Surrey (East Surrey CCG, Guildford & Waverley CCG, North West Surrey CCG, Surrey Downs CCG & Surrey Heath), Crawley CCG and Horsham & Mid-Sussex CCG

Prevention, Investigation and Treatment of Vitamin D Deficiency and Insufficiency in Adults

This document includes the following:

- Model pathways for treating vitamin D deficiency and insufficiency in adults **with and without bone disease**
- Section 1: Background
- Section 2: Prevention of vitamin D deficiency
- Section 3: Investigation and treatment of vitamin D deficiency and insufficiency in adults

Where patients are under the care of a specialist, clinicians may like to seek advice.

Document history:

This work is based on Vitamin D guidance produced by KSS HPSU with additional comments from local clinicians and adopted locally following PCN of February 2013.

The guidelines were reassessed by The Surrey Rheumatology Network in July 2013 in light of the published National Osteoporosis Society – Vitamin D and Bone Health: A Practical Clinical Guideline for Patient Management . The Network discussed the national guidance and recommend to the Prescribing Clinical Network that the current KSS model guidance used should be retained. This was discussed at the PCN in July 2013 who supported the recommendation from the rheumatology network to remain with the current Vitamin D guidance produced by KSS HPSU.

In November 2014, NICE published PH56 Vitamin D: increasing supplement use among at-risk groups which recommended that advice on dietary reference values for vitamin D intake in the UK population should be read in conjunction with any guidance published by the Scientific Advisory Committee on Nutrition (SACN). The SACN report Vitamin D and Health was published in July 2016 prompting review of Surrey guidelines.

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Pathway 1-Vitamin D Pathway for Adults (>18 years) in Primary Care-adapted from CKS

FOR PATIENTS WITHOUT BONE DISEASE

EXCLUSIONS: patients with chronic kidney disease (eGFR <30mmol/L), h/o renal stones, hypercalcaemia, sarcoidosis, liver disease, TB, lymphoma, metastatic cancer, parathyroid disorders, atypical biochemistry (persistent hypophosphatemia, elevated creatinine), pregnancy – **seek specialist advice**

FOR ALL PATIENTS – see **prevention advice** below and offer lifestyle advice including British Dietetic Association leaflet Food Fact Sheet on vitamin D

ROUTINE TESTING for at risk groups should NOT be undertaken (NICE PH56)

Does the patient have at least one **PERSISTENT SYMPTOM** suggesting vitamin D deficiency?

- Symptoms of osteomalacia, such as bone discomfort or pain (often throbbing) in lower back, pelvis, and lower extremities; impaired physical function; muscle aches and weakness (may be marked, usually most noticeable in the quadriceps and glutei, and can result in difficulty in rising from a seating position, or a waddling gait); symmetric lower back pain;
- chronic widespread pain.
- For patients with fragility fracture, osteoporosis, high risk of fracture or prior to initiating anti-resorptive drugs follow **Pathway 2-for patients with bone disease**

YES

It is appropriate to request a TEST for vitamin D deficiency and bone profile.
Vitamin D will naturally be lower October-March due to seasonal variation
Please note that labs may report levels and offer advice in different ways

NO

It is **NOT** appropriate to request a test for vitamin D deficiency

Vitamin D levels

0-30nmol/L (deficiency)

Prescribe on **Acute**
a **weekly** regimen of either

- *Colecalciferol 50,000iu/ml oral solution unit dose ampoules sugar free ONE weekly for 6 weeks **OR***
- *Colecalciferol 20,000iu capsules TWO weekly or 40,000iu capsules ONE weekly for 7 weeks*

OR a **daily** regimen of

- *Colecalciferol 3,200iu capsules **OR** **c**olecalciferol 4,000iu tablets ONE daily for 12 weeks*

30-50nmol/L (maybe **insufficient**)

Only prescribe if symptoms suggestive of vitamin D deficiency; or taking an antiepileptic drug/oral corticosteroid / on long-term treatment with other drugs known to cause vitamin D deficiency e.g. colestyramine; or have a malabsorption disorder

Prescribe on **Acute**
a **daily** regimen for up to 12 weeks

- *Colecalciferol 800iu capsules/tablets ONE daily*
- *Colecalciferol 1,000iu capsules/tablets ONE daily*

>50nmol/L

Consider other possible causes of symptoms

PREVENT deficiency by giving lifestyle advice and recommend **over the counter** supplement containing at least 400iu (10mcg) vitamin D daily especially during autumn and winter **for all adults**. At risk groups - people over 65, or pigmented skin or little/no sun exposure should consider taking a supplement all year round. Recommend a daily supplement to all pregnant and breast feeding women (PHE Guidance) - some may qualify for Healthy Start Vitamins.

