Main objectives for Vitamin D guidance

- Promote supplements for all children under 5 years of age.
- Adequate supplementation during pregnancy and breastfeeding.
- Optimise treatment for children and adults with symptomatic deficiency disorders.
- Safe advice on managing insufficiency.
- Improve information for practitioners and patients.
- Audit prevalence of vitamin D deficiency and treatment.

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- Structure / mechanism of action
- Sources of vitamin D
- Prevalence of deficiency
  - Measurement
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- Vitamin D associated diseases
- Vitamin D and adults
  - Symptomatic disease: osteomalacia
  - Asymptomatic vitamin D deficiency
  - Vitamin D insufficiency
- Vitamin D and children
- Special populations
  - Renal disease
  - Pregnancy and breastfeeding
  - Elderly and housebound
- Prescribing
  - Available preparations

Aim of Guidance

This summary guideline is designed to be used in primary care and outpatient settings to improve the management of patients with vitamin D deficiency and insufficiency.

The guideline draws on available national and local guidance on testing, treating and monitoring vitamin D disorders. At present there is insufficient evidence to make definitive evidence based statements in some areas of practice. Currently there are a number of trials in progress to clarify the best management of vitamin D deficiency states, and the safety of higher dosing regimes for routine supplementation.

This guideline aims to provide safe advice for clinicians in areas where clinical uncertainty remains.

References:

1. Committee on Medical Aspects of Food Policy (COMA) Department of Health 1991
2. Pearce S, Cheetham T, Diagnosis and management of vitamin D deficiency. BMJ. 2010; 340:142-7
4. St George’s Health care NHS trust. Vitamin D deficiency in adults. 2010
7. Primary vitamin D deficiency in adults. DBT. 2006; 44(4)
Structure and mechanism

In this guidance the term vitamin D refers to cholecalciferol (D$_3$) and ergocalciferol (D$_2$) which are the precursors of the active hormone 1α,25-dihydroxyvitamin D (1α,25(OH)$_2$D$_3$), also known as calcitriol. Vitamin D (from photosynthesis in the skin and from dietary sources) is hydroxylated in the liver, and further hydroxylated in the kidney and some other tissues to form calcitriol (see pathway diagram).

The active form of vitamin D, calcitriol, exerts its effect by binding to the vitamin D receptors (VDRs) which are widely distributed through many body tissues.

The major functions of vitamin D include:
- Calcium homeostasis
- Immune regulation
- Regulation of cell growth (cancer risk)
- Renin and insulin excretion affecting CVD risk

Pathway of vitamin D production, and effect on Calcium homeostasis

Vitamin D includes D$_3$, (Cholecalciferol) and D$_2$, (Ergocalciferol) collectively known as Calciferol. Vitamin D3 is formed in the skin by the action of UVB on 7-dehydrocholesterol (7DHC), or is ingested. Vitamin D2 mainly comes from plant sources. Vitamin D$_3$ and D$_2$ are hydroxylated in the liver by 25-hydroxylase to 25-hydroxyvitamin D, (25-OHD) or calcidiol. This is the major circulating form of vitamin D and is the target for assays measuring vitamin D status.

Calcidiol is further hydroxylated in the kidneys and other tissues to the active hormone 1α, 25-dihydroxyvitamin D (1α,25(OH)$_2$D$_3$) or calcitriol.

Renal production of calcitriol is regulated by parathyroid hormone (PTH), hypophosphataemia, hypocalcaemia and growth hormone.

Sources of vitamin D

The major natural source of vitamin D is sunlight, with a small amount coming from the diet. For white populations 20-30 minutes of sunlight exposure to the face and forearms in the middle of the day during summer generates approximately 2,000IU vitamin D. Two or three exposures a week are estimated to generate healthy levels during summer.

Populations with pigmented skin need 2-10 times the exposure of a fair skinned individual.

In the United Kingdom there is insufficient UVB of the necessary wavelength between October and March to generate vitamin D.

The figure below shows seasonal variation in vitamin D levels in the UK. Sun exposure for vitamin D production has to be balanced against the risk of skin cancer. Sunscreens with a sun protection factor of 15 or more block 99% of dermal vitamin D synthesis.

