Coexisting Osteoporosis and Vitamin D Deficiency - Double Trouble !

Parag Munshi*, Raman Toshniwal**

Introduction

Osteoporosis is a very common problem affecting women more than men in India. It is under recognised and under treated leading to long term chronic morbidity. 2015 census data suggests that prevalence of osteoporosis amongst women is rampant and of the 230 million Indians over the age of 50 years, 20% i.e.46 million women suffer with osteoporosis.[1] The cause for this is multifactorial - low calcium intake with extensive vitamin D deficiency, increasing lifespans, early menopause, genetic predisposition, lack of diagnostic facilities in rural areas and poor knowledge of bone health have all contributed to this problem.

Vitamin D is a very vital hormone with wide spread ramifications on several organ systems. Low vitamin D predisposes to a multitude of problems. When both pathologies coexist the symptoms get amplified and can get confusing for the physician to diagnose it clinically. Data suggests that prevalence of vitamin D deficiency in India is as follows: 70 to 100%.[2]

Indian Population	Prevalence of Vit.D deficiency (%)
Elderly	83.7
Pregnant women	67 - 96
Lactating women	47.8
Children < 5 years	61.4

*Consultant Orthopaedic and Joint Replacement Surgeon, ** Fellow in Joint Replacement Surgery, Dept. of Orthopaedics, Bombay Hospital Institute of Medical Sciences and Research Centre, 12, New Marine Lines, Mumbai - 400 020

The aim of this paper is to highlight this coexisting disease and how to treat it effectively.

Pathology

Osteoporosis is defined as a diffuse reduction in bone density that results when the rate of bone resorption exceeds the rate of bone formation. It is most commonly associated with ageing process in which the bone formation generally proceeds at a normal rate, but bone removal occurs at increased rate. The diagnosis of osteoporosis can be made when the bone mineral density is reduced by 2.5 standard deviations below the mean value for young normal individuals.

Histologically, this is seen as either diminished osteoblastic activity or excessive osteoclastic activity. The cortices are reduced in thickness and cancellous trabeculae become thinned as marrow spaces are widened (Fig 1).

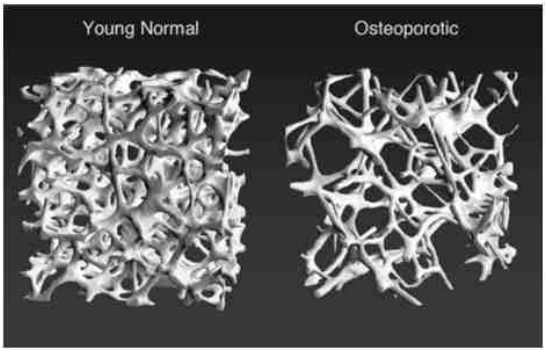

Fig.1: Bone architecture in Normal and osteoporotic condition

Vitamin D deficiency is very common

in the elderly. The prevalence varies strongly between different studies, depending on the population and definition used.[2] Vitamin D deficiency in older persons is caused by insufficient sunlight exposure, a decreased functional capacity of the skin to synthesise vitamin D3 and low dietary vitamin D intake.[3]

Pathophysiology of bone loss in vitamin D deficient patients

Vitamin D plays an important role in calcium homoeostasis.[3] The main effect of the active vitamin D metabolite 1, 25(OH)2D is to stimulate the absorption of calcium from the gut. The consequences of vitamin D deficiency are secondary hyperparathyroidism and bone loss, leading to osteoporosis and fractures, mineralisation defects which may lead to osteomalacia in the long term, and muscle weakness, causing falls and fractures.

