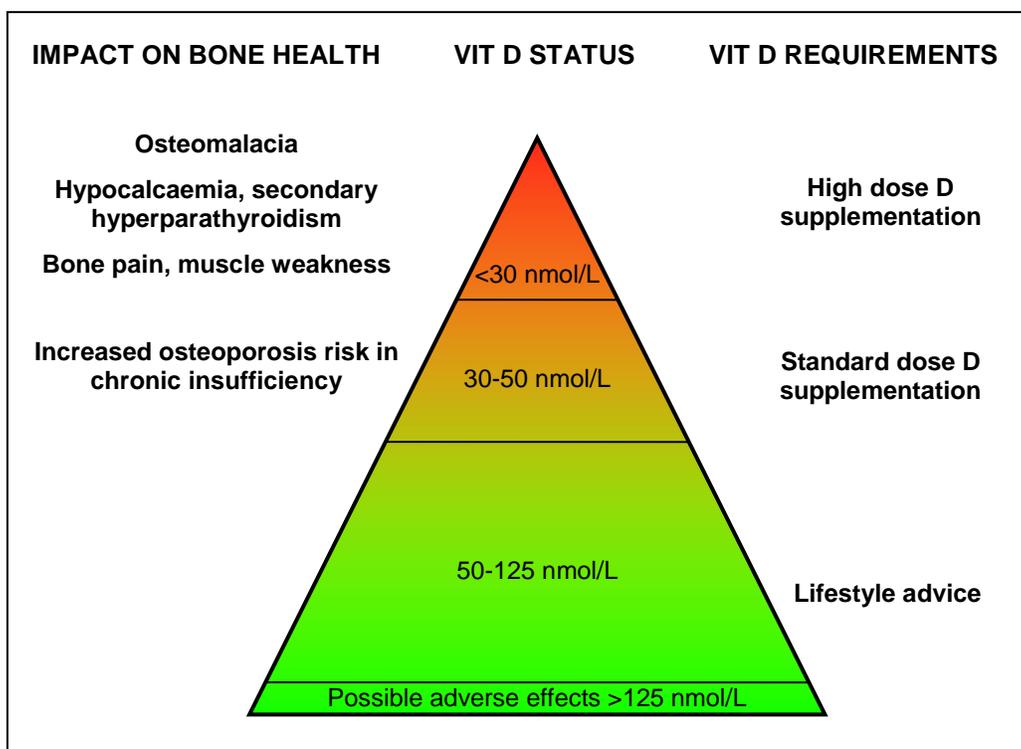


Sheffield Guidance on Optimising Vitamin D for Adult Bone Health

- **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 [signs/symptoms](#) of deficiency



- **Individuals with osteomalacia** or persisting level <30nmol/L despite treatment require further [investigation for underlying cause](#) and [impact on bone health](#)
- **Management** involves:
 - **For individuals with 25(OH)D <30 nmol/L** - Initial [high dose supplementation](#) and long-term [standard dose supplementation](#)
 - **For individuals with 25(OH)D 30-50 nmol/L** – long-term [standard 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. In the UK, exposure of the skin of the arms and face for approximately 20-30 minutes, 3 times each week over the summer months is sufficient for fair-skinned individuals to manufacture adequate vitamin D stores.

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 IU per daily dose). There are, however, a number of supplements containing calcium and vitamin D (up to 800 IU per daily dose) and vitamin D alone (up to 1000 IU per capsule) which are available over the counter. Cod liver oil and other fish oils are rich in vitamin D (up to 500 IU 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, D₃ (colecalciferol) and D₂ (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 (270-300 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)₂D). 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 functions. 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 the UK, recommended nutrient intake (RNI) for vitamin D of 10µg (400 IU) daily is only made for older adults (over age 65) and women who are pregnant or breastfeeding. The 2007 report of the Scientific Advisory Committee on Nutrition (SACN) highlighted the need for updated guidance on vitamin D requirements in the UK and a working party is due to report in Dec 2011. The SACN review will be informed by the recently published report by the Institute of Medicine (IoM) in the USA. In the interim, the IoM document provides the most comprehensive guidance.

The IoM recommended dietary allowances (RDA) represent the *levels meeting the needs of at least 97.5% of the population*. The RDA includes intake from diet and supplements. The recommendations for adults are summarized below. The table also shows the estimated average requirement (median) and the tolerable upper intake level – defined as *the highest average daily intake likely to pose no risk of adverse effects in the majority of individuals*.