Graph showing the seasonal variation in vitamin D levels in white men and women from the 1958 UK birth cohort (Hyponnen and Power 2007)
Dietary sources

There are few foods rich in vitamin D. The table below lists common dietary sources. Farmed fish may have lower levels than wild fish. Vegetable sources of vitamin D are insignificant.

In the UK margarine, infant formula milk and some cereals are modestly fortified with vitamin D.

Chewing Betel nut is associated with a reduction in circulating calcitriol.

Measurement

Vitamin D status is determined by measuring serum 25-hydroxyvitamin D (25 OHD). This has a circulating half life of one to two months, with levels actively replenished from fat stores.

In contrast, calcitriol (the active form of vitamin D) has a half life of one to two months, with levels actively replenished from fat stores.

Reference ranges for vitamin D (25 OHD)


<table>
<thead>
<tr>
<th>Vitamin D status</th>
<th>nmol/l</th>
<th>25(OH)D₂</th>
<th>25(OH)D₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td>nmol/l</td>
<td>deficient</td>
<td></td>
</tr>
<tr>
<td>30-80</td>
<td>nmol/l</td>
<td>insufficient</td>
<td></td>
</tr>
<tr>
<td>81-220</td>
<td>nmol/l</td>
<td>replete / normal</td>
<td></td>
</tr>
<tr>
<td>221-500</td>
<td>nmol/l</td>
<td>high</td>
<td></td>
</tr>
<tr>
<td>&gt;500</td>
<td>nmol/l</td>
<td>toxicity</td>
<td></td>
</tr>
</tbody>
</table>

Dietary reference values for vitamin D

Guidance from the Committee on Medical Aspects of Food and Nutrition Policy (COMA) states the recommended daily nutritional intake of vitamin D in certain groups needed to prevent rickets and osteomalacia. Such recommended intakes alone, without skin synthesis are unlikely to result in optimal status. Dietary surveys show vitamin D intake to be low, in the region of 80-160 IU per day.

Vitamin D supplements are advised by the DOH for specific groups:

- All pregnant / breastfeeding women: 400 IU/day
- All infants / toddlers from 6mths – 5yrs: 280 IU/day (unless drinking 500ml or more of infant formula)
- Breastfed babies 1mth – 6mths if mother is Vitamin D insufficient / deficient: 340 IU/day
- People with low sun exposure eg: confined indoors or with covered skin: 400 IU/day
- > 65 yrs old: 400 IU/day

These recommendations are thought by many authorities to be too low. In the absence of adequate skin synthesis these amounts will not maintain serum levels of vitamin D in the replete (or normal) range.

Prevalence of vitamin D deficiency and insufficiency

A recent UK survey among the white population showed 50% prevalence of insufficiency and 16% deficiency in the winter and spring (3).

The local prevalence, in a multiethnic population, shows much higher rates of deficiency. Among South Asians tested in routine clinical practice, >90% were found to have insufficient or deficient levels.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>% Deficient</th>
<th>% Insufficient</th>
<th>% Replete</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25nmol/l</td>
<td>17</td>
<td>63</td>
<td>20</td>
</tr>
<tr>
<td>25-74nmol/l</td>
<td>47</td>
<td>49</td>
<td>4</td>
</tr>
<tr>
<td>&gt;75nmol/l</td>
<td>42</td>
<td>54</td>
<td>3</td>
</tr>
<tr>
<td>&lt;16 years</td>
<td>45</td>
<td>48</td>
<td>7</td>
</tr>
<tr>
<td>16-64</td>
<td>38</td>
<td>56</td>
<td>6</td>
</tr>
<tr>
<td>&gt;64</td>
<td>37</td>
<td>56</td>
<td>12</td>
</tr>
</tbody>
</table>

Vitamin D values for 13,183 tests performed during 2009 in Tower Hamlets (population 250,692)
Causes of vitamin D deficiency

The main causes are summarised in the table below.