Calculate dietary calcium intake. Offer dietary advice (BDA Factsheet) to obtain optimum calcium intake and ONLY consider a calcium supplement if adequate dietary intake cannot be achieved (combined products are unsuitable for treatment of deficiency).

- At 4 weeks check for hypercalcaemia due to unmasked primary hyperparathyroidism
- Still symptomatic at 12 weeks?

YES

- Discuss concordance
- Repeat vitamin D level-wait for minimum of 3 months from starting treatment
- Refer non-responsive patients to 2ary care

NO

After treatment course for deficiency or insufficiency give lifestyle advice and recommend over the counter supplement as above. *However, prescribers may use discretion around continuing to prescribe a maintenance dose of colecalciferol 800-1000iu daily for institutionalized or housebound patients with ongoing risk of deficiency after treatment.*

Pathway 2- Vitamin D Pathway for Adults (>18 years) in Primary Care -adapted from CKS

FOR PATIENTS WITH BONE DISEASE

EXCLUSIONS: patients with chronic kidney disease (eGFR <30mmol/L), h/o renal stones, hypercalcaemia, sarcoidosis, liver disease, TB, lymphoma, metastatic cancer, parathyroid disorders, atypical biochemistry (persistent hypophosphatemia, elevated creatinine), pregnancy – **seek specialist advice**

FOR ALL PATIENTS – see **prevention advice** below and offer lifestyle advice including British Dietetic Association leaflet Food Fact Sheet on vitamin D

Who should I test?

- Is patient starting treatment where correcting vitamin D deficiency is appropriate e.g. antiresorptive therapy? (Do not start therapy until deficiency is corrected)
- Does the patient have a bone disease that may be improved with vitamin D treatment, such as osteomalacia, osteoporosis, or Pagets disease?
- Has the patient had a fall?

YES

It is appropriate to request a TEST for vitamin D deficiency and bone profile.
Vitamin D will naturally be lower October-March due to seasonal variation
Please note that labs may report levels and offer advice in different ways

Vitamin D levels

0-30nmol/L (deficiency)

Prescribe on **Acute**
a **weekly** regimen of either

- *Colecalciferol 50,000iu/ml oral solution unit dose ampoules sugar free ONE weekly for 6 weeks **OR***
- *Colecalciferol 20,000iu capsules TWO weekly or 40,000iu capsules ONE weekly for 7 weeks*

OR a **daily** regimen of either

- *Colecalciferol 3,200iu capsules **OR** **c**olecalciferol 4,000iu tablets ONE daily for 12 weeks*

30-50nmol/L (insufficiency)

Prescribe on **Acute**
a **daily** regimen for up to 12 weeks

- *Colecalciferol 800iu capsules/tablets ONE daily*
- *Colecalciferol 1,000iu capsules/tablets ONE daily*

>50nmol/L

PREVENT deficiency by giving lifestyle advice and recommend **over the counter** supplement containing at least 400iu (10mcg) vitamin D daily especially during autumn and winter **for all adults**. At risk groups -people over 65, or pigmented skin or little/no sun exposure should consider taking a supplement all year round. Recommend a daily supplement to **ALL** pregnant and breast feeding women (PHE Guidance) -some may qualify for Healthy Start Vitamins.

Calculate dietary calcium intake. Offer dietary advice (BDA Factsheet) to obtain optimum calcium intake and ONLY consider a calcium supplement if adequate dietary intake cannot be achieved (combined products are unsuitable for treatment of deficiency).

- At 4 weeks check for hypercalcaemia due to unmasked primary hyperparathyroidism
- Still symptomatic at 12 weeks?

