

# Vitamin D Deficiency including Osteomalacia and Rickets

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Adequate vitamin D<sub>3</sub> by synthesis in the skin and from dietary and supplemental sources is essential for bone health throughout life.<sup>[1]</sup> Rickets in children and osteomalacia in adults are the classic but extreme manifestations of severe **vitamin D** deficiency. Links have also been shown between poor vitamin D status and **breast cancer, bowel cancer, prostate cancer, lung cancer, metabolic syndrome, obesity, ischaemic heart disease and type 2 diabetes**. Similar associations have been found with **tuberculosis, type 1 diabetes, multiple sclerosis, dementia, pre-eclampsia and rheumatoid arthritis**.<sup>[2] [3]</sup>

Osteomalacia (adults) and rickets (children) are caused by inadequate mineralisation of bone matrix. Vitamin D deficiency causes low calcium and phosphate, which lead to **secondary hyperparathyroidism**. Osteomalacia results from a loss of skeletal mass caused by inadequate mineralisation of the normal osteoid tissue after the closure of the growth plates.<sup>[4]</sup> Rickets results from the same underlying process, occurring in children and adolescents before the growth plates have closed.

## Vitamin D

Normal bone mineralisation depends on adequate calcium and phosphate and this is maintained by vitamin D. Vitamin D is supplied either in the diet or produced from a precursor in the skin following exposure to ultraviolet light. Production of metabolically active vitamin D requires hydroxylation, which occurs first in the liver and then in the kidneys to produce 1,25-dihydroxyvitamin D<sub>3</sub>. The recommended daily intake of vitamin D in the UK is 400 IU (10 micrograms) per day for an adult, 280 IU (7 micrograms) for children aged between 6 months and 3 years, and 340 IU (8.5 micrograms) per day for infants under 6 months. These recommendations only provide sufficient vitamin D to prevent osteomalacia and rickets and, in the absence of skin synthesis, will not provide an optimal level of vitamin D.<sup>[5]</sup>

### Sunlight

Over 90% of vitamin D is derived from ultraviolet B light and the rest is obtained from the diet. In a fair-skinned person, 20-30 minutes of sunlight exposure on the face and forearms at midday is estimated to generate the equivalent of around 2,000 IU of vitamin D. Two or three such exposures to sunlight each week are sufficient to achieve healthy vitamin D levels during the summer. For people with pigmented skin and the elderly, the amount of sunlight exposure should be increased by a factor of between 2 and 10 in order to achieve the same level of vitamin D synthesis. Between October and April each year, 90% of the UK does not get sufficient exposure to the ultraviolet B necessary for vitamin D synthesis and so people are then reliant on dietary sources of vitamin D.<sup>[5]</sup>

### Dietary intake

Food sources of vitamin D include oily fish, liver, egg yolks, fortified margarine and fortified breakfast cereals. Only a few foods contain substantial amounts of vitamin D and the most significant dietary source is oily fish and cod liver oil. There is little or no vitamin D content in UK milk and dairy products. Only infant formula milk and margarine have statutory vitamin D supplementation in the UK.<sup>[2]</sup> Farmed fish may have less vitamin D content than wild fish. Egg yolk, liver, and wild mushrooms contain only small quantities of vitamin D.<sup>[5]</sup> Therefore, a low dietary vitamin D intake, combined with a lack of skin synthesis throughout the year, leads to a high prevalence of vitamin D insufficiency in the UK.

## Epidemiology

- Vitamin D deficiency continues to be common in children and adults. It has been estimated that 1 billion people worldwide have vitamin D deficiency.<sup>[6]</sup>
- A recent survey in the UK showed that more than 50% of the adult population have insufficient levels of vitamin D and that 16% have severe deficiency during winter and spring. The highest rates were found in Scotland, Northern England and Northern Ireland.<sup>[5]</sup>

- One study found the prevalence of rickets in non-Caucasian children to be 1.6%.<sup>[1]</sup>

