Vitamin D deficiency
Diagnosis and management of vitamin D deficiency

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Rickets in children and osteomalacia in adults are the classic manifestations of profound vitamin D deficiency. In recent years, however, non-musculoskeletal conditions—including cancer, metabolic syndrome, infectious and autoimmune disorders—have also been found to be associated with low vitamin D levels. The spectrum of these common disorders is of particular concern because observational studies have demonstrated that vitamin D insufficiency is widespread in many northern regions of the world, including industrialised countries. The increasing prevalence of disorders linked to vitamin D deficiency is reflected in the several hundred children with rickets treated each year in the UK. However, these children represent a small proportion of the individuals with a suboptimal vitamin D status in the UK population.

A recent nationwide survey in the United Kingdom 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 survey also demonstrated a gradient of prevalence across the UK, with highest rates in Scotland, northern England, and Northern Ireland. People with pigmented skin are at high risk, as are the elderly; obese individuals; those with malabsorption, short bowel, renal or liver disease; and individuals taking anticonvulsants, rifampicin, or highly active antiretroviral drugs.

In this article we discuss the diagnosis and management of vitamin D insufficiency and deficiency in children and adults according to evidence from descriptive and observational studies, randomised trials, and meta-analyses.

**Box 1| Sources of vitamin D**

- Ultraviolet B sunlight exposure
- >90% of human kind’s vitamin D supply is derived from ultraviolet B light
- Oily fish including trout, salmon, mackerel, herring, sardines, anchovies, pilchards, and fresh tuna
- Amount will depend on preparation, with smoked herring containing approximately 4 µg (160 IU) per 100 g and raw herring 40 µg (1600 IU) per 100 g
- Cod liver oil and other fish oils
- Egg yolks
  - 0.5 µg (20 IU) per yolk
- Mushrooms
  - Small quantities
- Supplemented breakfast cereals, mainly supermarket “own brands” in the UK
- Typically between 2 µg and 8 µg (80-320 IU) per 100 g
- Margarine and infant formula milk
- Statutory supplementation in the UK

**What are the sources of vitamin D?**

Vitamin D refers to the precursors of the active secosteroid hormone 1,25-dihydroxyvitamin D₃ (1,25-OH₃ D₃), also known as calcitriol. The major natural source of vitamin D is from skin photosynthesis following ultraviolet B solar irradiation (box 1).

In a fair skinned person, 20 minutes to 30 minutes of sunlight exposure on the face and forearms at midday is estimated to generate the equivalent of around 2000 IU of vitamin D. Two or three such sunlight exposures a week are sufficient to achieve healthy vitamin D levels in summer.

**Table 1| Serum 25-hydroxyvitamin D concentrations, health, and disease**

<table>
<thead>
<tr>
<th>Serum 25-OH concentration*</th>
<th>Vitamin D status</th>
<th>Manifestation</th>
<th>Management</th>
</tr>
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<tbody>
<tr>
<td>&lt;25 nmol/l</td>
<td>Deficient</td>
<td>Rickets</td>
<td>Treat with high-dose calciferol</td>
</tr>
<tr>
<td>25-50 nmol/l</td>
<td>Associated with disease risk</td>
<td>Osteomalacia</td>
<td>Vitamin D supplementation</td>
</tr>
<tr>
<td>50-75 nmol/l</td>
<td>Adequate</td>
<td>Healthy</td>
<td>Lifestyle advice</td>
</tr>
<tr>
<td>&gt;75 nmol/l</td>
<td>Optimal</td>
<td>Healthy</td>
<td>None</td>
</tr>
</tbody>
</table>

*To convert to µg/l divide by 2.5.
in the UK. For individuals with pigmented skin and, to a lesser extent, the elderly, exposure time or frequency need to be increased twofold to 10-fold to get the same level of vitamin D synthesis as fair skinned young individuals.\(^5\)\(^6\)\(^7\) Unfortunately, for six months of the year (October to April), all of Scandinavia, much of western Europe (including 90% of the UK), and 50% of the North American landmass lies above the latitude that permits exposure to the ultraviolet B wavelengths necessary for vitamin D synthesis,\(^8\)\(^9\) leaving millions of people reliant on exogenous sources of vitamin D.

