**PREVENTION, INVESTIGATION & TREATMENT OF VITAMIN D INSUFFICIENCY & DEFICIENCY IN ADULTS**

**Background**

- Vitamin D is essential for the absorption & utilisation of calcium and phosphorus in the body, both of which are necessary to maintain normal calcification of the skeleton & bone mineralization
- Vitamin D maintains neuromuscular function & various other cellular processes, including the immune system & insulin production
- Sun exposure is the main source of vitamin D, although it is also found in some foods & supplements. Vitamin D₃ (cholecalciferol) synthesised in skin through the action of UVB on cholesterol
- Greatest production in April - September in the UK:
  - Fair skinned individuals 20-30 minutes exposure of face & forearms between 10am & 3pm produces 2,000 IU vitamin D
  - Exposed 2-3x week produces healthy levels in the summer in the UK. Use of sunbeds is not recommended
  - Others (dark skinned, elderly) may need 2-10x this amount
  - Minimum erythema dose in a swimming costume produces 20,000 iu
- Converted to 25-OH vitamin D in liver - this is major storage form & what is measured in the majority of chemical pathology laboratories
- Vitamin D₃ is present in the diet, mainly in oily fish (trout, salmon, mackerel, herring, sardines, pilchards & tuna) but constitutes a maximum 20% of the daily requirement. Absorption is aided by fat, so vitamin D should be taken with meals
- Vitamin D₂ (ergocalciferol) is plant derived & has a shorter half life. Vitamin D₃ is superior to vitamin D₂ in achieving optimal levels

**To reduce vitamin D level testing and avoid long term prescribing of vitamin D supplements**

Public Health England advises that:

- In spring and summer, the majority of the population get enough vitamin D through sunlight on the skin and a healthy, balanced diet.
- During autumn and winter, everyone will need to rely on dietary sources of vitamin D.
- Since it is difficult for people to meet the 10 microgram recommendation from consuming foods naturally containing or fortified with vitamin D, people should consider taking a daily supplement containing 10 micrograms of vitamin D in autumn and winter.
- People whose skin has little or no exposure to the sun, like those in institutions such as care homes, or who always cover their skin when outside, risk vitamin D deficiency and need to take a supplement throughout the year.
- Ethnic minority groups with dark skin, from African, Afro-Caribbean and South Asian backgrounds, may not get enough vitamin D from sunlight in the summer and therefore should consider taking a supplement all year round.

Based on the information above, if vitamin D deficiency is suspected, treatment should be commenced **without** checking vitamin D levels.
Recommended levels

- Optimal bone health is achieved when vitamin D is >60nmol/L. This is needed to reduce rate of fracture. Supplementation of >800IU per day lowers risk of non-vertebral & hip fracture.

- A level >60nmol/L optimal to reduce the risk of falls. Supplementation with 700-1000 iu/day reduces falls by 20% in the elderly.

- 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.

- Recommended (UK Department of Health) daily intake 400iu/day (10μg) for an adult (child 6 months to 3 years 280iu/day [7μg/day], <6 months 340iu/day [8.5μg/day]).

- Recommendations for pregnant women & children can be found via the Department of Health website (www.dh.gov.uk) and the governments Healthy Start scheme (www.healthystart.nhs.uk).

- Average vitamin D requirement to achieve vitamin D 75nmol/l is 800-1,000/day.

