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Better bone health for everybody

Vitamin D and Bone Health:

A Practical Clinical Guideline for
Patient Management

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There is growing interest in the importance of vitamin D, not only in the maintenance of bone health but also in terms of its potential role in the prevention of non-skeletal disorders such as auto-immune disease, cancer, mental health problems and cardiovascular disease. Although there is no universal consensus on the criteria for vitamin D deficiency, it is common in the UK, particularly in older people and other people with limited exposure to sunlight. The awareness that vitamin D deficiency may contribute to the development of osteoporosis and to falls and fractures has resulted in a dramatic increase in requests for plasma 25-hydroxyvitamin D (25(OH)D) measurements. The previous lack of national guidance on the indications for 25(OH)D measurements, the interpretation of the results and the correction of vitamin D deficiency has resulted in confusion among patients and health-care professionals and the proliferation of conflicting guidelines and inconsistent practice across the UK. The Royal Osteoporosis Society therefore published a practical clinical guideline in 2013, on the management of vitamin D deficiency in adult patients with, or at risk of developing, bone disease.

The guideline has now been updated by a group of clinicians and scientists with expertise in vitamin D and osteoporosis, using evidence from the Institute of Medicine (IOM) Report in 2010 and the Scientific Advisory Committee on Nutrition (SACN) Report on Vitamin D and Health in 2016, supplemented by the identification of papers published subsequently.

Where clear-cut evidence was unavailable to inform the National Osteoporosis Society guideline, the authoring group have offered pragmatic advice, based on a consensus of their own views and experience. It is important to highlight that this is a clinical guideline intended to primarily inform patient management, rather than influence public health policy, which is the remit of the SACN, Public Health England and comparable organisations in the rest of the UK. This guideline is not for the general public with regards to maintaining good bone health, and does not address the management of vitamin D deficiency in childhood or adolescents, in pregnancy or in patients with severe or end-stage chronic kidney disease (CKD Stages 4–5), but the Royal Osteoporosis Society has recently updated the practical clinical guidance on vitamin D in children and young people.

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Publication date: December 2018

Date for review: December 2021

Funding: The development and printing of this document was funded by the National Osteoporosis Society, with sponsorship from Consilient Health, Internis Pharmaceuticals Ltd and Kyowa Kirin International Plc, which have had no input into its content. We are grateful to the authors for giving their time without charge.

Version: 2

Supported by:



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Glossary and abbreviations

Vitamin D	calciferol (either D ₂ or D ₃)
Vitamin D ₃	cholecalciferol
Vitamin D ₂	ergocalciferol
25-hydroxy vitamin D	25(OH)D calcidiol calcifediol
1,25-dihydroxy vitamin D	1,25(OH) ₂ D calcitriol
Chronic Kidney Disease	CKD
Parathyroid Hormone	PTH
Bone Mineral Density	BMD
Randomised Controlled Trial	RCT
Vitamin D Binding Protein	VDBP
High-Performance Liquid Chromatography (linked to either fluorescence or MS (Tandem MS))	HPLC
Mass Spectrometry	MS
3-epi-25(OH)D	C ₃ epimer
Scientific Advisory Committee on Nutrition	SACN
Institute of Medicine	IOM
Dietary Reference Value	DRV
Medicines and Healthcare Products Regulatory Agency	MHRA
European Food Safety Authority	EFSA
Upper Limit	UL
International Unit	IU
Ultraviolet B	UVB
Ultraviolet	UV

Conversion factors

10µg (micrograms) vitamin D = 400IU vitamin D

2.5 nmol/L plasma 25(OH)D = 1 ng/mL plasma 25(OH)D

Note

25(OH)D may be measured in plasma or serum

Key recommendations

- Measurement of plasma 25(OH)D is the best way of estimating vitamin D status.
- Plasma 25(OH)D measurement is recommended for:
 - patients with musculoskeletal symptoms that could be attributed to vitamin D deficiency
 - patients suspected of having bone diseases that may be improved with vitamin D treatment
 - patients with bone diseases, prior to specific treatment where correcting vitamin D deficiency may be necessary.
- In most cases routine vitamin D testing is unnecessary in patients with osteoporosis or fragility fracture, who may be co-prescribed vitamin D supplementation with an oral antiresorptive treatment.
- Following review of the Scientific Advisory Committee on Nutrition (SACN) and Institute of Medicine (IOM) reports, we propose that the following vitamin D thresholds are adopted by UK practitioners in respect to bone health:
 - plasma 25(OH)D < 25 nmol/L is deficient
 - plasma 25(OH)D of 25–50 nmol/L may be inadequate in some people
 - plasma 25(OH)D > 50 nmol/L is sufficient for almost the whole population.
- Oral vitamin D₃ is the treatment of choice in vitamin D deficiency.
- Where rapid correction of vitamin D deficiency is required, such as in patients with symptomatic disease or about to start treatment with a potent antiresorptive agent (zoledronate or denosumab or teriparatide), the recommended treatment regimen is based on fixed loading doses followed by regular maintenance therapy:
 - a loading regimen to provide a total of approximately 300,000 IU vitamin D, given either as separate weekly or daily doses over six to ten weeks
 - maintenance therapy comprising vitamin D in doses equivalent to 800–2,000 IU daily (occasionally up to a maximum of 4,000 IU daily), given either daily or intermittently at higher doses.
- Where correction of vitamin D deficiency is less urgent and when co-prescribing vitamin D supplements with an oral antiresorptive agent, maintenance therapy may be started without the use of loading doses.
- Adjusted plasma calcium is recommended to be checked one month after completing the loading regimen or after starting lower dose vitamin D supplementation in case primary hyperparathyroidism has been unmasked.
- Routine monitoring of plasma 25(OH)D is generally unnecessary but may be appropriate in patients with symptomatic vitamin D deficiency or malabsorption and where poor compliance with medication is suspected.
- Considering optimisation of bone health and the public health agenda, it is important to promote the relevance of adequate dietary calcium intake and consider use of 'calcium calculators' to help patients and primary-care clinicians (e.g. <http://www.rheum.med.ed.ac.uk/calcium-calculator.php>).

The role of vitamin D in bone health

Vitamin D is essential for musculoskeletal health as it promotes calcium absorption from the bowel, enables mineralisation of newly formed osteoid tissue in bone and plays an important role in muscle function^{1,2}. The main manifestation of vitamin D deficiency is osteomalacia in adults and rickets in children, which the Scientific Advisory Committee on Nutrition (SACN) suggests are generally associated with increased risk at plasma 25-hydroxyvitamin D (25(OH)D) concentrations below 20-25 nmol/L³. Less severe vitamin D deficiency, sometimes termed vitamin D insufficiency, may lead to secondary hyperparathyroidism, bone loss, muscle weakness, falls and fragility fractures in older people⁴⁻⁸.

Vitamin D and parathyroid hormone

Vitamin D status is currently best assessed by measurement of plasma 25(OH)D⁹. As there is a broad inverse relationship between plasma 25(OH)D and parathyroid hormone (PTH), the threshold plasma 25(OH)D concentration below which PTH increases above the normal range has been used to define biochemical criteria for vitamin D insufficiency^{9,10}. However, the inverse relationship between plasma 25(OH)D and PTH may be influenced by age, calcium intake, physical inactivity, renal function, ethnicity, magnesium status and vitamin D binding protein^{9,11-15}. Furthermore, the use of different assays for 25(OH)D and PTH may also influence the apparent threshold 25(OH)D concentration at which secondary hyperparathyroidism occurs^{9,16}. As a result, there is no clear consensus on the biochemical criteria that define vitamin D deficiency and insufficiency.