The active vitamin D metabolite 1, 25(OH) 2D opens up calcium channels in the gut, stimulates the formation of calcium binding protein in the intestinal cell, and thereby stimulates the absorption of calcium and phosphate from the gut. In this way, optimal environment for bone mineralisation is created. Mineralisation in itself is a passive process, once sufficient calcium and vitamin D are available. In case of vitamin D deficiency, the 1, 25(OH) 2D concentration may drop and less calcium will be available for bone mineralisation. The parathyroid hormone (PTH) level will increase, stimulating the hydroxylation of 25(OH) D in the kidney to 1, 25(OH) 2D. The increased serum PTH stimulates bone turnover, leading to bone loss.[3]

In the new steady state, serum 1, 25(OH) 2D is within the normal reference range and calcium absorption is restored, at the expense of increased bone resorption. In periods of protracted vitamin D deficiency bone loss is increased and this may lead to secondary osteoporosis (Fig. 2).

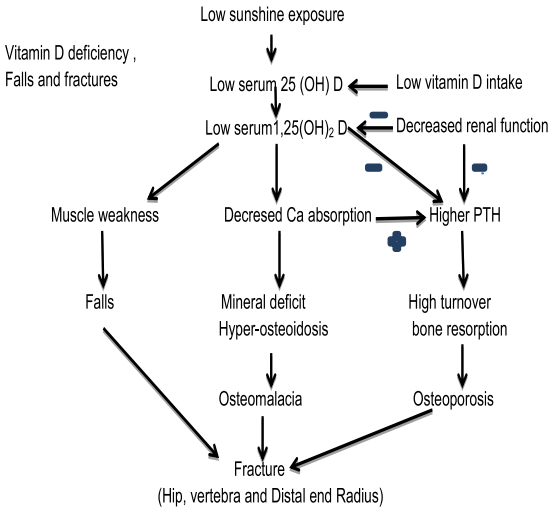

Fig. 2: The patho-physiologic pathways from vit.D deficiency to osteoporosis, osteomalacia, falls and fractures

Clinical Presentation

Osteoporotic discomfort presents with bone pains mainly in the back, rounded thoracic spine, stooped habitus, shortened stature, spontaneous fractures in previous deformities, compression fracture resulting from trivial trauma, frequent acute attacks of backache suggestive of minimal fractures which cannot be seen on X-ray. The acute onset, point of tenderness and relief with recumbency are the chief diagnostic features.

In osteoporosis, pain is a consequence of a low energy fracture or spontaneous fracture which points to late diagnosis. It

is a remarkable fact that about 50% of women aged over 50 years had no idea that they were suffering from vertebral fractures. Therefore, it is of particular importance in everyday clinical practice to recognise them early, because the intensity of pain is not in correlation with the presence and degree of vertebral fracture, and often is not linked with a known mechanical load. Moreover, some of these women felt no pain at all. Indeed, only 33% of vertebral fractures are considered to be diagnosed in clinical practice. On the other hand, not all patients who have proven osteoporosis get fractures during their lives, but 30-40% of patients with osteopenia had fractures with a T-score within the range of reference values.[4]

Osteoporotic postmenopausal women are at significantly greater risk of cardiovascular disease, cardio-vascular mortality and bone fractures than age-matched controls.[5,6]

Patients with lower bone density and Osteoporosis also have higher lipid levels, more severe coronary atherosclerosis, and a greater risk of stroke death.

Vitamin D deficiency presents with deformities in weight-bearing structures mainly in the leg and thigh, scoliotic and kyphotic deformities of spine, pressure over femoral heads produces coxa vara deformity, protrusion acetabula, generalised skeletal and muscular pain mainly in lower back and lower extremities, muscle weakness, and insufficiency fractures with ill-defined bone pains.

When both are present i.e. osteomalacia and osteoporosis, one should look for-

- Axial and pelvic aches and pains without an obvious fracture on X-ray,
- Insufficiency fractures in the pelvis
- Thigh pains with proximal muscular weakness.

Investigations

For investigating low vitamin D levels one needs to check 25-OH vitamin D levels in the random blood sample. The normal range is between 30-100 ng/ml.