<table>
<thead>
<tr>
<th>Reduced skin synthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Sunscreen use</td>
</tr>
<tr>
<td>- Skin pigmentation</td>
</tr>
<tr>
<td>- Ageing</td>
</tr>
<tr>
<td>- Season, latitude, time of day</td>
</tr>
<tr>
<td>- Patients with skin grafts</td>
</tr>
<tr>
<td>- Low UVB exposure among the housebound</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Decreased bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Malabsorption (Cystic fibrosis, Coeliac disease, Crohns, bypass surgery, medications that reduce cholesterol absorption)</td>
</tr>
<tr>
<td>- Obesity (possible reduced availability of vitamin D)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Increased catabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Drugs such as anticonvulsants and glucocorticoids activate the catabolism of both 25 OHD and calcitriol</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusive breast feeding &gt; 6/12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased Urinary loss</td>
</tr>
<tr>
<td>- Nephrotic syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Impaired vitamin D hydroxylation</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Liver failure</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Impaired vitamin D activation</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Chronic kidney disease</td>
</tr>
<tr>
<td>- Inherited enzyme deficiency</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acquired disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Primary hyperparathyroidism</td>
</tr>
<tr>
<td>- Granulomatous disorders (TB, sarcoidosis) are associated with increased activation of calcitriol</td>
</tr>
</tbody>
</table>

Vitamin D associated diseases

Classical diseases: Rickets & Osteomalacia
Vitamin D deficiency impairs the absorption of dietary calcium and phosphorus resulting in inadequate mineralisation of the bone matrix. The effects on muscle are equally important, causing loss of muscle mass, muscle weakness and abnormalities of contractility.

Non-classical disorders
There is a growing literature on the widespread tissue effects of vitamin D. Observational studies and meta-analyses suggest correlations between deficiency and a range of diseases. But data from large prospective interventionalal studies are currently lacking.

The following conditions are the most researched, but an exhaustive review is beyond the scope of this document.

Immunomodulation:
Many in vitro effects of vitamin D on the immune system have been described. Research suggests vitamin D enhances tolerance to autoimmune disease and increases antibacterial defence. Some observational studies have shown an association between reduction in type 1 diabetes in infants and provision of vitamin D supplements. A causative role in multiple sclerosis and Crohn’s disease has also been postulated.

Skin cathelicidins (antimicrobials) are induced by Vitamin D. Cathelicidin is also thought to have an important role in host response to mycobacterial and other respiratory infections.

Cancer:
Vitamin D has been shown in vitro to have effects on cell differentiation, proliferation and apoptosis.

Vitamin D deficiency has been linked to many forms of cancer. Observational data shows disparity in incidence and outcomes in individuals stratified by latitude, which is a surrogate marker of vitamin D status. Meta-analyses suggest that low vitamin D levels are related to breast, prostate and colorectal cancer risk. The association between vitamin D status and cancer outcomes remains uncertain.

Metabolic:
All aspects of the metabolic syndrome have been linked to vitamin D. Deficiency is associated with higher blood pressure, insulin resistance and obesity by effects on rennin, insulin and leptin levels.

Other:
Vitamin D receptor polymorphisms have been implicated in a number of diseases including asthma and chronic obstructive pulmonary disease.

Interventional studies in all these areas have been on a very small scale, and to date there is insufficient evidence to change clinical practice in these areas.

Vitamin D disorders in adults

Patients with vitamin D deficiency in whom there is suspicion of malabsorption, renal or hepatic disease, or where there is a co-existing condition leading to increased risk of toxicity with treatment, should be discussed with secondary care before initiating treatment.
Symptomatic deficiency: osteomalacia

In adults vitamin D deficiency (25OHD level less than 30nmol/l) can lead to osteomalacia. This often presents insidiously with bone pain, proximal muscle weakness and diffuse muscular aches. It is also associated with increased fracture risk. Biochemical abnormalities include hypocalcaemia, hypophosphataemia (both of which tend to be associated with longstanding symptomatic vitamin D deficiency) and raised alkaline phosphatase - which rises early in vitamin D deficiency.

