



Osteomalacia and Rickets

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Osteomalacia is a vitamin D deficiency in adults that results in a shortage or loss of calcium salts, causing bones to become increasingly soft, flexible, brittle and deformed. It is characterised by defective bone mineralisation, bone pain, increased bone fragility and fractures.

Rickets is the clinical syndrome that results when osteomalacia occurs in the growing skeleton and these patients develop bone deformity in addition to the above features.

Full-blown osteomalacia is now relatively rare in developed countries, but subclinical disease is still quite common, especially in people who have a poor diet or limited sunlight exposure such as elderly housebound individuals and Muslim women who live in northern latitudes. Four broad categories of osteomalacia and rickets can be identified based on the underlying cause, specifically:

1. Deficiency of vitamin D or defects in vitamin D metabolism
2. Hypophosphataemia
3. Drug-induced inhibition of bone mineralisation
4. Defects in pyrophosphate metabolism.

Pathogenesis

Maintenance of normal levels of vitamin D depends on ultraviolet sunlight exposure which permits formation of cholecalciferol (D) in the skin from 7-dehydrocholesterol. Lack of cholecalciferol due to inadequate sunlight exposure, dietary deficiency, malabsorption or a combination of these factors is accompanied by a reduction in 25(OH)D₃ synthesis in the liver. This causes reduced production of the biologically active metabolite 1,25(OH)₂D₃ in the kidneys, reduced intestinal calcium absorption and low serum calcium.

The low serum calcium level stimulates PTH secretion, resulting in secondary hyperparathyroidism and subsequent increased osteoclastic bone resorption, reduced renal calcium excretion and increased renal phosphate excretion.

This sequence of events represents an attempt by the parathyroid glands to restore serum calcium levels to normal; however this cannot be achieved with continuing vitamin D deficiency so there is progressive loss of both calcium and phosphate from bone and defective mineralisation.

Osteomalacia also occurs in association with inherited and acquired metabolic defects of vitamin D metabolism and function. Patients with chronic renal failure cannot synthesize the active metabolite of vitamin D (1,25(OH)₂D) due to renal damage and this causes secondary hyperparathyroidism and, in some cases, osteomalacia.

Osteomalacia also occurs in the inherited disorder vitamin D-resistant rickets type I, which is caused by inactivating mutations in the renal α -hydroxylase enzyme, rendering the enzyme unable to convert 25(OH)D to 1,25(OH)₂D. In type II vitamin D-resistant rickets, mutations in the vitamin D receptor occur, rendering it resistant to activation by 1,25(OH)₂D.

Clinical features

Rickets in children has many manifestations, including enlargement of epiphyses at the lower end of the radius, and swelling of the costochondral junctions ('rickety rosary').

Osteomalacia in adults presents much more insidiously and, when mild, can be relatively asymptomatic or mimic osteoporosis. With further progression, however, features of bone pain, pathological fractures and general malaise occur.

Proximal muscle weakness is prominent and the patient may walk with a waddling gait and experience difficulty in climbing stairs or getting out of a chair. Bone and muscle tenderness on pressure is common and focal bone pain may occur in association with fissure fractures of the ribs and pelvis.

Investigations and Diagnosis

Patients suspected of having osteomalacia should have a routine biochemical screen: renal function, serum calcium, phosphate, albumin, alkaline phosphatase and serum 25(OH)D and PTH levels.

A diagnosis of vitamin D-deficient osteomalacia should be suspected by the presence of low or low-normal calcium and phosphate, raised alkaline phosphatase, low 25(OH)D and raised PTH.

Radiological examination is of limited value in diagnosis. In advanced cases focal radiolucent areas (pseudofractures or Looser's zones) may be seen in the ribs, pelvis and long bones. Radiological osteopenia is common and the presence of vertebral crush fractures may cause confusion with osteoporosis.

In children, the pathognomonic feature is thickening and widening of the epiphyseal plate.

The diagnosis of osteomalacia can be confirmed by bone biopsy, which shows the pathognomonic features of increased thickness and extent of osteoid seams.

The clinical features of vitamin D-resistant rickets (VDRR) are similar to those of vitamin D-deficient rickets and the diagnosis is usually first suspected when patients fail to respond to vitamin D supplementation.

Biochemical features of type I VDRR are similar to vitamin D deficiency except that levels of 25(OH)D are normal and 1,25(OH)₂D is undetectable (reflecting failure of 1- α -hydroxylation of vitamin D).