Broad guidelines for diagnosing low vitamin D levels are as follows :

Mild hypovitaminosis D: 20-30 ng/ml

Moderate hypovitaminosis D: 10-20 ng/ml

Severe hypovitaminosis D: < 10 ng/ml.

While investigating for osteoporosis a DEXA scan or Bone Density Scan is usually asked for and values of T score below -2.5 standard deviation are suggestive of osteoporosis.

In a patient with low vitamin D levels, if a dexa scan is asked for without correcting preexisting vitamin D deficiency, the DEXA scan results will be erroneously amplified alarming the physician of very severe level of osteoporosis, wherein in reality that is not the case. Underlying secondary osteoporosis due to vitamin D deficient hyperparathyroidism is adding on to the wrong amplified results.

Treatment strategy

Vitamin D deficiency: Correcting vitamin D deficiency prior to starting osteoporosis treatment is vital however both can be started simultaneously as the colony forming units (CFU) regenerate over a period of 3 to 6 months. Vitamin D levels below 10 ng/ml should be treated with

injectable vitamin D supplements so as to bypass the gastric effect and to rapidly bring the levels up in order to prevent pathological fractures.

10-20 ng/ml levels can be brought up with oral medications / supplements and or injectables.

20-30 ng/ml levels can be brought up with oral tablets or syrups or sachets.

Osteoporosis treatment involves oral calcium, vitamin D supplements plus anti-resorptive agents or bone forming agents on a long term basis.

Drugs to treat osteoporosis

1. Oestrogen reduces bone turnover, prevents bone loss, and allows small increase in bone mass. Selective oestrogen response modulators (Raloxifene 60 mg/day)
2. Bisphosphonates: Alendronate 10 mg/day or 70 mg/week, Risedronate 35 mg/week, Ibandronate 150 mg/month
3. Calcitonin nasal spray: 200 IU/day
4. PTH analogue: Teriparatide (20 micrograms/day SC).
5. Receptor activator of nuclear factor kappaB (RANK) ligand inhibitor

Denosumab: inhibits osteoclast formation, given as 60 mg/ml SC twice yearly.

Once started, treatment should continue on a long term basis with yearly monitoring of bone mineral density with DEXA scan and if available blood markers. A combination of anti-resorptive and bone forming agents simultaneously can be tried as well. Recent data (2018) is suggestive of using this dual therapy with the advantage of a shorter overall duration of treatment and achieving optimal outcome with reduced dose of PTH analogue.[7]

Most patients with osteoporosis are currently treated with bisphosphonates. Calcium and vitamin D are added for several reasons. In a patient with severe vitamin D deficiency, bisphosphonate treatment alone may induce symptomatic hypocalcaemia.

A Japanese group treated 52 postmenopausal women with osteoporosis with alendronate 5 mg/d for 6 months without any supplements.[8] The increase of lumbar spine BMD was significantly lower in the patients with a serum 25(OH)D < 62.5 nmol/l (25 ng/ml), than in those with serum 25(OH) 62.5 nmol/l (3.3% Vs 6.8%, P ¼ 0.027).

In Italy, 1515 women with postmenopausal osteoporosis treated with bisphosphonates or Raloxifene were classified as vitamin D deficient or vitamin D replete. The mean annualised BMD increase in the lumbar spine was 0.22% in vitamin D deficient patients versus 2.11% in vitamin D replete patients (P ¼ 0.002). Similar differences were observed in the hip.[9]

This data confirms that the addition of vitamin D and calcium to anti-osteoporotic treatment is necessary. Anyhow, the recent recommendation of the Institute of Medicine for vitamin D is 600-800 IU/d depending on age.[10]

The addition of calcium should not be exaggerated, as a recent meta-analysis suggested that very high intakes might increase the risk of cardiovascular disease.[11]

Prevention of both

The reduction of fracture risk is by educating the patient about bone loss and reduction of modifiable risk factors. Hypothyroid state must be treated. Falls must be prevented by vision checkup and household modifications such as eliminating loose wires, curtain strings, slippery rugs and mobile beds and providing good light in bathrooms and wall railings. In postmenopausal women testing for BMD is based on risk profile while for women older than 65 years, measurement of BMD is recommended. Lifestyle changes include diet rich in calcium (1000 -1200 mg/day) exposure to sunlight to make vitamin D or vit.D supplementation to achieve 800-1000 IU/day. Regular weight bearing, muscle strengthening exercises are a must and avoid smoking and alcohol in excess.