Investigations

Renal function tests (U&E, eGFR)
Bone profile (Ca, PO4)
Liver function tests
Ferritin (to identify multiple vitamin deficiencies)
TFTs to exclude hypothyroidism
ESR where polymyalgia, inflammatory arthritis, or myeloma might be considered.

PTH will be elevated in vitamin D deficient states, but routine measurement is not indicated – except for patients with CKD (see below).
Persistently painful areas of bone may require further imaging to exclude other causes.

Treatment

Liquid “specials” of vitamin D (unlicensed) should NOT be routinely prescribed for adults. Cost effective alternatives are available.

Colecalciferol is the preferred form of vitamin D for treatment. It raises levels of 25 OHD more effectively than ergocalciferol.

Based on research into the response of serum 25 OHD to oral dosing with colecaciferol, a dose of 400 IU/day will elevate serum 25 OHD levels by approximately 10 nmol/l. Using 800IU a day (2x Calcichew D₃ Forte) it is estimated that osteomalacic bone may take a year to return to normal.

A single oral dose of 200,000 IU/day will raise serum 25 OHD to over 80 nmol/l, this effect starts within a week, and lasts for a maximum of two months. If the baseline level of 25 OHD is very low (<18nmol/l) a smaller loading dose (eg 100,000IU) may be insufficient to raise levels of 25 OHD into the optimal range.

The following loading dose treatment options are based on preparation strengths available at the time of publication (see table of preparations for further details)

- Colecalciferol 20,000IU / tablet.
  A loading dose of 5 tablets a day for 2 days (making a total dose of 200,000IU)
- A single Ergocalciferol 300,000IU / ml intramuscular injection. This is not first choice treatment in primary care, but can be used where oral therapy is not tolerated or concordance is likely to be poor.

The aim of treatment is to achieve 25 OHD levels of >80 nmol/l. If after 12 weeks the serum 25 OHD has not risen to a level of >80 nmol/l consider giving a repeat oral loading dose of 200,000IU followed by ongoing maintenance treatment.

Poor adherence to treatment is the most likely reason for a poor response to treatment though other causes, such as malabsorption, should be considered.

Following active treatment a daily maintenance dose of between 800 – 2000IU / day should be advised. This group of patients are likely to need long term preventative vitamin D supplementation.

This maintenance dose can be taken on a daily (e.g.1,000IU) or weekly basis (e.g.10,000IU once a week) depending on availability of preparations and patient preference. Daily dose medication mimics the body’s natural production of vitamin D most closely.

Monitoring

Vitamin D status and serum calcium should be checked at 8-12 weeks following active treatment with a loading dose.

Calcium levels should also be monitored at 4 and 8 weeks if:
- Risks of hypercalcaemia are higher than average such as in CKD, active TB, and patients on thiazide diuretics in combination with calcium supplements.
- Patients on digoxin and other cardiac glycosides – where drug effect may be accentuated by vitamin D
- Any symptoms or signs of hypercalcaemia (anorexia, nausea, thirst, polyuria, vomiting, diarrhoea, confusion)

There is no indication to monitor ALP routinely.

Management of asymptomatic vitamin D deficiency in adults (25 OHD <30nmol/L)

There is an absence of evidence on the value of active high dose treatment as for osteomalacia (see above) in those who have asymptomatic deficiency.

A daily supplement of 800-2,000IU a day (as a daily or weekly dose) will correct the vitamin D level over several months. As this group are likely to be at high risk of continuing deficiency they should remain on supplements long term.

An alternative approach is to treat as for osteomalacia with a 200,000IU oral loading dose. This is of questionable benefit in asymptomatic adults. This approach requires a review of vitamin D and serum calcium levels at 12 weeks, and a continuing maintenance dose long term.
Management of vitamin D insufficiency in adults (25 OHD 31-80nmol/L)

There is a lack of evidence on the functional outcomes of populations with insufficient levels of vitamin D.

Management should be with a long term vitamin D supplement at a dose range between 800-2000IU a day. In most instances (apart from the elderly in residential institutions) using a combination of calcium with vitamin D is unnecessary and unpalatable, reducing medication concordance.