Dietary sources

Vitamin D is found in a small number of foods including:

- oily fish, such as herring, mackerel, salmon, tuna & sardines
- red meat, such as liver (caution: high vitamin A content, so avoid in pregnancy)
- egg yolk
- mushrooms
- fortified foods including fat spreads, breakfast cereals & infant formula

Typical quantities found in these foods are given in the table below:

<table>
<thead>
<tr>
<th>Food</th>
<th>Vitamin D Content</th>
<th>Serving Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild salmon</td>
<td>600-2,000 iu D₃</td>
<td>per 3.5oz serving</td>
</tr>
<tr>
<td>Farmed salmon</td>
<td>100-200 iu D₂/D₃</td>
<td>per 3.5oz serving</td>
</tr>
<tr>
<td>Tinned salmon</td>
<td>300-600 iu D₃</td>
<td>per 3.5oz serving</td>
</tr>
<tr>
<td>Sardine, Mackerel, Tuna</td>
<td>250 iu D₃</td>
<td>per 3.5oz serving</td>
</tr>
<tr>
<td>Egg yolk</td>
<td>20 iu D₂/D₃</td>
<td>per yolk</td>
</tr>
<tr>
<td>Supplemented breakfast cereals</td>
<td>80-320 iu</td>
<td>per 100g</td>
</tr>
</tbody>
</table>

Dietary advice in vegetarians & vegans is probably better obtained via a Dietician.

Dietary reference ranges for calcium & vitamin D are available from the Institute of Medicine at the National Academies of Sciences in the US:

Implications & prevalence of vitamin D deficiency/insufficiency

- Vitamin D is essential for good bone health. Deficiency of vitamin D results in rickets in children and osteomalacia in adults. These are characterised by pathological defects in growth plate & bone matrix mineralization.
- Patients with osteomalacia often complain of multiple symptoms including bone, joint and muscle pain, hyperalgesia, muscle weakness & may develop a waddling gait.
- In children failure of bone mineralization gives rise to bone deformities; bones are painful & linear growth is reduced.
- Low vitamin D levels are associated with secondary hyperparathyroidism, low bone mineral density & therefore a higher risk of fracture.
- Some studies have suggested that low vitamin D levels are associated with an increased risk of certain cancers, such as bowel & breast, and chronic autoimmune diseases such as SLE, RA, type 1 diabetes & MS; however, evidence of causal associations are yet to be demonstrated.
- Low vitamin D levels may also be a risk factor for falls due to impaired neuromuscular function.

Risk Factors for Vitamin D Deficiency include:

- Inadequate UV light exposure
  - Northern latitude
  - Air pollution
  - Clothing (including hats and head garments)
  - Pigmented skin
  - Sunscreen (factor 15 & above, including some types of make-up)
  - Institution/Housebound
- Poor oral intake
  - Vegetarian/vegan
  - Malabsorption e.g. coeliac disease
  - Cholestatic liver disease
  - Cholestyramine
  - Bypass surgery
- Metabolic risk
  - Reduced synthesis
    - Elderly, liver disease
  - Increased breakdown
    - Drugs - anticonvulsants, glucocorticoids, rifampicin, HAART
    - Increased urinary loss - nephrotic syndrome
  - Reduced stores
    - Liver disease e.g. cirrhosis
    - Multiple short interval pregnancies

The National Diet & Nutrition Survey of British adults indicates that up to a quarter of people in the UK have low serum levels of vitamin D, which means they are at-risk of the clinical consequences of vitamin D deficiency.

Seasonal variations in vitamin D status are observed in the UK; levels are highest between July & September and lowest between January & March.
UK Prevalence:

- <25nmol/L: 16%
- <40nmol/L: 47%
- <75nmol/L: 87%

British Caucasian Adults (gradient North to South)

30% of men and 32.5% women over 65 years living in institutions

**Prevention of vitamin D deficiency in at-risk groups**

The Department of Health (DH) recommends at-risk groups should take vitamin D supplements as indicated in the table below:

<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 & drops for children. For further information on who qualifies for the scheme and where they can obtain vitamin supplements see [www.healthystart.nhs.uk](http://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.

**Investigation of vitamin D deficiency**

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.