Lips et al., classified vitamin D insufficiency into mild (plasma 25(OH)D 25–50 nmol/L), moderate (12.5–25 nmol/L) and severe (<12.5 nmol/L) insufficiency, which are broadly associated with <15%, 15–30% and >30% increases in PTH, respectively⁶. In contrast, investigators from North America have suggested that the optimal plasma 25(OH)D concentration may be as high as 80–100 nmol/L¹⁷.

The Institute of Medicine (IOM) Report on *Dietary Reference Intakes for Calcium and Vitamin D*

investigated the relationship between vitamin D status and bone health¹⁸ using evidence from two systematic reviews^{19,20}. These examined the relationship between plasma 25(OH)D as a marker of vitamin D status and PTH, calcium absorption, calcium balance, bone mineral density (BMD), fracture risk and rickets/osteomalacia as potential indicators of bone health. They also investigated the relationship between vitamin D status and physical performance, including falls.

From their analyses, the IOM highlighted that studies have demonstrated different threshold plasma 25(OH)D concentrations above which PTH reaches a plateau, ranging from <30 nmol/L to 100–125 nmol/L. The IOM also suggested that most people with a plasma 25(OH)D between 30 and 50 nmol/L have adequate calcium absorption.

The SACN Report on Vitamin D and Health reviewed the dietary reference values (DRVs) for vitamin D in the UK³. This examined the relationship between plasma 25(OH)D and health outcomes, together with the effect of vitamin D supplementation. As there was no clear evidence of a benefit on non-musculoskeletal health, musculoskeletal outcomes were considered as the basis for setting DRVs. There was a wide variation in 25(OH)D associated with poor musculoskeletal health, but the risk appeared to increase below 20–30 nmol/L. A plasma 25(OH)D above 25 nmol/L was therefore considered to be a population protective level, meeting the needs of 97.5% of the population.

Interpretation of studies of vitamin D supplementation and musculoskeletal outcomes

The problem with interpreting the results of RCTs of effect of vitamin D supplementation on falls and fractures is the heterogeneity of the individual studies regarding the concomitant use of calcium supplements; the type, dose and route of administration of vitamin D; the populations studied; and their baseline vitamin D status². This problem is compounded by the fact that, in most of the large RCTs of vitamin D supplementation, plasma 25(OH)D was only measured in a small sub-set of participants, often with different assays, making it difficult to ascertain the optimal concentration required to obtain the putative benefit on falls and fractures²¹.

Vitamin D and bone mineral density

The IOM Report concluded that there was fair evidence from observational studies to support an association between plasma 25(OH)D concentrations and BMD or changes in BMD at the femoral neck, but not at other sites. In contrast, the IOM reported that most of the RCTs of vitamin D supplementation showed no benefit on BMD. SACN identified a meta-analysis of 23 RCTs of vitamin D supplementation, which found a small improvement in femoral neck BMD, but no effect at the spine or total hip²². Two RCTs were not included in this meta-analysis, one reported beneficial effects of calcium and vitamin D supplementation on total body BMD²³, while the other showed significantly less bone loss from the hip with vitamin D supplementation²⁴. One cohort study showed an association between plasma 25(OH)D concentration < 50 nmol/L and greater bone loss from the hip²⁵ and another study recently found the effect of vitamin D 1,000 IU per day on BMD only in participants with a baseline 25(OH)D ≤ 30 nmol/L²⁶.

Vitamin D and muscle strength and function

SACN concluded that there was limited evidence from a small meta-analysis of seven interventional studies of a beneficial effect of vitamin D supplementation on muscle strength and function in younger adults with a plasma 25(OH)D < 30 nmol/L. In adults above the age of 50, the evidence from three meta-analyses of RCTs was mixed, but overall suggested that vitamin D supplementation improves muscle strength and function.

Vitamin D and falls

The IOM Report concluded that there was a lack of sufficiently strong evidence from RCTs of vitamin D supplementation, with or without calcium, on the risk of falls. This contrasts with the earlier meta-analyses by Bischoff-Ferrari et al.,^{27,28} the limitations of which were discussed in the IOM Report. A subsequent Cochrane Review demonstrated a 37% reduction in rate of falls with vitamin D supplementation in older people living in residential homes.²⁹ A second Cochrane Review showed no overall reduction in falls

in community dwelling older people,³⁰ but a post hoc analysis suggested a 43% reduction in rate of falls in trials recruiting subjects with low vitamin D levels. The SACN Report reviewed a number of meta-analyses and RCTs of the effects of vitamin D supplementation on falls risk and concluded that although the evidence was mixed, vitamin D supplementation appeared to reduce fall risk in community dwelling older adults, with mean baseline plasma 25(OH)D concentrations across a range of values.

Vitamin D and fractures

The IOM Report concluded that vitamin D supplementation alone did not reduce the risk of fractures, but combined supplementation with vitamin D and calcium decreased fractures in institutionalised older people. SACN reported that evidence from three meta-analyses of vitamin D supplementation and fracture prevention was mixed, but, on balance suggested that there was no reduction in fracture risk. A Cochrane Review showed no significant effect of vitamin D supplementation alone on fracture risk. Vitamin D and calcium marginally reduced the risk of hip fractures, but this benefit appeared to be restricted to those living in institutional care³¹. It is worthwhile highlighting the results of a study of annual administration of high dose vitamin D (12,500 µg/ 500,000 IU) over three to five years in community dwelling older people³². This showed an increased risk of falls and fractures in the three months after dosing, when plasma 25(OH)D concentrations were in the region of 90-120 nmol/L. Data from Bischoff-Ferrari et al., also showed increased risk of fracture with 60,000IU intermittent dosing³³.

Summary

After considering the data from their two systematic reviews, the IOM developed a schematic representation of the relationship between plasma 25(OH)D and integrated bone health outcomes (Figure 1).

As the relationship between plasma 25(OH)D and these outcomes is inconsistent, the IOM did not classify low, moderate and high concentrations in their schematic representation. Nevertheless, they

