Guidance on the Treatment of Vitamin D Deficiency & Insufficiency in Adult Patients

In line with the recommendations of The Greater Manchester Medicines Management Group (GMMMG). (1) NHS Trafford recommends high dose Vitamin D supplementation for the treatment of adult patients with proven Vitamin D deficiency.

GMMMG does NOT recommend the routine treatment of adult patients with Vitamin D insufficiency. (2)

**Background**

Vitamin D3 (colecalciferol) is normally synthesised in the skin through the action of ultraviolet light. In the UK, this usually can only occur from April to September. In order to exert its effects on bone metabolism and calcium absorption, vitamin D is first converted in the liver to 25-hydroxyvitamin D (25-OHD) which is the major storage form and then into the active form, calcitriol (1,25-OHD), in the kidney. 25-OHD is the form measured in the laboratory. Colecalciferol is also available in the diet, and is largely obtained from oily fish. In the absence of sunlight exposure, intake from dietary sources alone is insufficient to provide optimal levels in the absence of skin synthesis.

The adverse effects of vitamin D deficiency on bone health are well established (e.g. rickets, osteomalacia etc) and therefore treatment with high dose vitamin D is recommended for patients with proven vitamin D deficiency.

**High Risk Groups**

Patients at higher risk of vitamin D deficiency include (3,4):

- those with darker skin pigmentation,
- housebound or elderly (over 65 years)
- alcoholics
- vegetarians
- obese people (BMI>30)
- people who cover up e.g. Muslim women or extensive use of sunscreens.
- those with medical risk factors such as renal and hepatic disease, malabsorption and patients taking anticonvulsants or Highly active antiretroviral treatment (HAART).
- Pregnant or Breastfeeding women
- Children- See Children’s guidance
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**Lifestyle Measures**

People at high risk of Vitamin D deficiency should be advised to supplement their Vitamin D levels by.\(^{(2,3)}\)

**Increasing UV sunlight exposure.** Between early April to late October exposure of the face and forearms to sunlight (between 9am and 3pm) for 30 minutes twice per week is sufficient to replenish Vitamin D levels in light skinned subjects, although this may need to be doubled in those with heavily pigmented skin. Sun safety advice should be given; avoid prolonged periods of time in the sun as this can cause sunburn and skin damage. Further advice is available at: [http://www.nhs.uk/Conditions/Sunburn/Pages/Introduction.aspx](http://www.nhs.uk/Conditions/Sunburn/Pages/Introduction.aspx)

**Increasing dietary Vitamin D or over-the-counter Vitamin D supplementation.** Foods containing Vitamin D: oily fish, egg yolks, cod liver oil and fresh meat. Foods fortified with Vitamin D: cereals and some dairy products. Increasing the dietary intake of vitamin D alone will not avoid the need for supplementation in patients with vitamin D deficiency.

**When should I test for Vitamin D deficiency?**

Measurement of serum Vitamin D should *normally* only be performed when the clinical picture suggests Vitamin D deficiency. Testing is recommended for\(^{(4)}\):

- High risk patients (see above) with symptoms suggestive of vitamin D deficiency such as proximal muscle weakness or musculoskeletal aches and pains.
- Patients with rickets, osteomalacia or hypocalcaemia.
- Where abnormalities on laboratory investigations are suggestive of Vitamin D deficiency e.g. low calcium, low phosphate, raised ALP or raised PTH.

Patients with risk factors who are asymptomatic should not be routinely tested. These patients should receive lifestyle advice.

Patients with risk factors who are to be commenced on bisphosphonates and other drugs affecting bone metabolism should be tested to ensure they are calcium and vitamin D replete, in line with NICE guidance.
Who should I treat for Vitamin D deficiency?

Vitamin D status is most reliably determined by assay of serum 25-hydroxy Vitamin D (25-OHD).

If Total D2+D3 is\(^{(4)}\):
  - Below 10µg/l (25nmol/l) is Vitamin D deficiency and treatment is required.
  - 10-20µg/l (25-50nmol/l) is Vitamin D insufficiency, and routine treatment of patients is not recommended\(^{(2)}\).