Routine testing of vitamin D levels in at-risk groups is not recommended. However, vitamin D deficiency should be considered & measured 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
Possible indications for measurement of serum vitamin D levels include:

- Fragility fracture despite adequate treatment
- Fragility fracture <60 years
- In patients with osteoporosis starting IV bisphosphonates/denosumab
- Malabsorption e.g. coeliac disease (measure at least annually)
- Proximal myopathy and other relevant symptoms or signs of osteomalacia
- Patients with recurrent falls
- CKD stage 4 or 5
- Chronic musculoskeletal pain syndromes e.g. fibromyalgia (controversial)
- Systemic autoimmune disease e.g. SLE (measure at least annually)
- On bone modifying medication
  - Steroids (including high dose inhaled), anticonvulsants, aromatase inhibitors, HAART, cholestyramine, rifampicin

Interpretation (Remember optimum vitamin D level in Autumn):

Normal range 25-OH vit D at WSHFT: 70-200nmol/l (conversion factor µg/l x 2.5 =nmol/l)

<table>
<thead>
<tr>
<th>&lt;30 nmol/l</th>
<th>Deficiency: high dose treatment followed by long term maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-70 nmol/l</td>
<td>Insufficiency: Advise OTC vitamin D supplements &amp; give lifestyle advice</td>
</tr>
<tr>
<td>70-200 nmol/l</td>
<td>Replete</td>
</tr>
</tbody>
</table>

(These levels may differ from those specified by other CCG’s, but have been agreed on the advice of WSHfT Consultant Rheumatologists.)

Investigations:

Consider the following investigations in patients with true deficiency (<30nmol/l):

- FBC/ferritin/folate/B12 (iron deficiency commonly co-exists)
- U&Es (to exclude CKD)
- LFTs (to exclude hepatic failure)
- Serum intact PTH (must be analysed within 4 hours)
- Bone profile (Calcium, Phosphate, alkaline phosphatase)
- Anti-TTG or other coeliac antibodies (if hypocalcaemia, folate or iron deficient)

Treatment in adults

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 & has a longer duration of action

- Treatment relatively contraindicated if eGFR <30mL/min, history of calcium containing stones, hypercalcaemia; sarcoidosis
- Vitamin D levels plateau at 3 months
- Smaller response to treatment are seen with higher starting levels & in those with a higher BMI
- Vitamin D levels decrease with age but response to treatment does not vary
- Dietary calcium intake does not alter the response to vitamin D supplementation
• 100 iu vitamin D leads to an increase 25-OH vitamin D by:
  o 2.5nmol/l (1.75-2.75)
  o 1.0 ng/ml (0.7-1.1)
• 1000iu daily increases vitamin D by 25nmol/l
• Toxicity is rare unless vitamin D sustained >100µg/L(250nmol/l)

Treating deficiency (<30nmol/l):

Unlicensed preparations have variable availability and are potentially costly therefore licensed oral products may be preferable, for example:

- Colecalciferol 800iu capsules two capsules twice daily for 12 weeks
  or
- Colecalciferol 3200iu capsule once daily for 12 weeks

- Colecalciferol 1000iu tablets, 3-4 once daily for 12 weeks
  or
- Colecalciferol 25000iu tablets, two once weekly for 6 weeks
  or
- Colecalciferol 50000iu single dose oral solution (ampoule) once weekly for 6 weeks

Other options for patients with deficiency:

Cholecalciferol 20,000iu per capsule can be prescribed. Three capsules per week (60,000iu) for 4 weeks then three per month for 5 months.

Ergocalciferol 300,000iu (7.5mg/1ml) i.m. injection. Absorption via IM route can be unreliable, but it may be the preferable route in patients with GI malabsorption. Does not contain gelatin. Adheres to plastic syringes, so has to be given rapidly via 1-2.5ml Luer lock plastic syringe with blue needle or using glass syringe. Contents of the ampoule can be given orally.

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.

Monitoring:

Bone profile & U&Es at 4 weeks

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 suspected.

Patients who do not respond after 12 weeks of treatment may be considered for referral to secondary care.