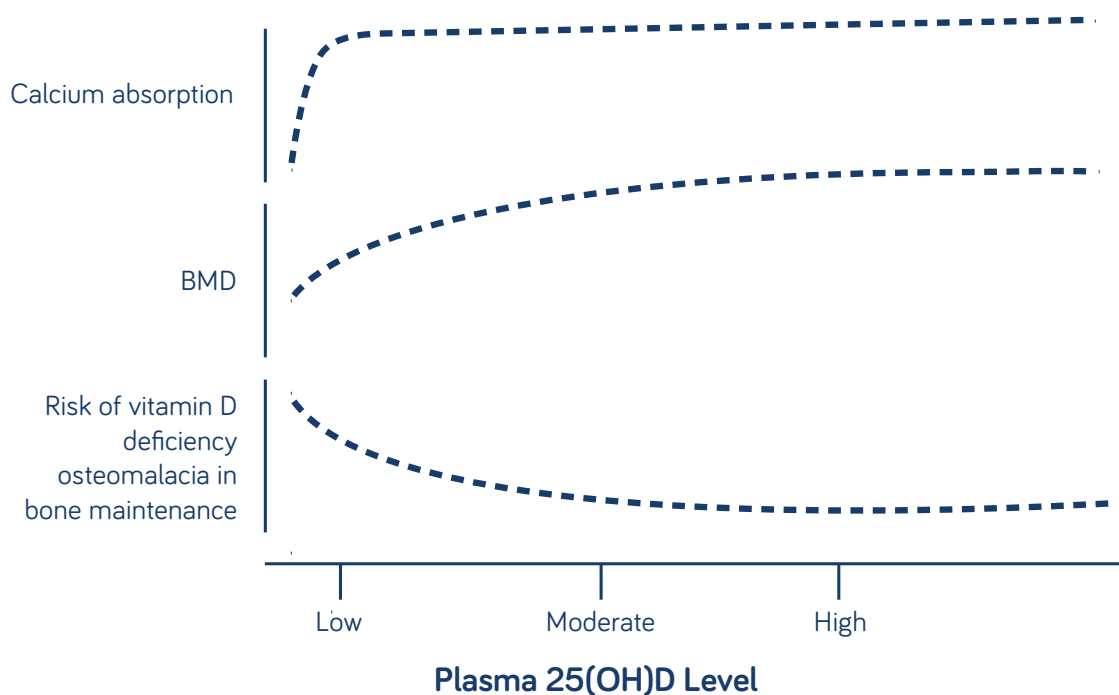


Figure 1 The relationship between vitamin D exposure as measured by plasma 25(OH)D and integrated bone health outcomes¹⁸. (Adapted from an IOM schematic representation.)

suggested that a plasma 25(OH)D of 40 nmol/L is sufficient to meet the vitamin D requirement for bone health in half the population, while 50 nmol/L would be sufficient for 97.5% of the population. They therefore concluded that people are at risk of deficiency when plasma 25(OH)D < 30 nmol/L, but suggested that some people are potentially at risk of inadequacy when plasma 25(OH)D is 30–50 nmol/L. Although a plasma 25(OH)D of 30–50 nmol/L has been termed ‘vitamin D insufficiency’, this may be misleading as half the people with a plasma 25(OH)D in this range have adequate vitamin D status. The IOM also suggested that practically everyone is sufficient in vitamin D when plasma 25(OH)D > 50 nmol/L.

SACN advocated that the general population have to achieve a plasma 25(OH)D of greater than 25 nmol/L throughout the year, to prevent poor musculoskeletal health. This was not considered to necessarily be a diagnostic criterion for vitamin D deficiency, but a marker of increased risk of poor musculoskeletal health.

The Endocrine Society Task Force published a clinical-practice guideline on the evaluation, prevention and treatment of vitamin D deficiency³⁴. This defined vitamin D deficiency as a plasma 25(OH)D < 50 nmol/L but advocated that 25(OH)D concentration exceed 75 nmol/L, to maximise the effect of vitamin D on calcium, bone and muscle metabolism. We are reluctant to encourage the achievement of such high 25(OH)D concentrations, as they potentially may be associated with adverse events, such as an increased risk of falls and fractures. Furthermore, this would conflict with public health guidance in the UK from SACN and Public Health England³.

Having reviewed the IOM and SACN Reports and the evidence base supporting them, we propose that the following pragmatic vitamin D thresholds are adopted by UK Clinicians in respect to bone health:

- plasma 25(OH)D < 25 nmol/L is deficient
- plasma 25(OH)D of 25–50 nmol/L may be inadequate in some people
- plasma 25(OH)D > 50 nmol/L is sufficient for almost the whole population

How should we assess vitamin D status?

Introduction

There are well over 40 identified metabolites of vitamin D³⁵. In practice, the vast majority of metabolites have a very short half-life in the circulation and so are currently of minimal interest. Although the parent sterol vitamin D has a half-life of close to 24 hours³⁶, this is relatively short compared to 25(OH)D, which has a half-life of 21–30 days^{37,38}. Therefore, measurement of 25(OH)D is a better indicator of vitamin D stores, whether obtained from sunlight (ultraviolet (UV) exposure) or dietary sources. The most potent physiologically active circulating metabolite produced by humans is 1,25(OH)₂D, which has a half-life of 4–15 hours^{39–42}, and while 25(OH)D circulates in nmol/L concentrations 1,25(OH)₂D is present in pmol/L concentrations.

25(OH)D production is dependent on the 25 hydroxylation that takes place in the liver.

This step is primarily dependent on the substrate concentration (vitamin D)^{43,44} and is the reason why the widely recognised seasonal variability related to UVB exposure exists. 1 α hydroxylation mainly takes place in the kidney but can also happen in placenta, bone, skin and granuloma tissue (sarcoid, tuberculosis) and many other tissues⁴⁵. It requires 25(OH)D as the substrate and the rate of 1,25(OH)₂D production by the kidney can be influenced by prevailing calcium and PTH concentration. For these reasons, as well as its short half-life, 1,25(OH)₂D is a poor indicator of overall vitamin D status as 25(OH)D needs to decrease to around 10 nmol/L for 1,25(OH)₂D to decrease significantly⁴⁶. Measurement of PTH will reflect deficiency of 25(OH)D sufficient to alter calcium homeostasis, but changes in PTH are affected by many factors other than 25(OH)D and hyperparathyroidism is caused by many factors⁴⁷.

