Model guidance
Prevention, investigation and treatment of vitamin D deficiency and insufficiency

This document includes the following:
- Model pathway for treating vitamin D deficiency and insufficiency in adults
- Section 1: Background
- Section 2: Prevention of vitamin D deficiency in at-risk groups
- Section 3: Investigation and treatment of vitamin D deficiency and insufficiency in adults

This model guidance does not apply to patients with osteoporosis.
Where patients are under the care of a specialist, clinicians may like to seek advice.

Document history:
This work is supported by a scoping report on vitamin D completed by the KSS HPSU and builds on guidance documents developed by KSS and other PCTs.

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Main changes/comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1</td>
<td>22 October 2012</td>
<td>First draft</td>
</tr>
<tr>
<td>V2</td>
<td>29 October 2012</td>
<td>Incorporated comments from medicines management</td>
</tr>
<tr>
<td>V3</td>
<td>6 February 2013</td>
<td>Incorporated comments from local clinicians</td>
</tr>
<tr>
<td>FINAL</td>
<td>15 February 2013</td>
<td>Incorporated additional comments from medicines management</td>
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</tbody>
</table>

These guidelines have been reassessed by The Surrey Rheumatology Network in July 2013 in light of the recent published National Osteoporosis Society – Vitamin D and Bone Health: A Practical Clinical Guideline for Patient Management http://www.nos.org.uk/document.doc?id=1352
The Network discussed the national guidance and recommend to the Prescribing Clinical Network that the current KSS model guidance used should be retained.
This was discussed at the PCN in July 2013 who supported the recommendation from the rheumatology network to remain with the current Vitamin D guidance produced by KSS HPSU.
Model pathway for treating vitamin D deficiency and insufficiency in adults

1. **Does the patient have a risk factor for vitamin D deficiency?**
   - **No**: No further action required
   - **Yes**: Does the patient have at least one symptom suggesting vitamin D deficiency?

2. **Does the patient have at least one symptom suggesting vitamin D deficiency?**
   - **No**: Lifestyle advice, Recommend OTC supplements*
   - **Yes**: Have other causes for symptoms been excluded?

3. **Have other causes for symptoms been excluded?**
   - **No**: Manage primary diagnosis
   - **Yes**: Test 25-hydroxyvitamin D (25[OH]D) status

   **If 25-hydroxyvitamin D < 25 nmol/L**
   - Prescribe a high dose vitamin D preparation for 12 weeks
   - Still symptomatic following 12 weeks treatment?
     - **No**: Vitamin D insufficiency (25-50 nmol/L)
     - **Yes**: Discuss concordance, Repeat 25(OH)D test, Refer non-responsive patients to secondary care

   **If 25-hydroxyvitamin D 25-50 nmol/L**
   - Lifestyle advice, Recommend OTC supplements*

*Ensure patients who are eligible for the Healthy Start Scheme are aware they can obtain vitamin supplements free of charge.
Section 1: Background

The role of vitamin D

Vitamin D is essential for the absorption and utilisation of calcium and phosphorus in the body, both of which are necessary to maintain normal calcification of the skeleton and bone mineralization\(^1\). Vitamin D maintains neuromuscular function and various other cellular processes, including the immune system and insulin production\(^1\). The main manifestation of vitamin D deficiency is rickets in children and osteomalacia in adults\(^2\). Sun exposure is the main source of vitamin D, however it is also found in some foods and supplements.

Sources of vitamin D

Sun exposure

The main source of vitamin D is usually considered to be skin photosynthesis following ultraviolet B sunlight exposure\(^3\). Environmental and personal factors greatly affect vitamin D production in the skin, making it difficult to recommend a one-size-fits-all level of exposure for the general population\(^4\). However, the best estimates suggest that for most people, everyday casual exposure to sunlight is enough to produce vitamin D in the summer months\(^4\). It has been suggested that during the summer, two or three exposures (of at least the face and arms without sunscreen and not behind glass) of 20 to 30 minutes between 10am and 3pm each week should provide adequate amounts of vitamin D for most individuals\(^5\). However this may not be sufficient for some groups who require increased exposure time or frequency to get the same level of vitamin D synthesis, for example those with heavily pigmented skin and the elderly. Studies have consistently shown that vitamin D can be efficiently and sufficiently produced at doses of UV below those which cause sunburn\(^4\).

