Background
Vitamin D compounds are fat soluble sterols which are essential for the absorption and utilisation of calcium and phosphorus (in the form of inorganic phosphate) in the body to maintain normal calcification of the skeleton and bone mineralisation. Along with parathyroid hormone (PTH) the active form of vitamin D (25 – OHD) regulates serum calcium concentration by altering serum calcium and inorganic phosphate blood levels as needed. It maintains neuromuscular function and various other cellular processes, including the immune system and insulin production.

Recommended daily intake
All UK Health Departments recommend:

- **All** pregnant and breastfeeding women should take a daily supplement containing 10 micrograms of vitamin D, to ensure that the mother’s requirements for vitamin D are met and to build adequate foetal 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 these requirements; Infants under 6 months 340 IU (8.5 micrograms) daily and 6 months – 5 years 280 IU (7 micrograms) daily. **NB:** Infants being 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. Breastfed 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.
- **Adults/adolescents** who are not exposed to much sun should also take a daily supplement containing 400 IU (10 micrograms).

The major natural source of vitamin D is from skin photosynthesis following ultraviolet B sunlight exposure. Over 90% of the body’s vitamin D is produced from the action of sunlight on the skin. Small amounts of vitamin D are also obtained from oily fish, egg yolks, mushrooms, fortified breakfast cereals, milk and margarine.

Risks factors for vitamin D deficiency
Vitamin D deficiency develops when there is inadequate exposure to sunlight or a lack of vitamin D in the diet and usually takes a long time to develop because of the slow release of the vitamin from body stores. Prolonged vitamin D deficiency in infants and children results in rickets. Less severe vitamin D deficiency (usually referred to as vitamin D insufficiency) is often associated with secondary hyperparathyroidism and increased bone loss, leading to high risk of fractures.

The Chief Medical Officer (CMO) has issued advice on vitamin D supplementation for people at risk of vitamin D deficiency. Risk factors for reduced vitamin D levels include:

- Dark/pigments skin colour e.g. black, Asian populations
- Routine use of sun protection factor 15 and above as this blocks 99% of vitamin D synthesis.
- Reduced skin exposure e.g. cultural reasons (clothing)
- Latitude (In the UK, there is no radiation of appropriate wavelength between October and March)
- Chronic ill health with prolonged hospital admissions e.g. oncology patients
- Children and adolescents with disabilities which limit the time they spend outside
- Institutionalised individuals
- Photosensitive skin conditions
- Reduced vitamin D intake
- Maternal vitamin D deficiency
- Infants that are exclusively breast fed
- Dietary habits – low intake of foods containing vitamin D
- Abnormal vitamin D metabolism, abnormal gut function, malabsorption or short bowel syndrome
- Chronic liver or renal disease
• Medicines including rifampicin, isoniazid and anti-convulsants e.g. phenytoin and carbamazepine, glucocorticoids and highly active anti-retroviral treatment.
• Genetic variation.  

**Indications for measurement of vitamin D**

**Symptoms and signs of rickets/osteomalacia**
- Progressive bowing deformity of legs
- Waddling gait
- Abnormal knock knee deformity (intermalleolar distance > 5 cm)
- Swelling of wrists and costochondral junctions (rachitic rosary)
- Prolonged bone pain (>3 months duration)

**Symptoms and signs of muscle weakness**
- Delayed walking
- Difficulty climbing stairs
- Cardiomyopathy in an infant

**Abnormal bone profile or x-rays**
- Low plasma calcium or phosphate
- Raised alkaline phosphatase
- Osteopenia or changes of rickets on x-ray
- Pathological fractures

**Disorders impacting on vitamin D metabolism**
- Chronic renal failure
- Chronic liver disease
- Malabsorption syndromes, for example, cystic fibrosis, Crohn’s disease, coeliac disease
- Older anticonvulsants, for example, phenobarbitone, phenytoin, carbamazepine

**Children with bone disease in whom correcting vitamin D deficiency prior to specific treatment would be indicated**
- Osteogenesis imperfecta
- Idiopathic juvenile osteoporosis
- Osteoporosis secondary to glucocorticoids, inflammatory disorders, immobility

**Measurement of vitamin D**

Confirmation of vitamin D deficiency is by measurement of serum levels of 25 – OHD, which is the main circulating form of vitamin D (also known as calcidiol).

