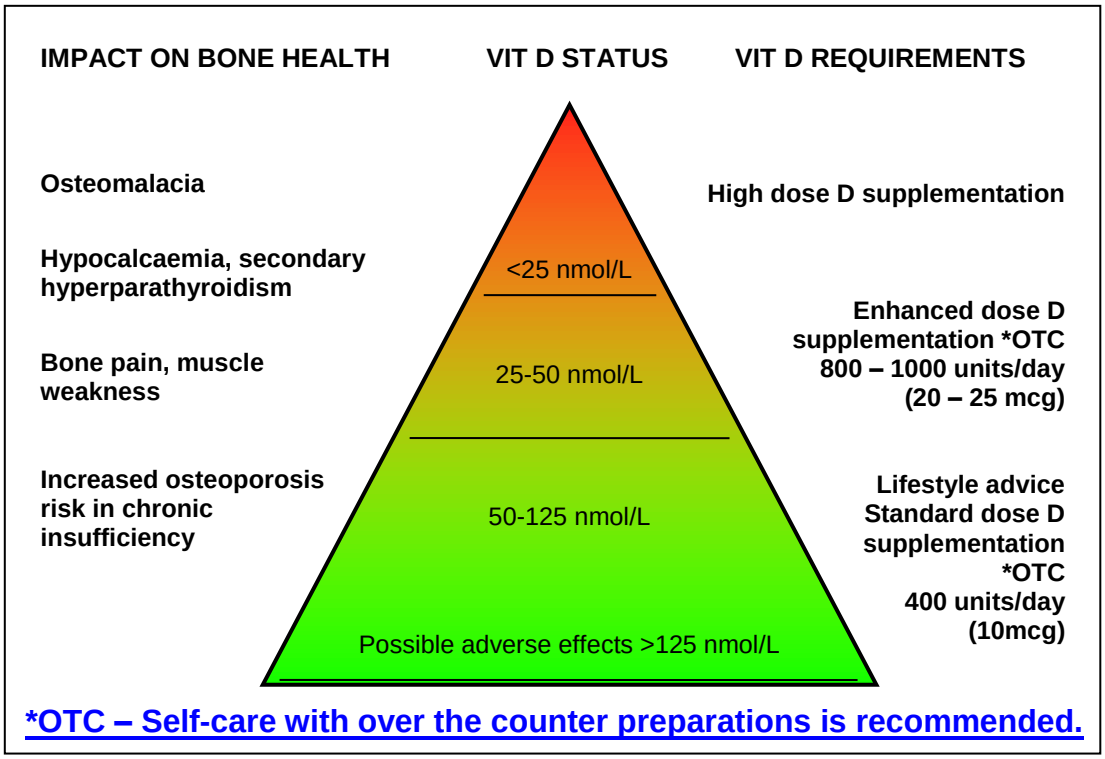
NHS
Sheffield
Clinical Commissioning Group

Sheffield Guidance on Optimising Vitamin D for Adult Bone Health

- **Raise awareness** of the importance of Vitamin D to bone health and make lifestyle advice available to all patients

- **Measure** "Vitamin D profile" only in at-risk individuals with sign and symptoms of deficiency



- **Individuals with osteomalacia or** persisting level <25nmol/L despite treatment require further investigation for underlying cause and impact on bone health

- **Management** involves:
  - For individuals with **25(OH)D <25 nmol/L**
    - Initial high dose supplementation and long-term enhanced dose supplementation
  - For individuals with **25(OH)D 25-50 nmol/L**
    - long-term enhanced dose supplementation
  - **Lifestyle advice for all**

Contact the Metabolic Bone Centre for further advice
0114 271 5340 or sht-tr.MetabolicBone@nhs.net

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What is Vitamin D and why is it important?

Vitamin D is a prohormone which is essential for skeletal health. It increases calcium absorption and facilitates bone mineralisation. Deficiency is associated with development of osteomalacia. Low Vitamin D levels are common and important even in the absence of overt osteomalacia as they are associated with an increased risk of falls and fracture.

Vitamin D may also have a role outside the musculoskeletal system and associations between low Vitamin D and many conditions including cancer, type 2 diabetes, hypertension and autoimmune diseases have been demonstrated but evidence for causal links have not yet been established.

Sources of Vitamin D

Vitamin D is primarily obtained from exposure of the skin to UVB light from the sun or artificial sources.

There are very few foods providing a natural source of Vitamin D. Consequently, dietary sources provide only approximately 10-15% of daily requirements. They include:

- Oily fish (such as sardines, pilchards, herring, trout, tuna, salmon and mackerel)
- Liver
- Egg yolk
- Mushrooms
- Cheese, milk and butter (small amounts)
- Fortified foods (some margarines and breakfast cereals in UK)

Most multivitamin preparations contain small amounts of Vitamin D (typically 100-200 units per daily dose). There are also a number of supplements containing varying amounts of calcium and Vitamin D. Cod liver oil and other fish oils are rich in Vitamin D (up to 500 units per daily dose) but also contain Vitamin A and the manufacturer's recommended dose should not be exceeded. For this reason, fish oil should not be recommended as a source of Vitamin D during pregnancy.

Vitamin D synthesis and metabolism

Vitamin D exists in two forms, D_3 (colecalciferol) and D_2 (ergocalciferol) that differ chemically only in their side-chain structure. Colecalciferol is synthesised in skin through the effect of UVB radiation on cholesterol precursors. UVB at the correct wavelength (280-315 nm) is present in sunlight when the UV index is greater than 3 (April to October in the UK) but is filtered out by glass and sunscreen with SPF>8. Only a minimal amount of UVB of the correct wavelength is generated by the UV lamps used in sunbeds and this is therefore not a recommended source. The cutaneous production of Vitamin D is regulated locally as a result of degradation which is dependent on the intensity and duration of the UV irradiation. This prevents Vitamin D toxicity from occurring in sunny climates. Ergocalciferol is synthesised by invertebrates, fungi and plants, also in response to UVB irradiation.