Given this periodic lack of photosynthesis at high latitudes, vitamin D is also a micronutrient. Only a relatively small number of foods contain substantial amounts of vitamin D, the most significant dietary sources being oily fish and cod liver oil.\(^7\) The farmed fish that is commonly consumed in the UK may have less vitamin D content than wild fish.\(^8\)\(^9\) Egg yolk, liver, and wild mushrooms contain small quantities of vitamin D. The amount in most vegetable sources is negligible.

The recommended daily intake of vitamin D in the UK is 400 IU (10 µg) per day for an adult, 280 IU (7 µg) for children aged between 6 months and 3 years, and 340 IU (8.5 µg) per day for infants under 6 months.\(^7\) However, these recommendations only provide sufficient vitamin D to prevent osteomalacia and rickets,\(^4\) and such an intake alone, in the absence of skin synthesis, will not provide optimal status. Accordingly, several learned bodies have recently increased their recommendations for vitamin D intake.\(^8\)\(^9\)

Food supplementation policies differ considerably between countries. Milk is widely fortified, but in the UK only infant formula milk and margarine have statutory vitamin D supplementation (1-2.5 µg (40-100 IU) per 100 kCal and 8 µg (320 IU) per 100 g, respectively). Thus, the typical UK diet, and that of many other countries, is profoundly lacking in vitamin D. A low dietary vitamin D intake, combined with the lack of skin synthesis for half of the year, is reflected in the disturbingly high prevalence of vitamin D insufficiency across the UK.\(^1\)\(^2\)

### How can vitamin D deficiency and insufficiency be determined?

Vitamin D status is most reliably determined by assay of serum 25-hydroxyvitamin D (25-OHD). Individuals with symptomatic osteomalacia or rickets have serum 25-OHD concentrations of less than 25 nmol/l (10 µg/l), reflecting profound vitamin D deficiency (table 1). A much larger proportion of the UK population (about 50% in spring) have vitamin D insufficiency, with serum 25-OHD concentrations between 25 nmol/l and 50 nmol/l (10-20 µg/l).\(^1\)\(^2\)

Several observational studies have shown that vitamin D insufficiency, although not enough to cause symptomatic bone and muscle disease, is associated with an increased risk of mortality\(^10\)\(^11\) and of several common diseases including cardiovascular disease,\(^12\)\(^13\) type 2 diabetes,\(^14\) bowel cancer, breast cancer,\(^14\)\(^15\) multiple sclerosis,\(^16\) and type 1 diabetes\(^17\) (table 2). An expert consensus is developing that optimal vitamin D status, reflected by optimal calcium handling and best health, is when serum concentrations of 25-OHD are 75 nmol/l (30 µg/l) or more.\(^18\)\(^19\) Serum 25-OHD has a circulating half life of two to three weeks, but levels are regularly replenished from fat stores.

Circulating active vitamin D (1,25-dihydroxyvitamin D, or calcitriol) has a short half life and is closely linked to parathyroid hormone production. Serum levels of calcitriol do not reflect vitamin D status and should not be measured unless abnormalities of vitamin D metabolism are suspected.

### Table 2 | Evidence for association of circulating 25-hydroxyvitamin D level or vitamin D supplementation with major health outcomes

| Type 1 | Ziptis and Akobeng, 2008\(^18\) | Meta-analysis of four case-control studies of vitamin D supplementation | 6455 | Supplemented v un-supplemented | OR 0.71 (0.60 to 0.84) |
| Type 2 | Pittas et al, 2007\(^14\) | Meta-analysis of four observational studies | 6784 (non-black) | Serum 25-OHD concentration 63-95 nmol/l v 25-58 nmol/l | OR 0.36 (0.16 to 0.80) |
| Breast | | | | | | |
Infants exclusively breast fed, particularly beyond six months of age, are at increased risk because the vitamin D content of breast milk will not meet their requirements. Delayed introduction of solid food, picky eating habits, and poor diet also raise the risk.

The Department of Health recommends daily supplemental vitamin D drops containing 400 IU of calciferol for all infants and preschool children, and this view is endorsed by the European Society for Paediatric Endocrinology. Supplementation is particularly important for infants in the north of the UK, those with darker skin pigmentation, and fussy eaters.