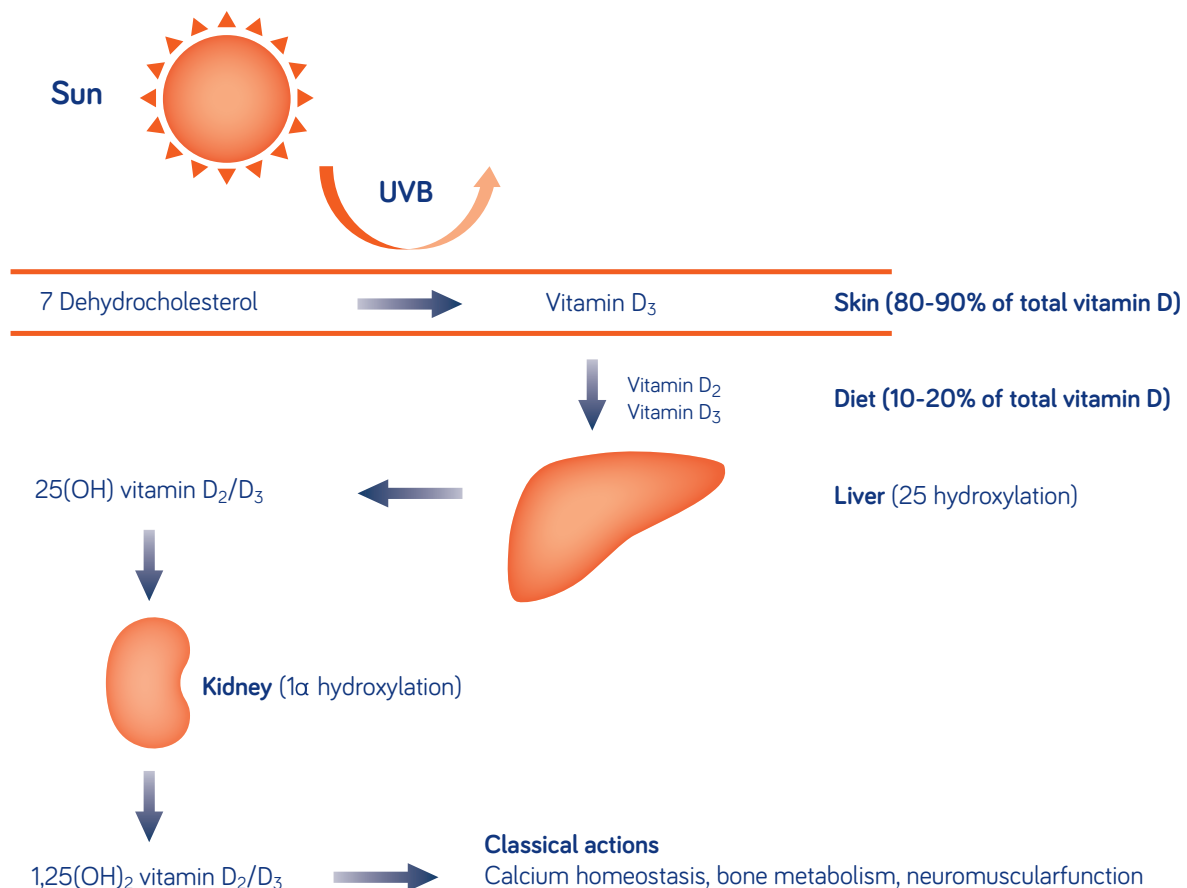


Figure 2 Metabolism of vitamin D (adapted from⁴⁸)

Biochemical assessment of vitamin D status

There are several factors that need to be taken into account when measuring 25(OH)D, including the concentration of vitamin D binding protein (VDBP) and albumin binding of vitamin D in the plasma. 25(OH)D (calcidiol) circulates in the blood as both the plant/fungi-derived (dietary) 25(OH)D₂ and the sunlight-derived and animal-derived (diet) 25(OH)D₃. For most people, the majority (80–90%) of circulating 25(OH)D is formed by 25 hydroxylation in the liver of vitamin D produced by the action of UVB on 7 dehydrocholesterol in the skin; the other 10–20% of 25(OH)D comes from the diet.

The main methods available to estimate 25(OH)D are immunoassay, HPLC attached to fluorescence or mass spectrometry (MS) detection (tandem MS).

Immunoassays are often automated and incorporated into large commercial analyser systems, which gives them excellent functionality and the ability to measure large numbers of samples routinely. Apart from issues of calibration and standardisation, a weakness of immunoassay is the inability to quantify vitamin D₂ and vitamin D₃ separately, which means they give an estimation of total 25(OH)D. Immunoassays do not necessarily identify all vitamin D₂. However, vitamin D₂ is normally low or undetectable in the majority of samples, unless the patient is receiving vitamin D₂ in the form of treatment or supplements.

Tandem MS assays are able to simultaneously give an estimate of 25(OH)D₂ and D₃. They tend to be more sensitive than immunoassays but are more labour intensive and require a greater level of technical expertise than immunoassays. Even with semi-automation of sample preparation, the number of samples that can be processed daily by tandem MS is significantly lower than in an automated immunoassay. Tandem MS assays can be subject to interference from metabolites such as the C₃ epimer, which is mainly synthesized by babies and younger children but has also been detected in adult populations⁴⁹.

Notwithstanding the various technical aspects of measuring vitamin D, there are a few simple considerations that need to be applied from a clinical perspective:

- measurement of plasma 25(OH)D is the best way of estimating vitamin D status.
- the assay should have the ability to recognise all forms of 25(OH)D (D₂ or D₃) equally. In practice, this means that it should use either HPLC or, more likely, tandem MS. None of the immunoassays offer the ability to recognise all forms of 25(OH)D.
- some laboratories restrict 25(OH)D measurements to patients in whom there has been shown to be an abnormality in adjusted plasma calcium, PTH or alkaline phosphatase. However, these changes occur late in the development of vitamin D deficiency and as markers are insufficiently sensitive to be used in this way. Accordingly, it is advised that where there are clinical grounds for suspecting vitamin D deficiency, 25(OH)D be measured without the need for any preliminary surrogate investigation.

Who should be tested for vitamin D deficiency?

The number of vitamin D measurements requested in the UK has increased in recent years, such that testing for vitamin D deficiency has become routine in clinical practice, despite considerable uncertainty about who to test and whether low results are related to the patient's symptoms or illness. In some areas, requests are made to measure plasma 25(OH)D for unclear clinical indications, resulting in large numbers of tests. The recommendations presented here provide a rational approach to 25(OH)D testing. Good-practice principles should always be adopted when considering testing for 25(OH)D. These include being able to justify that the result will affect clinical management, being aware that the relationship between the patients' symptoms and 25(OH)D concentration is not always consistent given the high prevalence of vitamin D deficiency, and being aware of how to interpret findings.

We have identified four groups with different health needs. The relevance of vitamin D testing is explored for each.

Patients with bone diseases (a) that may be improved with vitamin D treatment or (b) where correcting vitamin D deficiency prior to specific treatment would be appropriate

This group primarily comprises patients who have osteomalacia or osteoporosis. Patients with osteomalacia often complain of multiple symptoms including bone, joint and muscle pain, hyperalgesia, muscle weakness and a waddling gait. There is good evidence that correcting vitamin D is essential in osteomalacia, but it is also likely to be beneficial in osteoporosis. There are other bone diseases where correcting vitamin D deficiency before drug treatment is recommended, such as when treating Paget's disease with a bisphosphonate.

Correction of vitamin D deficiency is also required before starting osteoporosis treatment with a potent antiresorptive agent (zoledronate or denosumab or teriparatide), to avoid the development of hypocalcaemia. Nevertheless, in most cases