## Risk factors

- Dark skin, especially South Asian, African Caribbean and Middle Eastern; prevalence of vitamin D insufficiency is as high as 94% in otherwise healthy South Asian adults.<sup>[8] [9]</sup>
- Children and those aged over 65 years.
- Pregnancy.
- Obesity
- Routine covering of the face and body, eg wearing a veil.
- An infant who is exclusively breast-fed, particularly beyond six months of age.<sup>[5]</sup>
- Housebound or institutionalised.
- Poverty.
- Vegetarianism.
- Alcoholism.
- Living in countries at high latitude.
- Family history of vitamin D deficiency.<sup>[5]</sup>

## Causes

Vitamin D deficiency is most often caused by insufficient exposure to sunlight and nutritional deficiency but can be secondary to a wide range of other underlying causes, such as disorders of the gut, pancreas, liver and kidney.<sup>[10]</sup>

- Gastrointestinal malabsorption, eg surgery (stomach and bowel resections), other causes of short bowel syndrome, chronic pancreatic disease, cystic fibrosis, biliary disease (eg primary biliary cirrhosis, biliary fistulae, biliary atresia), Crohn's disease and coeliac disease.
- Liver disease, eg cirrhosis.
- Renal disease causing defective 1,25-dihydroxyvitamin D synthesis.
- Drug causes include anticonvulsants (particularly phenytoin, carbamazepine, phenobarbital), rifampicin, highly active antiretroviral therapy (HAART), colestyramine and cadmium.
- Severe dietary calcium deficiency can cause rickets despite adequate vitamin D.<sup>[11]</sup>
- Rare causes:
  - Hypophosphataemia: tumour-induced, Fanconi's syndrome, phosphate depletion, metals such as cadmium and lead that may lead to renal phosphate wasting.
  - Systemic acidosis, renal tubular acidosis.
  - Intoxication with diphosphonate, fluoride, aluminum (caused by excessive antacid ingestion, or in fluids used in dialysis).
  - Autonomous hyperparathyroidism presenting as vitamin D-deficient osteomalacia.
  - Mesenchymal tumour - oncogenic osteomalacia.
- Genetic causes:
  - Hypophosphataemic rickets: X-linked dominant disorder characterised by growth restriction, inadequate mineralisation of bone, hypophosphataemia, and renal defects in phosphate reabsorption and vitamin D metabolism.
  - Vitamin D-dependent rickets type I (failure of conversion of 25-hydroxyvitamin D (25-OHD) to 1,25-dihydroxyvitamin D) and II (end organ insensitivity to 1,25-dihydroxyvitamin D).
  - Adult-onset vitamin D-resistant hypophosphataemic osteomalacia (autosomal dominant).
  - Proximal renal tubule dysfunction: hereditary Fanconi's syndrome.

## Presentation<sup>[5]</sup>

Maintain a high index of clinical suspicion. People with suboptimal levels often have no symptoms and so awareness and prevention are very important, especially in young children, the elderly and pregnant women. Vitamin D deficiency should be suspected in children with known risk factors who are unwell with pain, irritability, and poor growth or skeletal deformity, and in all children with a seizure disorder.<sup>[5]</sup>

- Children:
  - Severe vitamin D deficiency may cause hypocalcaemic seizures or tetany, particularly in the neonatal period and during periods of rapid growth in adolescence.
  - From the age of 6 months, children with vitamin D deficiency often present with bony deformity (rickets). Bowing of the legs (genu varum) is typical, but knock knees (genu valgum) can also occur. Anterior bowing of the femur and internal rotation at the ankle are frequently found, along with swelling at the wrist, prominent costochondral joints, and a soft, deformable skull (craniotabes).
  - Children with vitamin D deficiency may be irritable and reluctant to weight-bear, and manifest impaired growth.
  - An increased susceptibility to infections and respiratory symptoms may be caused by a 'rachitic lung', with reduced lung expansion and muscle weakness.
  - Severe vitamin D deficiency can result in **cardiomyopathy** and potentially fatal heart failure.
- Adults:
  - Pain and **proximal muscle weakness** are the main features of vitamin D deficiency in adults. Symptoms may be mild and non-specific with a general lack of well-being.
  - Rib, hip, pelvis, thigh, and foot pain are typical.
  - More diffuse muscular aches and muscle weakness, including in the limbs and back, are also common.
  - Low bone density on dual-energy X ray absorptiometry (DEXA) scanning, **pathological fractures** or **osteopenia** on plain X-rays may reflect osteomalacia, and these findings warrant assessment of vitamin D status.