Maintenance following treatment for deficiency:

Colecalciferol at a dose of 1,000 to 2,000 IU daily 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. Options include:
- 800iu capsules, one to two daily
or
- 1000iu tablets, one to two daily
or
- 25000iu tablets, one per month
or
- Calcium 600mg + D3 400iu, one twice daily

Vitamin D prescriptions should only be continued following treatment for deficiency, in patients at high risk of recurrence, e.g. malabsorption or lupus/photosensitive skin disorders and in those with osteoporosis or osteomalacia (unless they are receiving a combined calcium/vitamin D preparation).

Patients who were previously prescribed calcium carbonate with colecalciferol can continue treatment with this where appropriate. Calcium replete patients should be advised to purchase appropriate vitamin D supplements over the counter (OTC).

Patient groups that do not receive adequate exposure to sunlight are exempt from these criteria e.g. nursing home residents.

Lifestyle advice should also be provided

<table>
<thead>
<tr>
<th>DRUG</th>
<th>FORM</th>
<th>STRENGTH</th>
<th>BRAND ON FORMULARY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colecalciferol</td>
<td>Capsules</td>
<td>800iu</td>
<td>Fultium D3</td>
</tr>
<tr>
<td>Colecalciferol</td>
<td>Capsules</td>
<td>3,200iu</td>
<td>Fultium D3</td>
</tr>
<tr>
<td>Colecalciferol</td>
<td>Capsules</td>
<td>20,000iu</td>
<td>Aviticol &amp; Fultium D3</td>
</tr>
<tr>
<td>Colecalciferol</td>
<td>Tablets</td>
<td>1,000iu</td>
<td>Stexerol D3</td>
</tr>
<tr>
<td>Colecalciferol</td>
<td>Tablets</td>
<td>25,000iu</td>
<td>Stexerol D3</td>
</tr>
<tr>
<td>Colecalciferol</td>
<td>Oral solution</td>
<td>50,000iu</td>
<td>Invita D3</td>
</tr>
<tr>
<td>Ergocalciferol</td>
<td>I/M injection</td>
<td>300,000iu</td>
<td>Generic</td>
</tr>
<tr>
<td>Calcium + D3</td>
<td>Chewable tablets</td>
<td>600mg + 400iu</td>
<td>Adcal D3</td>
</tr>
</tbody>
</table>

Click here for link to Coastal West Sussex Formulary.

Treating insufficiency (25(OH)D 30-70 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 colecalciferol at a dose of 1,000 to 2,000 IU daily. Vitamin D is present in a range of unlicensed OTC dietary supplements & licensed medicines, which can help to boost vitamin D levels. Oral supplements are available as either ergocalciferol (calciferol, vitamin D2) or colecalciferol (vitamin D3). Measured quantities of vitamin D in these preparations can vary considerably.

Cautions & contraindications

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

Contraindications include:
- Hypersensitivity to vitamin D or any of the excipients in the product
- Hypervitaminosis D
- Nephrolithiasis
- Diseases or conditions resulting in hypercalcaemia and/or hypercalciuria e.g. sarcoidosis
- Severe renal impairment
- Metastatic calcification

**Drug interactions:**
- 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 digoxin may be accentuated with the oral administration of calcium combined with vitamin D. Strict medical supervision is needed and, if necessary, monitoring of ECG & 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 & 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 rare, but may occur with sustained levels >250nmol/l. If toxicity is suspected, licensed vitamin D preparations or supplements should be withdrawn. Serum calcium & renal function should be checked urgently. Early signs of toxicity include symptoms of hypercalcaemia such as thirst, polyuria & constipation.

**Specialist advice:**

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

**Further reading**


Holick MF (2007) Vitamin D deficiency, NEJM, 357,3, 266-281


RCPCH (2012) Position statement vitamin D, online: [http://www.rcpch.ac.uk/positionstatements](http://www.rcpch.ac.uk/positionstatements)