No monitoring is required on these maintenance doses.

Vitamin D disorders in children

Any child whom you suspect to be hypocalcaemic secondary to vitamin D deficiency should be urgently referred to secondary care.

Paediatric reference ranges and definitions of deficiency are the same as for adults.

Children at risk of vitamin D deficiency/insufficiency:

- Maternal vitamin D deficiency
- Pigmented skin
- Lack of sunlight exposure
- Exclusively breast fed / delayed weaning
- Malabsorption e.g. cystic fibrosis
- Medications e.g. anticonvulsants

Rickets

The commonest cause of rickets is simple nutrient deficiency from low sun exposure combined with inadequate dietary intake. Malabsorption syndromes such as coeliac disease and cystic fibrosis should be considered, especially where there is a poor response to vitamin D treatment. Certain metabolic, renal and liver diseases can also lead to rickets.

Peak incidence of rickets is between 3 and 18 months of age. A deficient state exists for months before there are any signs on physical examination. Children with rickets are often miserable and in pain.

Symptoms and signs of rickets
- bowing of legs (genu varum) or knock knees (genu valgum)
- anterior bowing of the femur
- painful wrist swelling (distal radius)
- prominent costochondral joints “rickety rosary”
- softening of the skull with frontal bossing, and delayed fontanelle closure
- spinal curvature
- bone pain
- dental deformities (delayed tooth formation, enamel hypoplasia)

Investigations
Definitive diagnosis is based on specific radiological changes
Renal function tests (U&E, eGFR)
Bone profile (Ca, PO₄)
Liver function tests (raised ALP)
Hb and Ferritin (to identify multiple vitamin deficiencies)

Management of symptomatic vitamin D deficiency - Active Rickets

Treatment can be commenced in primary care. However if a child has bone deformities the child should be referred to the paediatric team.

Oral colecalciferol liquid is the treatment of choice.

Doses as recommended by the BNF:

- Child 1-6 months 3,000IU daily
- Child 6/12 – 12yrs 6,000IU daily
- Child 12-18yrs 10,000IU daily

These doses should be given for 8-12 weeks only. We advise they are not included on a ‘repeat medication’ list. The child should then be started on long term maintenance supplements.

In rare circumstances of poor concordance treatment with a bolus dose - 300,000IU colecalciferol in 2 divided doses for a child 1-12 years is indicated (Stoss therapy) 
*******Discuss with local paediatrician*******

Monitoring
After 3 months vitamin D, serum calcium and ALP should be rechecked.

The aim of treatment should be to reach a total Vitamin D level of >80nmol/l, normal ALP for age and resolution of radiological changes. If the vitamin D level is not >80nmol/l continue treatment for a further 2-3 months and recheck.

Once the total vitamin D level is within the normal range treatment should be changed to maintenance supplements as this group of children are likely to have ongoing risk factors for vitamin D deficiency.

The family and siblings of children with rickets are highly likely to be vitamin deficient. It is good practice to review family members and provide supplementation for those at high risk.

Daily maintenance supplements for children

- Neonate 400 IU/day
- Child 1 month-12 yrs 400-600 IU/ day

Suitable supplements are listed in the preparations table.

Management of asymptomatic vitamin D deficiency in children (25 OHD <30nmol/L)

There is a lack of evidence on the best treatment regime for children with 25 OHD levels of less than 30 nmol/l but without symptoms or clinical signs of rickets. These children are at very high risk of developing rickets and current advice is to provide treatment doses for 8-12 weeks (oral colecalciferol, see above) until the 25 OHD level is >80 nmol/l. (Check vitamin D and serum calcium at 3 months.) Maintenance supplements should then be continued long term.
Management of Vitamin D insufficiency in children (25 OHD 31-80nmol/l)

These children should receive daily preventative supplements at doses advised in the BNF (see above) there is no indication to monitor children on maintenance doses of vitamin D.

Safe sun exposure and dietary advice (including promoting adequate calcium intake) apply in all cases.