## Rickets

Classic presentation is a child with bony abnormalities such as leg-bowing and knock knees. There may be bony deformities of the chest, pelvis and skull, delayed dentition, poor growth, and **bone pain**.

- Softening of the skull (craniotabes) and frontal bossing in the first few months of life; delayed closure of fontanelles.
- Tender swollen joints.
- Enlargement of the ends of the ribs ('rachitic rosary') due to expansion of the costochondral junction in a 3-6 month-old child.
- Deformed bones, bowing of the legs, knock knees.
- **Delayed walking** or a **waddling gait**.
- Impaired growth; **short stature** and **poor weight gain**.
- The child is often miserable because of bone and **joint pain**.
- May present with **fractures** in severe cases.
- Dental deformities include delayed formation of teeth, enamel hypoplasia, and increased incidence of cavities in the teeth (**dental caries**).
- May present with symptoms of **hypocalcaemia** requiring urgent paediatric referral (eg **convulsions**, irritability, tetany, breathing difficulties with apnoea or stridor), cardiomyopathy or **cardiac arrest**, especially in very young infants.

## Osteomalacia

- Mildly affected patients may present with widespread bone pain and tenderness (especially **low back pain** and in the hips), proximal muscle weakness and lethargy.
- Signs of the underlying disease (eg **renal failure**, malabsorption) may predominate.
- Early symptoms include gradual onset and persistent fatigue, and bone and joint pain and tenderness.
- Later symptoms include muscular weakness (especially proximal) and paraesthesia.
- Severely affected patients may have difficulty walking and may have a waddling gait or a change in gait, with proximal muscle weakness and marked adductor spasm.
- Other signs include costochondral swelling (rachitic rosary), spinal curvature and signs of hypocalcaemia (eg tetany, carpopedal spasm).
- Tenderness over pseudofractures (which represent a lucent band of decreased cortical density, perpendicular to bone surface, often multiple, and with or without callus formation).
- The patient may experience multiple fractures which are often bilateral and symmetrical. Typical sites include the femoral neck, scapula, pubic rami, ribs and vertebrae.
- Skeletal deformity can occur in the vertebral bodies and skull. There may be forward projection of the breastbone (pigeon chest) and deformities of the spine, including **scoliosis** or **kyphosis**.
- Other signs include dental deformities and hyporeflexia.

## Possible long-term effects

- Low levels of vitamin D may be associated with increased cancer incidence and mortality in men, particularly for digestive-system cancers. <sup>[12]</sup>
- Vitamin D deficiency may contribute to atherosclerosis and increased cardiovascular morbidity and mortality. <sup>[13]</sup>

## Differential diagnosis

- The radiographic appearance of osteomalacia may be normal or similar to findings noted with osteoporosis.
- The differential diagnosis of generalised osteopenia includes osteomalacia, hyperparathyroidism, osteitis fibrosa, Paget's disease of bone and myeloma.
- Chronic excessive fluoride ingestion, etidronate overdose, aluminium toxicity.
- Other possibilities to exclude are rheumatoid arthritis, dermatomyositis, polymyositis, muscular dystrophy, malignant disease, polymyalgia rheumatica, hypothyroidism, hyperthyroidism and fibromyalgia.

## Investigations

### Initial investigations

- Blood biochemistry: renal function, electrolytes (including serum calcium and phosphate), LFTs, parathyroid hormone (PTH) level: <sup>[5]</sup>
  - More than 80% of adults with osteomalacia have a high concentration of serum alkaline phosphatase.
  - Hypocalcaemia, hypomagnesaemia and hypophosphataemia may be present, depending on the severity and chronicity of the disease and the patient's dietary calcium intake.
  - Elevation of plasma PTH (secondary hyperparathyroidism) is typical but not always found in patients with osteomalacia.
- FBC: anaemia suggests possible malabsorption.
- Serum vitamin D and PTH levels are not routinely recommended for high-risk symptomatic with clear clinical evidence of vitamin D deficiency but vitamin D levels are otherwise required for assessment. Vitamin D status is most reliably determined by assay of serum 25-hydroxyvitamin D (25-OHD): <sup>[5]</sup>
  - Vitamin D deficiency: individuals with symptomatic osteomalacia or rickets have serum 25-OHD concentrations of less than 25 nmol/L (10 micrograms/L).
  - A much larger proportion of the UK population have vitamin D insufficiency, with serum 25-OHD concentrations between 25 nmol/L and 50 nmol/L (10-20 micrograms/l).
  - Serum 25-OHD concentrations between 50-75 nmol/l are considered healthy but optimal vitamin D status is when serum concentrations of 25-OHD are 75 nmol/L (30 micrograms/L) or more.

