Box 1 | Sources of vitamin D

- Ultraviolet B sunlight exposure
  >90% of humankind’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 yolk
  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-di-hydroxyvitamin D₃ (1,25-OH₂D₃), 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 sufficient to achieve healthy vitamin D levels in summer.
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.\textsuperscript{6} \textsuperscript{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,\textsuperscript{8} 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.\textsuperscript{7} The farmed fish that is commonly consumed in the UK may have less vitamin D content than wild fish.\textsuperscript{8} 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.\textsuperscript{1} However, these recommendations only provide sufficient vitamin D to prevent osteomalacia and rickets,\textsuperscript{2} 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.\textsuperscript{3} \textsuperscript{4}

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.\textsuperscript{1,\textsuperscript{3}}

**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).\textsuperscript{1,\textsuperscript{5}}

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\textsuperscript{10-13} and of several common diseases including cardiovascular disease,\textsuperscript{11-13} type 2 diabetes,\textsuperscript{16} bowel cancer, breast cancer,\textsuperscript{15-16} multiple sclerosis,\textsuperscript{17} and type 1 diabetes\textsuperscript{18} (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.\textsuperscript{8-9} 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

<table>
<thead>
<tr>
<th>All cause mortality</th>
<th>Number of</th>
<th>Comparator</th>
<th>Odds/hazard ratio or relative risk(\times) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autier and Gandini, 2007\textsuperscript{10}</td>
<td>Meta-analysis of 18 vitamin D supplementation studies</td>
<td>57 311</td>
<td>Supplemented v unsupplemented</td>
</tr>
<tr>
<td>Ginde et al, 2009\textsuperscript{11}</td>
<td>Prospective observational study in individuals ≥65 years*</td>
<td>3265</td>
<td>Serum 25-OHD concentration &gt;100 nmol/l v 25-95 nmol/l</td>
</tr>
<tr>
<td>Dobning et al, 2008\textsuperscript{12}</td>
<td>Prospective cohort study with coronary angiography†</td>
<td>3258</td>
<td>Median serum 25-OHD concentration 70 nmol/l v 19 nmol/l</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ginde et al, 2009\textsuperscript{11}</td>
<td>Prospective observational study in individuals ≥65 years*</td>
<td>3265</td>
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<td>3258</td>
<td>Median serum 25-OHD concentration 70 nmol/l v 19 nmol/l</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>Zipitis and Akobeng, 2008\textsuperscript{14}</td>
<td>Meta-analysis of four case-control studies of vitamin D supplementation</td>
<td>6455</td>
</tr>
<tr>
<td>Type 2</td>
<td>Pittas et al, 2007\textsuperscript{15}</td>
<td>Meta-analysis of four observational studies</td>
<td>6784 (non-black)</td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>Yin et al, 2009\textsuperscript{16}</td>
<td>Meta-analysis of six case-control studies</td>
<td>3556</td>
</tr>
</tbody>
</table>

Breast
Box 2 | Risk factors for vitamin D insufficiency and deficiency

- Pigmented skin (non-white ethnicity)
- Lack of sunlight exposure or atmospheric pollution
- Skin concealing garments or strict sunscreen use
- Exclusively breast fed
- Multiparous, short interval pregnancies
- Elderly, obese, or institutionalised
- Vegetarian (or other non-fish eating) diet
- Malabsorption, short bowel, or cholestatic liver disease
- Use of anticonvulsants, rifampicin, cholestyramine, highly active antiretroviral treatment (HAART), or glucocorticoids

Box 3 | Preparations of calciferol available in the UK

**Solutions and drops**
- Dalivit (LPC Pharmaceuticals Ltd, Luton, Bedfordshire)*
  - Colecalciferol 400 IU per 0.6 ml
- Abidec (Chefaro UK, Huntingdon, Cambridgeshire)*
  - Colecalciferol 400 IU per 0.6 ml
- Healthy Start vitamin drops*
  - Colecalciferol 300 IU per 5 drops
- Ergocalciferol oily solution
  - 3000 IU/ml