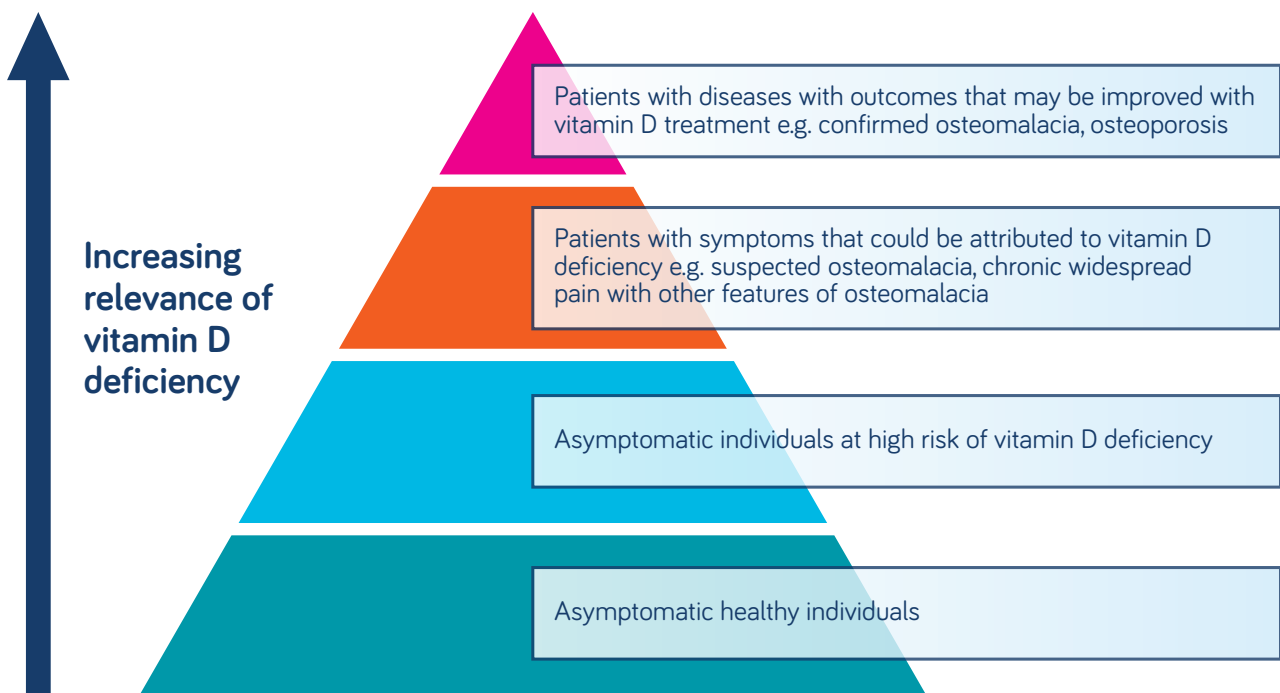


Figure 3 Schematic representation that helps to define broad groups for clinical consideration and decision making.

routine 25(OH)D testing is unnecessary in patients with osteoporosis or fragility fracture, where a decision has been made to co-prescribe vitamin D supplementation with an oral antiresorptive treatment.

Patients with musculoskeletal symptoms that could be attributed to vitamin D deficiency

Symptoms of vitamin D deficiency are unfortunately vague and it can be difficult to ascertain whether a low plasma 25(OH)D level is causal or a surrogate marker (e.g. of poor nutrition or a lack of activity). Nonetheless, if patients are suspected of having symptoms caused by osteomalacia, or have chronic widespread pain with other features of osteomalacia (e.g. proximal muscle weakness)⁵⁰⁻⁵², consider measuring plasma 25(OH)D as part of their clinical and laboratory evaluation.

Asymptomatic individuals at higher risk of vitamin D deficiency

There are a number of risk factors in asymptomatic individuals that predispose to lower levels of 25(OH)D. These individuals are more likely to be vitamin D-deficient and current UK guidance from the Department of Health and Social Care recommends that these individuals have a higher intake of vitamin D (see box below).

Recommendation:

Do not routinely test 25(OH)D levels in these groups.

Asymptomatic healthy individuals

The use of plasma 25(OH)D measurements in asymptomatic healthy individuals and the correction of deficiency to reduce the incidence of the diseases putatively associated with vitamin D deficiency have never been studied. This form of population screening has not been carried out and would not fulfil recognised criteria for screening⁵⁴. Although vitamin D deficiency is highly prevalent, universal screening of asymptomatic populations is not recommended.

Department of Health and Social Care Guidance⁵³

Adult groups at risk of vitamin D deficiency:

- older 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 who are confined indoors for long periods
- people who have darker skin, for example people of African, African-Caribbean or South Asian origin, because their bodies are not able to make as much vitamin D.

Recommendations:

- people aged 65 years and over and people who are not exposed to much sun should also take a daily supplement containing 10 µg (400 IU) of vitamin D.

Who will benefit from treatment?

It is advised that in those patients where 25(OH)D is tested (discussed in the previous section: 'Who should be tested for vitamin D deficiency?'), the results be acted upon as follows:

- plasma 25(OH)D < 25 nmol/L: treatment recommended.
- plasma 25(OH)D 25–50 nmol/L: treatment is recommended in patients with the following:
 - fragility fracture, documented osteoporosis or high fracture risk
 - treatment with antiresorptive medication for bone disease
 - symptoms suggestive of vitamin D deficiency
 - increased risk of developing vitamin D deficiency in the future because of reduced exposure to sunlight, religious/cultural dress code, dark skin, etc.
 - raised PTH
 - medication with antiepileptic drugs or oral glucocorticoids
- plasma 25(OH)D > 50 nmol/L: provide reassurance and give advice on maintaining adequate vitamin D levels through safe sunlight exposure and diet.

How should vitamin D deficiency be treated?

Practical aspects of vitamin D treatment must be central to any guidance relevant to clinical management in primary care. Treatment regimens must be acceptable to both non-expert primary care physicians and to patients. To achieve good patient adherence to treatment, it is important to consider both the complexity of the treatment regimen and patients' personal religious and cultural beliefs; specifically: the presence of gelatine in some preparations, whether the vitamin D is derived from animal or plant sources, and the presence of allergens in some preparations.

Primary care clinicians should have ready and easy access to supplies of appropriately priced, high-quality vitamin D formulations as well as to laboratory services to meet any monitoring requirements. Treatment of vitamin D deficiency should be effective in terms of assessment, biochemical testing and good adherence to treatment.

Key aims for treating vitamin D deficiency in patients with bone disease:

- use adequate doses to ensure correction of vitamin D deficiency (ideally >50 nmol/L).
- reverse the clinical consequences of vitamin D deficiency in a timely manner.
- avoid toxicity.

Vitamin D₃ or vitamin D₂?

There is considerable debate about the relative merits of treatment with animal-derived vitamin D₃ versus plant-derived D₂. Using biochemical parameters, vitamin D₂ does appear to have quicker clearance than vitamin D₃^{55–57}, especially after intermittent bolus dosing⁵⁸. The clinical relevance of this is not clear. However, in light of this controversy, guidance for both vitamins D₂ and D₃ is provided.

Recommendation:

- Based on the current medical consensus as well as problems related to the measurement of 25(OH)D₂, vitamin D₃ is recommended as the vitamin D preparation of choice for the treatment of vitamin D deficiency.

Oral or intramuscular administration?

While intramuscular administration results in 100% adherence, there are important factors to consider before usage, including an unpredictable bioavailability⁵⁹, slower onset of repletion⁵⁷ and the additional administration burden in comparison to oral preparations. Parenteral vitamin D is therefore not the first-line recommendation within the treatment guidance, primarily due to significant inter-individual variability in absorption.

Recommendation:

- Oral administration of vitamin D is recommended.

Fixed or titrated dosing strategy?

The concentration of 25(OH)D varies not only according to external factors such as exposure to sunlight (UVB) and diet but also by patient characteristics, including genetic factors⁶⁰ as well as body composition^{61,62}. These patient characteristics may also influence the subsequent pharmacokinetics and pharmacodynamics of vitamin D supplementation⁶³.

Therefore, a titrated treatment approach is likely to be more effective than a fixed approach when treating vitamin D deficiency. A titrated approach may either use baseline characteristics to predict the required dose⁶⁴ or monitor response to therapy to guide subsequent dose amount and/or frequency.

The potential benefits of a more refined repletion strategy in terms of reduced toxicity and improved repletion need to be balanced with the increased costs of titration testing and the effect of increasing complexity on physician and patient adherence. In light of the current absence of studies comparing the effectiveness of titrated against fixed dose strategies, we give preference to simpler, fixed-dose regimens.

Recommendation:

- Recommend treatment based on fixed-loading doses and maintenance therapy.

Lower daily dose or higher intermittent dose?

There is controversy concerning the need for and benefit of higher doses given intermittently as compared to daily dosing. In the few studies comparing both, one found that the intermittent dosing was less easily delivered by nursing staff in care homes and so less effective,⁶⁵ but that when different dosing regimens are consistently delivered they have equal biochemical efficacy⁶⁶.