Weaning foods frequently contain low quantities of calcium, and nutritional rickets (as a consequence of calcium and not vitamin D deficiency) has been reported in children with adequate levels of 25-OH D. Such findings reinforce the importance of focusing on the calcium content of a child’s diet in addition to vitamin D status.

Who is at risk of vitamin D insufficiency and deficiency?

At northern latitudes, the major risk factor for D insufficiency and deficiency at all ages is pigmented skin (box 2). This is also a key risk factor in sunnier climates such as Australia, where a large case series has demonstrated an increasing incidence of vitamin D deficiency in young people. This report and many European case series of children with vitamin D deficiency over the last 20 years have consisted primarily of immigrant children or first generation offspring of immigrant parents with dark skin. In a recent report from Denmark, however, half of very young patients with nutritional rickets were ethnic Europeans.

Sunscreen with a sun protection factor 15 or more blocks more than 99% of dermal vitamin D synthesis. Strict adherence to use of sunscreens when outdoors, or the use of a veil, headscarf, or other concealing clothing, places individuals with fair skin at similar risk of vitamin D deficiency to those with pigmented skin. Elderly and institutionalised individuals are at risk because of the relatively large amount of time such people spend indoors, as well as a reduced dermal capacity to generate vitamin D.

Numerous case series and some experimental studies highlight the fact that vitamin D deficiency may be present at birth, with neonatal and infant vitamin D status dependent upon maternal vitamin D status. Multiparity, short spacing between pregnancies, and non-white maternal skin are major risk factors for vitamin D deficiency.

Box 4 | Treatment of vitamin D deficiency and insufficiency

<table>
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<tr>
<th>Deficiency (25-OH D &lt;25 nmol/l)</th>
<th>Adult</th>
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<tr>
<td></td>
<td>10 000 IU calciferol daily or 60 000 IU calciferol weekly for 8-12 weeks* or</td>
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<td>Calciferol 300 000 or 600 000 IU orally or by intramuscular injection once or twice</td>
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<table>
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<tr>
<th>Insufficiency (25-OH D 25-50 nmol/l) or maintenance therapy following deficiency</th>
<th>Adult</th>
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<tbody>
<tr>
<td></td>
<td>1 000-2000 IU calciferol daily or</td>
</tr>
<tr>
<td></td>
<td>10 000 IU calciferol weekly</td>
</tr>
<tr>
<td>Child</td>
<td>Under 6 months: 200-400 IU calciferol daily†</td>
</tr>
<tr>
<td></td>
<td>Over 6 months: 400-800 IU calciferol daily*</td>
</tr>
</tbody>
</table>

*To convert IU to µg of calciferol, divide by 40. †One off high dose treatments are effective, but should be followed by a maintenance therapy dose of calciferol. ‡200 IU may be inadequate for breastfed babies with low vitamin D stores at birth.
Height is usually affected more profoundly than weight. An increased susceptibility to infections and respiratory symptoms in children with vitamin D deficiency may be a manifestation of “rachitic lung,” where respiratory function is compromised by a pliable rib cage and muscle weakness. Severe vitamin D deficiency can result in cardiomyopathy and potentially fatal heart failure.

Adults

Pain and proximal muscle weakness dominate the clinical picture of vitamin D deficiency in adults. 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 and may be labelled as “fibromyalgia” or as a somatisation of depression. Low bone density on dual energy x ray absorptiometry scanning, or osteopenia on plain radiography, may also reflect osteomalacia, and these findings warrant assessment of vitamin D status.

What investigations are necessary?

Children

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. Blood can be taken in primary care for measurement of levels of calcium, phosphate, alkaline phosphatase, and serum 25-OHD, which is the most robust marker for vitamin D status (table 1). Haemoglobin levels should also be measured because iron deficiency anaemia frequently coexists with rickets. Parathyroid hormone concentrations are typically elevated in neonates and young infants with vitamin D deficiency, but may be within the reference range.

