GUIDELINES FOR THE PRESCRIBING OF VITAMIN D IN ADULTS

This guidance has been adapted from the North of Tyne Guideline Group guidelines, published in 2011. The treatment of children has been removed, as this should be undertaken in conjunction with a paediatrician. In addition, slight changes have been made to the maintenance doses in light of the marketing of licensed preparations and also some of the guidance from the National Osteoporosis guidelines have been incorporated (http://www.nos.org.uk/document.doc?id=1352).

July 2013
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SUMMARY

This guideline aims to increase awareness of the prevalence and importance of vitamin D deficiency, to provide a structured approach to the management of those patients at risk of the deficiency with the intention of reducing morbidity from the condition.

This guideline makes recommendations for the diagnosis and management of vitamin D deficiency. The interventions should be offered to all people who are likely to benefit, irrespective of race, disability, gender, age, sexual orientation or religion. Information to be provided to patients in an accessible format and consideration should be given to any sensitive and cultural issues. Prescribers should review patients for contra-indications before initiating drug treatment.

This local guideline is intended for all clinicians in the Cumbria in the diagnosis and management of patients with vitamin D deficiently ensuring an integrated approach across primary and secondary care.

The Guidelines include recommendations for treatment and set out indications for treatment. Patients not assessed as requiring prescribed treatment should be given diet and lifestyle advice as recommended in the guidelines document.

A flow chat is included to aid implementation.
SUMMARY FLOWCHART

Vitamin D deficiency / insufficiency; Management Algorithm

Priority groups
- Pregnant
- Birth to 5 years old

Symptomatic individuals
- Rickets, osteomalacia or symptoms of hypocalcaemia
- High risk patient group with suggestive symptoms, e.g., proximal muscle weakness or musculoskeletal aches and pains

High risk groups (asymptomatic)
- Individuals with darker skin pigmentation
- Institutionalised
- Older/housebound people
- Vegetarian
- Medical risk

Check: Ca2+, PO4, Mg, Alk Phos

Measure serum 25-OHD

<25nmol/l
Vitamin D deficiency
High strength calcifediol for 6 to 10 weeks (or IM option)
Consider long-term supplementation

25-50nmol/l
Vitamin D insufficiency

>50nmol/l
Adequate vitamin D status

Advice on regular sunlight exposure, dietary sources of vitamin D and use of OTC vitamin D supplements
1. Introduction
This guideline aims to increase awareness of the prevalence and importance of vitamin D deficiency, to provide a structured approach to the management of those patients at risk of the deficiency with the intention of reducing morbidity from the condition across Cumbria.

1.1 Background
Osteomalacia is the classic manifestations of profound vitamin D deficiency in adults. However, in recent years, it has been recognised that there are many other adverse health consequences. The spectrum of these common disorders is of particular concern because suboptimal vitamin D status is widespread in Cumbria. Cancer, metabolic syndrome, infectious and autoimmune disease are all associated with moderately low vitamin D levels (1). Unequivocal links have been demonstrated between breast (2), bowel (3), prostate and lung cancer (4) and poor vitamin D status, as well as metabolic syndrome, obesity, ischaemic heart disease and type 2 diabetes. Similar associations have been found with several autoimmune and infectious conditions including tuberculosis, type 1 diabetes, multiple sclerosis and rheumatoid arthritis. (5-10).

1.2 Sources of Vitamin D
Vitamin D refers to the precursors of the active hormone, 1,25-dihydroxyvitamin D (1,25[OH]2D3). The major natural source of vitamin D (over 90% for most people) is from skin photosynthesis following ultraviolet (UV-B) solar irradiation. Unfortunately, for six months of the year (October to April), the North of England lies above the latitude that allows exposure to the UV-B wavelengths necessary for vitamin D synthesis (11), leaving our population reliant on exogenous sources of vitamin D. For this reason, vitamin D is also a micronutrient although 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. Contrary to popular perceptions, there is little or no vitamin D content in UK milk and dairy products. Indeed, only infant formula milk and margarine have statutory vitamin D supplementation in the UK. Thus, the prevalent diet 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 in our region, affecting over half the whole adult population during winter, with 16% showing severe deficiency. (Appendix 2) (12).