Dietary sources

Vitamin D is found in a small number of foods including\(^3,6\):

- oily fish, such as herring, mackerel, salmon, tuna, and sardines
- red meat, such as liver\(^7\)
- egg yolk
- mushrooms
- fortified foods including fat spreads, breakfast cereals and infant formula

\(^1\) Liver is also a rich source of vitamin A; consumption should therefore be limited to once a week to avoid toxicity and avoided entirely during pregnancy.
The potential contribution of diet to vitamin D supply is a topic of debate, however the general view is that it is difficult to get adequate levels of vitamin D from diet alone and the main source is skin synthesis on exposure to sunlight⁴.

**Supplements**

Vitamin D is present in a range of unlicensed dietary supplements and licensed medicines, which can help to boost vitamin D levels. Oral supplements are available as either ergocalciferol (calciferol, vitamin D2) or colecalciferol (vitamin D3). There is also an intramuscular ergocalciferol preparation. High doses of oral vitamin D supplements have been shown to have toxic effects. However, the threshold dose at which regular use becomes harmful is unclear³.

**Recommended daily intake**

In the UK, a recommended daily intake of vitamin D has not been set for individuals leading a normal lifestyle where they are exposed to solar radiation. For adults aged over 65, and pregnant and lactating women the reference nutrient intake (RNI) is 10µg per day⁷. The RNI for infants aged 0 to 6 months is 8.5µg per day, and for children aged 7 months to 3 years it is 7µg per day⁷.

**Implications and prevalence of vitamin D deficiency**

**Implications of vitamin D deficiency**

Vitamin D is essential for good bone health. Deficiency of vitamin D results in rickets in children and osteomalacia in adults; conditions characterised by pathological defects in growth plate and bone matrix mineralization³. Patients with osteomalacia often complain of multiple symptoms including bone, joint and muscle pain, hyperalgesia, muscle weakness and a waddling gait². In children failure of bone mineralization gives rise to bone deformities; bones are painful and linear growth is reduced³. Low vitamin D levels are associated with secondary hyperparathyroidism and low bone mineral density and, thus, a higher risk of fractures⁴. Some studies have suggested that low vitamin D levels are associated with an increased risk of certain cancers and other chronic diseases, however evidence of causal associations are yet to be demonstrated⁴.

**Prevalence**

The National Diet and Nutrition Survey of British adults⁸ indicates that up to a quarter of people in the UK have low levels of vitamin D in their blood, which means they are at-risk of the clinical consequences of vitamin D deficiency⁹. Seasonal variations in vitamin D status are observed in the UK; levels are highest between July and September and lowest between January and March³.
Factors affecting vitamin D status

Factors that potentially affect vitamin D status include\textsuperscript{3,6}:

- genetic factors
- adiposity
- factors affecting cutaneous synthesis of vitamin D such as:
  - skin pigmentation and ethnicity
  - age
  - season and latitude
  - melanin concentration
  - clothing and use of sunscreens
  - atmospheric pollution
  - ability to spend time outdoors
- medical conditions:
  - malabsorption or short bowel syndrome
  - cholestatic liver disease
  - chronic kidney disease
- medications:
  - some anticonvulsants e.g. carbamazepine
  - rifampicin
  - cholestyramine
  - glucocorticoids
  - HAART therapy
Section 2: Prevention of vitamin D deficiency in at-risk groups

The Department of Health (DH)\(^9\) recommends at-risk groups should take vitamin D supplements as per Table 1.