### Further investigations

- Urine microscopy to help determine whether the patient has underlying renal failure.
- In children with low vitamin D levels identified, a wrist X-ray is required to diagnose rickets (definitive diagnosis of rickets requires radiography of a long bone which shows cupping, splaying and fraying of the metaphysis - for example, champagne glass wrist). <sup>[14]</sup>
- Radiology is unnecessary for adults if the diagnosis is clear but may include:
  - Plain X-ray of weight-bearing bones (neck of femur, pelvis, pubic rami, ribs, outer border of the scapulae and metatarsals) may show characteristic features such as coarsened trabeculae, osteopenia, pseudofractures ('Looser's zones' - linear areas of low density surrounded by sclerotic borders) and fractures; pseudofractures are particularly seen at the lateral border of the scapula, inferior femoral neck and medial femoral shaft.
  - Low bone density on DEXA scanning. <sup>[2]</sup>
  - MRI scanning helps to evaluate the soft tissues for ligament rupture.
  - CT scanning can help to evaluate pathological fractures.
  - Bone scan will show increased skeletal uptake of radioactive isotope ('hot spots') in the ribs and near joints.

- Iliac bone biopsy will show a failure of mineralisation and wide osteoid seams but bone biopsy is now rarely required. [8]

Assessment must be made for a possible underlying cause of vitamin D deficiency if suspected, eg coeliac disease or cystic fibrosis causing malabsorption.

- All children with rickets should be referred to a paediatrician. [14]
- Referral of adults is not routinely needed but should be considered where there is doubt about the diagnosis, if the biochemistry is atypical (eg low vitamin D and high calcium) or if the patient fails to respond to treatment. [2]

## General management

- Education: dietary advice (refer to a dietician).
- Encourage exposure to sunlight.
- Vitamin D supplementation.
- Treatment of any underlying condition.
- Treatment of pain.
- Orthopaedic intervention may be required.

## Specific treatment [5]

- Children:
  - Oral **calciferol** in the form of either **ergocalciferol** or **colecalciferol** is the treatment of choice for children with rickets.
  - Children aged less than 6 months should be treated with 3,000 IU of calciferol daily, increasing to 6,000 IU daily after 6 months of age. The daily dose for those aged 12-18 years should be 10,000 IU. [2]
  - Calcium supplementation is advisable during the first weeks of therapy for a growing child. [2]
  - A maintenance dose of 400 IU calciferol daily is appropriate for a child of any age.
  - A relatively rapid biochemical response is typically seen in children, with normalisation of alkaline phosphatase levels within three months.
  - It is likely that the mother, siblings, and other family members of a child with rickets are also vitamin D-deficient. A maintenance dose of calciferol is recommended for other family members (who should be investigated for vitamin D deficiency and may require therapeutic doses).
- Adults:
  - Calciferol treatment, in a daily dose of 10,000 IU or a weekly dose of 60,000 IU, will lead to restoration of body stores of vitamin D over 8 to 12 weeks. A maintenance dose of 1,000-2,000 IU calciferol daily or 10,000 IU weekly is adequate. Combined calcium and vitamin D preparations should be avoided in the long term, as the calcium component is usually unnecessary.
  - Short-acting, potent vitamin D analogues such as 1-alpha calcidol or **calcitriol** are ineffective in correcting vitamin D deficiency and may lead to **hypercalcaemia**.
  - In adults with severe malabsorption, or those in whom concordance with oral therapy is suspect, an intramuscular dose of 300,000 IU calciferol monthly for three months followed by the same dose once or twice a year may be considered.
  - Pathological lesions in the bone are characterised by inadequate mineralisation and may take many months to heal. Levels of serum alkaline phosphatase and PTH will start to decline during the first three months of treatment in adults, but may take a year to fall into the reference range.
  - Few adults have truly reversible risk factors for vitamin D deficiency and so lifelong supplementation will be required.
  - Vitamin D is contra-indicated in patients with hypercalcaemia or metastatic calcification. Relative contra-indications include **primary hyperparathyroidism**, **renal stones**, and severe hypercalciuria. [8]
  - Caution is required when prescribing vitamin D for patients also taking certain drugs, including thiazide **diuretics** (which impair calcium excretion) and **digoxin** (enhance the effect of digoxin).