NO

After treatment course for deficiency or insufficiency give lifestyle advice and recommend over the counter supplement as above. *Prescribers may use discretion around prescribing a maintenance dose of colecalciferol 800-1000iu daily for institutionalized or housebound patients at ongoing risk of deficiency after treatment (or a calcium and vitamin D supplement if dietary intake of calcium is inadequate).* However, **all** patients on **oral bisphosphonates, iv zoledronic acid or denosumab** should receive supplemental calcium and vitamin daily (see local osteoporosis guidelines), unless dietary intake of calcium is adequate.

YES

- Discuss concordance
- Repeat vitamin D level-wait for minimum of 3 months from starting treatment
- Refer non-responsive patients to 2ary care

Section 1: Background

The role of vitamin D

Vitamin D is essential for the absorption and utilisation of calcium and phosphorus in the body, both of which are necessary to maintain normal calcification of the skeleton and bone mineralization[1]. Vitamin D maintains neuromuscular function and various other cellular processes, including the immune system and insulin production[1]. The main manifestation of vitamin D deficiency is rickets in children and osteomalacia in adults[2]. Sun exposure is the main source of vitamin D, however it is also found in some foods and supplements. Dietary sources are essential when sunlight containing UVB radiation is limited (e.g. during the winter months) or exposure to it is restricted (e.g. due to lack of time spent outdoors or little skin exposure)[3].

Sources of vitamin D

Sun exposure

The main source of vitamin D is usually considered to be skin photosynthesis following ultraviolet B sunlight exposure. Exposure of skin to UVB radiation is influenced by many factors; these include time of day, season, latitude, altitude, cloud cover, air pollution, clothing and sunscreen use. At latitudes below 37°N, UVB radiation is sufficient for year round vitamin D synthesis. At higher latitude, vitamin D is not synthesized during the winter months. **In the UK, sunlight-induced vitamin D synthesis is only effective between late March/early April and September and not from October onwards throughout the winter months**.[3]

Efficiency of cutaneous vitamin D synthesis may be lower in people with dark skin and in older people but the evidence is limited.

The British Phototherapy Group/British Association of Dermatologists has produced guidance around ultraviolet radiation, skin cancer and vitamin D[4]. Sun exposure is a major source of vitamin D in the UK, but particularly when excessive, is known to be the main cause of both melanoma and non-melanoma skin cancers, which continue to escalate in number in the UK.

- Environmental, physical and personal factors influence risk/benefit of sunlight exposure. **In white-skinned people, casual short sun exposures a few times per week, taking particular care not to burn and avoiding deliberate tanning, can help provide the benefits of vitamin D while minimising risks.**

- Sunbed use increases the risk of skin cancer, and is not recommended as a method for enhancing vitamin D status.

NICE NG34 Sunlight exposure:risks and benefits (2016)[5] recommends that people who choose to expose their skin to strong sunlight to increase their vitamin D status should be aware that prolonged exposure (for example, leading to burning or tanning) is unlikely to provide additional benefit. Exposing commonly uncovered areas of skin such as forearms and hands, for short periods when in strong sunlight provides vitamin D. (Longer periods of exposure may be needed for those with darker skin.)

Dietary sources

Dietary sources of vitamin D are in the UK are very limited and oily fish is the only significant source.

- Oily fish such as salmon, sardines, pilchards, trout, herring, kippers and eel contain reasonable amounts of vitamin D
- Cod liver oil contains a lot of vitamin D (avoid if pregnant)
- Egg yolk, meat, offal and milk contain small amounts but this varies during the seasons (liver is also a rich source of vitamin A and consumption should be limited to once a week to avoid toxicity and avoided entirely during pregnancy)
- Fat spreads, some breakfast cereals, infant formula milk and some yoghurts have added or are 'fortified' with vitamin D[6,7]

Supplements

Vitamin D is present in a range of unlicensed dietary supplements and licensed medicines, which can help to boost vitamin D levels. Oral supplements are available as either ergocalciferol (calciferol, vitamin D2) or colecalciferol (vitamin D3). Vitamin D supplements and multivitamins are now widely available to buy from pharmacies, supermarkets and health food shops. Some women who are pregnant or breastfeeding and children aged six months to four years may qualify for **Healthy Start** vitamins which contain vitamin D.