Vitamin D is 25-hydroxylated in the liver to calcidiol (25(OH)D) which is fat soluble and acts as the main transport and storage form. This process continues even in the presence of significant hepatic disease. Calcidiol is stored in hepatocytes and adipocytes and transported in the circulation bound to Vitamin D binding protein. Circulating calcidiol is further hydroxylated in the kidney to the main active metabolite calcitriol (1,25-$(OH)_2$D). Synthesis of calcitriol is reduced with ageing and markedly reduced in renal impairment. This leads to reduced calcium absorption and secondary hyperparathyroidism.

Activation of Vitamin D is regulated predominantly by the action of parathyroid hormone on the kidney. Its effects are mediated by the Vitamin D receptor (VDR), located in the nuclei of target cells. VDR are present in many tissues but activation in bone, gut, parathyroid and kidney is mainly responsible for maintaining calcium and phosphate homeostasis. Activation of Vitamin D to calcitriol may also occur extra-renally, for example by cells of monocyte-macrophage lineage. This may occur in pathological situations such as sarcoid granuloma and lead to hypercalcaemia.

Role of Vitamin D

The main actions of calcitriol are to increase intestinal absorption of calcium and phosphate and facilitate mineralisation of bone. Vitamin D is therefore an important component in the regulation of calcium homeostasis acting to increase serum calcium.

Consequences of Vitamin D deficiency

Low Vitamin D leads to a reduction in the fractional calcium absorption in the gut. The decrease in serum calcium is detected by the calcium-sensing receptors in the parathyroid glands leading to an increased synthesis and release of parathyroid hormone (PTH). PTH restores serum calcium through effects of increased bone resorption, increased renal retention of calcium and by increasing activation of Vitamin D. Serum calcium can therefore be maintained by secondary hyperparathyroidism until Vitamin D deficiency is severe and prolonged. Chronic secondary hyperparathyroidism is a risk factor for osteoporosis as a consequence of increased bone resorption causing bone loss.

Vitamin D has other roles including modulation of cell growth, neuromuscular and immune function and anti-inflammatory function. Many genes encoding proteins that regulate cell proliferation, differentiation and apoptosis are, at least in part, regulated by Vitamin D. Vitamin D receptors are present on many cell types and some cell types have the ability to activate Vitamin D outside the kidney. The consequences of Vitamin D deficiency and supplementation on these processes remain to be elucidated.

Recommended Vitamin D intake for adults

In July 2016, Public Health England (PHE) changed their advice based on the recommendations from the Scientific Advisory Committee on Nutrition (SACN) following its review on Vitamin D and Health. They provided the following recommendations:

- In spring and summer, the majority of the population obtains enough Vitamin D through sunlight and diet. However during autumn and winter, it is advised everyone in the UK should consider taking a daily 400 units (10mcg) supplementation.
- Those whose skin has little or no sun exposure including those who cover their skin for cultural reasons, who are housebound or confined indoors for long periods and those of darker skin i.e. Africa, African Caribbean and South Asian origin should consider taking a supplement containing 400 units (10mcg) all year round.
- In addition to this, previous advice from the UK Chief Medical Officers and NICE Guidance still stands that recommends all pregnant and breastfeeding women, especially teenagers and young women should also take a daily 400 unit (10mcg) supplement.
- See link for local guidance and advice around children

Causes of Vitamin D deficiency

In the UK, inadequate sun exposure is the most common cause of low Vitamin D levels. This may be exacerbated by the presence of additional risk factors and it is important to consider if any of these are present, especially if a sub-optimal response to treatment is observed.

- **Inadequate sunlight exposure**
    - Pigmented skin
    - Occlusive garments
    - Housebound or prolonged institutional care
    - Habitual use of high factor sunscreen (>SPF 8)
- **Restricted intake**
    - Malabsorption or short bowel syndromes including those with Cystic Fibrosis and Inflammatory Bowel Disease
    - Cholestatic liver disease
    - Cholestyramine use
- **Reduced synthesis / storage problems**
    - Elderly
    - Chronic renal or liver disease
    - Multiple, close pregnancies
    - Obesity
- **Increased degradation**
    - Medication causing induction of hepatic enzymes, e.g. anticonvulsants

Who is at risk?

At-risk groups may be summarised as below.

- Elderly, particularly housebound or institutionalised
- Limited sunlight exposure including dark skin, occlusive clothing, high-factor sunscreen
- Malnutrition states including those with Cystic Fibrosis and Inflammatory Bowel Disease
- Renal or hepatic disease, medication causing induction of liver enzymes
- Obese
- Pregnant and breastfeeding women (see separate guidance)
- Children (see separate guidance)

In addition to this, NICE PH56 ‘Vitamin D: increasing supplement use among at-risk groups’ recommends primary care should promote this message whenever possible through routine appointments and health checks.

Definitions of Vitamin D status

The Vitamin D status is established from measurement of the serum level of 25(OH)D. This represents the Vitamin D produced cutaneously and that obtained from the diet and supplements. 25(OH)D has a fairly long half-life (15 days) and functions as a good marker of exposure. Circulating 1,25-$(OH)_2$D is not a good indicator of Vitamin D status as it has a short half-life (15 hours) and levels do not decrease until deficiency is severe.