**IMPORTANT**- Different laboratories may report in different units. µg/l is equivalent to ng/ml; do not confuse with nmol/L

**Note**- Very low Vitamin D2 and D3 levels cannot be measured and are reported as below. Levels reported in this way should be assumed to be zero when calculating total D2 and D3 to establish the need for treatment.

<table>
<thead>
<tr>
<th>Vitamin D2</th>
<th>Lower level for measurement</th>
<th>Reported as</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 nmol/L</td>
<td>10 µg/l (4 µg/l)</td>
<td>&lt;10 nmol/L (4 µg/l)</td>
</tr>
<tr>
<td>Vitamin D3</td>
<td>15 nmol/L (3.75µg/l)</td>
<td>&lt;15 nmol/L (3.75µg/l)</td>
</tr>
</tbody>
</table>

Who should I refer?

Referral of adults is not normally needed. Referral to the relevant consultant for further investigation should be considered where there is doubt about the diagnosis or in the following sets of patients;\(^{(8,9,10)}\)

- Patients with atypical biochemistry e.g. vitamin D is low but calcium is high
- Patients who fail to respond to treatment or where symptoms worsen on treatment
- Patients with severe renal impairment (eGFR <30) (Vitamin D requires hydroxylation by the kidney and colecalciferol may be less effective and close monitoring is required).
- Patients with abnormal LFTs/Patients with liver failure. (NB raised alkaline phosphate with normal GGT is common in vitamin D deficiency)
- Patients deficient in vitamin D in the absence of known risk factors
- Patients with tuberculosis, lymphoma, parathyroid disorders, short stature, metastatic cancer, renal stones, sarcoidosis, pre-existing hypercalcaemia, deficiency due to malabsorption.
- Patients with unexplained weight loss or focal bone pain
- Patients with skeletal deformity
- Pregnant or breastfeeding women
What should I prescribe for patients with proven Vitamin D deficiency?

Adult treatment

Treatment can be given by one of the different regimes as outlined below\(^4\):

**Treatment regimes**

- 20,000 IU Pro D³\(^\text{®} \) (colecalciferol) **three times a week** for 8-12 weeks [unlicensed product]

  or

- 60,000 IU Pro D³\(^\text{®} \) (colecalciferol) **weekly** for 8-12 weeks [unlicensed product]

Vitamin D levels should be checked at the end of the treatment course to check for adequate replacement. If levels haven’t increased to above 20ug/l at 12 weeks compliance should be queried and referral to a specialist considered. After treatment most patients will require vitamin D supplementation for life or lifelong during the winter months unless a cause has been found and treated.\(^4\)

**Alternative treatment regimes used by local hospitals**

The following regime may be recommended by local hospitals and can be prescribed. It is recommended that this is prescribed as Pro D³\(^\text{®} \) 20,000 IU capsules where possible.

- 40,000 IU Colecalciferol **daily for 10 days** then 20,000 IU per week (Prescribe as Pro D3 [unlicensed product])

If maintenance treatment is required the following regimes can be recommended\(^4\):

**Maintenance regimes**

- 800 IU-2000 IU colecaciferol daily **purchased** over the counter.

If prescription is necessary give:

- Fultium\(^\text{®} \) 800 IU (colecalciferol) **1-2 capsules daily** [licensed product but contains arachis oil and is not suitable for patients with peanut or soya allergy]

- Pro D³\(^\text{®} \) 20,000 IU (colecalciferol) **one capsule once a week**. [unlicensed product]
Which preparation should I prescribe?

- **Prescribe Pro D3 capsules.** These are unlicensed but are manufactured in the UK, marketed as a nutritional supplement and packs contain an English product information leaflet. Patients should be informed of the unlicensed status and informed consent obtained and recorded in the patient’s clinical notes. Pro D3 is suitable for vegetarians, do not contain peanut oil and are halal approved and are therefore suitable for Muslims. Cost of 10 week treatment course (30 x 20,000 IU capsules) is £19.99. Cost of maintenance is £1.33 per month (2 x 20,000 IU once per month) or £2.66 (20,000 IU, once weekly).