Table 1. IoM recommendations for vitamin D in adults

	Estimated average requirement (IU/day)	Recommended dietary allowance (IU/day)	Upper level (IU/day)
Adult up to age 70	400	600	4000
Adult over age 70	400	800	4000
Pregnant/lactating	400	600	4000

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
 - 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, eg 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
- Renal or hepatic disease, medication causing induction of liver enzymes
- Obese

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)₂D 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. The recent recommendations from the Institute of Medicine advise that a level of 25(OH)D of 50 nmol/L (20 ng/mL) covers the bone health requirements for over 97.5% of the population. Levels below 30 nmol/L may be associated with a significant risk of osteomalacia. There are limited data regarding the long-term effects of levels chronically raised above 125 nmol/L and a suggestion of adverse outcomes including increased all-cause mortality with levels persistently elevated above 125 nmol/L (50 ng/mL). Caution is therefore advised in order to avoid potential over-supplementation.

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
 - eg malabsorption
- Low trauma fracture
 - May have history of prodromal pain
 - Typical sites include ribs, sacrum, pelvis, hip
 - Vertebral fractures classically present with biconcave appearance of several vertebrae

Investigation

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

- [Signs/symptoms](#) or
- [Abnormalities](#) on laboratory investigations suggestive of D deficiency

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.

The profile consists of:

- 25(OH)D, Ca, PO₄, alkaline phosphatase, albumin, creatinine

Results are reported as follows:

- <30 nmol/L – Suggest high dose supplementation
- 30-50 nmol/L – If bone health an issue, suggest standard-dose supplementation. No repeat vitamin D measurement required
- 50-125 nmol/L – 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. If there is no secondary hyperparathyroidism this may simply require lifestyle advice. 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 <30 nmol/L)

Investigations for an underlying cause of D deficiency

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

- Malabsorption screen (eg 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 (www.sheffield-kidney-institute.org)

Investigations to evaluate the impact of D deficiency

- **Parathyroid hormone (PTH)**
 - Elevated in >60% of cases of vitamin D deficiency
 - Useful in follow-up if increased at baseline
- **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 30 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 <30 nmol/L, repletion usually occurs over 3 months with monthly high dose treatment (ie 4 doses)
 - A single bolus may be considered if levels are 30-50nmol/L

- **Implement long-term maintenance**
 - Lifestyle modification
 - [Standard dose](#) 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
 - Face and arms exposed without sunscreen
 - This will enable sufficient vitamin D production in most fair-skinned individuals
- Any individual who has insufficient sun exposure should consider taking a supplement containing vitamin D (400 to 600 IU daily as per [IoM recommendations](#))
 - Housebound, dark skin, occlusive clothing, high SPF sunscreen
 - This is particularly important in those over age 65 as indicated in guidance from the Department of Health (DoH, Feb 2012)

Vitamin D Supplements

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

- **Colecalciferol or ergocalciferol**
- **Formulation**

- Choosing the preparation suitable for the individual patient characteristics to optimise efficacy and compliance
- **Dosing options**
 - High dose preparations
 - Low 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 D₃) is manufactured by the UV irradiation of 7-dehydrocholesterol from lanolin and ergocalciferol (vitamin D₂) 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 D₂ and vitamin D₃ are identical. Both effectively raise serum 25(OH)D levels. However, there is a suggestion that whilst at nutritional doses vitamins D₂ and D₃ are equivalent, at high doses the effects of vitamin D₂ may be less potent and persistent. There are differences in licensing status in the UK and currently the choice is driven by availability.

Ergocalciferol is licensed in the UK for administration at high dosage via oral or IM routes. It is also licensed for oral administration at low dosage, and is available in combination with calcium. High dose colecalciferol preparations are not, however, licensed in the UK despite the fact that this is the form of vitamin D in the majority of the combination products eg Adcal D₃.

Unfortunately, the licensed high-dose oral ergocalciferol preparation is no longer manufactured and the IM preparation is sporadically unavailable due to manufacturing problems. Consequently, it is currently recommended that oral colecalciferol be used for high dose supplementation. There is considerable variability in the cost of available preparations which may be prescribed as “specials” and new preparations are becoming

available on a frequent basis so the choice of [recommended supplements](#) will be kept under review.

Formulations

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

- **Vegetarians, or avoidance of gelatin for religious reasons**
 - Use IM ergocalciferol if available
 - 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.
 - Other Muslims accept gelatin in medication ([information sheet](#))
- **Vegans**
 - IM ergocalciferol is the most appropriate preparation if available
- **Allergy to excipients**
 - Many products contain gelatin which can be of meat or fish origin and in some cases is Halal
 - Colecalciferol is sourced from lanolin (sheep wool)
 - Many 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
- **Malabsorption**
 - IM preparation is the most suitable – if unavailable, 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 – current recommended products

High dose

[High dose](#) treatment is usually used to achieve vitamin D repletion by administering intermittent high doses for a few months. Levels are subsequently maintained using standard low dose preparations.