Table 1 – DH recommendations for preventing vitamin D deficiency in at-risk groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Recommended supplementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant women</td>
<td>Daily supplement containing 10 micrograms of vitamin D to build adequate fetal stores for early infancy</td>
</tr>
<tr>
<td>Breastfeeding women</td>
<td>Daily supplement containing 10 micrograms of vitamin D</td>
</tr>
<tr>
<td>Infants and young children</td>
<td>Infants and young children aged between 6 months and 5 years of age 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 vitamin D per day. However 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. 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.</td>
</tr>
<tr>
<td>People aged 65 years and over</td>
<td>Daily supplement containing 10 micrograms of vitamin D</td>
</tr>
<tr>
<td>People who have low or no exposure to the sun</td>
<td>Daily supplement containing 10 micrograms of vitamin D</td>
</tr>
</tbody>
</table>

Women and children from families who are eligible for the Government’s Healthy Start scheme can get free vitamin supplements including vitamin D in the form of tablets for women and drops for children\(^9\). For further information on who qualifies for the scheme and where they can obtain vitamin supplements see www.healthystart.nhs.uk.

Individuals who do not qualify for the Healthy Start scheme should be advised to purchase vitamin D supplements at the appropriate strength.
Section 3: Investigation and treatment of vitamin D deficiency and insufficiency in adults

It is worthwhile providing all patients with risk factors – even those not exhibiting symptoms – with lifestyle advice in order for them to make changes where appropriate.

Indications for testing vitamin D status

Routine testing of vitamin D levels in at-risk groups should not be undertaken\(^2\).

Vitamin D deficiency should be considered and checked where patients have:

- one or more risk factor for vitamin D deficiency **AND**
- clinical features of vitamin D deficiency **AND**
- other causes for symptoms have been excluded

See Table 3 for examples of risk factors and clinical features of vitamin D deficiency and other causes for symptoms that should be excluded – these are not exhaustive lists and should not be treated as such. Table 2 sets out tests that may be carried out when vitamin D deficiency is suspected.

Table 2 – Tests that may be carried out when vitamin D deficiency is suspected\(^2,5,10\)

<table>
<thead>
<tr>
<th>Test</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaline phosphatase (ALP) and phosphate</td>
<td>Hypophosphatemia may indicate long standing vitamin D deficiency</td>
</tr>
<tr>
<td>C-reactive protein (CRP)</td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>To exclude hypercalcaemia and provide a baseline for monitoring</td>
</tr>
<tr>
<td>Creatine kinase (CK)</td>
<td>Raised CK with non-specific myalgia indicates vitamin D deficiency</td>
</tr>
<tr>
<td>Full blood count (FBC)</td>
<td>Anaemia may be present if there is malabsorption</td>
</tr>
<tr>
<td>Liver function tests</td>
<td>To exclude hepatic failure</td>
</tr>
<tr>
<td>Parathyroid hormone (PTH)(^ii)</td>
<td>Vitamin D deficiency can lead to secondary hyperparathyroidism</td>
</tr>
<tr>
<td>Renal function</td>
<td>To exclude renal failure</td>
</tr>
<tr>
<td>Urea &amp; electrolytes (U&amp;E)</td>
<td></td>
</tr>
</tbody>
</table>

\(^ii\) Phlebotomy needs to take place at the site where the assay is processed because the blood test for PTH is unstable.
Table 3 – Risk factors and clinical features of vitamin D deficiency in adults and other causes for symptoms that should be excluded

