

East Lancashire Health Economy Guideline

Diagnosis and Management of Vitamin D Deficiency for Non-Specialists

Aims of Guideline

- 1) Advice on the diagnosis and management of Vitamin D deficiency in adults and children.
2. Clinical and cost effective investigation of suspected Vitamin D deficiency.
- 3) Clinical and cost effective prescribing of Vitamin D therapy and choice of supplements.
- 4) An appropriate balance between patient lifestyle, self management and medical treatment.

Vitamin D physiology

Vitamin D₃ (Cholecalciferol) is normally synthesized in the skin through the action of ultraviolet light on cholesterol. In the UK, this can only occur from April to September. Vitamin D is converted in the liver to 25OH Vitamin D which is the major storage form and what is measured in the laboratory.

Cholecalciferol is also available in the diet, and largely obtained from seafood and its derivatives. It is unusual to get more than 20% of total intake from a normal diet. Dietary supplements of a plant derived sterol (Ergocalciferol, Vitamin D₂) are also available. Vitamin D₂ has equal potency but a shorter half life.

In order to exert its effects on bone metabolism and calcium absorption, Vitamin D must first be converted to 1-25 OH Vitamin D, which occurs through the action of parathyroid hormone (PTH). This is a self regulating process, evidence of Vitamin D deficiency then being manifest through high levels of PTH.

At present, most of our knowledge and evidence base for management of Vitamin D related issues comes from effects on bone metabolism. Until large prospective studies have reported on emerging issues in relation to the potential for reducing heart disease, diabetes and cancer risk, no specific guidance is given here.

Treatment is not the same as supplementation: the recommended daily amount of 400 IU vitamin D will be insufficient to ‘treat’ an adult or child with osteomalacia or rickets respectively.

Risk factors for Vitamin D deficiency

Inadequate UV light exposure	Poor oral intake	Metabolic risk
Northern latitude Air pollution Occlusive garments Pigmented skin Habitual sunscreen use Institutionalised or housebound	Vegetarian (or fish-free diet) Malabsorption, short bowel, or cholestatic liver disease Cholestyramine use Breast fed infant	Reduced synthesis Elderly Increased Breakdown Drugs (Rifampicin, anticonvulsants, HAART therapy, glucocorticoids). Reduced stores Liver disease Multiple, short interval pregnancies

Clinical features of Vitamin D deficiency

SYMPTOM, SIGN, BIOCHEMISTRY	CHILDREN	ADULT
Seizures	√	√
Tetany	√	√
Hypocalcaemia	√	√
Irritability	√	
Leg bowing	√	
Knock knees	√	
Impaired linear growth	√	
Delayed walking	√	
Limb girdle pain	√	√
Muscle pain	√	√
Proximal myopathy	√	√

Assessing the 'patient'

Population screening by measuring Vitamin D levels is unnecessary even in high risk populations.

Patient characteristics	Advice and management
Healthy, no risk factors, symptom free	No investigations required Lifestyle advice Consider preventive therapies
Risk factors only (see above)	Lifestyle advice Consider long term preventative therapies
Risk factors AND symptoms/signs	Lifestyle advice Investigations Therapeutic intervention Long term preventative treatment

Investigations

Test	Reason
Renal function	Exclude renal disease
Liver function (albumin)	
FBC	Iron deficiency commonly co-exists
Parathyroid hormone	
Calcium	
Phosphate	
Alkaline phosphatase	
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25OH Vitamin D levels	See below for guidance on whether to assay
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1-25OH Vitamin D levels	ONLY if granulomatous disease suspected
24h urine calcium	ONLY where Vitamin D excess suspected

Measurement & Interpretation of serum 25-hydroxyvitamin D concentrations

Is it necessary to always assay serum 25-hydroxyvitamin D concentrations?

Children – Yes, all children with suspected vitamin D deficiency should have their levels assayed.

Adults – Not necessarily. Vitamin D deficiency can be assumed for those adults presenting with classical symptoms/signs of vitamin D deficiency AND with known risk factors AND with abnormal biochemistry (e.g. raised Alk Phos). They can be started on empirical 'maintenance' treatment with vitamin D. However, not all patients with symptoms/signs of vitamin D deficiency will have abnormal biochemistry, and in these cases assaying of vitamin D levels is the definitive diagnostic method.

Serum 25-hydroxyvitamin D concentrations, status and management	
<10ng/mL	Deficiency: high dose treatment initially, then long term maintenance treatment required.
10-20ng/mL	Insufficiency: long term maintenance treatment required
20-30ng/mL	Healthy, give lifestyle advice
>40ng/mL	Optimal

Referral to a specialist is advised for the following groups of patients.