Long-term intermittent (eg 3-monthly) high dose treatment may be considered if compliance with standard dose supplementation is a problem (when treatment may be supervised if necessary) and is sometimes required in patients with resistant deficiency such as those with malabsorption.

Indications for high dose vitamin D

- At diagnosis of vitamin D deficiency / osteomalacia to replete body stores
 - Monthly treatment with colecalciferol 100 000 IU following [flowchart](#)
 - Alternatively 20 000 IU per week may be used
 - Concomitant prescription of standard dose calcium and vitamin D supplementation
- At baseline if vitamin D is between 30 and 50 nmol/L
 - Single bolus of colecalciferol 100 000 IU at initiation of standard dose supplements may be considered:
 - If vitamin D is at lower end of this range
 - In winter months
- In patients requiring vitamin D supplementation who are unwilling to take or unable to tolerate standard calcium and vitamin D supplements, in which case advice should also be given to increase dietary calcium intake
 - If a patient in this situation is unable to take a daily colecalciferol preparation, colecalciferol 100 000 IU every 3 months (supervised if necessary) may be used to maintain levels (equates to approximately 1100 IU daily)

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 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 IU ergocalciferol at the start of the winter
- An annual supplement given as a bolus of colecalciferol 500 000 IU was associated with an increased risk of falls and fractures in the 3 months after administration (JAMA 2010; 303: 1815-1822)

Low dose

There are several combined preparations containing calcium and vitamin D, usually as colecalciferol. A licensed preparation containing colecalciferol 800 IU alone is now available as well as a 1000 IU supplement which may be prescribed or purchased OTC.

There are an increasing number of vitamin D supplements available over the counter. Vitamin D alone may be useful for patients who cannot tolerate (and hence do not comply) with combined preparations, or for whom these are contraindicated. Wherever feasible, patients should be encouraged to buy low dose vitamin D supplements over the counter. Prescription is indicated if there is concern about regular compliance, particularly in an individual with bone disease.

Combined preparations

1. **Calcium and colecalciferol** – most products provide 800 to 1000 mg calcium and 800 IU cholecalciferol 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 500mg and colecalciferol 800 IU** in a single tablet is useful if a lower calcium dose is required
3. **Calcium and ergocalciferol** (Ca 97 mg and ergocalciferol 400 IU)
 - Suitable if a low calcium content is required
 - Tablets may be swallowed

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.

Vitamin D alone

These products are well-tolerated and particularly suitable for patients who have a good dietary calcium intake or in whom additional calcium is contraindicated.

Colecalciferol is available from pharmacies, health food shops and online. Recommend preparations providing 25 micrograms (1000 IU) vitamin D. A licensed product is now available on prescription (however this is a lower dose – 800 IU/ capsule). A 1000 IU supplement (in capsule form) can also be obtained on prescription.

Ergocalciferol

- There are no preparations providing a standard dose of ergocalciferol on its own

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

- **Hypercalcaemia**
 - 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.

- **Metastatic calcification**
- **Sarcoidosis and other granulomatous disease**
 - as vitamin D may be metabolised to the active metabolite and cause hypercalcaemia

Treatment in these situations should be monitored carefully and discussion with the metabolic bone team may be helpful.

In addition, the manufacturer's information for ergocalciferol 300 000 IU states that use is contra-indicated in patients with decreased renal function.

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. 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

Drug interactions with vitamin D

- 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
- Medications which increase vitamin D metabolism
 - eg barbiturates, carbamazepine, phenytoin or primidone
 - Higher doses of vitamin D may be required in these patients

Contraindications to low dose vitamin D

Product-specific contra-indications can be checked in the individual product literature.

- 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 low 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.

Special situations

Pregnant and breastfeeding women

- **All** pregnant and breastfeeding women are recommended to receive vitamin D 400 IU (10µg) per day (1994 DoH COMA report, 2012 CMO letter)
 - This is most reliably given through supplementation
 - Depending on dietary calcium intake, the use of a combined preparation eg Adcal D₃, 1 tablet daily may be used (500 mg calcium, 400 IU vit D) or women may take an over the counter preparation of appropriate dosage.
 - Women already taking supplementation and who have been demonstrated to be vitamin D replete on this should continue their usual dose during pregnancy
 - NICE guidance also advises that women are informed about the importance of adequate vitamin D in pregnancy and while breastfeeding and indicates that women may choose to do this via supplements
 - See www.healthystart.nhs.uk for further information including patient literature