If there is diagnostic uncertainty—because of atypical clinical manifestations, a lack of risk factors, atypical biochemistry, focal pain, or asymmetrical deformity—then radiographs should be arranged to confirm rickets. In addition, a small number of children have hereditary or renal rickets. These rarer diagnoses need to be considered in the absence of known risk factors, in the presence of atypical biochemistry (for example, persistent hypophosphataemia, normal alkaline phosphatase, or elevated creatinine), and in children who fail to reduce alkaline phosphatase levels or respond clinically following vitamin D treatment. Referral for specialist assessment is appropriate in these circumstances.

The clinician must be vigilant for a secondary cause of vitamin D deficiency in both children and adults, such as covert coeliac disease or cystic fibrosis causing malabsorption.

Adults

More than 80% of adults with osteomalacia have a high concentration of serum alkaline phosphatase. Hypocalcaemia and hypophosphataemia are less consistently present, depending on the severity and chronicity of the disease and the patient’s dietary calcium intake. Elevation of plasma parathyroid hormone—secondary hyperparathyroidism—is typical of osteomalacia but is not found in about 20% of adults with vitamin D insufficiency. It is good practice to image areas of focal pain in adults, particularly if they persist or worsen during treatment (suggesting bony metastases).

UNANSWERED QUESTIONS

- How much does vitamin D insufficiency contribute to north/south health inequality in the UK?
- Would eradication of vitamin D insufficiency in the UK reduce cancer incidence and improve cancer outcomes?
- Does poor vitamin D status cause obesity, or is it a consequence of obesity?
- Are individuals genetically susceptible to vitamin D insufficiency or toxicity?

ONGOING RESEARCH

More than 150 clinical trials of vitamin D are listed on ClinicalTrials.gov. Some key trials include:
- The ViTAm in D and omegA-3 Trial (VITAL)
- A study of colecalf erol 2000 IU daily, fish oil, or placebo in 20 000 older individuals (65+ yrs), with cardiovascular disease and cancer incidence as outcomes.
- Vitamin D and Calcium Homeostasis for Prevention of Type 2 Diabetes (CaDDM) (NCT00436475)
- Treatment of vitamin D insufficiency: does vitamin D increase calcium absorption, bone mass and muscle mass and function in women past menopause who have mildly low vitamin D levels? (NCT00933244)
- Evaluation of vitamin D requirements during pregnancy (NCT00292591)
- Development of vitamin D as a therapy for breast cancer—phase II (NCT00656019)
- Vitamin D supplement in preventing colon cancer in African Americans with colon polyps (NCT00879061)
- Health benefits of vitamin D and calcium in women with PCOS (polycystic ovarian syndrome) (NCT00743574)
- Vitamin D3 supplementation and the T cell compartment in multiple sclerosis (MS) (NCT0094719)

How should rickets and osteomalacia be treated?

Children

Oral calciferol in the bioequivalent forms of either ergocalciferol (yeast derived vitamin D₃) or colecalf erol (fish or lanolin derived vitamin D₃) is the treatment of choice for children with rickets. The principal aim of therapy is to replenish vitamin D stores; patients are then continued on a lower maintenance dose. Large bolus doses are also equally effective. Tablet, capsule, or oily suspensions of calciferol are available.

Children aged less than 1 year should be treated with 3000 IU of calciferol daily, increasing to 6000 IU daily after 1 year of age (box 4). Calcium supplementation (50 mg/kg a day) is advisable during the first weeks of therapy in the growing child. 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. At a minimum, a maintenance dose of calciferol is recommended for other family members.

Adults

Calciferol has a high therapeutic index. It has been estimated that a regular daily dose of 1000 IU raises serum 25-OHD by 25 nmol/L; however, vitamin D toxicity occurs
at 25-OHD values above 500 nmol/L. In adults, calciferol treatment, in a daily dose of 10000 IU or a weekly dose of 60 000 IU, will lead to restoration of body stores of vitamin D over eight to 12 weeks. Thereafter, a maintenance dose of 1000–2000 IU calciferol daily or 10 000 IU weekly is adequate. Short acting, potent vitamin D analogues such as 1–25 calcidiol or calcitriol are ineffective in correcting vitamin D deficiency and may lead to hypercalcaemia. Clinicians should avoid giving combined calcium and vitamin D preparations in the long term because the calcium component is usually unnecessary, makes for unpalatability, and reduces concordance. 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 is an alternative treatment approach. Pathological lesions in the bone are characterised by undermineralisation and may take many months to heal. Levels of serum alkaline phosphatase and parathyroid hormone will start to decline during the first three months of treatment in adults, but may take a year to fall into the reference range. Given that few adults have truly reversible risk factors for vitamin D deficiency, the assumption should be that supplementation will be needed life long, or life long during winter months (dependent upon latitude and dress habits).