All children under 1 year	Atypical biochemistry	Atypical clinical manifestations or biochemistry
Deficiency due to malabsorption	Failure to respond to treatment after 3 months	Focal bone pain
Liver disease	Lymphoma	Metastatic cancer
Parathyroid disorders	Renal disease	Renal stones
Sarcoidosis	Short stature	Skeletal deformity
Tuberculosis	Unexplained deficiency	Unexplained weight loss

Advice on prescribing of Vitamin D and calcium supplements for ADULTS

Daily treatment with Vitamin D (either Cholecalciferol or Ergocalciferol) is associated with a rise in measured vitamin D levels, representing an increased amount of stored Vitamin D. In adults, each 100 units of vitamin D taken daily will normally raise vitamin D levels by 1 ng/ml. Provided basic investigations are undertaken before treatment and renal disease, liver disease, primary hyperparathyroidism and inflammatory conditions have been excluded, then Vitamin D toxicity is very rare. Toxicity is normally only seen when the blood level exceeds 90ng/ml (220nmol/l). Extremely large daily doses in excess of 250 mcg or 10,000 units are generally required to achieve this (Hathcock et al 2007).

Patient characteristics	Advice and management
<p>‘Deficiency’ in adults (<10ng/ml)</p> <p><small>*To convert international units to micrograms of ergocalciferol, divide by 40.</small></p>	<p>Dekristol® (cholecalciferol) capsules 20 000 international units [unlicensed import]. Prescribe 15 capsules (15 x 20,000 international units) as a single dose (or can be taken over a number of days) = 300,000 international units total dose. N.B. Likely to contain gelatin. <i>Once corrected remember to then give long term maintenance treatment below.</i></p> <p>Alternatively Ergocalciferol 300,000 (or 600,000) international units* single dose by intramuscular injection (4). The injection is gelatin free and may be preferred for some populations. <i>Then give long term maintenance treatment below.</i></p>
<p>‘Insufficiency’ in adults** (10- 20ng/ml)</p> <p>OR</p> <p>long term maintenance therapy following treatment of deficiency in adults</p> <p><small>**this includes those with known risk factors AND signs/symptoms AND abnormal biochemistry without assaying vitamin D levels</small></p>	<p>Advise self treatment with ‘over the counter’ high strength vitamin D preparation of up to 2000-2500 international units daily (equivalent to 50 to 62.5 micrograms daily).</p> <p>OR</p> <p>Prescribe Dekristol® (cholecalciferol) capsules 20 000 international units [unlicensed import]. Prescribe 2 capsules (2 x 20,000 international units) each MONTH. N.B. Likely to contain gelatin.</p> <p>Alternatively Ergocalciferol 300,000 international units single dose by intramuscular injection once or twice a YEAR (4).</p>
<p>Healthy, no risk factors, symptom free (Intake and synthesis presumed adequate)</p>	<p>Life style advice. Can consider daily self treatment with purchased supplement of 400-800 units vitamin D daily – amount likely to prevent rickets, but unlikely to significantly raise vitamin D levels to ‘optimal’ in most people.</p>

Prescribing responsibility for adults: GREEN Traffic light.

Dekristol® capsules contain gelatin. The ergocalciferol injection is gelatin free and may be administered safely using a plastic syringe.

Intestinal Malabsorption/Chronic liver disease

Vitamin D deficiency in intestinal malabsorption or in chronic liver disease often requires higher doses of pharmacological vitamin D than for primary deficiency (see BNF). The BMJ article suggests doses such as ergocalciferol 300,000 international units by intramuscular injection monthly for 3 months, followed by 300,000 international units by intramuscular injection once or twice a year is suggested.

Should adult patients be advised to take Calcium supplements also?

Clinicians should avoid giving combined calcium and vitamin D preparations in the long term because the calcium component is usually unnecessary, makes for unpalatability, and reduces concordance. Where there is severe deficiency accompanied by hypocalcaemia, leading to secondary hyperparathyroidism, treatment with Vitamin D should be accompanied at least initially by Calcium supplementation 1-2 grams daily – consider referral for advice. Much more vigilant monitoring of calcium levels is required to prevent hypercalcaemia – see ‘monitoring’ requirements. Dietary calcium deficiency is common in some patient groups (low meat and milk product intake) and may be significantly exacerbated where there is a high dietary intake of phytate (chapatti flour, wholegrain and wholemeal flour) which binds calcium in the intestine. These patients should be advised to take 1-2 grams of calcium daily long term which can be purchased over the counter.

Advice on prescribing of Vitamin D and calcium supplements for CHILDREN.

If a child has vitamin D insufficiency or deficiency it is probable the mother and other siblings are similarly affected. They will need testing and may need therapy as well.