There is considerable controversy over the level of 25(OH)D required for optimal bone health. Some experts, particularly in the US, advocate levels of 75 or even 100 nmol/L.

SACN advises that the risk of poor musculoskeletal health is increased at serum 25(OH)D concentrations below 25 nmol/L and, to protect musculoskeletal health, levels should not fall below this level at any time of year. The American Institute of Medicine advises that a level up to 50nmol/L may be inadequate in some people and a level above 50nmol/L is sufficient for almost the whole population.

Vitamin D is associated with an inverse gradient of risk for adverse effects on bone health. This can be further defined through clinical evaluation and additional investigation.

Clinical presentation of Vitamin D deficiency

There is a gradient of risk with an increasing likelihood of signs and symptoms with very low levels of Vitamin D, particularly if these are longstanding. Symptoms are generally gradual in onset. They may be seasonal and more marked over the winter months. Characteristic features include:

- Bone pain without preceding mechanical injury
    - Commonly affects back or lower limbs
    - Gradual onset, persistent
- Proximal muscle weakness
    - Difficulty with stairs, standing after sitting in a low chair
    - Waddling gait
- Signs/symptoms of underlying condition
    - e.g. malabsorption (i.e. Inflammatory Bowel Disease)
- Low trauma fracture
    - May have history of prodromal pain
    - Typical sites include ribs, sacrum, pelvis, hip

Vertebral fractures associated with Vitamin D deficiency classically present with biconcave appearance of several vertebrae

Investigation

Indicated in an at-risk individual with clinical suspicion of deficiency because of:

- Signs and/or symptoms consistent with Vitamin D deficiency
- Abnormalities on laboratory investigations suggestive of Vitamin D deficiency e.g.
    - Hypocalcaemia
    - Increased PTH
    - Increased alkaline phosphatase of bone origin (i.e. with normal GGT)

Screening for Vitamin D deficiency in individuals in at-risk groups who are well is **not** supported by the evidence and is discouraged

Initial investigation – Vitamin D profile (STH lab)

Request "Vitamin D profile" (gold top blood sample) to the STH clinical chemistry laboratory which consists of:

- 25(OH) Vitamin D, Ca, PO_4, alkaline phosphatase, albumin, creatinine

Results are reported as follows:

- <25 nmol/L – Suggest high dose supplementation
- 25-50 nmol/L – If bone health an issue, suggest OTC enhanced dose supplementation. No repeat Vitamin D measurement required
- 50-125 nmol/L – Reassure - No action required

Remember that Vitamin D levels are seasonal. A very high proportion of individuals in the UK will have evidence of borderline low Vitamin D levels at the end of the winter months. A low level at the end of the summer months, however, suggests the individual is likely to develop overt deficiency in the winter and warrants more aggressive supplementation.

Vitamin D measurement is usually only required at baseline and should only be considered in the follow-up of patients who require high dose supplementation (those with baseline values <25nmol/L)

Investigations for an underlying cause of Vitamin D deficiency

This will depend on the clinical presentation. Consider the following:

- Malabsorption screen (e.g. FBC, coeliac antibodies)
- If alkaline phosphatase is increased, measure liver function tests (LFT) and GGT to assess whether this is of liver or bone origin
    - Isolated increase in alkaline phosphatase with normal LFT and GGT suggests bony cause
- Renal disease – this will be indicated by increased creatinine and secondary hyperparathyroidism. Further investigation should be undertaken in accordance with Sheffield Kidney Institute guidance.

Investigations to evaluate the impact of Vitamin D deficiency

- **Parathyroid hormone** (PTH)
    - Elevated in >60% of cases of Vitamin D deficiency
    - PTH measurement is not required for all patients with low Vitamin D but is helpful in situations e.g. abnormal serum calcium, CKD 3 or below
    - If it is measured and is increased at baseline, then useful in follow-up
- **Bone density measurement (DXA)** if chronic deficiency is suspected
    - Chronic deficiency/insufficiency is a risk factor for osteoporosis. This is mediated by chronic secondary hyperparathyroidism and increased bone resorption
    - Defer measurement until Vitamin D replete for at least 6 months to allow remineralisation to occur
- **Imaging** if severe bone pain is present (X-rays or NM scan)
- **24 hour urinary calcium excretion**
    - Not required routinely – may be useful in malabsorption states and in sub-optimal response to treatment

Abnormal biochemical measurements suggesting Vitamin D deficiency

- Hypocalcaemia (if present on rechecking and hypomagnesaemia excluded)
- Increased PTH with normal or low serum calcium
- Increased alkaline phosphatase of bone origin (ie with normal GGT)

Interpretation of laboratory investigations

Vitamin D levels below 25 nmol/L indicate an increased risk of osteomalacia. The severity of the bone disease will be suggested by the Vitamin D level but needs to be interpreted in light of other investigations:

- **Secondary hyperparathyroidism** is present in the majority but not all patients with deficiency. Increased PTH is produced in response to decreasing serum calcium to prevent hypocalcaemia. PTH increases calcium absorption (via Vitamin D activation), increases bone resorption and reduces renal calcium loss
    - Providing renal function is normal, the higher the PTH, the more severe is the deficiency and this increases the likelihood of symptoms and bone fragility
    - Raised PTH may be useful in monitoring as the levels will decrease with successful treatment of Vitamin D deficiency
    - Patients who have had prolonged deficiency may occasionally develop autonomous PTH production. This will be manifest as persistent elevation of PTH despite Vitamin D repletion, or occasionally the development of overt primary hyperparathyroidism
- **Serum calcium** generally remains normal until deficiency is severe when symptomatic hypocalcaemia may develop
    - Serum calcium should be interpreted with caution in renal impairment and in individuals with hypoalbuminaemia
    - If serum calcium is low with normal PTH levels consider checking serum magnesium

    - Serum phosphate may also be decreased as absorption is also dependent on Vitamin D

- **Increased alkaline phosphatase** of bone origin (suspected if isolated increase with normal LFT and GGT, confirmed by measurement of bone isoform) in a patient with D deficiency may indicate overt osteomalacia
- **Urinary calcium excretion** reduces early and is generally the first biochemical abnormality detectable in deficiency and the last to resolve with treatment. Measurement involves collection of 24 hour urine samples and is not recommended as a routine investigation in primary care

Individuals with borderline Vitamin D levels frequently have evidence of secondary hyperparathyroidism but other investigations are generally normal.