There is no agreed definition for vitamin D deficiency. A plasma concentration of <25 nanomol/L for 25-OHD levels has been used as the lower limit of adequacy of vitamin D status i.e. deficiency. There is no consensus on optimal levels of serum 25 – OHD, some experts suggest that a desirable 25 – OHD concentration is > 75 nanomol/l. Insufficiency falls between deficient and desirable levels. There are no defined limits, so insufficiency can be quoted as any of the following: 25 – 50 nanomol/l, 25 – 75 nanomol/l or > 35 nanomol/l.

**Vitamin D levels, effects on health and management of deficiency**

<table>
<thead>
<tr>
<th>Serum 25 – (OH) D concentration level</th>
<th>Vitamin D status</th>
<th>Manifestation</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 25 nmol/l (10 micrograms/l)</td>
<td>Deficient</td>
<td>Rickets, osteomalacia</td>
<td>Treat with high dose vitamin D</td>
</tr>
<tr>
<td>25 – 50 nmol/l (10 – 20 micrograms/l)</td>
<td>Insufficient</td>
<td>Associated with disease risk</td>
<td>Vitamin D supplementation OTC – Not to be prescribed</td>
</tr>
<tr>
<td>50 – 75 nmol/l (20 – 30 micrograms/l)</td>
<td>Adequate</td>
<td>Healthy</td>
<td>Lifestyle advice</td>
</tr>
<tr>
<td>&gt; 75 nmol/l (30 micrograms/l)</td>
<td>Optimal</td>
<td>Healthy</td>
<td>None</td>
</tr>
</tbody>
</table>
Flowchart for children with suspected Vitamin D deficiency

Does the child have any risk factors or symptoms?
- No
  - No investigations required
  - Lifestyle advice

- Yes
  - Risk Factors Only
    - Children under the age of 5 years: Lifestyle advice* and vitamin D supplementation**. Purchase OTC or via Healthy Start
      - Under 1 year: 200 units vitamin D once daily
      - 1 - 4 years: 400 units vitamin D once daily
    - Under 1 year: 200 units vitamin D once daily
    - 1 - 4 years: 400 units vitamin D once daily
    - Children 5 years and over – offer lifestyle advice
  - Risk Factors AND Symptoms/Signs
    - Lifestyle advice*
    - Investigations
    - Therapeutic intervention
    - Arrange Investigations
      - Renal function, Calcium, Phosphate, Magnesium (infants), Alkaline phosphatase, 25-OH Vitamin D levels, Urea and electrolytes. Parathyroid hormone.

Does the patient meet all the criteria for management in Primary Care?
- No significant renal impairment
- Normal calcium (If <2.1 mmol/l in infants refer as risk of seizures)
- Any other abnormal results of concern
- Yes
  - Management of insufficiency (25-OHD 25 – 50 nmol/L)
    (Patients to purchase OTC, not to be prescribed) or maintenance therapy following treatment for deficiency (prescribe on FP10)
      - Lifestyle advice* and vitamin D supplementation*
        - < 6 months: 200 – 400 units daily ±
        - Over 6 months – 18 years: 400 – 800 units daily
        ± 200 units may be inadequate for breastfed babies.

- Treatment of deficiency (25 - OHD < 25 nmol/L)
  - Prescribe on FP10
  - Lifestyle advice* AND vitamin D (ideally colecalciferol)*
    - 0 - 6 months: 3,000 units daily
    - 6 months – 12 yrs: 6,000 units daily
    - 12 – 18 yrs: 10,000 units daily
  - Course length is 8 – 12 weeks followed by maintenance therapy.

  - If any issues are encountered with compliance, consideration should be given for referral to Secondary care, as a high dose Stoss regimen may be appropriate.

- Further assessment is required consider referral to specialist.
  - See criteria for referral to secondary care specialist.

