS

In summary, secondary osteoporosis, while less common than primary osteoporosis merits special attention as the treatment is not to start anti-osteoporosis medications straight away but to address the underlying disorder. It is sometimes challenging and elusive to diagnose, especially in patients with a paucity of symptoms or who have less common clinical presentation and hence, there is a need for regular follow-up, re-appraisal of patients' clinical progress and joint partnership between primary and specialist care.

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#### **LEARNING POINTS**

- Perform basic secondary osteoporosis screen for patients diagnosed with osteoporosis.
- Do not start anti-osteoporosis medications if uncertain about secondary osteoporosis.
- To refer patients with suspected or confirmed complex secondary osteoporosis to a specialist.