Vitamin D deficiency is common in the UK, the prevalence may be increasing and it often goes unrecognised. The authors discuss current vitamin D serum levels used in diagnosis and the recommended treatment of a range of conditions.

Figure 1. Rickets is a sign of severe vitamin D deficiency and is diagnosed in several hundred children in the UK every year.

Vitamin D (calciferol) is a fat-soluble vitamin, the main sources of which are dermal synthesis and fortified foods.

Few foods contain vitamin D (oily fish, cod-liver oil, supplemented breakfast cereals, margarine and infant formula milk, with lesser amounts in egg yolks, liver and mushrooms) such that there is significant risk of deficiency in populations with limited exposure to sunlight. Nutritional rickets is diagnosed in several hundred UK children annually.

Deficiency in adults is common and it often goes unrecognised. In addition to being the cause of nonspecific symptoms and increased fracture risk, low levels of vitamin D have been associated with an increased risk of malignancy. Relationships between vitamin D deficiency and risk of autoimmune disease are also being studied.

Metabolism

In humans >80 per cent of available vitamin D (in the form of D3) is synthesised in the skin from 7-dehydrocholesterol on exposure to ultraviolet radiation (UVB) in sunlight.

The length of exposure to sunlight required to obtain sufficient levels of vitamin D varies depending upon skin type, time of day, season and latitude. It has been estimated that a fair-skinned person would generate 2000IU of vitamin D3 following exposure of the face and forearms for 20–30 minutes, and this two to three times per week would be sufficient. Those with pigmented skin and the elderly would require more exposure.

Unfortunately, for six months of the winter 90 per cent of the UK lies above the latitude that would allow this exposure to UVB.

The diet provides lesser amounts of both vitamin D2 and D3.

Vitamin D from the diet and skin is biologically inactive and
requires enzymatic conversion to its active metabolites (see Figure 2). It is converted to 25-hydroxyvitamin (25OH) D (calcidiol) that is the major circulating form of vitamin D by the 25-hydroxylase enzyme in the liver, and then to 1,25-dihydroxyvitamin (1,25OH) D (calcitriol), the active form of vitamin D, by 1-alpha hydroxylase in renal tubular cells.

One alpha hydroxylase is expressed by other cell types in vitro but 1,25OH-D is absent from the circulation in anephric subjects, indicating the importance of the kidney.

**Actions**

1,25OH-D binds to a nuclear receptor to activate vitamin D response elements within target genes. It promotes enterocyte differentiation and the intestinal absorption of calcium. It also stimulates intestinal phosphate absorption, directly suppresses parathyroid hormone (PTH) release from the parathyroids and regulates osteoblast and osteoclast activity.

These functions play a vital role in the maintenance of normal calcium and phosphate concentrations in the blood and in the mineralisation of newly formed bone. Vitamin D is also thought to have a direct effect on muscle which is relevant in the elderly (see below).

**Diagnosis of vitamin D deficiency**

The clinical features of vitamin D deficiency are nonspecific and include muscle and bone pain and proximal myopathy. Thus a high index of suspicion is required to make this diagnosis.

In practice, measurement of vitamin D concentrations is usually confined to individuals with suggestive biochemistry (low serum calcium and phosphate, raised PTH and, in advanced cases, raised alkaline phosphatase) or those who fall into at-risk categories (see Table 1).

Vitamin D levels are measured by estimation of 25OH-D. Measurements of 1,25OH-D should not be used for this purpose because in vitamin D deficiency one-alpha hydroxylation is promoted by the secondary hyperparathyroidism that occurs.

There is no clear consensus on the optimal level of 25OH-D for skeletal health. The Institute of Medicine (IOM) recommends a serum level above 50nmol per litre (20ng per ml).

Other authorities (The Endocrine Society, The International Osteoporosis Foundation) suggest that a minimum level of 75nmol per litre (30ng per ml) is necessary in older adults to minimise the risk of falls and fracture.5,6

Thus, concentrations between 50 and 75nmol per litre may be insufficient. Serum levels <50nmol per litre certainly indicate deficiency.

Levels below 25nmol per litre represent severe deficiency and may be accompanied by clinical rickets or osteomalacia.
Treatment
The elderly
In the elderly there is a consensus supporting supplementation as standard practice without prior measurement of vitamin D levels. Scottish Intercollegiate Guidelines Network (SIGN) guidelines recommend the housebound elderly receive 1000mg calcium and 800IU of vitamin D daily.7

There are several meta-analyses showing the reduction in falls with treatment in the elderly, especially when baseline vitamin D levels are very low.8 The beneficial effect of vitamin D on muscle is likely to contribute to this.

Long-term treatment with such doses of vitamin D and calcium is used for primary prevention of osteoporotic fracture. Many of the trials of antiresorptive therapies also had patients on calcium and vitamin D.

Pregnancy and breast-feeding
In pregnancy and when breast-feeding 400IU (10g) of vitamin D daily is now recommended as routine.9

Mild to moderate deficiency
Mild to moderate vitamin D deficiency can occur in many settings and can be treated with preparations containing 400–800IU vitamin D with or without calcium.