However, more than one supplement containing vitamin D, which includes cod-liver oil, should not be taken. A supplement tailored to the age group or condition should be recommended, as fish liver oils and high dose multivitamin supplements often contain vitamin A, too much of which can cause liver and bone problems, especially in very young children, and the elderly.[7]

Recommended daily intake

In 2010, the Scientific Advisory Committee on Nutrition (SACN) agreed to consider whether the Dietary Reference values (DRVs) for vitamin D intake were still appropriate in the context of public health advice to stay out of the sun and to wear sunscreen and because a substantial amount of new evidence had accumulated since its previous considerations.

In a change to previous advice, SACN guidance published in 2016 is now recommending an RNI for vitamin D of 10micrograms per day (400 iu/day), throughout the year for everyone in the general UK population aged 4years and above.[3]

This recommendation **includes pregnant and lactating women and population groups at increased risk of vitamin D deficiency**. Since there was insufficient data to set RNIs for children aged under 4 years, **Safe Intakes** are being recommended for this age group (8.5-10 micrograms/340-400 IU per day for all infants under 1 year and 10micrograms/400 IU per day for ages 1 up to 4 years). The RNI/Safe Intakes have been developed to ensure that the majority of the UK population has a satisfactory vitamin D status (as measured by blood levels) throughout the year, in order to protect musculoskeletal health. It was not possible to quantify and take account of sunlight exposure in setting the DRVs because of the number of factors that affect endogenous vitamin D synthesis.

Biomarkers of vitamin D exposure

Plasma/serum 25(OH)D concentration is widely used as a biomarker of vitamin D status because it reflects vitamin D supply from cutaneous synthesis and diet but also because it has a long half-life in the circulation (about 2-3 weeks) and is not under tight homeostatic control. A limitation of its use is that it has been observed to decrease in response to acute inflammation, so low concentrations (e.g., observed in conditions such as cancer) may reflect an underlying inflammatory state.

The relationship between vitamin D exposure and serum 25(OH)D concentration may also be influenced by Body Mass Index and genetic variation. There are also limitations associated with the methods used for measurement of serum 25(OH)D concentration, since measurements can vary considerably (15-20%) depending on the type of assay used. In addition, there is considerable variation between different laboratories using the same methods[3].

Implications and prevalence of vitamin D deficiency

Vitamin D and Health Outcomes

SACN reviewed the evidence for a relationship between vitamin D and various health outcomes which were considered to be of public health concern. Assessment of the evidence was divided into musculoskeletal (rickets, osteomalacia, bone health indices, fracture prevention, risk of falls and muscle health) and non-musculoskeletal (pregnancy and lactation, cancers, CVD & hypertension, all-cause mortality, immune modulation, infectious diseases, neuropsychological functioning, oral health and age-related macular degeneration) health outcomes.

An important limitation to this task was that there is no clear consensus on the threshold serum 25(OH)D concentration used to define vitamin D deficiency or low status and cut-offs varied across studies and were predefined according to different criteria for deficiency. As a consequence, the selected cut-offs were insecure and made it difficult to assess if there was a dose-response relationship.[3]

Implications of vitamin D deficiency

Vitamin D is essential for good bone health. Deficiency of vitamin D results in rickets in children and osteomalacia in adults; conditions characterised by pathological defects in growth plate and bone matrix mineralization[3]. Patients with osteomalacia often complain of multiple symptoms including bone, joint and muscle pain, hyperalgesia, muscle weakness and a waddling gait[2]. In children failure of bone mineralization gives rise to bone deformities; bones are painful and linear growth is reduced[3]. Low vitamin D levels are associated with secondary hyperparathyroidism and low bone mineral density and, thus, a higher risk of fractures.

Evidence overall suggests that risk of poor musculoskeletal health is increased at serum 25(OH)D concentrations below about 20-30 nmol/L. The current threshold for increased risk of vitamin D deficiency, of <25nmol/L has therefore been retained by SACN. [3]

However, NOS[2] and recent CKS guidelines suggest treating deficiency at levels below 30nmol/L and this is the level that has been agreed locally.