Management

The aims of management are to:

- **Identify underlying cause**
  - Modify any reversible contributory causes
- **Achieve Vitamin D repletion**
  - Initial high dose treatment if required
    - In patients with baseline Vitamin D <25 nmol/L, repletion usually occurs over 3 months
    - A single dose of a high dose preparation may be considered if levels are 25 - 50nmol/L e.g. in winter months
- **Implement long-term maintenance**
  - Lifestyle modification
  - Enhanced dose OTC supplementation: This is generally required for life as few underlying causes are fully reversible, There are exceptions such as individuals with newly diagnosed coeliac disease who demonstrate a good response to gluten-free diet

Lifestyle advice

Lifestyle advice about the importance of Vitamin D for bone health and how to maintain a healthy Vitamin D level should be made available to all individuals.

- Diet provides, at most, 15% of daily requirements
  - Dietary sources of Vitamin D include oily fish, dairy foods, liver
  - Some margarines and breakfast cereals in the UK contain small amounts of supplemental Vitamin D
- Exposure to sunlight is the main source of Vitamin D in most individuals
  - Aim to spend 20-30 minutes outdoors 3 times a week between April and October. This includes face and arms exposed without sunscreen
  - Consider the use of daily Vitamin D supplementation containing 400 units (10mcg) all year round, in particular during late October to March
- Any individual who is in a risk group for Vitamin D deficiency should follow SACN advice. (In adults a daily supplementation with 400 units (10 mcg) of Vitamin D).

Vitamin D Supplements

When choosing which supplement to use there are a number of considerations, including:

- **Colecalciferol or ergocalciferol**
- **Over the counter (OTC) or prescribe**
- **Formulations**
    - Choosing the preparation suitable for the individual patient characteristics to optimise efficacy and compliance
- **Dosing options**
    - High dose preparations
    - Standard and enhanced dose preparations
        - Vitamin D in combination with calcium
        - Vitamin D alone

Active metabolites of Vitamin D (alfacalcidol and calcitriol) should *not* be used in the routine treatment of Vitamin D deficiency. They have a high potential for toxicity and require frequent monitoring. Their use is only required in the management of Vitamin D deficiency in patients with renal disease which is severe enough to impair hydroxylation to the active metabolite and this needs to be undertaken under close supervision.

Colecalciferol or Ergocalciferol?

Colecalciferol (Vitamin D_3) is manufactured by the UV irradiation of 7-dehydrocholesterol from lanolin and ergocalciferol (Vitamin D_2) is manufactured by the UV irradiation of ergosterol from yeast. The two forms have historically been regarded as equivalent based on their ability to cure rickets and indeed, most steps involved in the metabolism and actions of Vitamin D_2 and Vitamin D_3 are identical. Both effectively raise serum 25(OH)D levels. However, there is a suggestion that whilst at nutritional doses Vitamins D_2 and D_3 are equivalent, at high doses the effects of Vitamin D_2 may be less potent and persistent. Licensed preparations are available in low and high strengths.

Colecalciferol is therefore the preparation of choice in the majority.

Ergocalciferol is licensed in the UK for administration at high dosage via the IM route. There are also unlicensed ergocalciferol preparations for oral administration available.

The licensed high-dose IM ergocalciferol preparation is a relatively expensive option to prescribe. Increases in 25(OH)D following IM ergocalciferol injection are unpredictable and short-lived. Consequently, it is currently only recommended in patients with malabsorption or if there is another reason for using a parenteral preparation. See UKMi Q and A for further information Which Vitamin D preparations are suitable for a vegetarian or vegan diet?

Over the counter or prescribe?

The indications for prescribing Vitamin D include:

- A patient requiring treatment of deficiency (symptoms plus Vitamin D level < 25 nmol/L)
- Intramuscular injections of ergocalciferol are required (e.g. malabsorption, inability to take oral treatment or non-compliance with oral treatment)
- Those who have a malabsorption condition where Vitamin D deficiency is more prevalent i.e. those with Cystic Fibrosis or Inflammatory Bowel Disease.
- In patients requiring calcium supplementation in combination with Vitamin D who have active bone disease (e.g. osteoporosis)
- If there is concern about regular compliance in an individual with active bone disease

If the patient has Vitamin D insufficiency or needs maintenance supplementation after treatment of deficiency then the patient should be advised to purchase a supplement from their local pharmacy, health food shop or supermarket.

Formulations

The choice of preparation needs to take account of patient characteristics:

- **Vegetarians, or avoidance of gelatin for religious reasons**
    - Colecalciferol is sourced from lanolin (from sheep wool) and is acceptable to many vegetarians but some capsules contain gelatin from an animal source
    - The gelatin in some preparations is Halal and therefore acceptable to Muslims.