In VDRR type II, 25(OH)D is normal but PTH and 1,25(OH)₂D values are raised.

Management

Rickets and osteomalacia caused by vitamin D deficiency respond rapidly to treatment with: 25(OH) (50 μ g daily) or active vitamin D metabolites (1- α -(OH)D 1-2 μ g daily or 1,25(OH)₂D 0.25-1.5 μ g daily) and calcium supplementation (500-1000 mg daily).

Higher doses or systemic administration may be required in patients with malabsorption. Healing of the bone disease is accompanied by rapid clinical improvement, normalisation of biochemical abnormalities and radiographic improvement. After 3-4 months, treatment can generally be stopped or the dose of vitamin D reduced to a maintenance level of 10-20 μ g cholecalciferol for those in whom underlying disease or lifestyle factors put them at risk of recurrence.

Osteomalacia secondary to chronic renal failure and VDRR type I require treatment with active vitamin D metabolites (1- α -(OH)D or 1,25 (OH)₂D) since these bypass the metabolic defect in 1- α -hydroxylation of 25(OH)D.

Management of VDRR type II is difficult as the defect is at the receptor level, but a partial response to high doses of vitamin D metabolites and parenteral calcium and phosphate may be observed. During treatment of osteomalacia it is important to measure serum calcium, alkaline phosphatase and renal function on a regular basis to screen for development of hypercalcaemia.

Healing of osteomalacia is reflected by a return of alkaline phosphatase values to normal.

Osteomalacia in Old Age

Increased risk in housebound individuals due to lack of sunlight exposure and poor diet. Around 15% of older people in the community in the UK and USA have low levels of 25(OH)D. The diagnosis should be considered in patients with bone pain and muscular weakness who have low serum levels of 25(OH)D and raised alkaline phosphatase levels. Bone biopsy should be considered in patients in whom the above investigations are inconclusive. The symptoms and signs of osteomalacia respond rapidly to treatment with calcium and vitamin D.

Hypophosphataemic Rickets

Osteomalacia and rickets can occur as the result of renal phosphate wasting in the absence of vitamin D deficiency. Hypophosphataemic rickets is most often caused by inherited defects in key genes that regulate phosphate metabolism but can also arise in patients who develop tumours that secrete phosphaturic substances.

Serum phosphate levels in normal individuals are primarily regulated by modulation of phosphate reabsorption in the renal tubules. One of the most important regulators is the circulating phosphaturic hormone, fibroblast growth factor 23 (FGF23), the levels of which, in turn, are regulated by the enzyme PHEX which degrades FGF23

X-linked hypophosphataemic rickets (XLH) is caused by inactivating mutations in the PHEX gene preventing degradation of FGF23.

Autosomal dominant hypophosphataemic rickets (ADHR) is caused by mis-sense mutations in the FGF23 gene that render FGF23 hormone resistant to PHEX-mediated inactivation – thus raising bioactive levels of FGF23 in the circulation.

Most cases of tumour-induced osteomalacia appear to be due to 'ectopic' production of FGF23 by mesenchymal tumours, sometimes in combination with other phosphaturic factors.

The diagnosis of XLH and ADHR is often made on the basis of the family history.

Both conditions are characterised by:

- severe hypophosphataemia
- phosphaturia
- raised alkaline phosphatase levels
- normal or low-normal serum calcium levels and normal 25(OH)D and 1,25(OH)D levels.

Patients with tumour-induced osteomalacia present with a similar biochemical picture, but with a later age at onset and no family history. In most cases, the causal tumour is clinically occult and whole-body MRI or CT may be required for localisation.

Treatment of hypophosphataemic rickets is with phosphate supplements (1-4 g daily), combined with active metabolites of vitamin D to promote intestinal calcium and phosphate absorption (1- α -(OH)D 1-2 μ g daily or 1,25(OH)₂D 0.25-1.5 μ g daily).

The aim is to ameliorate symptoms, restore normal growth, maintain serum phosphate levels within the normal range and normalise alkaline phosphatase levels. Levels of calcium, phosphate, alkaline phosphatase and renal function should be monitored during treatment.

Whilst tumour-induced osteomalacia can also be managed medically, it is best treated by localisation and removal of the causal tumour.

Other Causes of Osteomalacia

Aluminium intoxication - often seen in renal patients on dialysis. Aluminium has a direct inhibition of mineralization.

Bisphosphonates.

Fluoride - Excessive intake of fluoride causes osteomalacia due to direct inhibition of mineralisation.

Hypophosphatasia.