In addition to musculoskeletal health, SACN reviewed the relationship between vitamin D and non-musculoskeletal health outcomes including cancer, Type 1 diabetes, multiple sclerosis and heart disease but found insufficient evidence to draw any firm conclusions. NICE CG186 Multiple sclerosis in adults:management advises not to offer vitamin D solely for the purpose of treating MS.[8]

Prevalence of vitamin D deficiency

The National Diet and Nutrition Survey of British adults[9] suggests that almost a fifth of UK adults have a low vitamin D status (below 25nmol/L 25(OH)D). Seasonal variations in vitamin D status are observed in the UK; levels are highest between July and September and lowest between January and March[3].

Section 2: Prevention of vitamin D deficiency

In the UK, individuals in population groups at increased risk of having a serum 25(OH)D concentration < 25 nmol/L are those with minimal sunshine exposure as a result of not spending time outdoors (e.g. frail and institutionalised people) or habitually wearing clothing that covers most of the skin while outdoors and those from minority ethnic groups with dark skin.

Factors that potentially affect vitamin D status include[3,6,10,11]

- Pregnant and breastfeeding women, especially teenagers and younger women
- People aged 65 years and over
- People who have low or no exposure to the sun, for example those who cover their skin for cultural reasons, who are housebound or confined indoors for long periods
- Clothing and use of sunscreens
- People who have darker skin, for example people of African, African-Caribbean and South Asian origin
- Obese people (BMI>30)
- Diet that restricts the major food sources of vitamin D
- Family history of vitamin D deficiency / osteomalacia
- Liver or renal disease
- Intestinal malabsorbtion or short bowel syndrome
- Multiple, short interval pregnancies
- Taking anticonvulsants, cholestyramine, rifampicin, glucocorticoids, or antiretrovirals

National recommendations to avoid vitamin D deficiency

It is now recommended that the RNI/Safe Intakes are applicable throughout the year, as a precautionary measure, to cover population groups in the UK identified to be at risk of having a serum 25(OH)D concentration < 25 nmol/L as well as unidentified individuals in the population at risk of having a serum 25(OH)D concentration < 25 nmol/L in summer.

The RNI is the average amount needed by 97.5% of the population to maintain a serum 25(OH)D concentration ≥ 25 nmol/L when UVB sunshine exposure is minimal. It refers to average intake over a period of time (e.g. a week) and takes account of day to day variations in vitamin D intake. The RNI/Safe Intake for vitamin D refers to intakes from all dietary sources: natural food sources; fortified foods (including infant formula milk); and supplements[3].

Public Health England (PHE) has based its latest advice on the SACN recommendations[12].

- Since it is difficult for people to meet the 10 microgram recommendation from consuming foods naturally containing or fortified with vitamin D, PHE recommend that people should consider taking a daily supplement containing 10 micrograms of vitamin D in autumn and winter. Between late March/April to the end of September, the majority of people aged five years and above will probably obtain sufficient vitamin D from sunlight when they are outdoors. So they may choose not to take a vitamin D supplement during these months.
- People whose skin has little or no exposure to the sun, like those in institutions such as care homes, or who always cover their skin when outside, risk vitamin D deficiency and need to take a supplement throughout the year. Ethnic minority groups with dark skin, from African, Afro-Caribbean and South Asian backgrounds, may not get enough vitamin D from sunlight in the summer and therefore should consider taking a supplement all year round.
- Children aged 1 to 4 years should have a daily 10 microgram vitamin D supplement.
- A newborn baby's vitamin D status is largely determined by the mother's level of vitamin D during pregnancy. Infants from birth to one who are exclusively breastfed, or who have less than 500ml a day of infant formula, should be given a daily supplement containing 8.5 to 10µg of vitamin D, to make sure they get enough. Babies fed infant formula do not need a vitamin D supplement until they are receiving less than 500ml (about a pint) of infant formula a day, since it is fortified with vitamin D.