2. Recommendations to Achieve Adequate Vitamin D Levels

2.1 Sun exposure
For a fair-skinned person, 20 to 30 minutes of (‘sub-erythematos’) sunlight exposure at midday on the face and forearms two or three times weekly between April and October are sufficient to achieve healthy vitamin D levels in summer in the UK. However, for individuals with pigmented skin, and to a lesser extent the elderly, exposure time or frequency needs to be increased two-to ten-fold to get the same vitamin D synthesis (depending upon skin pigmentation). While recognising the importance of avoiding sunburn and sunbeds, total avoidance of sun exposure is a clear risk factor for vitamin D deficiency.

2.2 Dietary sources of vitamin D:
- 2-3 portions (100-150 grams per portion) weekly of oily fish including trout, salmon, mackerel, herring, sardines, anchovies, pilchards or fresh tuna. Because of the concerns of heavy metal contamination in the marine food chain, it is recommended that these amounts should not be exceeded in pregnancy, or in women who may conceive.
- Cod liver oil and other fish oils.
- Egg yolk.
• Some breakfast cereals (mainly supermarket ‘own brands’ – which are manufactured for the EU market where several countries have obligatory minimum levels in cereals) are supplemented.
• Margarine and infant formula milk have statutory supplementation in the UK.

3. Who Becomes Deficient or Insufficient?

The following are groups at increased risk:
• Anyone with dark skin.
• People who cover up, e.g., Muslim women, people with skin photosensitivity (e.g., azathioprine, chlorpromazine) or history of skin cancer.
• Pregnant women, or those who have recently had children, particularly multiparous women with short intervals between pregnancies.
• Housebound, institutionalised and certain older people.
• Chronic disease (liver, kidney, malabsorption including coeliac disease, short bowel).
• All babies, particularly those who have had prolonged breast feeding without supplementation.
• Family history of vitamin D deficiency.
• Vegetarian (or other non-fish eating) diet.
• Anticonvulsant, rifampicin, colestyramine, HAART, corticosteroid use.
• Obese – risk increases with increasing obesity.

The prevalence of vitamin D insufficiency has a natural seasonal pattern, being most prevalent in winter and spring, and least frequent in the autumn. Individuals who work outdoors or who have regular outdoor leisure activity are at less risk.

4. How Does Vitamin D Deficiency Present in Adults?

In adults:
• Non-specific musculoskeletal aches and pains which can be localized (rib, hip, pelvis, thigh and foot pain or low back), generalized, or migratory
• Proximal muscle weakness – difficulty rising from chair or climbing stairs
• Weakness and pain may be mislabelled as ‘fibromyalgia’ or as a somatisation of depression
• Low bone density on DEXA scanning
• Osteopenia may be seen on plain X-ray
• Incidental findings on routine biochemistry, such as raised alkaline phosphates, raised PTH, hypocalcaemia, hypomagnesaemia, hypophosphataemia.

5. How to Investigate

In someone with suggestive symptoms and from an at risk category, vitamin D deficiency is best confirmed by direct measurement of serum 25-OHD. Measurement of serum 25-hydroxyvitamin D (25-OHD) is the most reliable indicator of vitamin D status, it is worthwhile measuring bone chemistry, but parathyroid hormone estimation is not routinely required.

It is an expensive assay and many patients can be advised to change their lifestyle (sun exposure and diet) or to take a supplementary dose of vitamin D without measuring serum 25-OHD.

Serum 25-OHD measurement is recommended for:
• patients with bone diseases that may be improved with vitamin D treatment
patients with bone diseases, prior to specific treatment where correcting vitamin D deficiency is appropriate

patients with musculoskeletal symptoms that could be attributed to vitamin D deficiency.

Routine vitamin D testing may be unnecessary in patients with osteoporosis or fragility fracture, who may be co-prescribed vitamin D supplementation with an oral antiresorptive treatment.