<table>
<thead>
<tr>
<th>Risk factors of vitamin D deficiency in adults&lt;sup&gt;5, 9&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant and breastfeeding women, especially teenagers and younger women</td>
</tr>
<tr>
<td>People aged 65 years and over</td>
</tr>
<tr>
<td>People who have low or no exposure to the sun, for example those who cover their skin for cultural reasons, who are housebound or confined indoors for long periods</td>
</tr>
<tr>
<td>People who have darker skin, for example people of African, African-Caribbean and South Asian origin</td>
</tr>
<tr>
<td>Obese people (BMI&gt;30)</td>
</tr>
<tr>
<td>Diet that restricts the major food sources of vitamin D</td>
</tr>
<tr>
<td>Family history of vitamin D deficiency / osteomalacia</td>
</tr>
<tr>
<td>Liver or renal disease</td>
</tr>
<tr>
<td>Intestinal malabsorption or short bowel</td>
</tr>
<tr>
<td>Multiple, short interval pregnancies</td>
</tr>
<tr>
<td>Taking anticonvulsants, cholestyramine, rifampicin, glucocorticoids, or antiretrovirals</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical features of vitamin D deficiency in adults&lt;sup&gt;5, 6,10&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insidious onset, widespread or localised bone pain or tenderness without preceding mechanical injury</td>
</tr>
<tr>
<td>Proximal muscle weakness or muscle aches</td>
</tr>
<tr>
<td>Swelling, tenderness and redness at pseudo-fracture sites</td>
</tr>
<tr>
<td>Insufficiency fractures / fragility fracture</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Possible causes for symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercalcaemia</td>
</tr>
<tr>
<td>Metastatic calcification</td>
</tr>
<tr>
<td>Renal stones (calculi)</td>
</tr>
<tr>
<td>Severe hypercalciuria</td>
</tr>
<tr>
<td>Stage 4 chronic kidney disease or eGFR &lt;30ml/minute</td>
</tr>
<tr>
<td>Primary hyperparathyroidism</td>
</tr>
<tr>
<td>Low bone mineral density</td>
</tr>
<tr>
<td>PMR / myositis (morning stiffness)</td>
</tr>
<tr>
<td>Myeloma</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Polymyalgia rheumatica</td>
</tr>
</tbody>
</table>

<sup>iii</sup> These are no exhaustive lists and should not be treated as such
Assessing vitamin D status

Assay of 25-hydroxyvitamin D (25[OH]D) should be undertaken to assess vitamin D status.

There is no universal consensus on the criteria for vitamin D deficiency\(^2\). Thresholds outlined in Table 4\(^iv\) are consistent with the current DH guidelines\(^11\).

### Table 4 – Serum 25-hydroxyvitamin D concentrations, health and disease

<table>
<thead>
<tr>
<th>25(OH)D concentration</th>
<th>Vitamin D status</th>
<th>Manifestation</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25 nmol/L</td>
<td>Deficient</td>
<td>Rickets, osteomalacia</td>
<td>Treat with high dose calciferol</td>
</tr>
<tr>
<td>25-50 nmol/L</td>
<td>Insufficient</td>
<td>Associated with risk of disease</td>
<td>Advise OTC vitamin D supplementation</td>
</tr>
</tbody>
</table>

Adapted from Pearce & Cheetham (2010)\(^5\)

There is no agreement on optimal 25(OH)D levels\(^12\).

**Treating vitamin D deficiency (25(OH)D <25 nmol/L)**

Patients with vitamin D deficiency should be treated with high-dose vitamin D.

Colecalciferol (vitamin D3) is considered preferable to ergocalciferol (vitamin D2) because the former raises vitamin D levels more effectively and has a longer duration of action\(^2\).

Unlicensed preparations have variable availability and are potentially costly therefore licensed oral products may be preferable, for example:
- Fultium\(^®\) 800 IU 4 capsules daily for 12 weeks (note: contains peanut oil)
- Desunin\(^®\) 800 IU up to 5 tablets daily for 12 weeks

Oral administration of vitamin D is recommended in most cases\(^2\); injections should be reserved for patients with malabsorption due to high cost and availability issues.

Treatment for deficiency will be for a maximum of 12 weeks before review; it is recommended therefore to avoid putting vitamin D onto repeat prescriptions.