- **Prescribe Pro D3 by brand.** If generic colecalciferol is specified any brand may be dispensed and many are unlicensed imports which are considerably more expensive and may not contain instructions in English.

- **Prescribe the treatment course as a one-off acute prescription.** Do not put on repeat.

- **Do not prescribe ergocalciferol capsules or liquid** due to prohibitive cost and also reports that it does not raise serum Vitamin D levels as effectively as colecalciferol. Ergocalciferol is equipotent to colecalciferol but has a shorter half life.

- Do NOT prescribe intramuscular calciferol which has variable absorption and should only be given in specialist units.

- Do NOT prescribe hydroxylated derivatives of Vitamin D, such as alfacalcidol or calcitirol, without specialist advice, as these may lead to hypercalcaemia. (3)

- **Avoid giving combined calcium and vitamin D supplements long term** as calcium is usually unnecessary, makes for unpalatability, reduces concordance and is more expensive. (3) Much more vigilant monitoring of calcium levels is required to prevent hypercalcaemia.
The following products can be recommended in special circumstances:

<table>
<thead>
<tr>
<th>Special circumstance</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swallowing difficulties</td>
<td></td>
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</tbody>
</table>

Pro-D3 [unlicensed product] are powder filled capsules and contents could be mixed with food, although against manufacturers recommendations as stability is unknown. Cost £19.99 for 30 capsules (10 week treatment course) with £3.65 handling fee if ordered direct and cost <£100. Can be ordered via all major warehouses at no extra cost except for Alliance healthcare where Phoenix account should be used instead.

Pro D3 [unlicensed product] is available as an alcohol and PEG free liquid in a strength of 100 IU per drop (2.5µg per drop) which is equivalent to 2,000 IU per ml. Specify 3 x 100ml for 10 week treatment course. Cost £67.50 + £3.65 handling fee if orders <£100 (Note: Other pack sizes of Pro-D3 are considerably more expensive):

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Pack size</th>
<th>Cost per pack</th>
<th>Cost per treatment (10 week course)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pro D3 liquid 2000 IU/ml</td>
<td>100ml</td>
<td>£22.50</td>
<td>£67.50</td>
</tr>
<tr>
<td>Pro D3 liquid 2000 IU/ml</td>
<td>50ml</td>
<td>£16.80</td>
<td>£100.80</td>
</tr>
<tr>
<td>Pro D3 liquid drops 100 IU/drop</td>
<td>20ml</td>
<td>£9.80</td>
<td>£147</td>
</tr>
<tr>
<td>Pro D3 Forte 3000 IU/ml</td>
<td>50ml</td>
<td>£18.90</td>
<td>£75.60 but dose difficult to measure</td>
</tr>
</tbody>
</table>

Dekristol® 20,000 IU capsules [unlicensed product] can be pierced with a needle and the contents squeezed out. Not suitable for patients with peanut allergy. Cost of 50 capsules around £23.90+ £6.50-15.45 handling fee if orders less than £30-£75, but cost can be considerably higher depending on how sourced. (11)

<table>
<thead>
<tr>
<th>Special circumstance</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vegetarians</td>
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</table>

Pro D3 is suitable for vegetarians and is available as a 20,000 IU capsule for treatment. It is also available as a 1,000 IU and a 400 IU preparation which can be purchased from pharmacies or direct from the manufacturers.

<table>
<thead>
<tr>
<th>Vegans</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Colecalciferol (vitamin D3) is derived from wool fat therefore ergocalciferol (vitamin D2) is needed. Seek advice.</td>
<td></td>
</tr>
</tbody>
</table>

| Patients not wishing to consume gelatin from animal sources for religious or ethical reasons |         |
| Pro-D3 (colecalciferol) all strengths are suitable for vegetarians, Muslims (halal), kosher and are gelatine free. |         |

| Patients with peanut allergy |         |
| Pro-D3 (colecalciferol) all strengths are suitable for patients with peanut allergy |         |
What should I recommend for patients with Vitamin D insufficiency?