Deficiency treatment in children (<10ng/ml)

Child OVER 1 year: Ergocalciferol 300,000 international units single dose by intramuscular injection.
Alternatively: Dekristol® (cholecalciferol) capsules 20 000 international units [unlicensed import]. Prescribe 3 capsules (3 x 20,000 international units) daily for 5 days then stop. N.B. Capsules cannot be opened or crushed.

Prescribing responsibility for children over 1 year: GREEN Traffic light: Primary care professionals may be asked to prescribe and administer the IM injection for children over 1 year as a single dose in primary care. The injection has been widely administered using plastic syringes 'off label' without significant problems or additional adverse events.

Assessment of response: See *monitoring requirements*. In some children depending on response, a repeat dose may be required after 2-3 months. Responders should be offered long term maintenance treatment with vitamin D, see below.

*To convert international units to micrograms of ergocalciferol, divide by 40.

Child UNDER 1 year: Ergocalciferol injection will be prescribed and administered based on the age and weight of the child in a secondary care setting.

Alternatively: Under 6 months: 3000 international units ergocalciferol solution daily for 8-12 weeks. Prescribe 3 x 20ml ergocalciferol solution 1500 international units per mL for each months supply. [unlicensed special]

6 months to 1 year: 6000 international units ergocalciferol solution daily for 8-12 weeks. Prescribe 6 x 20ml ergocalciferol solution 1500 international units per mL for each months supply. [unlicensed special]

Prescribing responsibility for children under 1 year: RED Traffic light (Specialist only): Children under 1 year will receive the single dose of IM ergocalciferol in a secondary care setting, or will be prescribed with 2-3 months of ergocalciferol solution by the paediatrician. This will be dispensed by ELHT pharmacy in monthly installments. The injection has been widely administered using plastic syringes 'off label' without significant problems or additional adverse events.

Assessment of response: See *monitoring requirements*. In some children depending on response, a repeat dose may be required after 2-3 months. Responders should be offered long term maintenance treatment with vitamin D, see below.

Calcium supplementation for children with vitamin D deficiency

Calcium supplementation (50mg/kg a day – see BNF) is advisable during the first 2 weeks of vitamin D therapy in the growing child.⁴ In those who are hypocalcaemic, calcium supplementation may be needed for longer, but close monitoring is required to prevent hypercalcaemia and it is advisable to refer to the paediatricians. See *monitoring requirements* below.

Insufficiency (10-20ng/ml) or Maintenance therapy following deficiency treatment in children

Child UNDER 1 year: Healthy Start Vitamins (offered to all children up to age of 5 years locally). Alternatively Abidec® drops 0.3mL daily (= ergocalciferol 200 international units/day). To be continued until 5yrs of age, with the dose increased to 0.6mL after the age of 1 year. ‡

Child OVER 1 year: Healthy Start Vitamins (offered to all children up to age of 5 years locally). Alternatively prescribe as Abidec® drops 0.6mL daily (= ergocalciferol 400 international units/day). To be continued until puberty (after age of 5 years Abidec® has to be used in place of Healthy Start vitamins).

‡ 200 international units may be inadequate for breastfed babies with low vitamin D stores at birth.

Supplementary Information

Monitoring requirements

Important. All patients receiving therapy for vitamin D deficiency should be monitored as follows:

- 1 month: plasma-calcium concentration checked
- 3 months: plasma-calcium, phosphate, alkaline phosphatase and parathyroid hormone* checked.

*Measuring PTH is difficult in the community because the sample has to reach the lab within four hours. Ensure sample taken at correct time to allow transport to lab for analysis, and sample is clearly labelled.

Important. All patients receiving calcium supplementation for hypocalcaemia, in addition to pharmacological doses of vitamin D need more frequent monitoring of plasma-calcium every 1-2 weeks in the first months of treatment to determine length of time calcium supplementation is needed and to avoid hypercalcaemia. Patients or carers should be informed about the symptoms of hypercalcaemia e.g. weight loss, sickness, vomiting, headache, abdominal pain, apathy, polyuria.

Available Vitamin D preparations

The BNF lists two single ingredient products of high dose ergocalciferol (e.g. Ergocalciferol tablets 10,000 & 50,000 international units). Due to ongoing supply problems neither of these preparations are currently available in the UK. As such, the recommendations below outline the range of alternative products which may be available, the doses recommended, and the cost. See below & above.

Special considerations in relation to the preparation used.

- Ability to take or absorb oral medication (e.g. malabsorption)
- Gelatin excipients in capsules may be of Porcine origin (see 'supplemental information' overleaf)
- Tolerability in selected patients
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Supplies of higher dose vitamin D preparations:

There are two preparations that could be imported and are considered of suitable strength for intermittent dosing in primary vitamin D deficiency:

Preferred product: Colecalciferol (Dekristol®) 20,000 units x 50 capsules (£16 approx) [Unlicensed import]. (Dekristol®, MIBE, Brehna, Germany). Likely to incur additional delivery charge.