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iv Alternative thresholds for vitamin deficiency have been suggested. For example, recent guidelines recommend defining deficiency as a 25(OH)D <50 nmol/L (Endocrine Society Task Force\(^13\)) or <30 nmol/L (National Osteoporosis Society\(^2\)). The DH Scientific Advisory Committee on Nutrition is currently reviewing the evidence and new advice is due to be issued next year.
Monitoring following treatment for vitamin D deficiency
Serum calcium should be checked one month after starting treatment for vitamin D deficiency to allow detection of subclinical primary hyperparathyroidism.²

Routine monitoring of serum 25(OH)D is unnecessary but may be appropriate 12 weeks following commencement of treatment where patients are still symptomatic, have malabsorption, or where poor concordance is suspected². Patients who do not respond after 12 weeks of treatment may be considered for referral to secondary care.¹⁴

Maintenance following treatment for vitamin D deficiency
Colecalciferol at a dose of 1,000 to 2,000 IU daily⁵ may be required once deficiency has been corrected for those patients who are still considered at-risk. In some cases this may be lifelong therapy. Patients who were previously prescribed AdcalD3 or equivalent can continue treatment with this preparation where appropriate. Calcium replete patients should be advised to purchase appropriate vitamin D supplements over the counter (OTC). Lifestyle advice should also be provided.

Treating insufficiency (25(OH)D 25-50 nmol/L)
In contrast to treating vitamin D deficiency, there is no good evidence to demonstrate that treating vitamin D insufficiency leads to improved clinical outcomes. Therefore it is recommended that patients are given lifestyle advice and are advised to purchasing OTC coleccalciferol at a dose of 1,000 to 2,000 IU daily⁵.

Cautions
The information provided below does not replace the necessity to refer to the summary of product characteristics and patient information leaflet provided by the manufacturer.

Contraindications
Contraindications include¹⁰,¹⁵,¹⁶:
- Hypersensitivity to vitamin D or any of the excipients in the product
- Hypervitaminosis D
- Nephrolithiasis
- Diseases or conditions resulting in hypercalcaemia and/or hypercalciuria
- Severe renal impairment
- Metastatic calcification
**Drug interactions**

Drug interactions are as follows\textsuperscript{15,16}:

- Concomitant treatment with phenytoin or barbiturates can decrease the effect of vitamin D because of metabolic activation.
- Concomitant use of glucocorticoids can decrease the effect of vitamin D.
- The effects of digitalis and other cardiac glycosides may be accentuated with the oral administration of calcium combined with vitamin D. Strict medical supervision is needed and, if necessary, monitoring of ECG and calcium.
- Thiazide diuretics reduce the urinary excretion of calcium. Due to the increased risk of hypercalcaemia, serum calcium should be regularly monitored during concomitant use of thiazide diuretics.
- Simultaneous treatment with ion exchange resins such as cholestyramine or laxatives such as paraffin oil may reduce the gastrointestinal absorption of vitamin D.
- The cytotoxic agent actinomycin and imidazole antifungal agents interfere with vitamin D activity by inhibiting the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D by the kidney enzyme, 25-hydroxyvitamin D-1-hydroxylase.
- Patients should avoid taking vitamin D at the same time of day as orlistat as this reduces absorption.

**Vitamin D toxicity**

Vitamin D toxicity is rarely seen\textsuperscript{2} however if toxicity is suspected, vitamin D should be withdrawn and serum calcium and renal function checked urgently\textsuperscript{10}. Early signs of toxicity include symptoms of hypercalcaemia such as thirst, polyuria and constipation\textsuperscript{10}.

**Specialist advice**

Where patients are under the care of a specialist, clinicians may like to seek advice.
References


[16] SPC Fultium-D3 800IU capsules, online: http://www.medicines.org.uk/emc/medicine/25664/SPC

Acknowledgements