It is worthwhile providing all patients with lifestyle advice in order for them to make changes where appropriate, for example the British Dietetic Association Food Fact Sheet on Vitamin D.[7] **A supplement may contain vitamin D alone or contained in multi-vitamin products and should be purchased over the counter.** Women and children from families who are eligible for the Government's Healthy Start scheme can get free vitamin supplements including vitamin D in the form of tablets for women and drops for children. For further information on who qualifies for the scheme and where they can obtain vitamin supplements see www.healthystart.nhs.uk.

NICE also recommend that health professionals recommend and record vitamin D supplement use among at-risk groups whenever possible, for example during registration appointments, vaccine and screening appointments or other health checks[6].

Table 1-Who needs a Vitamin D supplement? National guidance

Group	Recommended Supplementation
All adults and children over 1	**Consider taking a daily supplement containing 10 micrograms (400 iu) of vitamin D especially during Autumn and Winter**
At-risk groups ▪ **People whose skin has little or no exposure to the sun,eg in care homes,** ▪ **People who always cover their skin when outside** ▪ **Ethnic minority groups with dark skin, from African, Afro-Caribbean and South Asian backgrounds,**	**Should take daily supplement containing 10 micrograms (400 iu) of vitamin D throughout the year**
Pregnant and breast feeding women	**Consider taking a daily supplement containing 10 micrograms (400 iu) of vitamin D**
Children aged 1-4 years	**Daily supplement containing 10micrograms (400 iu) vitamin D unless receiving >500ml infant formula per day**
Babies under 1 year	**Daily supplement containing 8.5micrograms-10micrograms/day unless receiving >500ml infant formula per day**

Section 3: Investigation and treatment of vitamin D deficiency and insufficiency in adults

Indications for testing vitamin D status

Routine testing of vitamin D levels in at-risk groups should not be undertaken[2]. NICE recommends that health professionals should not test people's vitamin D status unless:

- They have symptoms of deficiency
- They are considered to be at particularly high risk of deficiency (for example, they have very low exposure to sunlight)
- There is a clinical reason to do so (for example, they have osteomalacia or have had a fall).[6]

Table 2 sets out tests that may be carried out when vitamin D deficiency is suspected and Table 3 lists clinical features of vitamin D deficiency and other causes for symptoms that should be excluded – **these are not exhaustive lists and should not be treated as such**.

Table 2 – Tests that may be carried out when vitamin D deficiency is suspected [2, 10, 13]

Test	Notes
Alkaline phosphatase (ALP) and phosphate	Hypophosphatemia may indicate long standing vitamin D deficiency
C-reactive protein (CRP)	
Calcium	To exclude hypercalcaemia and provide a baseline for monitoring
Creatine kinase (CK)	Raised CK with non-specific myalgia indicates vitamin D deficiency
Full blood count (FBC)	Anaemia may be present if there is malabsorption
Liver function tests	To exclude hepatic failure
Parathyroid hormone (PTH)[i]	Vitamin D deficiency can lead to secondary hyperparathyroidism
Renal function	To exclude renal failure
Urea & electrolytes (U&E)	

[i] Phlebotomy needs to take place at the site where the assay is processed because the blood test for PTH is unstable.

Table 3 Clinical features of vitamin D deficiency in adults and other causes for symptoms that should be excluded

Clinical features of vitamin D deficiency in adults[10,11,13]

- Insidious onset, widespread or localised bone pain or tenderness without preceding mechanical injury
- Proximal muscle weakness or muscle aches
- Swelling, tenderness and redness at pseudo-fracture sites
- Insufficiency fractures / fragility fracture

Possible causes for symptoms

Hypercalcaemia

- Metastatic calcification
- Renal stones (calculi)
- Severe hypercalciuria
- Stage 4 chronic kidney disease or eGFR <30ml/minute
- Primary hyperparathyroidism
- Low bone mineral density
- PMR / myositis (morning stiffness)

  Myeloma
- Rheumatoid arthritis
- Polymyalgia rheumatica

Assessing vitamin D status

Assay of 25-hydroxyvitamin D (25[OH]D) should be undertaken to assess vitamin D status. There is high inter-assay and inter-laboratory variation in serum 25(OH)D concentration measurements. Vitamin D deficiency is defined by the Department of Health as a plasma concentration of 25(OH)D below 25 nmol/L (equal to 10ng/ml). A level above 25 nmol/L is considered to be sufficient for the majority of the preparation to maintain musculoskeletal health. However, levels of 25-50 nmol/L **may** be considered inadequate in some people[2,10]. NOS[2] and recent CKS guidelines suggest treating deficiency at levels **below 30nmol/L** and this is the level that has been agreed locally. There is no agreement on optimal 25(OH)D levels[14]. **Prescribers should be aware that locally, there may be variation in the way that laboratories report vitamin D status**.