Population wide prevention of rickets
The DOH recommends daily vitamin D supplements in the following groups of children:

- All children from 6m – 5yrs
- Breastfed babies 1m – 6m if the mother is vitamin D deficient / insufficient

Local audits of vitamin D and multivitamin prescriptions for children aged 6m-5 years show low rates of uptake (around 10%).

Improving the availability and uptake of vitamin supplements for children in multiethnic populations is essential to the strategy of rickets prevention.

Practice audits on vitamin prescribing rates are easy to undertake in EMIS Web.

Summary of management guidance

<table>
<thead>
<tr>
<th>Serum 25 OHD level</th>
<th>Vitamin D status</th>
<th>Manifestation</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30 nmol/l</td>
<td>Deficient</td>
<td>Osteomalacia</td>
<td>Treat with vitamin D loading dose followed by supplementation</td>
</tr>
<tr>
<td>31-80 nmol/l</td>
<td>Insufficient</td>
<td>Associated with disease risk</td>
<td>Supplementation and diet/sunshine advice</td>
</tr>
<tr>
<td>&gt;80 nmol/l</td>
<td>Optimal</td>
<td>Healthy</td>
<td>None</td>
</tr>
</tbody>
</table>

Vitamin D and renal disease

In CKD there is decreased activation of vitamin D in the kidney, along with decreased gut calcium absorption and increased phosphate retention. As the eGFR declines these processes may trigger secondary hyperparathyroidism with bone reabsorption, pathological fractures and metastatic calcification leading to an increased risk of CVD.

Up to 30% of CKD stage 3 patients will have some disturbance of calcium metabolism.

1. Check the PTH (NR 1-6pmol/l) when the eGFR falls to about 45.

2. If the PTH is raised (> 7 pmol/l) check vitamin D levels (25 OHD). If this is low, indicating vitamin D deficiency treat with a dose aimed at achieving optimal levels (1,000IU a day)

3. Repeat PTH and 25 OHD at around three months.

4. If the PTH remains high (>10 pmol/l) and vitamin D levels are replete suggesting secondary hyperparathyroidism, refer or discuss with nephrologist.

As the eGFR declines further there will be inadequate production of active vitamin D (calcitriol). For these patients replacement with alphacalcidol will be needed under the supervision of the renal department.
Pregnancy and breastfeeding

Pregnancy
There is a direct correlation between maternal vitamin D status and that of the infant. If a mother is deficient at delivery the infant is at considerable risk of deficiency and the development of rickets.

There are few available national data on the vitamin D status of pregnant and breastfeeding women, but local data on ethnic minority groups show vitamin D deficiency to be common. Vitamin D status measured on 500 unselected antenatal women showed 74% to be deficient, 11% to be insufficient and 15% to have a normal vitamin D level.

The current NICE guidance (2008) on routine supplementation states:

“There is a need for research into the effectiveness of routine vitamin D supplementation for pregnant and breastfeeding women...although there is some evidence of benefit from vitamin D supplementation for pregnant women at risk of vitamin D deficiency; there is less evidence in the case of pregnant women currently regarded as being at low risk of deficiency.”

In summary there is a lack of evidence concerning:

- optimal levels of vitamin D during pregnancy and breastfeeding.
- what supplementation is required to reach those levels.
- functional outcomes both for the pregnancy and for the infant following vitamin D supplementation.
- possible harms of high-dose supplementation.

Preparations of vitamin D which also contain vitamin A (e.g. vitamins capsules) should not be prescribed during pregnancy as excessive vitamin A is associated with foetal CNS malformations.

Breastfeeding
The vitamin D content of breast milk is related to the mothers’ exposure to UV light and her dietary intake of vitamin D. While there is concern that a daily supplement of 400IU/day for lactating mothers will not raise vitamin D levels to the normal range, there is evidence that these amounts will prevent neonatal hypocalcaemia and rickets.

More evidence is required on the benefits and safety of high dose vitamin D supplements, before these can be routinely advised for pregnant and breast feeding mothers.

Vitamin D and the elderly

The elderly are at increased risk of vitamin D deficiency due to a combination of factors. These include lower sun exposure, and decreased skin synthesis of vitamin D especially in the residential home population, poor nutrition and lower levels of renal hydroxylation. The DoH (1991) recommend a dietary intake of 400IU in the population over 65 years.