- As in the non-pregnant state, vitamin D profile should be measured in pregnant women who are suspected of being vitamin D deficient:
 - On the basis of risk factors and signs/symptoms
 - Measurement should not be performed routinely in all pregnant women
- Vitamin D levels below 30 nmol/L during pregnancy can lead to significant morbidity in both mother and foetus. Prevention of deficiency is preferable as there is no evidence-base for the safety of high-dose supplementation in pregnancy. However, treatment using [high dose supplementation](#) is considered appropriate in symptomatic deficiency and should not be avoided. The IoM recommends an upper limit of 4000 IU daily in pregnancy (which equates to the intermittent dosing described in this document)
- Vitamin D levels of 30-50 nmol/L should be treated as in the non-pregnant state with [standard dose supplementation](#)
- The infants of vitamin D deficient mothers should receive supplements themselves, especially if they are breastfed (refer to Sheffield paediatric vitamin D guidelines and www.healthystart.nhs.uk)

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.

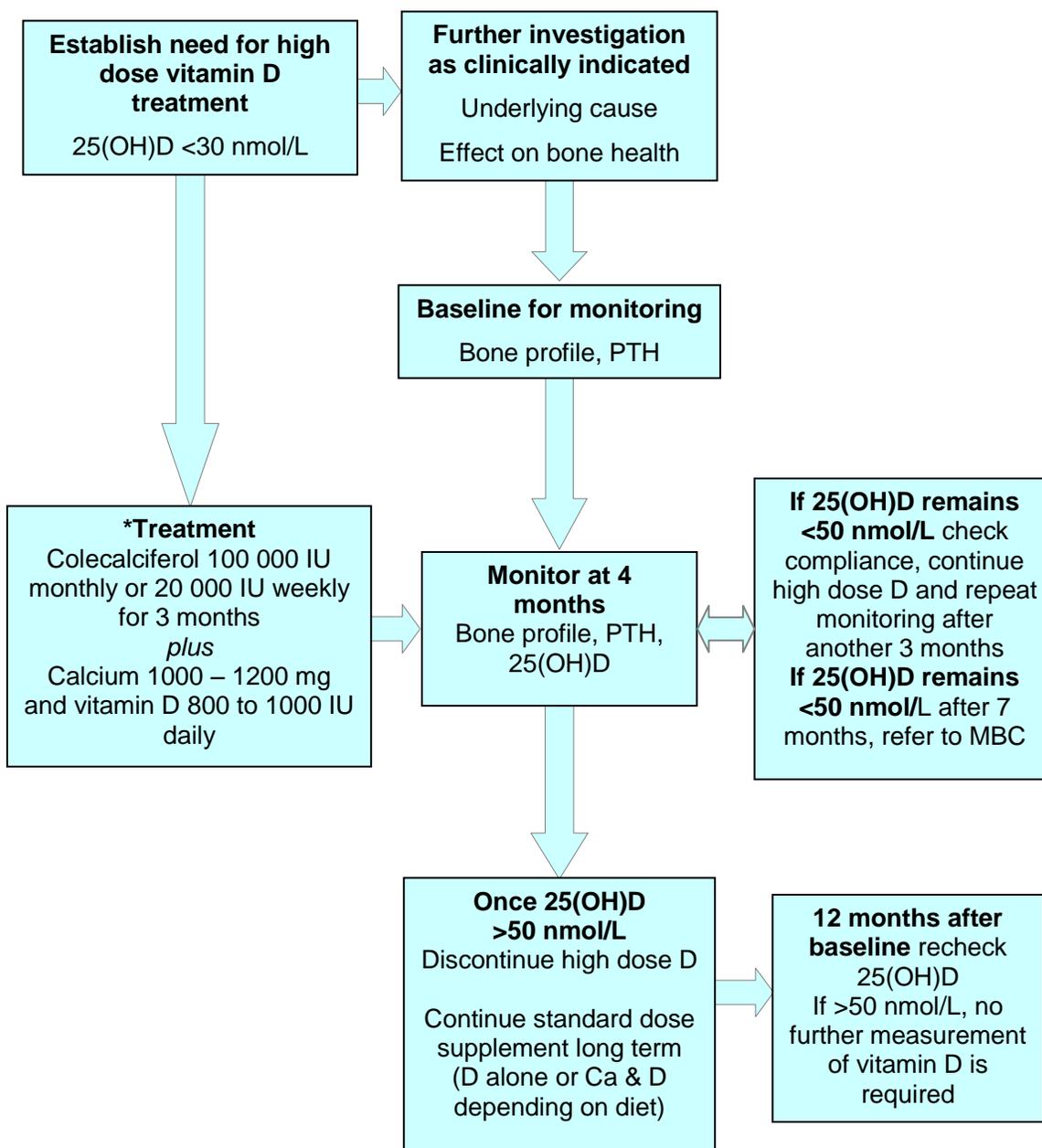
Further reading

1. Ross AC et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *J Clin Endocrinol Metab* 2011;96:53-58
2. www.sacn.gov.uk
3. www.iom.edu/vitamins
4. Dawson-Hughes B et al. IOF position statement: vitamin D recommendations for older adults. *Osteoporosis Int* 2010;21:1151-4
5. Pearce SHS and Cheetham TD. Diagnosis and management of vitamin D deficiency. *BMJ* 2010;340:142-147
6. Rosen C Vitamin D insufficiency. *NEJM* 2011;364:248-54
7. Primary vitamin D deficiency in adults. *Drug and therapeutics bulletin* 2006;4:25-29
8. Hanley DA et al. Vitamin D in adult health and disease: a review and guideline statement from Osteoporosis Canada. *Canadian Medical Association Journal* 2010;182:1864-73
9. www.healthystart.nhs.uk

About this document

This guidance was developed by Dr Nicola Peel, Consultant in Metabolic Bone Medicine, STHFT in collaboration with Louise White and Heidi Taylor, medicines management pharmacists, NHS Sheffield, on behalf of the Sheffield Working Group for Osteoporosis and Bone Health. The authors are grateful to the many colleagues in primary and secondary care who have contributed to the guidance development and in particular, to those who have shared practice guidelines.

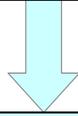
High-dose oral vitamin D supplementation and monitoring



- ***Treatment options** – see [summary](#) of products and [guidance on vitamin D supplementation](#) for details
- Refer to document for [contra-indications](#) and [side-effects](#)