All patients should be given advice on regular sunlight exposure, dietary sources of vitamin D and the use of over the counter vitamin D supplements.

Patients should not be routinely prescribed vitamin D supplements and should be advised to purchase over the counter high strength vitamin D treatments (800-2000 IU daily). Where it is important that patients are vitamin D and calcium replete e.g. when starting bisphosphonate or other bone modifying agents, prescribing may be considered.

Patients should be reviewed after an appropriate interval, and if levels have improved lifestyle advice should be reinforced; if no improvement then patients can be prescribed a maintenance dose of colecalciferol.

Pregnancy and breast feeding

- The Department of Health recommends that all pregnant and breast feeding women should take 10µg (400IU) of Vitamin D daily to prevent Vitamin D deficiency. (Available as Healthy Start 91p for 56 tablets or available free to eligible women under the Healthy Start scheme www.healthystart.nhs.uk/)\(^{(7)}\).

- Refer pregnant women in whom Vitamin D deficiency is suspected to secondary care for investigation and management.

- Breast milk of women taking pharmacological doses of vitamin D can cause hypercalcaemia if given to an infant and additional monitoring is required.

- Breast fed 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.\(^{(12)}\)
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References:


3. Diagnosis and management of Vitamin D deficiency. BMJ 340:142-147 16th Jan 2010


5. East Lancashire Health Economy Guideline. Diagnosis and Management of Vitamin D Deficiency for Non-Specialists. May 2010


11. NHS Manchester Prescribing Policy: Treatment of Vitamin D Deficiency and Insufficiency

12. CMO letter CEM/CMO/2012/04 2nd February 2012: Vitamin D- Advice on Supplements for At Risk Groups. www.dh.gov.uk/health/2012/02/advice-vitamin-d/
Appendix 1 - Flow chart for the treatment of Vitamin D deficiency in adults

#### Symptomatic individuals
- Rickets, osteomalacia or symptomatic hypocalcaemia
- High risk patient group with suggestive symptoms such as proximal muscle weakness or musculoskeletal aches and pains

#### Arrange Investigations
Renal function, liver function (albumin), calcium phosphate, alkaline phosphatase, 25-OH vitamin D levels

#### Does the patient meet all the criteria for management in primary care?
- No significant renal impairment
- Normal calcium
- Normal LFT's or an isolated elevation of Alk Phos (raised alk phos is common in vitamin D deficiency)
- No contraindications to treatment
- Diagnosis certain
- Not pregnant

#### If TOTAL D2+D3 is:

- **≤ 25nmol/l (≤10µg/l)**
  - Vitamin D Deficiency

- **25-50nmol/l (10-20µg/l)**
  - Vitamin D Insufficiency

#### Treatment of deficiency:
- 20,000 IU Pro D3® (colecalciferol) three times a week for 8-12 weeks, or
- 60,000 IU Pro D3® (colecalciferol) weekly for 8-12 weeks

#### Maintenance following treatment:
800 IU-2000 IU colecalciferol daily purchased over the counter
If prescription is necessary give:
- Fultium® 800 IU (colecalciferol) one or two capsules daily [licensed product but contains arachis(peanut) oil] or
- Pro D3® 20,000IU (colecalciferol) one capsule once a week

#### ≥ 50nmol/l (≥ 20µg/l)
- Adequate Vitamin D Status

#### High risk individuals without symptoms
- Dark skinned patients
- Institutionalised/ housebound or elderly (>65yrs)
- Alcoholics
- Vegetarians and vegetarians
- Obese BMI>30
- People who cover up (e.g. muslims, sunscreen use)
- Medical risk

Further assessment required consider referral to specialist

Advice on regular sunlight exposure, dietary sources of vitamin D and use of over the counter vitamin D supplements.

Give all patients advice on regular sunlight exposure, dietary sources of vitamin D and use of over the counter vitamin D supplements.

Patients should be reviewed and if levels have improved lifestyle advice should be reinforced; if no improvement then consider prescribing maintenance dose of colecalciferol.