The evidence for lower dose daily dosing is based primarily on the clinical trial studies for drugs used to treat osteoporosis⁶⁷. However, few of these patients were severely deficient and the high level of adherence to daily vitamin D preparations has not been matched in community-based studies⁶⁸.

One recent study has shown that 60,000 units of vitamin D₃ once per month resulted in a higher incidence of falls over 12 months compared with those receiving a monthly dose of 24,000 units. More evidence is required but for maintenance doses higher than 24,000 units per month it may be prudent to opt for a shorter dosing interval³³.

In the past it was advocated that a single large dose (300,000 IU or higher) of vitamin D (stoss therapy) 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 therapeutic option for vitamin D insufficiency in the elderly⁶⁹. However, more recently it has been suggested that large doses of vitamin D given intermittently are ineffective⁷⁰ and might actually increase fracture risk³².

In the absence of further studies, such single-loading-dose strategies are not recommended; instead we recommend a split-dose loading regimen followed by a maintenance phase.

The treatment replacement schedule (Appendix 1) involves a loading phase with high doses of vitamin D₃ (or D₂) over many weeks and then moves into a maintenance phase with options of daily supplements

or less frequent 'top ups' according to individual patient needs or wishes. There may also be sub-groups of patients identified (e.g. those with gastrointestinal disorders) who are unable to maintain adequate vitamin D status and so require a more aggressive replacement or maintenance schedule provided under specialist supervision in a secondary-care setting.

Recommendations:

- Where correction of vitamin D deficiency is less urgent and when co-prescribing vitamin D supplements with an oral antiresorptive agent, maintenance therapy may be started without the use of loading doses .
- Where rapid correction of vitamin D deficiency is required, such as in patients with symptomatic disease or about to start treatment with a potent antiresorptive agent (zoledronate or denosumab or teriparatide), the recommended treatment regimen is based on fixed loading doses followed by regular maintenance therapy.

Example Regimens

1. Loading regimens for treatment of deficiency up to a total of approximately 300,000 IU given either as weekly or daily split doses. The exact regimen will depend on the local availability of vitamin D preparations but will include:
 - 50,000 IU (tablets, capsules or liquid) given weekly for six weeks (300,000 IU)
 - 40,000 IU given weekly for seven weeks (280,000 IU)
 - 1,000 IU tablets, four a day for 10 weeks (280,000 IU)
 - 800 IU capsules, five a day given for 10 weeks (280,000 IU).

This list is not exhaustive.

The following should be borne in mind:

- advise that calcium/vitamin D combinations not be used as sources of vitamin D for the above regimens, given the resulting high dosing of calcium.

2. Maintenance regimens should generally be started one month after loading with doses equivalent to 800 to 2,000 IU daily (up to a maximum of 4,000 IU daily), given either daily or intermittently at a higher equivalent dose. The strategies below have been demonstrated not to work or to have a high risk of being ineffective or causing toxicity, and are therefore not to be recommended:
 - annual depot vitamin D therapy either by intramuscular injection or orally
 - use of activated vitamin D preparations (calcitriol and alfacalcidol).

Calcium supplementation

The use of calcium supplements at doses between 400 and 800 mg is associated with poor persistence⁶⁸ and efficacy⁷¹. It had been suggested that there may be adverse cardiovascular outcomes associated with combination therapy, but this was not supported by the MHRA, nor the Biobank study in over half a million men and women⁷²⁻⁷⁴. It is also reassuring to note that an individual-patient-data meta-analysis of the anti-fracture studies suggests that combined calcium and vitamin D supplementation is associated with an improvement in mortality, which is not observed with vitamin D supplementation alone⁷⁵.

Recommendation:

- Considering optimisation of bone health and the public health agenda, it is important to promote the relevance of adequate dietary calcium intake and consider use of 'calcium calculators' to help patients and primary-care clinicians (e.g. <http://www.rheum.med.ed.ac.uk/calcium-calculator.php>).

Monitoring

It is well known that vitamin D treatment, particularly combined with calcium supplementation, can unmask previously undiagnosed primary hyperparathyroidism⁷⁶. It is important that the clinician is aware of this.

Although the dosing regimen is unlikely to result in toxicity, it ought to be recognised that certain groups may be at increased risk of this or adverse side effects and they ought to be monitored. This is usually done by measuring adjusted plasma calcium levels.

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. Monitoring is an integral component of the proposed treatment algorithms as the requirements for repeat testing may be different according to the approaches used.

There is limited evidence for when to monitor response to therapy, but the aims are to:

1. detect those who remain deficient after loading
2. detect those who become deficient during maintenance
3. detect those patients in whom vitamin D therapy uncovers sub-clinical primary hyperparathyroidism.

Assessment of improvement in 25(OH)D status on replacement therapy

There is considerable variability between the results of studies examining the dose response to vitamin D supplementation, but it appears that much of this inconsistency results from the confounding effects of UV exposure in the summer months. When consideration is confined to the results of studies that examined the effect of supplementation on winter 25(OH)D levels, the results are more consistent: a daily supplement of 20 to 25 µg (800 to 1,000 IU) calciferol will cause an increase in 25(OH)D of 24 to 29 nmol/L. Most of these studies have suggested that a new steady-state 25(OH)D level is reached by

about three months. While this is in line with what would be expected given the elimination half-life of 25(OH)D, a more recent study has found that the steady-state levels are not obtained until after six months of treatment. Accordingly, it is a waste of resources to measure vitamin D levels too soon after the therapy has started. A minimum of three months treatment must be given and it may be more prudent to wait until six months have passed.

Recommendation:

- Routine monitoring of plasma 25(OH)D is unnecessary but may be appropriate in patients with symptomatic vitamin D deficiency or in situations where malabsorption or poor compliance with medication is suspected or in patients taking antiresorptive therapy who have extremely low levels at baseline assessment.
- Repeat testing of 25(OH)D may be indicated prior to sequential doses of potent antiresorptives.

Based on the pharmacokinetics of 25(OH)D, assessment of adjusted plasma calcium levels within one month after the administration of the last loading dose are recommended to be undertaken to detect those with primary hyperparathyroidism. The presence of hypercalcaemia ought to lead to cessation of further vitamin D supplementation prior to investigation of the hypercalcaemia.

Recommendation:

- Adjusted plasma calcium is recommended to be checked one month after completing the loading regimen or after starting lower dose vitamin D supplementation in case primary hyperparathyroidism has been unmasked.

Vitamin D toxicity

Excessive oral intakes of vitamin D can lead to toxic effects⁷⁷. Cutaneous synthesis of vitamin D is regulated so that prolonged sunshine exposure does not lead to excess production^{78,79}. Overt vitamin D toxicity manifests itself through chronic hypercalcaemia (elevated plasma calcium). It is rarely seen unless the vitamin D dose is very high, either through inappropriate high-dose treatment or accidental overdosing⁸⁰. Less severe symptoms of vitamin D toxicity include prolonged hypercalciuria, which is a potential risk for renal stones⁸¹. There is weak evidence for other adverse events (mortality⁸² and cancer⁸³) but these are unlikely to be a problem when the aim is to correct vitamin D deficiency.