## Monitoring

- Serum calcium concentrations should be checked regularly for a few weeks after starting treatment for vitamin D deficiency and then vitamin D, PTH and calcium concentrations should be checked after 3-4 months of treatment to assess efficacy and adherence to therapy. Vitamin D and calcium concentrations should be checked every 6-12 months. [8]
- Renal disease: 1,25-dihydroxycholecalciferol with response monitored until alkaline phosphatase level returns to normal, when therapy should be reduced to maintenance. **Alfacalcidol** (1-hydroxy derivative of calciferol) can be used in vitamin D deficiency due to renal disease.
- **Renal tubular disorders** and hypophosphataemia: the acidosis needs to be corrected by giving bicarbonate and an adequate phosphate intake of 3-5 g/day. Small doses of 1,25-dihydroxycholecalciferol may also be required.
- Hypocalcaemic tetany requires urgent treatment with intravenous **calcium gluconate** (10 mmol of a 10% solution initially).

Once vitamin D deficiency has been treated, prevention is required to prevent recurrence. This includes correction of any underlying cause, lifestyle advice (diet, sunshine) and often long-term vitamin D supplements:

- Babies aged under 1 year: 200 units (5 micrograms) daily.
- Children aged over 1 year: 280-400 units (7-10 micrograms) daily.
- Adults: 400 units (10 micrograms) daily (more for certain groups, eg those who get no sunshine, elderly, taking anticonvulsant medications, liver or kidney disease).

## Prognosis

- This depends on the underlying cause but the outcome of treatment of vitamin D deficiency is generally very good.
- Treatment of simple deficiency with vitamin D replacement and/or sunlight and correction of predisposing factors should lead to dramatic improvements.
- Rickets and osteomalacia should respond rapidly to vitamin D. Increased mobility with increase in muscle strength may be the first clinical response but there may be a temporary increase in bone pain.
- Some groups (eg those in long-term institutional care) may require long-term maintenance therapy.
- As long as there is no specific resistance to treatment then bone healing often begins within a few weeks of starting treatment and complete healing within six months.

## Prevention

Information about appropriate sunlight exposure, the use of vitamin D supplements, and eating oily fish should be made available to the whole population. [5]

- Education: dietary advice, advice about the importance of sun exposure.
- Either colecalciferol or ergocalciferol can be used to prevent primary vitamin D deficiency. A daily dose of 400 IU (10 micrograms) prevents simple vitamin D deficiency in otherwise healthy adults at risk of deficiency (those adults at high risk of vitamin D deficiency may require higher doses, eg 800 IU daily). [8]
- Early diagnosis and treatment of potential causes such as **intestinal malabsorption** or renal failure.

In February 2012 the Chief Medical Officers for the United Kingdom issued the following recommendations: [15]

- All pregnant and breast-feeding women should take a daily supplement containing 10 micrograms of vitamin D, to ensure the mother's requirements for vitamin D are met and to build adequate fetal stores for early infancy.
- All infants and young children aged 6 months to 5 years should take a daily supplement containing vitamin D in the form of vitamin drops, to help them meet the requirement set for this age group of 7-8.5 micrograms of vitamin D per day. However, those infants who are fed infant formula will not need vitamin drops until they are receiving less than 500ml of infant formula a day, as these products are fortified with vitamin D. Breast-fed infants may need to receive drops containing vitamin D from one month of age if their mother has not taken vitamin D supplements throughout pregnancy.
- People aged 65 years and over and people who are not exposed to much sun should also take a daily supplement containing 10 micrograms of vitamin D.

## Further reading & references

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