- **Vegans**
    - The Vegan Society has additional information on supplementing Vitamin D.
    - There are some preparations suitable for use in Vegans, see separate advice
    - Recommend OTC wherever possible. IM ergocalciferol is an option for those where considered appropriate.
- **Allergy to excipients**
    - Some preparations may contain traces of soy or peanut oil. Whilst allergic reactions are thought to be highly unlikely due to the small traces involved, these products must be avoided in the case of significant allergy
    - Most preparations contain sweeteners including lactose, sucrose and artificial sweeteners
    - Most preparations contain artificial flavourings and some contain colourings
    - See individual Summary Product Characteristics for licensed preparations – link to eMC
- **Malabsorption**
    - IM preparation is the most suitable – if unavailable/impractical, may need higher or more frequent doses of oral preparations
- **Use of anticonvulsant medication**
    - Vitamin D may be metabolised more rapidly and higher doses may be required
- **Problems swallowing tablets/capsules**
    - IM product or liquid preparation may be used
- **Renal impairment**
    - As renal function decreases, the ability to activate Vitamin D decreases and patients may require Vitamin D metabolites. This is likely if renal impairment is severe or if PTH remains elevated after supplementation. Advice from secondary care (renal or metabolic bone physicians) should be sought.

Dosing options

1) High dose

*****High dose treatment for 6-12 weeks is usually used to achieve Vitamin D repletion. Levels are subsequently maintained using standard enhanced dose preparations (800 - 1000 units / 20-25mcg).

Long-term intermittent high dose treatment (e.g. monthly supplementation with licensed oral preparations) may be considered if compliance with daily OTC supplementation is a problem. IM ergocalciferol is sometimes required in patients with resistant deficiency such as those with malabsorption i.e. Cystic Fibrosis or Inflammatory Bowel Disease.

Low BMI

*For those with a low BMI (<20kg/m^2) a lower treatment dose is recommended. Treatment should deliver a total dose of approximately 150,000 units over 6 – 12 weeks e.g. 25,000 units weekly for 6 weeks. This is 50% of the usual recommended treatment dose. This advice is based on local recommendation from colleagues at the Metabolic Bone Clinic, Northern General Hospital. Vitamin D is a fat soluble vitamin and those patients with a lower BMI may get higher concentrations of vitamin D in the blood due to less body fat. High concentrations of vitamin D has been associated with an increase risk in fractures.

Indications for high dose Vitamin D

- At diagnosis of Vitamin D deficiency / osteomalacia to replete body stores
    - Course of high dose supplementation over ~2-3 months
    - Consider calcium requirements and need for concomitant prescription for calcium supplementation
- At baseline if Vitamin D is between 25 and 50 nmol/L
    - Single dose of a high strength preparation of colecalciferol (20 000 to 100 000 units depending on level and risk factors) at initiation of enhanced dose supplements may be considered:
        - If Vitamin D is at lower end of this range
        - In winter months

The use of high dose Vitamin D is also appropriate in a number of specific clinical circumstances. In these cases treatment would generally be initiated within secondary care or in discussion with the metabolic bone team:

- Patients with complex metabolic bone problems such as those with a combination of primary hyperparathyroidism and Vitamin D deficiency in whom it is not desirable to administer additional calcium

- Patients with renal failure with documented Vitamin D insufficiency particularly if the secondary hyperparathyroidism is disproportionate to the degree of renal disease. These cases are commonly reviewed in the renal/bone MDT meetings and treatment with both colecalciferol and an active Vitamin D metabolite may be used

Annual treatment

An annual bolus of high dose Vitamin D has previously been advocated as a potential treatment for some at-risk groups such as the elderly housebound or those in institutional care. This approach is **not**, however, recommended for two reasons:

- Benefit in terms of a reduction in falls or fractures has not been demonstrated in randomized controlled studies with an annual IM bolus of 300 000 units ergocalciferol at the start of the winter
- An annual supplement given as a bolus of colecalciferol 500 000 units was associated with an increased risk of falls and fractures in the 3 months after administration (JAMA 2010; 303: 1815-1822)

Contraindications and cautions in use of high dose Vitamin D

High dose Vitamin D treatment should be used with extreme caution in certain circumstances and only in the presence of documented deficiency and with reference to individual SPC**.**

The details below are not a complete list and the BNF and the SPC remain authoritative

- **Hypercalcaemia and / or hypercalciuria**
    - Patients who are hypercalcaemic due to primary hyperparathyroidism are at increased risk of D deficiency due to increased metabolism. This will exacerbate their bone disease and should be treated. Vitamin D in this situation generally does not lead to further increase in serum calcium and may lead to a decrease in PTH.
- **Serious renal impairment**
    - manufacturer's information for ergocalciferol 300 000 unit states that use is contra-indicated in patients with decreased renal function
- **Nephrolithiasis and/or nephrocalcinosis**
- **Hypervitaminosis D**
- Hypersensitivity to the active substance or excipients

- **Pseudohypoparathyroidism** - the Vitamin D requirement may be reduced due to phases of normal Vitamin D sensitivity, involving the risk of prolonged overdose

Special warnings and precautions for use with high dose Vitamin D:

- **Metastatic calcification**
- **Impaired renal function -** Vitamin D should be used with caution in patients with impairment of renal function and the effect on calcium and phosphate levels should be monitored. The risk of soft tissue calcification should be taken into account**.**
- **Sarcoidosis and other granulomatous disease,** due to a possible increase in the metabolism of Vitamin D in its active form. In these patients the serum and urinary calcium levels should be monitored.
- **Those with a low BMI** <20kg/m^2 as detailed above.