Alternative: Ergocalciferol capsules 1.25mg (50 000 units) x 50 (£273 approx) [Unlicensed import]. Likely to incur additional delivery charge.

Colecalciferol capsules are the more readily available and the cheaper preparation. Both of these products are likely to contain gelatin. Community pharmacists can obtain these preparations from an import company (see BNF for details), with delivery taking about two days.

Injection

There is a licensed UK injection of ergocalciferol. This is gelatin free and is currently available. An intermittent regimen for primary vitamin D deficiency would be off-label (see previously).

Ergocalciferol, 7.5 mg (300 000 units)/mL in oil, Injection for intramuscular use only. 1-mL amp = £7.45, 2-mL amp = £8.95.

NOT RECOMMENDED: Named patient liquid 'specials' of vitamin D (unlicensed) for adults in primary care should NOT be routinely prescribed.

Due to the exorbitant cost of some of these preparation in primary care (e.g. up to £500 for 30ml) these should NOT be routinely prescribed. A named patient supply of an unlicensed liquid preparation of vitamin D should only be used in exceptional circumstances where patients are unable to use colecalciferol capsules or the injection above (e.g. PEG feeding & needle phobic).

An ergocalciferol or colecalciferol oral solution can be obtained by a community pharmacist from a specials manufacturer. The manufacturer will prepare any strength and volume required. These solutions are very expensive (the price being determined by the strength and volume ordered) and have a short shelf life of one to two months from the date of manufacture. These solutions would be gelatin free. Oral solutions could be given on a daily basis depending on the strength.

Only where absolutely necessary: Cholecalciferol solution 1500 units/ml 20mL (e.g. Uvesterol D®) or 10,000 units/mL both unlicensed specials [usually 28 day expiry] are available from specials manufacturers. Details of such companies and others can be found in the BNF.

Alfacalcidol/Calcitriol (Specialist initiation only)

Alfacalcidol and Calcitriol have no routine place in the management of primary vitamin D deficiency and should be reserved for use in renal disease, liver disease and primary hypoparathyroidism. Vitamin D requires hydroxylation, by the kidney and liver, to its active form therefore the hydroxylated derivatives alfacalcidol (or calcitriol) should be prescribed on the advice of a specialist only (see BNF). Ordinarily these short acting, potent vitamin D analogues such as alfacalcidol and calcitriol are ineffective in correcting vitamin D deficiency and may lead to hypercalcaemia.(2)

Pregnancy & Breastfeeding

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

High dose intermittent regimes are not suitable in pregnancy, and daily dosing is preferred:

- Deficiency in adults: 1 x 20,000 international units Dekristol® capsule on alternate days for 8-12 weeks. [unlicensed imported product]
- Insufficiency in adults or maintenance following deficiency: 1000-2000 international units daily

Gelatin Free & Halal Products

Most vitamin D preparations contain gelatin which is an animal derived product. Not all gelatin products are forbidden to Muslims; porcine-derived gelatin and that from non-Halal sources are not allowed. Fish gelatin is considered Halal and is acceptable. Similarly, gelatin of bovine origin is acceptable if the source is Halal. However, it is difficult to determine whether the gelatin used in the manufacture of pharmaceutical products is Halal. Manufacturers generally do not have this information. There is pragmatic advice available in the form of a WHO statement agreed with the Islamic Organisation for Medical Sciences which advises that all gelatin used in pharmaceuticals can be considered Halal (1). This makes the choice of agent more straightforward. However, some Imams do not agree with this statement, so number of other options are detailed below. To ensure a pharmacological dose of vitamin D which is devoid of gelatin (preventing use of the imported colecalciferol capsules) the options include:

- ❖ the licensed IM ergocalciferol injection– which is gelatin free
- ❖ prescribe or advise to purchase an over the counter gelatin free product for daily dosing – see below
- ❖ as a last line resort – prescribe an unlicensed oral solution made by a specials manufacturer – which would be gelatin-free

Alternatively, patients can be directed to buy Solgar® (Vitamin D3 – Cholecalciferol) vegetarian capsules in two strengths: 600 international units priced at £6.90 for a pot of 60 capsules, and 2200 international units priced at £8.09 for a pot of 50 capsules. It appears that this product does not include any animal-derived ingredients and as such may be more acceptable to Muslim and other patients. These products are available from health food shops. Solgar® is not listed in Part XVIII A of the Drug Tariff (the 'black list') as of April 2010; it can therefore legally be prescribed on an NHS FP10 prescription, but not all community pharmacies maybe able to obtain it as it is not listed in the Chemist & Druggist.

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