- An [annual bolus](#) of high dose vitamin D is *not* recommended

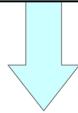
Standard-dose vitamin D supplementation

Establish need for standard dose supplementation
25(OH)D between 30 and 50 nmol/L
or
At-risk individual without signs/symptoms of deficiency



***Treatment options**

Combined supplement Ca 1000 to 1200mg and vitamin D 800 IU daily
or
Combined supplement Ca 500 and vitamin D 800 IU daily if good calcium intake
or
Daily vitamin D 1000 IU with good dietary calcium intake
or
Daily high strength fish oil supplement (approx 500 IU) with good dietary calcium intake. *Not adequate for patients with results at lower end of this range*



Monitor tolerability and persistence with treatment at 1-2 months and then annually
If PTH increased at baseline consider repeat at 6 months to assess treatment response

Vitamin D measurement does **not** need to be repeated in these patients

- ***Treatment options** – see [summary](#) of products and [guidance on vitamin D supplementation](#) for details
- Refer to document for [contra-indications](#) and [side-effects](#)
- An [annual bolus](#) of high dose vitamin D is not recommended

Summary of recommended products

[Details of suppliers in primary care and prescribing details](#)
[Summary of preparations on Sheffield Teaching Hospitals Formulary](#)

High dose vitamin D

Oral colecalciferol

- Synthesized from lanolin (sheep wool) so unsuitable for strict vegans
- In primary care, advise issuing monthly prescription to avoid supply problems and to help in monitoring compliance

Pro D₃ – 20 000 IU capsules

- First choice preparation in primary and secondary care
- Gelatin free
- Does not contain arachis oil or soy
- Manufactured as a nutritional supplement
 - Manufactured in the UK to full Good Manufacturing Practice (GMP)
 - Certificate of Analysis available upon request

Pro D₃ Liquid - 2000 IU/ml

- First choice liquid preparation in primary and secondary care
- Gelatin free
- Does not contain arachis oil or soy
- Manufactured as a nutritional supplement
 - Manufactured in the UK to full Good Manufacturing Practice (GMP)
 - Certificate of Analysis available upon request

IM Ergocalciferol

- There have been sporadic problems with the manufacture of the licensed product for IM administration for some time resulting in intermittent supply problems
- Unlicensed “specials” may be obtained but at very high cost and should not therefore be used

Low dose vitamin D

Colecalciferol

Colecalciferol alone is a suitable alternative for patients who cannot tolerate, or for whom it is inappropriate to prescribe, combined calcium and vitamin D products.