**Vitamin D (25-OHD) Levels should be interpreted as below:**

<table>
<thead>
<tr>
<th>25-OHD Level</th>
<th>Status</th>
<th>Manifestation</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25 nmol/L</td>
<td>Deficiency</td>
<td>Rickets / Osteomalacia</td>
<td>Treat</td>
</tr>
<tr>
<td>25-50 nmol/L</td>
<td>Insufficiency</td>
<td>Associated with disease risk</td>
<td>*Lifestyle advice, diet and sun exposure</td>
</tr>
<tr>
<td>50-75 nmol/L</td>
<td>Adequate</td>
<td>Healthy</td>
<td>Lifestyle advice</td>
</tr>
<tr>
<td>&gt;75 nmol/L</td>
<td>Optimal</td>
<td>Healthy</td>
<td>None</td>
</tr>
</tbody>
</table>

* Levels of 25-OHD between 25 and 50 nmol/L are a grey area and advice to take vitamin D supplementation will depend upon the level within this range, the season (of blood testing) and likelihood of other sources of vitamin D being effective (e.g., sunlight exposure, dietary change)

*Give leaflet on vitamin D sources including sun exposure, diet and supplementation (available at: [http://www.bda.uk.com/foodfacts/VitaminD.pdf](http://www.bda.uk.com/foodfacts/VitaminD.pdf)). There is no level 1 evidence that prescribing supplements to this group will produce health benefits.

6. Other Biochemical Features of Deficiency

- High serum alkaline phosphates
- Low serum calcium
- Low serum phosphate
- High serum parathyroid hormone

A high serum alkaline phosphatase is almost universal in children with D deficiency rickets and is also found in 80% or more of adults with osteomalacia. This occurs early and vitamin D deficiency should be considered within the differential diagnosis for unexplained raised alkaline phosphatase. An additional biochemical feature pointing to a bony origin is if the serum alkaline phosphatase is relatively more elevated than the γ-glutamyl transferase. In vitamin D deficiency, 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, caused by secondary hyperparathyroidism, is typical but may not be found in neonates and young infants or in about a quarter of adults with vitamin D insufficiency.

7. Further Investigation and Referral

Referral of adults in not routinely needed. It should be considered where there is doubt about the diagnosis, if biochemistry is atypical (e.g., low vitamin D and high calcium) or if the patient fails to respond to treatment.

Follow up blood tests after treatment are not needed unless there are on-going symptoms, doubts about compliance or co-morbidities. In particular, monitoring serum vitamin D levels during treatment or supplementation of uncomplicated sunlight / dietary deficiency is not usually worthwhile.
8. Treatment of Deficiency

The treatment of choice is oral calciferol in the form of either ergocalciferol (yeast derived vitamin D2) or colecalciferol (fish or lanolin derived vitamin D3). Tablets, capsules and oily suspensions are available. Short-acting, potent vitamin D analogues such as alfacalcidol (1α-hydroxycholecalciferol, One-Alpha®) or calcitriol are ineffective in correcting vitamin D deficiency and may lead to dangerous hypercalcaemia in this situation.

The usual principle of therapy is to replenish the vitamin D stores over 8 to 12 weeks with high does calciferol therapy and then to continue a lower maintenance dose. Large bolus doses are also highly effective. Oral treatment is believed to be better absorbed than IM.

There is a high therapeutic index for calciferol. It has been estimated that a regular daily dose of 1000 IU raises serum 25-OHD by 24nmol/L; vitamin D toxicity has only been observed with 25-OHD values above 500nmol/L.

Few, if any, people have significant contra-indications to calciferol therapy and toxicity (hypercalcaemia) is very rare. Pre-existing hypercalcaemic disorders, generally hyperparathyroidism or sarcoidosis, do however require liaison with secondary care before any treatment is instituted. Individuals with renal stones or nephrocalcinosis can safely be given vitamin D, but concomitant calcium therapy should be avoided.

For adults with deficiency, a loading dose of approximately 300,000 IU is given in divided doses over 6 to 10 weeks (see Section 8 for regimes). Patients should be aware of the need to supplement their diet thereafter.

In adults with severe malabsorption, or those in whom concordance with oral therapy is suspect, an intramuscular does of 300,000 IU monthly for 3 months followed by the same dose every 2-3 months is an alternative.

Adjusted serum calcium should be checked 1 month after completing the loading regimen or after starting vitamin D supplementation in case primary hyperparathyroidism has been unmasked.

Routine monitoring of serum 25-OHD is generally unnecessary but may be appropriate in patients with symptomatic vitamin D deficiency or malabsorption and where poor compliance with medication is suspected.

As few adults have truly reversible risk factors for vitamin D deficiency, the assumption should be that supplementation will be needed lifelong following treatment for deficiency, or lifelong during winter months (dependent upon latitude and dress habits).