Allowances should be made for the total dose of Vitamin D in cases associated with treatments already containing Vitamin D, foods enriched with Vitamin D, cases using milk enriched with Vitamin D, and the patient's level of sun exposure**.**

Side effects and toxicity with high dose Vitamin D

Side-effects are extremely uncommon providing the dosing schedules described in this document are not exceeded and generally relate to hypercalcaemia due to excessive treatment. **The details below are not a complete list and the BNF and the SPC remain authoritative**

Symptoms include:

- Polydipsia and polyuria
- Nausea & vomiting
- Constipation
- Headache

Severe toxicity presents with overt hypercalcaemia and in addition to the above may lead to confusion, dehydration and even coma

2) Standard and enhanced doses

Standard (400units / 10mcg) and enhanced dose (800 - 1000 unit / 20 - 25mcg) Vitamin D preparations are readily available at low cost over the counter from pharmacies, supermarkets and health food shops. If Vitamin D supplementation is recommended then patients should be signposted to buy low dose Vitamin D supplements over the counter. There are also several combined preparations containing calcium and Vitamin D, usually as colecalciferol for those who have a poor dietary calcium intake. A prescription may be indicated if there is concern about regular compliance in an individual with active bone disease.

Vitamin D alone

Colecalciferol is available from pharmacies, health food shops and online. Licensed preparations are now available on prescription (800 units / tablet), although self-care with OTC is first choice (see Appendix 1). There are no licensed preparations providing a standard dose of ergocalciferol on its own.

Combined preparations

Combined calcium and Vitamin D products may all contain a variety of excipients which can include gelatin, artificial sweeteners, flavourings and soya-bean or arachis oil. The components can alter over time and the current SPC should be consulted for confirmation.

1. ***Calcium and colecalciferol*** – most products provide 800 to 1000 mg calcium and 800 unit colecalciferol in daily dose (generally 2 tablets daily)
    - "Chewable" tablets
        - Patients often prefer one brand to another on basis of taste/texture – start with cheapest
    - Soluble preparations
    - Caplets
        - Tablets which can be swallowed – may be helpful with tolerability and compliance
2. ***Calcium 500 mg and colecalciferol 800 unit*** in a single tablet is useful if a lower calcium dose is required
3. ***Calcium and ergocalciferol*** (Ca 97 mg and ergocalciferol 400 unit)

- Not as cost effective as other variations so prescribe in exceptional cases
- Suitable if a low calcium content is required
- 'Zanza Pharmaceuticals' produce a tablet that is suitable for Vegans

Contraindications to standard and enhanced dose Vitamin D

The details below are not a complete list and the BNF and the SPC remain authoritative

- Vitamin D in combination with calcium is contraindicated in hypercalcaemia or hypercalciuria
    - Vitamin D without calcium may be needed in hypercalcaemia if deficiency is diagnosed, eg in primary hyperparathyroidism
- Vitamin D in combination with calcium should be used with caution in patients with a history of renal calculi
- Sensitivity to any excipients

Side effects of standard and enhanced dose Vitamin D

Side-effects are common with combined calcium and Vitamin D supplements and are almost always caused by the calcium salt. Gastro-intestinal symptoms are the most frequent complaint and include nausea, bloating, abdominal pain and constipation.

Many patients discontinue treatment because they dislike the taste or texture of an individual preparation. It is often helpful to switch to an alternative preparation to alleviate side-effects and improve compliance.

Drug interactions with Vitamin D

The details below are not a complete list and the BNF and the SPC remain authoritative

- Thiazide diuretics
    - BNF advises of an increased risk of hypercalcaemia when Vitamin D is given with thiazides and related diuretics
    - In practice, this is only of relevance with high dose Vitamin D treatment
- Drugs containing digitalis and other cardiac glycosides - the use of digitalis glycosides in the presence of hypercalcaemia due to Vitamin D administration

might result in arrhythmias. Strict medical supervision is needed, together with serum calcium concentration and electrocardiographic monitoring if necessary.

- Medications which increase Vitamin D metabolism
    - e.g. barbiturates, carbamazepine, phenytoin or primidone
    - Higher doses of Vitamin D may be required in these patients

Special situations

Pregnant and breastfeeding women

- **See separate guidance**

Renal impairment

Renal impairment becomes increasingly common with age, and patients may need treatment with an active metabolite of Vitamin D. Individuals with CKD 4 and 5 may have renal bone disease and require supervision of their treatment by the renal physicians in association with the metabolic bone team.

CKD 3 is often associated with secondary hyperparathyroidism which becomes increasingly more severe as renal function deteriorates. This reflects reduced clearance of PTH fragments as well as the effects of Vitamin D deficiency and impaired hydroxylation of Vitamin D to the active metabolite.

Introduction of Vitamin D in CKD 3 should be monitored using PTH measurements. If PTH remains elevated after adequate Vitamin D therapy this may indicate the need to introduce a small dose of an active metabolite. It is recommended that this is discussed with the renal and/or metabolic bone teams.

Low BMI

See above.