- Pro D₃ 1000 IU capsules
 - Gelatin and nut-free
 - This product is unlicensed and marketed as a nutritional supplement in the UK - it may be prescribed or bought over the counter
 - Community pharmacies can obtain Pro D₃ through AAH or Phoenix Healthcare
- Fultium- D₃ 800 IU capsules
 - This product contains gelatin and peanut oil
 - Licensed in the UK and can be prescribed on the NHS

Several other low dose vitamin D preparations are also available from pharmacies, health food shops and online, check individual products for full list of excipients. Examples include:

- Boots Bone Health Vitamin D₃ tablets 25 mcg (1000 IU) £5.10 for 90*
- Holland and Barrett Sunvite D₃ 25 mcg (1000 IU) caplets £7.65 for 100*
- Solgar Vitamin D₃ softgels (capsules) 25 mcg (1000 IU) £7.05 for 100*
- Sunvit D₃ capsules 25 mcg (1000 IU) gelatin-free £10.56 (including P&P) for 180* from www.sunvitd3.co.uk

*Prices correct at time of publication (March 2012)

Ergocalciferol

- There are no preparations containing standard dose ergocalciferol without calcium
- Calcium and ergocalciferol tablets, which have a low calcium content (97 mg) are available from www.newhealthcare.co.uk and other online suppliers

Combined preparations of calcium and vitamin D

Calcium and colecalciferol (800 to 1000 mg calcium and 800 IU colecalciferol in daily dose, usually 2 tablets daily but see notes)

“Chewable” tablets

- Adcal D₃ should be used first line on basis of cost

- NB Adcal D₃ caplets are the same price
- Alternatives include Calcichew D₃ Forte, Calceos, Natecal D₃
 - Consider these if the patient is intolerant of, or non-compliant with Adcal D₃

Soluble preparations

- Adcal D₃ Dissolve (2 tablets/day), Calfovite D₃ (1 sachet daily)

“Swallowable” caplets

- Adcal D₃ caplets
 - *The equivalent dose to the chewable Adcal D₃ is 2 caplets twice daily*
 - These are the same price as the original chewable tablets
 - Gelatin free
 - Nut and soya free
- Calcichew D₃ caplets
- Accrete D₃ film coated tablets

Calcium 500mg and colecalciferol 800 IU in single tablet

- Kalcipos-D
 - May be indicated if a lower dose of calcium is required

***Calcium and ergocalciferol* (Ca 97 mg and ergocalciferol) 400 IU**

- Suitable if a very low calcium content is required but will not provide adequate calcium if dietary intake is low

Combined calcium and vitamin D products may contain a variety of excipients which can include gelatin, lactose, artificial flavourings and sweeteners and soya-bean or arachis oil. The components are sometimes altered and the current SPC should be consulted for confirmation.

Details of suppliers and prescribing details for Primary Care High strength colecalciferol products

These products are unlicensed medicines and as such should be prescribed in line with the “Sheffield Guidance on Optimising Vitamin D for Adult Bone Health” or the “Sheffield Children’s Guidance on Vitamin D”

Details are provided for Pro D₃ products only as these cover the range of requirements in this document.

- Pro D₃ are gelatin and nut free, are suitable for vegetarians, and people following Halal and Kosher diets
- Pro D₃ products can be obtained readily and are listed in the Chemist and Druggist so costs can be managed
 - Pro D₃ products are currently the most cost effective preparations in primary care.
- Pro D₃ is manufactured in the UK to full Good Manufacturing Practice (GMP) requirements and pharmacies, upon request, can obtain a certificate of analysis (NHS Sheffield would recommend community pharmacies do this for each batch obtained)

Products included in this section will be kept under regular review and updated accordingly.

Product	Strength and form	Distributor and cost including delivery or handling fee*	How to prescribe	Other information
Pro D ₃	Colecalciferol 20,000 IU capsules	AAH Phoenix Healthcare (NB. Alliance customers can obtain Pro D ₃ products through their Phoenix Healthcare access account) Synergy biologics - 0845 5197401 £19.99 / 30 capsules (+ VAT)	SystemOne Prescribe as Pro D ₃ 20,000 IU capsules EMIS Prescribe as Pro D ₃ 20,000 IU capsules	Gelatin free Halal approved Does not contain arachis oil Does not have UK marketing authorisation Marketed as a nutritional supplement
Pro D ₃	Colecalciferol 2000 IU /ml	AAH Phoenix Healthcare (NB.	SystemOne Prescribe as Pro D ₃	Gelatin free Halal approved

	Liquid	Alliance customers can obtain Pro D ₃ products through their Phoenix Healthcare access account) Synergy biologics - 0845 5197401 £16.80 / 50ml (+ VAT) £22.50 / 100ml (+ VAT)	2000 IU /ml Liquid EMIS Prescribe as Pro D ₃ 2000 IU/ml Liquid	Does not contain arachis oil Does not have UK marketing authorisation Marketed as a nutritional supplement
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***Prices accurate January 2012**

NB. In general, UK licensed products and imported products licensed in a country of origin with a strong regulatory framework (eg another EU country) should be considered of high quality. In the same vein, UK manufactured special products made in MHRA-licensed facilities would be considered to offer an improved risk position compared with imported products not licensed in the country of origin. Nutritional supplements are generally subject to food safety labelling legislation and whilst this excludes them from a formal licensing process they may be considered a potentially useful option in some circumstances following a consideration of the risks.