Deficiency Treatment Regimens (25-OHD <25nmol/L)

Where rapid correction of vitamin D deficiency is required, such as in patients with symptomatic disease or about to start treatment with a potent antiresorptive agent (zoledronate or denosumab), the recommended treatment regimen is based on fixed loading doses followed by regular maintenance therapy.

Where correction of vitamin D deficiency is less urgent and when co-prescribing vitamin D supplements with an oral antiresorptive agent, maintenance therapy may be started without the use of loading doses.
Loading regimens for treatment of deficiency up to a total of approximately 300,000 IU given either as weekly or daily split doses. The exact regimen will depend on the local availability of vitamin D preparations but will include:

<table>
<thead>
<tr>
<th>Dose</th>
<th>Frequency</th>
<th>Duration</th>
<th>Total dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>50,000 IU</td>
<td>Once weekly</td>
<td>6 weeks</td>
<td>300,000 IU</td>
</tr>
<tr>
<td>20,000 IU</td>
<td>Twice weekly</td>
<td>7 weeks</td>
<td>280,000 IU</td>
</tr>
<tr>
<td>800 IU</td>
<td>Five a day</td>
<td>10 weeks</td>
<td>280,000 IU</td>
</tr>
</tbody>
</table>

See Appendix 1 for recommended preparations.

Supplements should be taken with food to aid absorption.

Calcium/vitamin D combinations should not be used as sources of vitamin D for the above regimens, given the resulting high dosing of calcium.

Maintenance regimens may be considered 1 month after loading with doses equivalent to 800 to 2000 IU daily (occasionally up to 4,000 IU daily), given either daily or intermittently at a higher equivalent dose. Fultium® and Desunin® are licensed preparations suitable for maintenance therapy.

9. What About Prevention?

People at risk and those demonstrated to have suboptimal serum 25-OHD levels should be targeted for lifelong lifestyle advice, especially about sun exposure and diet, and advice on vitamin D supplementation.

There is no clear evidence of cost effectiveness in the insufficiency group, supplementation has no evidence that it prevents long term sequelae. Therefore prescription is not advised.

How to identify people for advice on supplementation and lifestyle in the general population

- All non-Caucasian individuals
- All people with restricted sun exposure (e.g., doesn’t have outdoor activity through work or leisure, agoraphobia, wears a veil, uses sun-block regularly, photosensitive skin disorder, previous skin cancer)
- People with limited dietary fish intake (particularly vegetarians, those with poor diet)

In addition the following groups need particular attention (Department of Health recommendation):

Pregnant and breastfeeding women

We recommend that all pregnant women take a supplementation dose of vitamin D in the form of Healthy Start Women’s vitamins throughout their pregnancy. This is in accordance with NICE recommendations, as women in the North are at risk due to poor sunlight exposure (15). Eligible groups for free Healthy Start vitamins are those on Income Support, Income based Jobseekers or Child tax credit (but not Working tax credit). All pregnant women / girls under 18 years old also qualify. Anyone at risk not eligible for Healthy Start vitamins (for example asylum seekers) should be prescribed oral calcium and vitamin D supplementation.
Housebound, institutionalised and older people (including those with fracture risk)

Institutionalised, housebound and at risk older people (as defined above) should be advised on supplementation. A number will be on calcium and vitamin D prophylaxis and osteoporosis.

Anticonvulsant, rifampicin and Highly Active AntiRetroviral Therapy (HAART) use

Routine supplementation with 800 to 1600 units of vitamin D daily should be given advice and a leaflet, in individuals on enzyme inducing antiepileptic medications (particularly phenytoin, carbamazepine, and phenobarbital). Similar supplementation is advised during prolonged rifampicin and HAART use. In addition patients should be given a leaflet and advice on diet and lifestyle.

References

Appendix 1 - Preparations of Calciferol available in the UK

Preparations recommended for treatment

The recommended preparations are:

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Strength</th>
<th>License status</th>
<th>Cost of full course (12 weeks)</th>
<th>Handling fee</th>
<th>Total cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dekristol®</td>
<td>20,000 IU</td>
<td>Medicine (Germany)</td>
<td>Between £7.49 to £11.85</td>
<td>Between £6.50 and £14.45</td>
<td>Pharmarama £13.99, Martindale £26.50, UL medicines £20.76</td>
</tr>
<tr>
<td>Pro D3®</td>
<td>400 IU</td>
<td>Food</td>
<td>£23.99</td>
<td>None</td>
<td>£23.99</td>
</tr>
</tbody>
</table>