Table 4 – Serum 25-hydroxyvitamin D concentrations, health and disease

25(OH)D concentration	Vitamin D status	Manifestation	Management
<30 nmol/L	Deficient	Rickets, osteomalacia	Treat with high dose colecalciferol-**see flowcharts**
30-50 nmol/L	May be insufficient in some people. Only treat if symptomatic in patients without bone disease. Treat patients with bone disease.		Advise potential benefits of purchasing vitamin D supplement in line with national guidance. Prescribe vitamin D 800-1000 micrograms daily for 12 weeks ONLY in certain circumstances with product licensed to treat insufficiency-**see flowcharts**

Treating vitamin D deficiency (25(OH)D <30 nmol/L)

Patients with vitamin D deficiency should be treated with high-dose vitamin D**.** Vitamin D is administered as either D2 (ergocalciferol) or D3 (colecalciferol) which are both physiologically inactive and have to be hydroxylated in the liver and kidneys to form active compounds. Colecalciferol and ergocalciferol are considered to have equal potency although colecalciferol has been reported to raise serum vitamin D concentrations more effectively than ergocalciferol due to higher affinities of colecalciferol and its metabolites for liver enzymes, plasma vitamin D binding protein and vitamin D receptors. Based on the current medical consensus as well as problems related to the measurement of 25(OH)D2, **colecalciferol is recommended** as the preferred choice. Supplements containing colecalciferol are obtained from animal sources (usually as a by-product of wool fat) and are not suitable for strict vegetarians (vegans) whereas ergocalciferol is obtained from plant sources.[1]

In the past there has been a reliance on unlicensed medicines and food supplements to meet prescribing needs, however there are now many licensed vitamin D products and unlicensed preparations **should no longer be prescribed.** There is a licensed ergocalciferol 300,000iu/ml IM injection which results in 100% adherence, however it has unpredictable bioavailability, slower onset of repletion and additional administration burden and is therefore **not recommended**.

Treatment for deficiency will be for a maximum of 12 weeks before review; it is recommended therefore to avoid putting vitamin D onto repeat prescriptions.

Suggested Treatment Strategies for Vitamin D deficiency

In the past it was advocated that a single large dose (300,000 IU or higher) of vitamin D might lead to sustained correction of vitamin D deficiency and potentially avoid adherence problems with regular lower dose supplementation. This was initially proposed for the treatment of rickets and osteomalacia but has also been suggested as a possible option for vitamin D insufficiency in the elderly. However, more recently it has been suggested that large doses of vitamin D given intermittently are ineffective and might actually increase fracture risk. In light of the current absence of studies comparing the effectiveness of titrated dose strategies, NOS recommend use of simpler, fixed-dose regimens.[2] **See flow charts for recommended products**.

Contraindications include[13] (consult product SPCs for full information)

- Hypersensitivity to vitamin D or any of the excipients in the product
- Hypervitaminosis D
- Nephrolithiasis
- Diseases or conditions resulting in hypercalcaemia and/or hypercalciuria
- Severe renal impairment (eGFR <30ml/min) -consider advice from local nephrologist if not already under their care[16]
- Metastatic calcification

Drug interactions (consult product SPCs for full information)

Drug interactions are as follows[15]

- Concomitant treatment with phenytoin or barbiturates can decrease the effect of vitamin D because of metabolic activation.
- Concomitant use of glucocorticoids can decrease the effect of vitamin D.
- The effects of digitalis and other cardiac glycosides may be accentuated with the oral administration of calcium combined with vitamin D. Strict medical supervision is needed and, if necessary monitoring of ECG and calcium.
- Thiazide diuretics reduce the urinary excretion of calcium. Due to the increased risk of hypercalcaemia, serum calcium should be regularly monitored during concomitant use of thiazide diuretics.