Upper limit of intake

The Food and Nutrition Board of the IOM has summarised the evidence from a number of supplementation studies of vitamin D¹⁸, which covered a range of doses (800 to 300,000 IU per day) and duration (months to years). They concluded that vitamin D below 10,000 IU per day is not usually associated with toxicity, whereas doses equal to or above 50,000 IU per day for several weeks or months are frequently associated with toxicity. The IOM set the Upper limit (UL) for long-term intake at 4,000 IU (100 µg) per day. Similarly, the European Food Safety Authority (EFSA) and the UK Scientific Advisory Committee on Nutrition (SACN) reviewed the evidence and concluded that an upper limit of 4,000 IU (100 µg) per day is safe for adults and children over 11 years of age including pregnant and lactating women⁸⁴. In addition, SACN concluded that doses of 7,500 µg (300,000 IU) at intervals of three months or longer would not be expected to cause adverse effects in adults. However, SACN acknowledged that there was greater uncertainty about the effects of larger doses, which might cause hypercalcaemia in some individuals.

The ULs for vitamin D intake may not apply to individuals with medical disorders that predispose to hypercalcaemia. These include normocalcaemic hyperparathyroidism, granulomatous diseases such as sarcoidosis and tuberculosis and genetic predispositions.

Hypercalcaemia

High intakes of either vitamin D₂ or vitamin D₃ can cause toxicity through hypercalcaemia. The high plasma calcium potentially leads to soft tissue calcification and resultant renal and cardiovascular damage. There is evidence that higher levels of vitamin D₂ can be tolerated compared to vitamin D₃¹⁸. Patients with granulomatous disease are at risk of hypercalcaemia because of increased 1α-hydroxylase activity (which converts 25(OH)D to active 1,25(OH)₂D). Toxicity has been reported during vitamin D treatment of tuberculosis and in patients with active sarcoidosis with lower dosages than those that are associated with toxicity in healthy people⁸⁵. It is advised that specialist advice be sought before starting these patients on vitamin D therapy.

Hypercalciuria and renal stones

There is no strong evidence that correcting vitamin D deficiency with vitamin D alone will increase the risk of renal stones on healthy people. Patients with active or a history of nephrolithiasis are recommended to be managed on a case by case basis.

A recent meta-analysis of long-term (>24weeks) vitamin D supplementation studies concluded that vitamin D supplementation (without any calcium), is not associated with an increased risk of renal stones, when the effect of supplemental calcium was considered,⁸¹ although the risk of hypercalcaemia and hypercalciuria was increased. These findings are supported by observational studies, reporting that there is increased risk of renal stones with supplemental calcium intake, whereas dietary calcium intake may protect against this^{86,87}. These results correct findings of two Cochrane meta-analyses that reported a 17% increased risk of kidney stones from vitamin D supplementation^{31,82}. These analyses were however dominated by the reported increased incidence of renal stones in the Women's Health Initiative study⁸⁸ in those who were taking vitamin D with calcium supplements (1,000 mg plus 10 µg (400 IU) of vitamin D for up to seven years). In these analyses the effect of calcium supplementation was not considered.

High bolus dosing of vitamin D and falls and fractures

In recent years, a number of studies have been conducted supplementing individuals with intermittent, high-dose vitamin D. Several of those RCTs reported an increase rather than the anticipated decrease in the risk of falls and fractures^{32,33,89,90}. In all of the studies that reported increase falls, these predominantly occurred in after the start of the supplementation, which suggest a link with a change in vitamin D metabolism. The mechanism of action is however not yet understood.

Thus, the evidence from clinical trials is conflicting and other factors such as the falls rate prior to recruitment and baseline 25(OH)D level may be of significance.

Based on the current evidence, there seems to be no rationale to recommend bolus doses in the majority of patients, unless urgent correction of vitamin D status is required. These patients are recommended to be monitored and be under medical supervision. For the majority of patients, as there are no convincing benefits that are likely to outweigh potential risks, lower dose schemes are recommended.

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Appendix 1: Guidance for treatment of vitamin D deficiency

Principles:

1. Treatment of vitamin D deficiency should be effective in terms of assessment and testing, with easy availability of vitamin D formulations, good patient treatment adherence and practical requirements for monitoring a chronic condition.
2. Based on current medical consensus, vitamin D₃ is recommended as the vitamin D preparation of choice for treatment of vitamin D deficiency. However, D₂ is to be used in those who cannot take D₃ for cultural, dietary or religious reasons because of the animal vs. plant sourcing of vitamin D or the use of gelatine in some preparations. Where, D₂ is given, it is recognised that there is a greater rise in 25(OH)D with D₃ than with D₂ supplementation⁹¹.
3. The oral supplementation route is recommended in preference to the parenteral route.
4. A titrated treatment approach is likely to be more effective than a fixed approach when treating vitamin D deficiency. However, the complexity of regimens and the paucity of evidence limits this approach.
5. The treatment replacement schedule includes a loading phase with high doses of vitamin D₃ (or D₂) over several weeks and then moves into a maintenance phase with options of daily supplements or less frequent 'top ups' according to individual patient needs.
6. There may be sub-groups of patients identified who are unable to maintain adequate vitamin D status. These may require a more aggressive replacement or maintenance schedule provided under specialist supervision in a secondary-care setting.
7. 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.
8. Use of a single mega-dose (300,000 IU or higher) for loading patients, while an attractive option with good adherence, has been shown to be either ineffective⁷⁰ or associated with higher rates of falls and fractures³². In the absence of further studies, such single-loading-dose strategies are not recommended.

Example regimens:

1. Loading regimens for the treatment of deficiency up to a total of approximately 300,000 IU given either as weekly or daily split doses. The exact regimen will depend on the local availability of vitamin D preparations but will include:
 - 50,000 IU (tablets, capsules or liquid) once weekly for six weeks (300,000 IU)
 - 40,000 IU given weekly for seven weeks (280,000 IU)
 - 1,000 IU tablets, four a day for 10 weeks (280,000 IU)
 - 800 IU capsules, five a day given for 10 weeks (280,000 IU).

This list is not exhaustive.

The following should be borne in mind:

- advise that calcium/vitamin D combinations not to be used as sources of vitamin D for the above regimens, given the resulting high dosing of calcium. However, some calcium supplementation may be required, especially where a patient's dietary calcium intake is low or osteomalacia is suspected. However, giving calcium may increase the risk of hypercalcaemia in rare cases where primary hyperparathyroidism is unmasked.
2. Maintenance regimens should generally be started one month after loading with doses equivalent to 800 to 2,000 IU daily (occasionally up to 4,000 IU daily), given either daily or intermittently at a higher equivalent dose.

The strategies below have been demonstrated not to work or to have a high risk of being ineffective or causing toxicity, and are therefore not to be recommended:

- annual depot vitamin D therapy either by Intramuscular injection or orally
- use of activated vitamin D preparations (calcitriol and alfacalcidol).