Summary of products on Sheffield Teaching Hospitals Formulary

High dose colecalciferol

- Pro D₃ 20 000 IU capsules
 - Use for all patients unless a liquid preparation is required
 - Gelatin and nut-free
- Pro D₃ Liquid 2000 IU/ml - prescribe as 20 000 IU (10 mL) weekly for the period of high dose supplementation if a liquid preparation is required

High dose ergocalciferol

- IM ergocalciferol 300 000 IU/mL (limited supplies)

Combined calcium and vitamin D products

- Adcal D₃ chewable tablets
 - Standard dose is 1 tablet bd
- Adcal D₃ caplets
 - Standard dose is 2 caplets bd
 - Caplets are gelatin-free
 - Caplets are nut and soya-free
- Calfovit D₃ sachets
 - Standard dose is 1 sachet daily
- Calcium and ergocalciferol
 - Contain low dose of calcium
 - Standard dose is 1 tablet bd

Low dose colecalciferol

- Pro D₃ 1000 IU capsules
 - Gelatin and nut-free

Patient resources

Recommended online resources

National Osteoporosis Society

The NOS provides extensive information about bone health including a free booklet “Healthy bones – facts about food” which can be downloaded from the website (www.nos.org.uk). The NOS also offers a telephone helpline staffed by nurses (0845 450 0230) and an online discussion forum.

Arthritis Research UK

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

Other resources

[Patient information about gelatin in medicines](#)

www.healthystart.nhs.uk

Patient Information about gelatin in medicines

A lot of medicines contain gelatin which is derived from animal sources. Thank you for taking the time to read this information. You are not obliged or expected to take a medicine containing gelatin if you are not happy to do so after reading this sheet.

Not all gelatin products are forbidden to Muslims. Gelatin from pork and 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 often difficult to find out whether the gelatin used in the manufacture of pharmaceutical products is Halal.

The Islamic Organisation for Medical Sciences has given practical advice in a statement agreed with the World Health Organisation. This was agreed in a Seminar in 1995 attended by the Mufti's of Egypt, Tunisia and Oman and many other eminent Muslim theologians and medical professionals. This states that all gelatin used in pharmaceuticals can be considered Halal (1).

It discusses the process of transformation which causes one object to change into another with totally different properties and characteristics, so what is deemed to be unclean becomes a clean object. This means that gelatin manufactured to hold together medicines is clean and permissible for consumption because it has become totally different from the animal part from which it was first made.

This statement is available in full from the web link listed below, in English and Arabic. You can access the internet free at any library if you do not have it at home and a librarian will usually help you if you are unsure what to do.

With capsules, the gelatin is usually a binding agent in the capsule rather than in the medicine itself. A simple alternative can be to split open powder-containing capsules and sprinkle the contents onto a spoon or to pierce liquid-containing capsules and squeeze the liquid onto a spoon.

1. World Health Organisation. Regional Office for the Eastern Mediterranean. July 2001. Full document available at

http://www.ganfyd.org/images/1/11/Porcine_gelatine_medications_Islam_WHO_2003.doc

Vitamin D – information for patients

What is vitamin D and why is it important?

Vitamins are compounds that our bodies need to grow and remain healthy. Vitamin D is essential for bone health. Vitamin D is needed to absorb calcium and other nutrients from our diet and helps to keep bones strong. Vitamin D may also help to keep us healthy in other ways, for example by helping the immune system, but the evidence for this is not clear.

Where does vitamin D come from?

Vitamin D is made in our bodies in response to sunlight on the skin. We also absorb vitamin D from our diet but we can only obtain a small amount (about 10%) of the vitamin D we need in this way because very few foods contain vitamin D.

Foods that do contain small amounts of vitamin D include:

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

Vitamin D is also available in some food supplements that you can buy from the chemist, supermarket or health food shop. Supplements which contain vitamin D include:

- Multivitamins
- Cod liver oil and other types of fish oil
- Vitamin D supplements – which sometimes also contain calcium and other minerals such as magnesium

These different supplements contain different amounts of vitamin D which will be shown on the label. If you are unsure how much vitamin D is present you could talk to your pharmacist.

How much vitamin D do I need?

The latest recommendations suggest that 600 IU (international units), or 15 micrograms, of vitamin D each day is enough for nearly all adults and children over 1 year old. Older adults (over 70 years of age) need about 800 IU (20 micrograms) daily. These amounts include the vitamin D from sunshine, from our food and from any supplements we take, all added together.