- Simultaneous treatment with ion exchange resins such as cholestyramine or laxatives such as paraffin oil may reduce the gastrointestinal absorption of vitamin D

- The cytotoxic agent actinomycin and imidazole antifungal agents interfere with vitamin D activity by inhibiting the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D by the kidney enzyme, 25-hydroxyvitamin D-1-hydroxylase.

- Patients should avoid taking vitamin D at the same time of day as orlistat as this reduces absorption.

Treating vitamin D deficiency in pregnancy

A re-emergence of rickets has been seen in the UK, with cases mainly affecting children from ethnic minorities; this is probably related to both maternal and infant diet and lifestyle in particular groups (for example, in women who cover their skin). Women should have adequate vitamin D stores for their own requirement, for their developing foetus and to build stores for early infancy particularly if they plan to breast-feed. During pregnancy, maternal vitamin D deficiency can lead to deficiency in the infant. Correction of vitamin D deficiency should begin in the 2nd or 3rd trimester because of the lack of safety or outcome data in first trimester, and because the majority of skeletal growth and development is thought to occur in the 2nd or 3rd trimester. Products that are licensed in pregnancy should be used and the recent UKMi document "Which oral vitamin dosing regimens correct deficiency in pregnancy?" should be consulted.[17]

Monitoring following treatment for vitamin D deficiency

Serum calcium should be checked one month after starting treatment for vitamin D deficiency to allow detection of subclinical primary hyperparathyroidism[2,15].

Routine monitoring of serum 25(OH)D is unnecessary but may be appropriate at least 12 weeks following commencement of treatment where patients are still symptomatic, have malabsorption, or where poor concordance is suspected[2]. Patients who do not respond after 12 weeks of treatment may be considered for referral to secondary care.

Treating insufficiency (25(OH)D 30-50 nmol/L)

In contrast to treating vitamin D deficiency, there is no good evidence to demonstrate that treating vitamin D insufficiency leads to improved clinical outcomes. However, some patients may be symptomatic at levels considered to be "insufficient". Therefore it is recommended that **symptomatic patients without bone disease, those on drugs known to cause vitamin D**

deficiency or with malabsorption disorders and those with bone disease are prescribed an appropriate vitamin D preparation licensed for the treatment of insufficiency for 12 weeks only.

Maintenance following treatment for vitamin D deficiency or insufficiency

Once deficiency has been corrected, patients should follow national guidance around prevention of vitamin D deficiency and should be advised to purchase an over the counter supplement containing at least 400iu (10 micrograms) colecalciferol daily if they are calcium replete. A prescriber may use discretion around prescribing a maintenance dose of colecalciferol 800-1000iu daily where it is considered that it is not practical for a patient to purchase an over the counter supplement, for example residents of care homes or other institutions **and** they are considered at risk of future deficiency following treatment. For those with bone disease this may be in the form of a calcium and vitamin D supplement if dietary intake of calcium is inadequate. All patients on oral bisphosphonates, iv zoledronic acid or denosumab should receive a calcium and vitamin D supplement unless dietary intake of calcium is adequate.

Vitamin D toxicity

Vitamin D is the most likely of all vitamins to cause overt toxicity. There is wide variation in tolerance to vitamin D. As more patients are treated, it is likely that patients with increased sensitivity to vitamin D therapy because of genetic abnormalities in vitamin D metabolism, co-morbidities such as CKD, granuloma-forming diseases or hyperparathyroidism will be identified and require lower subsequent dosing . Excessive intake leads to hypercalcaemia and its associated effects. These include apathy, anorexia, constipation, diarrhoea, dry mouth, fatigue, headache, nausea and vomiting, thirst and weakness. Later symptoms are often associated with calcification of soft tissues and include bone pain, cardiac arrhythmias, hypertension, renal damage (increased urinary frequency, decreased urinary concentrating ability; nocturia, proteinuria), psychosis (rare) and weight loss. The treatment of toxicity consists of stopping all intake of vitamin D and rehydration [1]

Specialist advice

Where patients are under the care of a specialist, for example a rheumatologist or nephrologist, clinicians may like to seek advice.

References

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