Exercise reduces bone loss and has a beneficial effect on the neuromuscular function thereby improving coordination, balance, strength, thus reducing the risk of falling and associated fractures. Excessive immobilisation is best avoided.

Vitamin D deficiency prevention: Prophylaxis consists chiefly of administration of vit. D and exposure to sunlight. As per the latest guidelines issued by Institute of Medicine (IOM), the RDA recommended daily allowance for vitamin D is 800 IU for children and elderly more than 70 yrs. of age and 600 IU for all other age groups, provided the preexisting baseline serum 25-hydroxyvitamin D level of at least 20 ng/ml(50 nmol/l).

Conclusion

1. Vitamin d deficiency should preferably be treated prior to imaging for osteoporosis.
2. Osteomalacia and osteoporosis when diagnosed concomitantly have to be treated aggressively for the duration of 2-3 years
3. Newer RANK ligand inhibitors (Denosumab) are looking promising and combination usage with Teriparatide perhaps will be the long term solution for effective osteoporotic treatment.

References

1. Khadilkar AV, Mandlik RM. Epidemiology and treatment of osteoporosis in women: an Indian perspective. *International journal of women's health*. 2015;7:841.
2. Gupta A. Vitamin D deficiency in India: prevalence, causalities and interventions. Nutrients. 2014 Feb;6(2):729-75.
3. Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. *Endocrine reviews*. 2001 Aug 1;22(4):477-501.
4. Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. *The Lancet*. 2002 Jun 1;359(9321):1929-36.
5. Von der Recke P, Hansen MA, Hassager C. The association between low bone mass at the menopause and cardiovascular mortality. *The American journal of medicine*. 1999 Mar 1;106(3):273-8.
6. Martins D, Wolf M, Pan D, Zadshir A, Tareen N, Thadhani R, Felsenfeld A, Levine B, Mehrotra R, Norris K. Prevalence of cardiovascular risk factors and the serum levels of 25-hydroxyvitamin D in the United States: data from the Third National Health and Nutrition Examination Survey. *Archives of internal medicine*. 2007 Jun 11;167(11):1159-65.
7. Lou S, Lv H, Li Z, Zhang L, Tang P. Combination therapy of anabolic agents and bisphosphonates on bone mineral density in patients with osteoporosis: a meta-analysis of randomised controlled trials. *BMJ open*. 2018 Mar 1;8(3): e015187.

8. Ishijima M, Sakamoto Y, Yamanaka M, Tokita A, Kitahara K, Kaneko H, Kurosawa H. Minimum required vitamin D level for optimal increase in bone mineral density with alendronate treatment in osteoporotic women. *Calcified tissue international*. 2009 Nov 1;85(5):398.
9. Adami S, Giannini S, Bianchi G, Sinigaglia L, Di Munno O, Fiore CE, Minisola S, Rossini M. Vitamin D status and response to treatment in post-menopausal osteoporosis. *Osteoporosis International*. 2009 Feb 1;20(2):239-44.
10. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, Durazo-Arvizu RA, Gallagher JC, Gallo RL, Jones G, Kovacs CS. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *The Journal of Clinical Endocrinology & Metabolism*. 2011 Jan 1;96(1):53-8.
11. Bolland MJ, Avenell A, Baron JA, Grey A, MacLennan GS, Gamble GD, Reid IR. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ*. 2010 Jul 29;341:c3691.