Preparations used for maintenance

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Daily Dose</th>
<th>License status</th>
<th>Peanut oil</th>
<th>Cost of 1 month’s treatment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fultium-D3®</td>
<td>800 IU</td>
<td>Medicine</td>
<td>No</td>
<td>£3.60</td>
<td>Contains 4.8mmol calcium</td>
</tr>
<tr>
<td>Desunin®</td>
<td>800 IU</td>
<td>Medicine</td>
<td>No</td>
<td>£3.60</td>
<td></td>
</tr>
<tr>
<td>Pro D3®</td>
<td>800 IU (2 x 400 IU caps)</td>
<td>Food</td>
<td>No</td>
<td>£9.98</td>
<td></td>
</tr>
<tr>
<td>Calcium + vitamin D tablets</td>
<td>2 x 400 IU (as ergocalciferol)</td>
<td>Medicine</td>
<td>No</td>
<td>£16.78</td>
<td>Contains 4.8mmol calcium</td>
</tr>
<tr>
<td>Calcichew-D₃ Forte® tablets</td>
<td>800 IU (2 tabs)</td>
<td>Medicine</td>
<td></td>
<td>£4.24</td>
<td>Contains 25mmol calcium</td>
</tr>
<tr>
<td>Adcal-D₃ tablets</td>
<td>800 IU (2 tabs)</td>
<td>Medicine</td>
<td></td>
<td>£3.84</td>
<td>Contains 30mmol calcium</td>
</tr>
<tr>
<td>Colecalciferol oily solution</td>
<td>600 IU (1mL)</td>
<td>Special (by Martindale)</td>
<td></td>
<td>£102.16</td>
<td></td>
</tr>
</tbody>
</table>

Information is available to check the suitability for vegetarians and vegans and for peanut and soya allergy.
Appendix 2 - The seasonal and geographical variation in the prevalence of hypovitaminosis in Great Britain

![Seasonal and geographical variation in the prevalence of hypovitaminosis D (25-hydroxyvitamin D <40 nmol/L) in Great Britain.]

Appendix 3 - Dekristol® information sheet for primary care and community pharmacies

Dekristol® is included in the Lothian Joint Formulary for treatment of severe vitamin D deficiency, where standard calcium + vitamin D would be inadequate or the calcium component is undesirable.

Although Dekristol® is not listed in the BNF, it has been included as an option because the alternate licensed products (Colecalciferol 10,000 IU and Ergocalciferol [D2] 50,000 IU) are no longer being imported into the UK.
Appendix 4 - Vitamin D Guidelines: Summary Information

Sources

The significant sources of vitamin D are sunlight and oily fish, including cod liver oil.

Common groups at risk of vitamin D deficiency/insufficiency

- Non-white skin, lack of sunlight exposure (including concealing clothing), vegetarians (non-fish eaters)
- Pregnant women, babies, children and adolescents, older housebound or institutionalised people
- Liver and renal disease, anticonvulsant, rifampicin, HAART use

Management

In a patient with symptoms/deformity confirm clinical suspicion by measuring serum 25-hydroxyvitamin D (25OHD):

- 25-OHD below 25nmol/L = deficiency - requires high dose calciferol treatment
- 25-OHD between 25 and 50nmol/L = insufficiency - lifestyle (sun exposure and diet) and supplementation advice
- 25-OHD above 50nmol/L = sufficient (reinforce dietary and lifestyle advice)

Universal supplementation

- Recommended in pregnancy
- Important for breast-fed babies and recommended for all infants and children <5yrs

Target for supplementation and lifestyle advice

- All non-Caucasian individuals
  PLUS
- All people with restricted sun exposure (e.g., doesn’t have outdoor activity through work or leisure, wears a veil, uses sun-block regularly, photosensitive skin disorder, previous skin cancer)

AND / OR

- People with limited dietary fish intake (particularly vegetarians, those with poor diet)

Refer

- If lack of clinical response to vitamin D therapy
- Persistent focal bone pain
- Suspicion of unrecognised underlying problem (e.g., malabsorption).

Key points

- Vitamin D insufficiency/deficiency is very common in children and adults with non-white skin
- Supplementation will often need to be lifelong, as lifestyle changes may not be effective.