People with fair skin who spend plenty of time out of doors and who regularly eat foods containing vitamin D will get enough vitamin D from their lifestyle. People who cannot make enough vitamin D from the sunshine will generally need to take supplements, even if they eat plenty of vitamin D-rich foods.

Can I have too much vitamin D?

Yes – it is possible to have too much vitamin D but this is very rare. It is not possible to make too much vitamin D from the sunshine, even if you spend lots of time in strong sunlight, for example on holiday abroad. This is because your body controls the amount of vitamin D it makes and when it has made enough it breaks down any more as soon as it is produced in the skin.

In the UK, it is not possible to take too much vitamin D in the diet. In some countries such as USA, where many more foods are fortified with vitamin D, this can occasionally happen. If somebody has too much vitamin D it causes too much calcium to be absorbed. This makes the calcium level in the blood too high (hypercalcaemia) and causes symptoms. Symptoms of hypercalcaemia include nausea, vomiting, abdominal pain and constipation.

Vitamin D supplements are generally very safe and providing you take the recommended dose you will not get too much vitamin D. Doses up to 4000 IU (100

micrograms) daily are considered safe and most people need much less than this to keep their bones healthy.

How will it affect me if I have a shortage of vitamin D?

Adults with very low levels of vitamin D for a long time develop a condition called osteomalacia. In this condition, calcium is lost from the bones. The bones become softened and painful and broken bones (fractures) can occur without an injury. In osteomalacia, the muscles also become weak making it hard to walk. Children who have very low vitamin D develop a similar condition called rickets.

Low levels of vitamin D that are not low enough to cause osteomalacia are still important. Calcium can gradually be lost from the bones and result in osteoporosis. Osteoporosis increases the risk of broken bones.

Am I at risk of low vitamin D?

Some people are at greater risk of vitamin D deficiency than others. This may be because they cannot produce enough vitamin D from the effect of sunshine on the skin, because their diet is low in vitamin D, or a combination of these. At-risk groups include:

- Older people, especially those who are housebound
- People who have dark skin or who remain covered up when they go outdoors. This includes people who regularly use high-factor sunscreen

Your doctor will know if you are at risk because of any medical conditions you have or because of medications you take.

What can I do to improve my vitamin D levels and do I need a supplement?

The best way to increase vitamin D levels for most people is by spending time out of doors over the summer months. Exposing the skin on your arms and face to sunlight for 20-30 minutes a day, 3 times each week is enough for most people with fair skin to make the vitamin D they require. This should be without sunscreen and,

in order to avoid sunburn, exposure should not be in the middle of the day when the sun is hot. As we get older we need more sunlight to produce enough vitamin D and people with darker skin also need to spend more time in the sun. This is why these groups are at greater risk of vitamin D deficiency.

It is also important to eat foods which contain vitamin D regularly. However, this cannot make up for lack of sunlight exposure. This is why many people are advised to take vitamin D supplements.

Why have I been given supplements containing calcium as well as vitamin D?

Vitamin D helps to keep bones healthy by helping us to absorb calcium. If you have been short of vitamin D for a long time you will need extra calcium while your bones are healing. Even after that, if you have a diet low in calcium your doctor may advise you to continue taking the combined supplement. This makes sure that you are getting the right amounts of both calcium and vitamin D for your bone health.

Many foods contain calcium but our bodies absorb the calcium from dairy foods such as milk and cheese more easily than from some other foods. Many people try to limit their intake of dairy foods, for example if they have high cholesterol levels. These people can have quite a low intake of calcium.

Why have I been given a course of high-dose vitamin D supplements?

If your doctor has found that you are very short of vitamin D the quickest way to increase the level back to a healthy level is with a course of high dose supplements. These are usually given as capsules or medicine which are taken once a month (sometimes once a week). The high dose treatment is usually only needed for about 3 months. After that, you will need to continue to take normal supplements to prevent you from becoming short of vitamin D again in the future.

Sometimes, high dose treatment is given as an injection. This is particularly helpful for people who do not absorb medication well. These people may need to have long term treatment with vitamin D injections which are usually given every 3 months.

If you are treated with high dose vitamin D it is important that it is taken as prescribed. If you have been given high dose vitamin D by your GP you should tell any doctors that you see at the hospital that you have had this so you are not given extra treatment that you don't need.

How long will I need to take vitamin D for?

Unless there is a short-term reason for you to have low vitamin D levels, such as an illness preventing you from going outdoors, then you will need to continue taking supplements for life. By continuing your supplements you will maintain healthy levels of vitamin D and this will help you keep your bones healthy.