How should moderate vitamin D insufficiency be managed?

From a public health perspective, primary prevention of vitamin D deficiency in a country such as the UK is socially as well as medically justifiable. The key groups for healthcare professionals to target are infants, children, adolescents, and pregnant women, particularly those with dark skin. Many individuals of non-white ancestry living in the Midlands and north of the UK are at particularly high risk of vitamin D insufficiency (including doctors). Most elderly and institutionalised people in other areas of the UK are also at high risk. Fair skinned people who eat oily fish twice weekly or who get regular suberythematosunlight exposure through outdoor work or leisure activity may have adequate vitamin D status; most other fair skinned people will be vitamin D insufficient, particularly in the winter and spring.

Given the clear and mounting evidence of the substantial disease burden associated with moderate vitamin D insufficiency (table 2), information about appropriate sunlight exposure, the use of vitamin D supplements, and eating oily fish should be made available to the whole population. In particular, health visitors and midwives can implement current Department of Health recommendations by distributing children’s vitamin drops, which should be universally available through Healthy Start, Sure Start, and similar government schemes. Furthermore, we believe that a more robust approach to statutory food supplementation with vitamin D (for example, in milk) is needed in the UK, as this measure has already been introduced successfully in many other countries at similar latitude.

Conclusions

Vitamin D deficiency and insufficiency are common in the UK. Health professionals have been slow to respond to this problem even though the issue has been highlighted in the literature for a number of years. Rickets and osteomalacia are entirely preventable diseases that are becoming increasingly common in the UK population, and vitamin D insufficiency now seems unequivocally linked to several other common and morbid conditions. Local initiatives have been implemented to address this issue, but the high number of patients presenting with symptomatic vitamin D insufficiency highlights the fact that we have some way to go. A change in UK public health policy is long overdue.

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References

A congenital anomaly in a preterm newborn

1. The Apgar score consists of the following items, each of which can be scored 0, 1, or 2 points: heart rate; respiratory effort; muscle tone; reflex irritability; and colour.
2. Oesophageal atresia can be seen on the chest radiograph (figure). The radio-opaque nasogastric tube is curled up in a blind, dilated upper oesophageal pouch.
3. A double lumen catheter (“Replique suction catheter”) should be placed in the upper oesophageal pouch to suction secretions and prevent their aspiration. Administration of parenteral nutrition and fluid replacement should be initiated. Surgical repair of the oesophageal atresia and ligation of any associated tracheo-oesophageal fistula is indicated.
4. The majority of associated anomalies involve one or more of the components that constitute VACTERL association: vertebral anomalies, anorectal atresia or stenosis, cardiovascular defects, tracheo-oesophageal atresia, renal defects, and limb abnormalities.
5. The umbilical catheter was, unintentionally, positioned in an umbilical artery, which is not the preferred route for administration of parenteral nutrition.

Annotated chest and abdominal radiograph. (A) Nasogastric tube curled up in a blind, dilated upper oesophageal pouch. (B) Fingers of the nurse holding the patient. (C) Cardiorespiratory monitoring electrodes. (D) Holes in the incubator roof. (E) Air in the digestive tract. (F) Arterial umbilical catheter

Diagnostic difficulties with a lipaemic blood sample

1. The suspected diagnosis is acute pancreatitis secondary to hypertriglyceridaemia.
2. Hypertriglyceridaemia interferes with the serum amylase assay and can produce a falsely low result—serum amylase can seem to be within normal limits despite clinical and radiological evidence of acute pancreatitis.
3. Urine amylase to creatinine ratio can be measured to diagnose acute pancreatitis, and the result of this test is less likely to be affected by hypertriglyceridaemia. Alternatives are the removal of lipids before serum amylase measurement by using ultracentrifugation.
4. This patient has ongoing severe epigastric pain and a computed tomography scan of the abdomen (considered the “gold standard” test in the diagnosis of acute pancreatitis) should be organised.