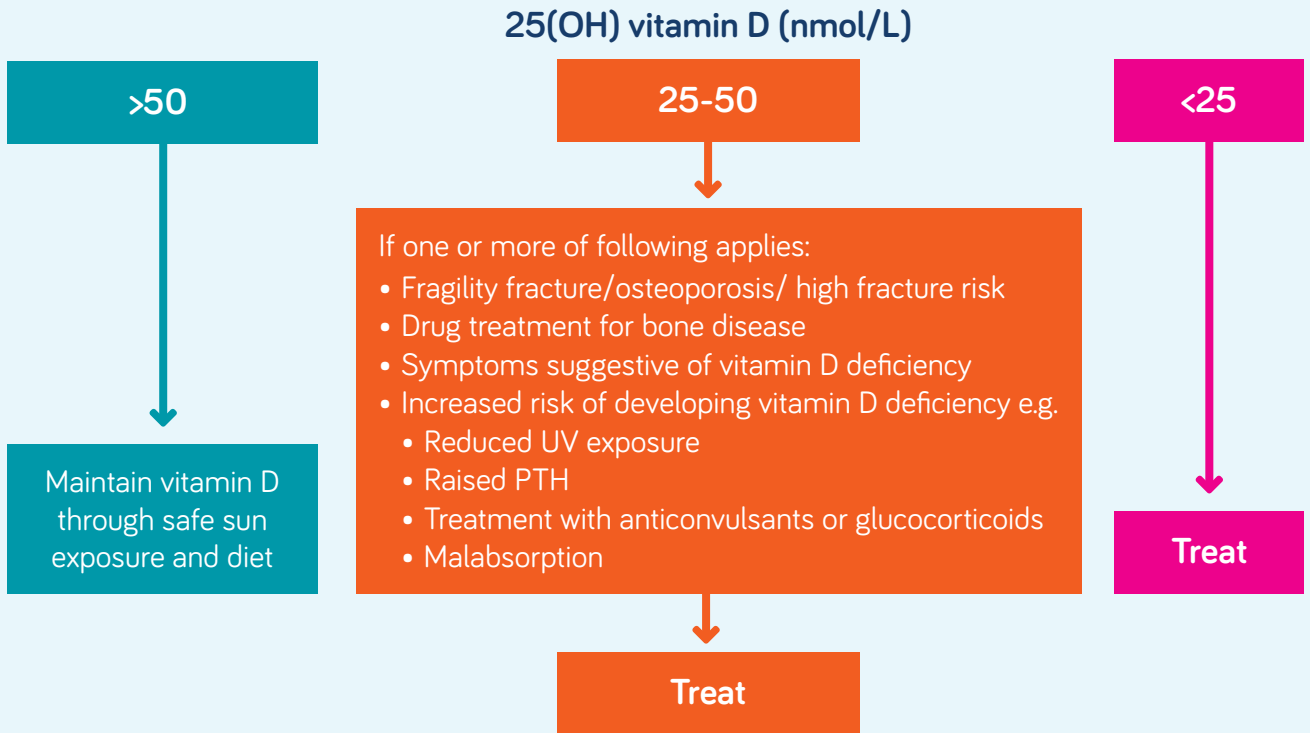
Monitoring:

1. Assess plasma calcium levels one month after administration of last loading dose.
2. Routine monitoring of plasma 25(OH)D is generally unnecessary but may be appropriate in patients with symptomatic vitamin D deficiency or malabsorption and where poor compliance with medication is suspected.

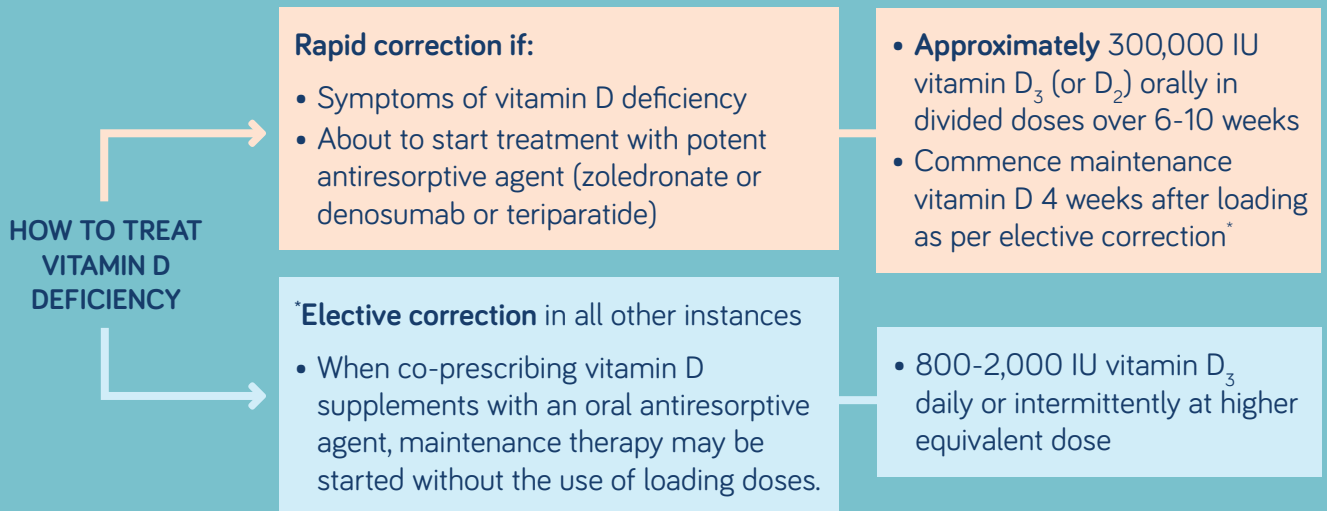
TEST

- Patients with diseases with outcomes that may be improved with vitamin D treatment e.g. confirmed osteomalacia, osteoporosis
- Patients with symptoms that could be attributed to vitamin D deficiency e.g. suspected osteomalacia, chronic widespread pain with other features of osteomalacia
- Before starting patients on a potent antiresorptive agent (zoledronate or denosumab or teriparatide)

INTERPRET



TREAT



FOLLOW UP

CAUTION

- Check serum adjusted calcium one month after treating with loading doses of vitamin D. Vitamin D repletion may unmask primary hyperparathyroidism
- Routine repeat vitamin D testing is generally unnecessary

Example regimens are given in Appendix 1 of the full guideline

About us

The Royal Osteoporosis Society is the only UK-wide charity dedicated to ending the pain and suffering caused by osteoporosis. The Charity works tirelessly to help and support people with the condition as well as promoting good bone health to prevent osteoporosis. We do this by:

- Providing a range of information resources covering all aspects of osteoporosis for health professionals and the public.
- Providing a free helpline staffed by nurses with specialist knowledge of osteoporosis and bone health.
- Investing in research to ensure future generations are freed from the burden of osteoporosis.
- Influencing government and campaigning to improve and maintain essential services.
- Educating Health Professionals to ensure they are kept up to date about osteoporosis – through events, accredited training courses and our leading conference on osteoporosis and bone health.
- Working in partnership with the NHS to set up and improve Fracture Liaison Services which can reduce the number of fractures caused by osteoporosis.

To find out more about our information, support and services, visit our website: theros.org.uk

Professional Membership

Professional membership of the Royal Osteoporosis Society will ensure you become better informed and able to deliver the best care possible to people with osteoporosis or fractures.

As a professional member, you'll have all the information you need at your fingertips and will stay up to date on best practice, care, delivery, new treatments and the latest news on osteoporosis research findings.

You'll also feel proud to be part of an organisation working hard to help those affected by osteoporosis.

To join a growing network of professional members like you, call our membership team on **01761 473287** or visit theros.org.uk/professionals



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01761 471771 (General Enquiries)



0808 800 0035 (Specialist Nurse Helpline)



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Reviewed February 2020

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