SIGN guidance (2002) suggests the use of calcium with vitamin D for everyone over 65, as there is evidence for the reduction of hip fractures. This has been confirmed in a systematic review. It remains unclear whether vitamin D alone offers the same protection as the combination product.

Calcium plus vitamin D is cheap and safe at the suggested dose of 400 – 800IU, and may be a cost-effective intervention in these groups. This is an evolving area and further trials will inform practice in the future.

Until further research becomes available all pregnant and lactating women should be advised to take vitamin D 400IU a day. Healthy start vitamins are recommended (if available).

This dose is known to be adequate for the prevention of neonatal hypocalcaemia and infantile rickets.

Start infant supplements at 1 month (400IU a day) in breastfed babies if the mother is vitamin D insufficient / deficient. Healthy start vitamins are recommended (if available).

No monitoring is required for these doses.
A range of Vitamin D products available on prescription

Vitamin D products (loading/treatment doses):

<table>
<thead>
<tr>
<th>Product</th>
<th>Strength</th>
<th>Contents</th>
<th>Approximate Annual Cost per patient*</th>
<th>Suitability for vegans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colecalciferol capsules</td>
<td>20,000IU</td>
<td>D₃</td>
<td>Varying (from £15 to ~£90 for 50 capsules)</td>
<td>No</td>
</tr>
<tr>
<td>Ergocalciferol i.m. injection</td>
<td>7.5mg (300,000 IU) per 1ml</td>
<td>D₂</td>
<td>1ml ampoule - £8.50 2ml ampoule - £9.85</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Based on information in the British National Formulary 60, September 2010 and suppliers quoted

Vitamin D products (maintenance doses):

<table>
<thead>
<tr>
<th>Products</th>
<th>Strength</th>
<th>Contents</th>
<th>Approximate Annual Cost per patient*</th>
<th>Suitability for vegans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colecalciferol capsules/tablets</td>
<td>1,000IU/tablet</td>
<td>D₃</td>
<td>Varying (from £7.15 upwards for 100 tabs/caps) Can also be bought OTC e.g. Solgar, Biolife, Sunvite</td>
<td>Varying, prescribe “gelatin free” if required.</td>
</tr>
<tr>
<td>Calcichew D₃ capsules</td>
<td>200IU/tablet</td>
<td>D₃</td>
<td>£55.26</td>
<td>No</td>
</tr>
<tr>
<td>Calcichew D₃ Forte chewable tablets</td>
<td>400IU/tablet</td>
<td>D₃</td>
<td>£56</td>
<td>No</td>
</tr>
<tr>
<td>Adcal D₃ chewable tablets</td>
<td>400IU/tablet</td>
<td>D₃</td>
<td>£46.68</td>
<td>No</td>
</tr>
<tr>
<td>Adcal D₃ Dissolve tablets</td>
<td>400IU/tablet</td>
<td>D₃</td>
<td>£59.88</td>
<td>No</td>
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<tr>
<td>Calceos chewable tablets</td>
<td>400IU/tablet</td>
<td>D₃</td>
<td>£43.44</td>
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</tr>
<tr>
<td>Cacit D₃ effervescent granules</td>
<td>440IU/sachet</td>
<td>D₃</td>
<td>£97.44</td>
<td>No</td>
</tr>
<tr>
<td>Calfovit D₃ powder</td>
<td>800IU/sachet</td>
<td>D₃</td>
<td>£103.68</td>
<td>No</td>
</tr>
</tbody>
</table>

* Based on information in the British National Formulary 60, September 2010 and suppliers quoted

Examples of children’s products (licensed):