* Lifestyle advice – refer to Appendix 1

**Vitamin D formulations – refer to Appendix 2
• Criteria for management in primary care not met
• Deficiency established with absence of known risk factors
• Atypical biochemistry (persistent hypophosphataemia, elevated creatinine)
• Failure to reduce alkaline phosphatase levels within 3 months
• Family history (parent, siblings) with severe rickets
• Infants under one month with calcium <2.1mmol/l at diagnosis as risk of seizure
  Check vitamin D level of mothers in this group immediately and treat, particularly if breast feeding.
• If compliance issues are anticipated or encountered during treatment.
• Satisfactory levels of vitamin D not achieved after initial treatment.

Contraindications
• Hypercalcaemia
• Evidence of vitamin D toxicity
• Metastatic calcification

Adverse effects
If the recommended doses are adhered to side effects are rare. Side effects are generally associated with excessive intake of Vitamin D leading to the development of raised levels of calcium and phosphate in plasma. The symptoms of hypercalcaemia include anorexia, nausea and vomiting, headache, dry mouth, fatigue, muscle weakness, lassitude, diarrhoea or constipation, weight loss, polyuria, sweating, vertigo.

Interactions
• Magnesium-containing antacids: hypermagnesaemia may develop in patients on chronic renal dialysis
• Digitalis glycosides: hypercalcaemia in patients on digitalis may precipitate cardiac arrhythmias
• Anti-convulsants: vitamin D requirements may be increased in patients taking anti-convulsants (e.g. carbamazepine, phenobarbital, phenytoin and primidone)

Checking of levels
As Vitamin D has a relatively long half-life levels will take approximately 6 months to reach a steady state after a loading dose or on maintenance therapy. Check serum calcium levels at 3 months and 6 months, and 25 – OHD repeat at 6 months. Review the need for maintenance treatment. If the treatment is initiated by the GP, it is also their responsibility to ensure that levels are measured. For patients who fall into the criteria for referral to secondary care, or where treatment is initiated by a hospital Consultant, it is the responsibility of the Consultant to ensure that levels are measured.

<table>
<thead>
<tr>
<th>Serum 25 OHD after 3 months treatment</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 80 nmol/mL</td>
<td>Recommend OTC prophylaxis and lifestyle advice. Review need for further treatment after 6 months.</td>
</tr>
<tr>
<td>50 - 80 nmol/mL</td>
<td>Continue with current treatment dose and reassess in 3 months.</td>
</tr>
<tr>
<td>&lt; 50 nmol/mL</td>
<td>Increase dose or, in case of non-adherence/concern refer to secondary care.</td>
</tr>
</tbody>
</table>

Relapse prevention
To prevent relapse, preventative measures should be taken long term after pharmacological treatment of deficiency. During April-September sunlight advice should be followed (please see Appendix 1)

Outside these months consider:
• Children: multivitamin drops (Abidec® / Dalvit®) as detailed above. For those at risk and under the age of 5 years a dose of 0.6ml once daily is advisable (Under 1 year 0.3ml). This should be purchased OTC.
Appendix 1
Lifestyle Advice

- **Sunlight**
  Exposure of face, arms and legs for 5-10 mins (15-25 mins if dark pigmented skin) would provide good source of Vitamin D. In the UK April to September between 11am and 3pm will provide the best source of UVB. Application of sunscreen will reduce the Vitamin D synthesis by >95%. Advise to avoid sunscreen for the first 20-30 minutes of sunlight exposure. Persons wearing traditional black clothing can be advised to have sunlight exposure of face, arms and legs in the privacy of their garden.

- **Diet**
  Vitamin D can be obtained from dietary sources (salmon, mackerel, tuna, egg yolk) fortified foods (cow, soy or rice milk) and supplements. There are no plant sources that provide a significant amount of Vitamin D naturally.

Appendix 2
Available Products and Supplements:
- There are currently a number of supply issues surrounding Vitamin D preparations, with the limited number of licensed preparations available being confined to high strength injections for treatment of adult deficiency and oral vitamin drops for paediatric insufficiency. However these may be difficult to obtain
- Licensed products should be used where available; however, unlicensed or special products may be suitable following proper consideration of potentially increased risks associated with such medicines as well as what may be substantial costs
- Vitamin D supplements can be bought from pharmacies, health food shops and on the internet by patients in dosages ranging from 400 units up to 1000 units per tablet/capsule.
- Some patients also wish to avoid gelatin which is used in some available preparations
- Colecalciferol (Vitamin D₃) is the preparation of choice as it is the natural vitamin in humans

Calcium and vitamin D preparations e.g. Adcal D₃ tablets 600mg calcium and 400 units colecalciferol. Unsuitable for treating vitamin D deficiency because they contain sub-therapeutic quantities of vitamin D and may also result in hypercalcaemia. They may be used for prophylaxis for vitamin D deficiency if calcium supplements are also required.