Further reading

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4. Rosen C Vitamin D insufficiency. NEJM 2011;364:248-54
5. Primary Vitamin D deficiency in adults. Drug and therapeutics bulletin 2006;4:25-29
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7. National Health Service. Healthy Start website
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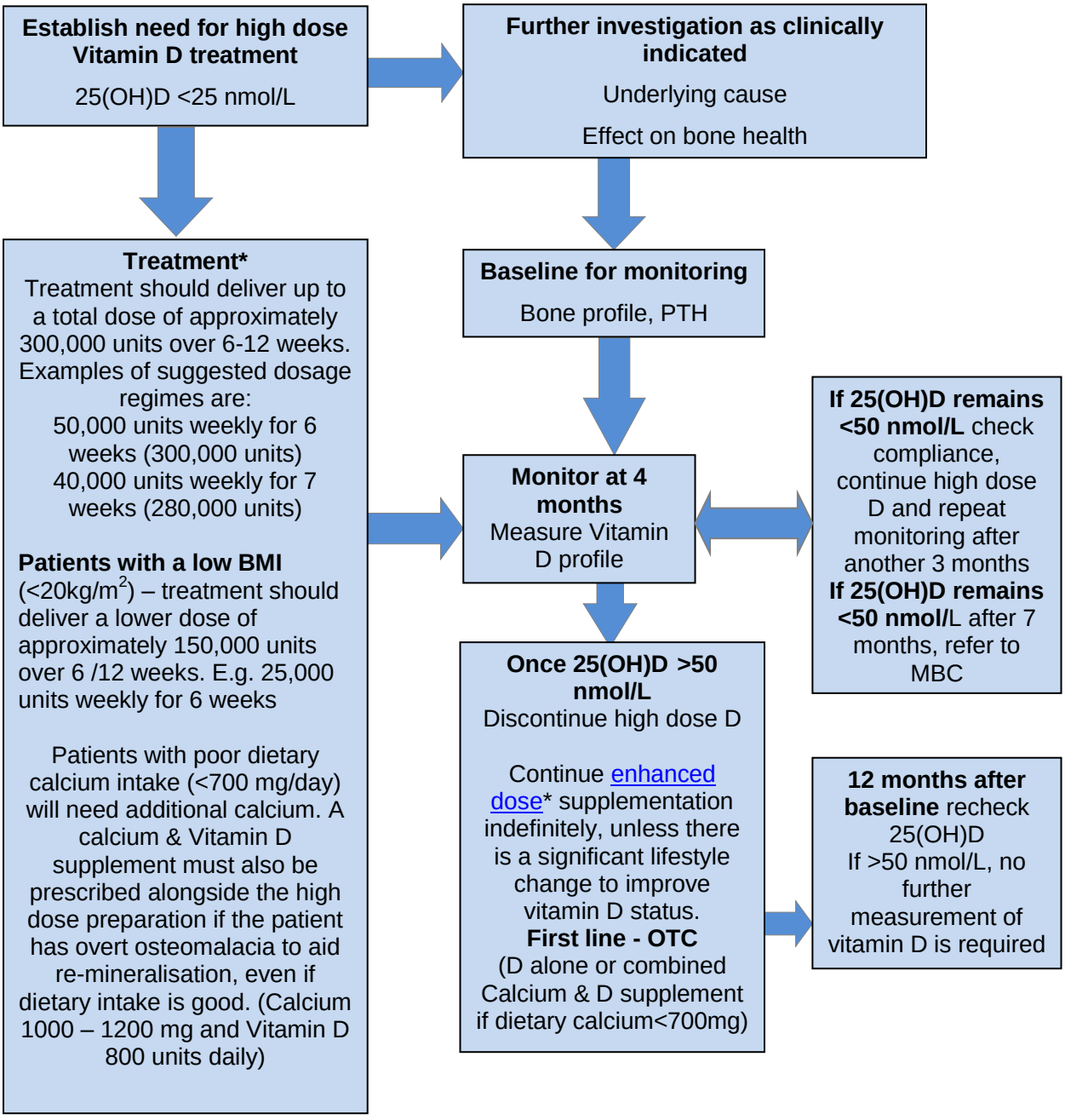
11. Scientific Advisory Committee on Nutrition (SACN) Vitamin D and Health Report 2016
12. Public Health England. Public Health England publishes new advice on Vitamin D (July 2016)
13. NICE Clinical Knowledge Summaries Vitamin D deficiency in adults – treatment and prevention https://cks.nice.org.uk/vitamin-d-deficiency-in-adults-treatment-and-prevention