<table>
<thead>
<tr>
<th>Products (Branded)</th>
<th>Strength</th>
<th>Contents</th>
<th>Approximate Annual Cost per patient*</th>
<th>Suitability for vegans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketovite liquid</td>
<td>400IU, 5ml OD</td>
<td>D₃ (+multivitamins)</td>
<td>£32.40</td>
<td>Yes</td>
</tr>
<tr>
<td>Dalivit drops</td>
<td>400IU, 0.6ml OD</td>
<td>D₃ (+multivitamins)</td>
<td>£35.76</td>
<td>Yes</td>
</tr>
<tr>
<td>Abidec drops</td>
<td>400IU, 0.6ml OD</td>
<td>D₃ (+multivitamins)</td>
<td>£26.40</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Special liquids (unlicensed):

<table>
<thead>
<tr>
<th>Products</th>
<th>Strength and daily dose of vitamin D</th>
<th>Contents</th>
<th>Approximate Annual Cost per patient**</th>
<th>Suitability for vegans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colecalciferol liquid</td>
<td>3,000IU/ml***</td>
<td>D₃</td>
<td>£1013</td>
<td>Yes</td>
</tr>
<tr>
<td>Ergocalciferol liquid</td>
<td>3,000IU/ml***</td>
<td>D₂</td>
<td>£1708</td>
<td>Yes</td>
</tr>
</tbody>
</table>

** Average cost at PCT level taking from ePACT data
***No other strength of Specials liquid is recommended, nor are liquid specials recommended for adults
Over the counter preparations

A wide range of vitamin D preparations, in varying strengths, is available from health food shops and pharmacists. Many of these are suitable for vegans. Examples include Solgar Vitamin D, 25μg (1,000IU) or 55μg (2,200IU), BioLife Vitamin D, 25μg (1,000IU) suitable for vegetarians, Sunvite Vitamin D, 25μg (1,000IU) or 50μg (2,000IU), Holland & Barrett colecalciferol 10μg (400IU) or 25μg (1,000IU).

Safety of vitamin D preparations

Prolonged sunlight exposure does not lead to excess production of vitamin D as a regulation mechanism exists to destroy excess pre-vitamin D in the skin. However, high doses of vitamin D supplements can be toxic (resulting in hypercalcaemia and renal failure). This is only likely to occur if high dose formulations (used as initial treatment loading doses) are taken over a prolonged period of time, or if alfacalcidol or calcitriol are given in error.

There is a small risk of hypercalcaemia developing in the presence of undiagnosed sarcoidosis or primary hyperparathyroidism.

<table>
<thead>
<tr>
<th>Symptoms of overdose (hypercalcaemia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>anorexia, nausea, vomiting, diarrhoea, constipation, lassitude, vertigo, polyuria, thirst, sweating, headache and weight loss</td>
</tr>
<tr>
<td>Patient who are symptomatic and hypercalcaemic should have their management discussed with specialist clinicians without delay.</td>
</tr>
</tbody>
</table>

- Vitamin D treatment doses are contraindicated in patients with hypercalcaemia or metastatic calcification, or where there may be significant interactions with other medications.
- Vitamin D requirements are possibly increased with concomitant use of Barbituates, carbamazepine, phenytoin and primidone.
- Supplements of vitamin D containing vitamin A should not be prescribed in pregnancy as excessive vitamin A doses are associated with foetal CNS malformations.
- Alfacalcidol and calcitriol should NOT be prescribed for vitamin D deficiency.

Advice for clinicians

<table>
<thead>
<tr>
<th>Barts and the London NHS trust</th>
<th>Endocrine telephone advice clinic</th>
<th>Telephone the referral to 020 346 55044 (24-hour answer phone)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paediatric endocrine advice</td>
<td>General paediatric advice</td>
<td>020 7377 7468</td>
</tr>
<tr>
<td>Paediatric endocrine advice</td>
<td>General paediatric advice</td>
<td>020 7377 7000 bleep paediatric registrar on call</td>
</tr>
<tr>
<td>Homerton hospital NHS trust</td>
<td>Mr Peter Timms, consultant clinical biochemist</td>
<td>O20 8510 7886</td>
</tr>
<tr>
<td>Newham university hospital NHS trust</td>
<td>Mr Peter Timms, consultant clinical biochemist</td>
<td>O20 8510 7886</td>
</tr>
</tbody>
</table>

Acknowledgements

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