**Tablets and capsules**
- Calcium and vitamin D (400 mg calcium and 400 IU ergocalciferol)
- Colecalciferol 20 000 IU (Dekristol; MIBE, Brehna, Germany)
- Ergocalciferol 10 000 IU or 50 000 IU (UCB Pharma, Slough, Berkshire)

**Parenteral**
- Ergocalciferol 300 000 IU per ml

*Multivitamin preparations; not suitable for prolonged high dose therapy owing to the risk of vitamin A toxicity.
†Other ergocalciferol and colecalciferol preparations are available off prescription.

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.20 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 children have vitamin D deficiency,21 and this view is endorsed by the European Society for Paediatric Endocrinology.22 Supplementation is particularly important for infants in the north of the UK, those with darker skin pigmentation, and fussy eaters.23

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.22 Delayed introduction of solid food, fussy eating habits, and poor diet also raise the risk.

The Department of Health recommends daily supplementary vitamin drops containing 400 IU of calciferol for all infants and preschool children.21 and this view is endorsed by the European Society for Paediatric Endocrinology.24 Supplementation is particularly important for infants in the north of the UK, those with darker skin pigmentation, and fussy eaters.23

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-OHD.25 Such findings reinforce the importance of focusing on the calcium content of a child’s diet in addition to vitamin D status.26

How do patients with vitamin D deficiency present?

Children

Severe vitamin D deficiency may cause hypocalcaemic seizures or tetany, particularly in the neonatal period and again during the phase of rapid growth in adolescence. From the age of 6 months, children with vitamin D deficiency commonly 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 (craniofaci).25 Children with vitamin D deficiency may be irritable and reluctant to weight bear, and manifest impaired growth.21,22

Box 4 | Treatment of vitamin D deficiency and insufficiency

**Deficiency (25-OHD <25 nmol/l)**

**Adult**
- 10 000 IU calciferol daily or 60 000 IU calciferol weekly for 8-12 weeks*
- or
- Calciferol 300 000 or 600 000 IU orally or by intramuscular injection once or twice

**Child**
- Under 6 months: 3000 IU calciferol daily for 8-12 weeks
- Over 6 months: 6000 IU calciferol daily for 8-12 weeks or
- Over 1 year: 300 000 IU calciferol, as a one off high dose therapy (Stoss regimen)*

**Insufficiency (25-OHD 25-50 nmol/l) or maintenance therapy following deficiency**

**Adult**
- 1000-2000 IU calciferol daily
- or
- 10 000 IU calciferol weekly

**Child**
- Under 6 months: 200-400 IU calciferol daily
- Over 6 months: 400-800 IU calciferol daily

*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.\textsuperscript{21} 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.\textsuperscript{20} Severe vitamin D deficiency can result in cardiomyopathy and potentially fatal heart failure.\textsuperscript{21}

**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.\textsuperscript{26} 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.\textsuperscript{412} 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 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).\textsuperscript{22}

**How should rickets and osteomalacia be treated?**

**Children**

Oral calciferol in the bioequivalent forms of either ergocalciferol (yeast derived vitamin D\textsubscript{2}) or colecalciferol (fish or lanolin derived vitamin D\textsubscript{3}) is the treatment of choice for children with rickets.\textsuperscript{9,23,27} The principal aims 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 (box 3).

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).\textsuperscript{22,24} Calcium supplementation (50 mg/kg a day) is advisable during the first weeks of therapy in the growing child.\textsuperscript{22,20} A maintenance dose of 400 IU calciferol daily is appropriate for a child of any age.\textsuperscript{22} 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.\textsuperscript{9} 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\textsuperscript{25}; however, vitamin D toxicity occurs
at 25-OHD values above 500 nmol/L. In 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 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-α calcidol 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 health-care 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 suberythematosus sunlight 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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**PICTURE QUIZ**

**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 (“Replogle 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.

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**CASE REPORT**

**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.