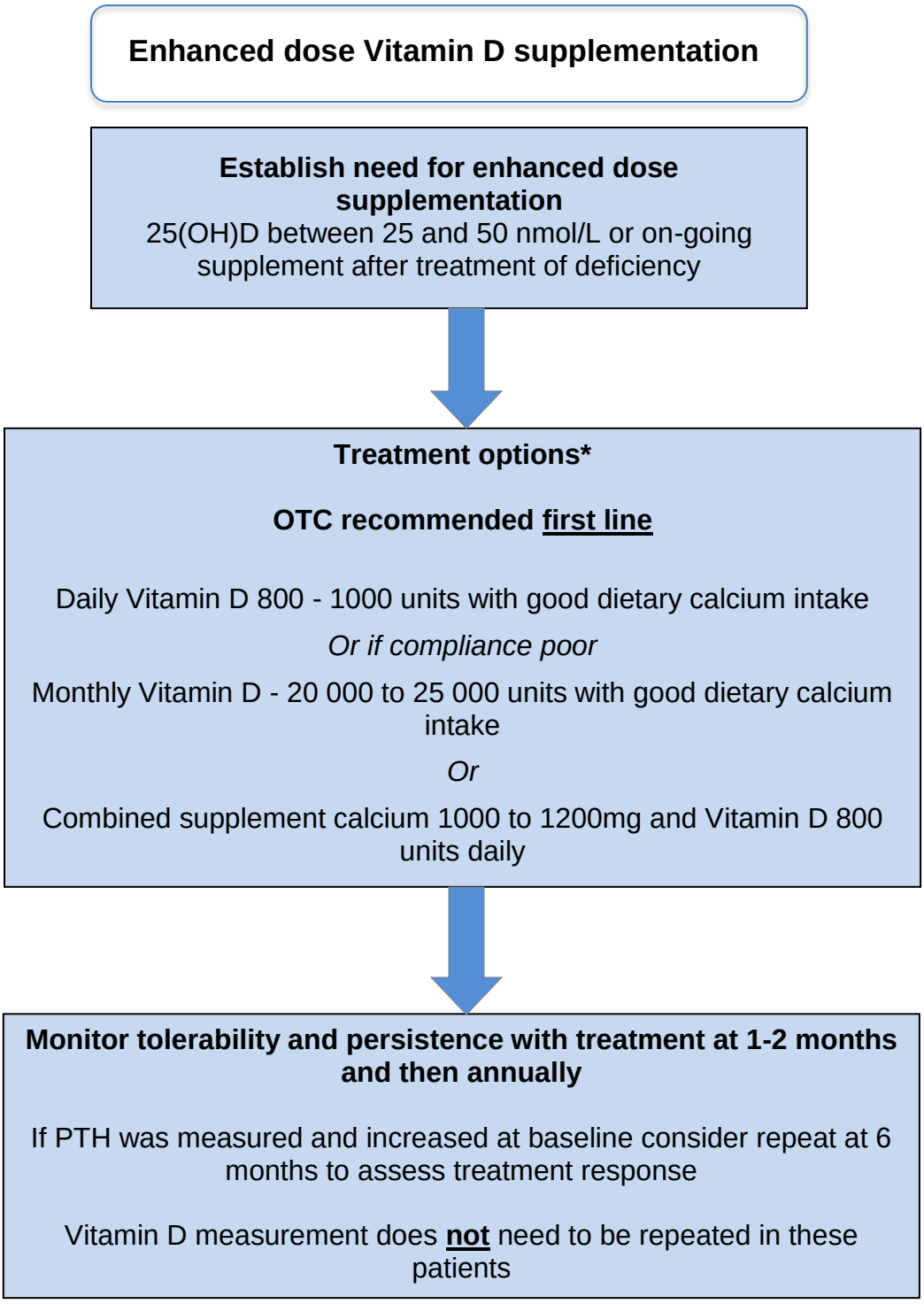
About this document

This guidance was developed by Dr Nicola Peel, Consultant in Metabolic Bone Medicine, STHFT in collaboration with Heidi Taylor, Clinical Effectiveness Pharmacist, NHS Sheffield *CCG*, on behalf of the Sheffield Working Group for Osteoporosis & Bone Health. This version has been updated by Kirsty Burdett, Clinical Practice Pharmacist, NHS Sheffield CCG. Amendment made: November 2018, December 2019 (added in info on low BMI dosing).

High-dose oral Vitamin D supplementation and monitoring



- ***Treatment options – see Sheffield Formulary.**
- **NB: An annual bolus of high dose Vitamin D is *not* recommended**



- ***Treatment options – see Sheffield Formulary.**
- **Refer to document for contra-indications and side-effects**
- **NB: An annual bolus of high dose Vitamin D is *not* recommended**

Patient Resources

Recommended online resources

National Osteoporosis Society

The NOS provides extensive information about bone health including a number of information leaflets, a telephone helpline staffed by nurses (0808 800 0035) and an online discussion forum.

Leaflets:

Further Food Facts and Bones – looking beyond calcium and Vitamin D

Vitamin D Supplements and Tests

Arthritis Research UK

AR UK publish a very useful booklet on osteomalacia which can be downloaded free from their website (www.arthritisresearchuk.org).

Healthy Start

www.healthystart.nhs.uk

Local Resources

Vitamin D A4 Leaflet

Vitamin D Easy Read Leaflet

This leaflet is also available in a number of different languages: Arabic, Punjabi, Slovak, Somali and Urdu

Appendix 1: Over the Counter Preparations

OTC preparations can be obtained from pharmacies, major supermarkets and health food shops. The table below lists some examples of preparations available along with current prices to support discussions with patients. Please note these vitamin supplements are often on offer, which reduces price further. As per individual manufacturer's advice, preparations annotated with a (V) are suitable for vegetarians those with (H) have been certified as Halal. Note those annotated with a (H) or (V) are suitable for those following Halal diets. Also see separate advice

Examples of OTC preparations	Cost (August 2018)/pack size
Vitamin D 400 unit (10 microgram) preparations	
Boots - Vitamin D 400 unit (V)	**£2.29/90 (*76p/month*)**
Healthy Start - Vitamins for Women (V)	**Around £1.15/60 (58p/month) – available from all Children's Centres**
Holland and Barrett - Vitamin D 400 unit tablets	**£3.59/100 (£1.07/month)**
Holland and Barrett - Vitamin D 400 unit vegetarian capsules (V)	**£4.99/100 (£1.50/month)**
Pro D3 400 unit capsules (V) (H)	**£7.99/30 (£7.99/month)**
Vitamin D 1000 unit (25 microgram) preparations	
ASDA - High strength Vitamin D 25 microgram food supplement tablets	**£2.00/60 (£1.00/month)**
Boots - Vitamin D 1000 unit (25 microgram) tablets (V)	**£4.99/90 (£1.67/month)**
Holland and Barrett - Vitamin D3 1000 unit (25 microgram) tablets	**£8.19/100 (£2.45/ month)**
Pro D3 1000 unit capsules (V) (H)	**£9.99/30 (£9.99/month)**
Sainsbury's Vitamin D 25 microgram (1000 unit) tablets	**£2.50/90 (83p/month)**
Sunvit D3 1000 unit tablets (V) (H)	**£4.79 /30 (£4.79 / month) (plus post and packaging)**
Tesco – High strength Vitamin D – 1000 unit (25 microgram) tablets (V)	**£3.50/90 (£1.17/month)**
Valupak 1000 unit tablets - available from most community pharmacies (V)	**£0.99/60 (50p/month)**