Vitamin D preparations

Doses of vitamin D are expressed in ‘units’ of antirachitic activity: 400 units = 10 micrograms.

Colecalciferol (D₃) and ergocalciferol (D₂) are the main dietary sources sources of vitamin D and can be used for prophylaxis and treatment. Doses are equivalent, however for indications other routine supplementation/prophylaxis, ideally ergocalciferol should only be prescribed if colecalciferol is unavailable, as colecalciferol is more effective at raising serum 25-OHD levels.

Alfacalcidol and calcitriol (1,25(OH)₂ vitamin D) are not suitable for the management of nutritional rickets and vitamin D deficiency as they can cause hypercalcaemia and do not correct the deficiency. These preparations should be reserved for patients with severe renal or hepatic impairment.

Other vitamin D preparations are available but it is important to check the constituents with manufacturer as some contain peanut oil.
<table>
<thead>
<tr>
<th>Preparations, manufacturers and distributors</th>
<th>Cost (BNF list price or from the manufacturer)</th>
<th>Availability as of January 2013</th>
<th>Licensing and risk considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Liquid preparations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy Start vitamin drops. Multivitamin preparation containing colecalciferol 300 units per 5 drops.</td>
<td></td>
<td></td>
<td>Free of charge for patients eligible for the Government’s Healthy Start scheme. Supply outlets can be identified using the Healthy Start website <a href="http://www.healthystart.nhs.uk">www.healthystart.nhs.uk</a></td>
</tr>
<tr>
<td>Liquids containing 400 units/0.6ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dalivit® multivitamin drops containing <strong>400 units colecalciferol per 0.6ml</strong> Available via normal wholesaling routes</td>
<td>25ml £2.98 50ml £4.85</td>
<td>Available</td>
<td>Product has a UK marketing authorisation. Recommended in patients with peanut allergies. Dalivit® contains plant source of Vitamin D₂ - suitable for vegetarians, orthodox Jews, practicing Hindus / Muslims if keen to avoid animal source.</td>
</tr>
<tr>
<td>Abidec® multivitamin drops containing <strong>400 units ergocalciferol per 0.6ml</strong> Available via normal wholesaling routes (contains Arachis oil) 25ml</td>
<td>£2.20</td>
<td>Available</td>
<td>Product has a UK marketing authorisation. Contains arachis oil; avoid in peanut allergy. (Abidec® contains peanut oil)</td>
</tr>
<tr>
<td>Liquids containing 3,000 units/ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colecalciferol liquid 3000 iu/ml. 100ml. Unopened expiry 18 months. No opened expiry. Available from Sterling Pharmaceuticals (0121 446 6113)</td>
<td>100ml £18.10</td>
<td>Available</td>
<td>Unlicensed product  Sugar free, lactose free, alcohol free. Suitable for vegetarians and vegans. Does not contain peanut oil.</td>
</tr>
<tr>
<td>Liquid containing 10,000 units/ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zymad® (colecalciferol) drops 10,000 IU/ml. Each drop contains 300 units. Available from IDIS (01932 824 100) 10ml 3 month expiry after opening</td>
<td>£4.14</td>
<td>Available</td>
<td>Does not have UK marketing authorisation Manufactured in Novartis, France</td>
</tr>
<tr>
<td><strong>Capsules</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fultium D₃® capsules 800 units of colecalciferol.</td>
<td>Available Used at NGH</td>
<td>Licensed in UK for children &gt; 12 years. Contains peanut oil Should be swallowed whole not chewed.</td>
<td></td>
</tr>
</tbody>
</table>

Table adapted from: Vitamin D Deficiency and insufficiency, using appropriate available products, January 2011, East and South East England Specialist Pharmacy Services.
References