It should be noted that certain groups of patients need higher doses of vitamin D to achieve the same target levels (obese individuals,10 patients with malabsorption, use of medications affecting vitamin D metabolism: liver enzyme inducers, glucocorticoids).

The factors causing deficiency, particularly lack of exposure to sunlight, often affect whole families, and therefore consideration should be given to screening siblings.

Severe deficiency
In severe deficiency (total serum vitamin D <25nmol per litre) a course of high-dose therapy is required to replenish stores in a reasonable timescale. Endocrine Society guidelines recommend 50 000IU per week of either vitamin D2 or D3 for eight weeks to increase the levels of 25O H-D above 75nmol per litre (30ng per ml).5 This should be followed by maintenance therapy of 1500–2000IU per day, usually indefinitely.

The safety of this regimen is not sufficiently studied in pregnant and lactating women, and there is a concern that high-dose therapy can result in hypercalcaemia in the infant. Hence, a more cautious regimen is adopted in these patients with supplementation of 600–800IU per day.

Other conditions
The management of hypoparathyroidism and some malabsorptive conditions, eg short bowel syndrome following surgery, requires large doses of vitamin D. Malabsorption or chronic liver disease may require 40 000IU per day. The hypocalcaemia of hypoparathyroidism will require doses up to 100 000IU per day to achieve normocalcaemia.

One-alpha hydroxycholecalciferol (alfacalcidol) and calcitriol (1,25O H-D) are most useful in those with chronic renal failure or in type I vitamin D-dependent rickets (due to an inactivating mutation in the 1-hydroxylase gene). Calcitriol is available in capsule form whereas alfacalcidol can be administered both orally and parenterally.

Dangerous levels of hypercalcaemia can occur, particularly with alfacalcidol, if the dose is not appropriately titrated or with declining renal function over time. Some authorities recommend regular monitoring of serum calcium levels in patients treated with one-alpha hydroxylated vitamin D metabolites.

In patients with vitamin D deficiency and co-existing primary hyperparathyroidism, there has been no clear consensus until

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Table 1. Risk factors for and indicators of possible vitamin D deficiency

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<th>Risk Factor</th>
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<td>• individuals with limited sun exposure due to concealing clothing, particularly if dark skinned</td>
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<td>• obesity (BMI &gt;30)</td>
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<td>• vegetarian (no fish) diet</td>
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<td>• elderly individuals with history of falls: fractures following minimal trauma are particularly suggestive</td>
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<td>• institutionalised individuals</td>
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<td>• pregnant and lactating women</td>
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<td>• exclusive breast feeding</td>
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<td>• medications that accelerate the metabolism of vitamin D: liver enzyme inducers (eg anticonvulsants, rifampicin, antiretroviral therapy, glucocorticoids)</td>
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<td>• malabsorption due to small bowel disease: inflammatory bowel disease, coeliac disease, radiation enteritis, bariatric surgery, short bowel syndrome following surgery</td>
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<td>• pancreatic disease: chronic pancreatitis, cystic fibrosis, pancreatectomy</td>
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<tr>
<td>• chronic kidney disease</td>
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<td>• chronic liver disease</td>
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<td>• osteoporosis</td>
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recently with regards to the replenishment of vitamin D.

The 3rd International Workshop on Asymptomatic Primary Hyperparathyroidism recommended measuring 25OHD in all patients with primary hyperparathyroidism and repleted those with low levels (<50nmol per litre, 20ng per ml). Close monitoring of these patients when on vitamin D therapy is required.

There is no clear consensus on whether vitamin D treatment might reduce cancer risk. Vitamin D is antiproliferative, thus calcitriol (Silkis), calcipotriol and tacalcitol (Curatoderm) are used topically in the treatment of psoriasis.

**Available preparations**

Repletion of vitamin D can be achieved using either ergocalciferol (vitamin D2) or colecalciferol (vitamin D3).

Many preparations – flavoured, effervescent, chewable – are available in which vitamin D3 400–800IU is combined with calcium. Calcium is often not needed and in some cases makes preparations unpalatable.

Desunin tablets and Fultium-D3 capsules contain 800IU vitamin D3. Vitamin D 25µg (1000IU) tablets are available without prescription from Boots.

For larger doses, Dekristol tablets containing 20 000IU have been used but are not licensed and available only on special order. Ergocalciferol (D2) tablets containing 10 000 and 50 000IU are listed but difficult to obtain. Parenteral ergocalciferol 300 000IU per ml is available.

One-alpha hydroxylated vitamin D (alfacalcidol) and calcitriol, used primarily in chronic renal disease, are not appropriate for patients with simple vitamin D deficiency and can cause hypercalcaemia as described above.

**Conclusion**

Vitamin D deficiency is common and the prevalence may be increasing. There has been controversy over what serum level indicates deficiency but it seems that, unless oily fish are consumed twice weekly or there is regular sun exposure, a majority of UK adults will have some degree of vitamin D deficiency.

It has been suggested that the public health response to this has been inadequate, although the precise consequences of mild deficiency remain uncertain.

The UK national recommendation of an intake of 400IU (10g) per day is sufficient to prevent osteomalacia and rickets but may not be adequate for optimum health.

Higher-dose therapeutic preparations have been difficult to obtain but are clearly required in some clinical situations.

**References**


**Declaration of interests**

None to declare.

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