

Vitamin D and Bone Health: A Practical Clinical Guideline for Patient Management

National Osteoporosis Society Practical Guides

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Vitamin D and Bone Health: A Practical Clinical Guideline for Patient Management

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 nonskeletal 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. 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 serum 25 hydroxyvitamin D (25OHD) measurements. The lack of national guidance on the indications for 25OHD measurements, on the interpretation of the results and on the correction of vitamin D deficiency has resulted in confusion among patients and health-care professionals and in the proliferation of conflicting guidelines and inconsistent practice across the UK. As a result, the National Osteoporosis Society has developed this practical clinical guideline on the management of vitamin D deficiency in adult patients with, or at risk of developing, bone disease. This guideline does not address the management of vitamin D deficiency in childhood, in pregnancy or in patients with severe or end-stage chronic kidney disease (CKD Stages 4–5).

The guideline was developed by a group of clinicians and scientists with expertise in vitamin D and osteoporosis. The group used evidence from the Institute of Medicine (IOM) report in 2010, supplemented by literature reviews to identify papers published subsequently. The IOM report itself sought evidence from two systematic reviews from the Agency for Healthcare Research and Quality (AHRQ), based in Tufts University and Ottawa. 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 inform patient management but not to influence public health policy. The latter is the remit of the Department of Health Scientific Advisory Committee on Nutrition (SACN), which is currently reviewing the dietary reference values for vitamin D.

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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	25OHD 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	HPLC (linked to either fluorescence or MS (Tandem MS))
mass spectrometry	MS
3-epi-25(OH)D	C ₃ epimer

Conversion factors

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

2.5 nmol/L serum 25OHD = 1 ng/mL serum25OHD

Key recommendations

- Measurement of serum 25OHD is the best way of estimating vitamin D status.
- Serum 25OHD measurement is recommended for:
 - patients with bone diseases that may be improved with vitamin D treatment
 - patients with bone diseases, prior to specific treatment where correcting vitamin D deficiency is appropriate
 - patients with musculoskeletal symptoms that could be attributed to vitamin D deficiency.
- Routine vitamin D testing may be unnecessary in patients with osteoporosis or fragility fracture, who may be co-prescribed vitamin D supplementation with an oral antiresorptive treatment.
- In agreement with the Institute of Medicine (IOM), we propose that the following vitamin D thresholds are adopted by UK practitioners in respect to bone health:
 - serum 25OHD < 30 nmol/L is deficient
 - serum 25OHD of 30–50 nmol/L may be inadequate in some people
 - serum 25OHD > 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), 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 6 to 10 weeks
 - maintenance therapy comprising vitamin D in doses equivalent to 800–2000 IU daily (occasionally up to 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 serum calcium should be checked 1 month after completing the loading regimen or after starting vitamin D supplementation in case primary hyperparathyroidism has been unmasked.
- Routine monitoring of serum 25OHD is generally unnecessary but may be appropriate in patients with symptomatic vitamin D deficiency or malabsorption and where poor compliance with medication is suspected.



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 Department of Health suggests are generally associated with a serum 25 hydroxyvitamin D (25OHD) concentration of less than 20 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 serum 25OHD⁹. As there is a broad inverse relationship between serum 25OHD and parathyroid hormone (PTH), the threshold serum 25OHD 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 serum 25OHD 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 25OHD and PTH may also influence the apparent threshold 25OHD 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 classified vitamin D insufficiency into mild (serum 25OHD 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 (including Holick, Heaney and Vieth) have suggested that the optimal serum 25OHD concentration may be as high as 80–100 nmol/L¹⁷.

The IOM report *Dietary Reference Intakes for Calcium and Vitamin D* investigated the relationship between vitamin D status and bone health¹⁸, using evidence from two systematic reviews commissioned by the Agency for Healthcare Research and Quality (AHRQ), from the University of Ottawa¹⁹ and the Tufts Evidence-Based Practice Centre²⁰. These examined the relationship between serum 25OHD 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. The two AHRQ groups also investigated the relationship between vitamin D status and physical performance, including falls.

From these analyses, the IOM highlighted that studies have demonstrated different threshold serum 25OHD 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 serum 25OHD between 30 and 50 nmol/L have adequate calcium absorption.

Vitamin D and bone mineral density

AHRQ-Ottawa found fair¹ evidence to support an association between serum 25OHD and changes in BMD, but the serum 25OHD concentration below which increased bone loss occurred from the hip ranged from 30 to 80 nmol/L. Nevertheless, the IOM commented that these observational studies may have been confounded by age, dietary calcium intake, physical activity and other factors. AHRQ-Ottawa identified that rickets was consistently associated with a serum 25OHD concentration below 27.5 nmol/L, but most of the studies they analysed were from developing countries, where dietary calcium intake is low. The IOM highlighted that clinically significant osteomalacia is not found unless serum 25OHD is below 30 nmol/L. From their analysis of randomised controlled trials (RCTs), AHRQ-Tufts concluded that there is good² evidence that combined vitamin D and calcium supplementation increased BMD modestly, but it was unclear whether vitamin D alone had a beneficial effect on BMD.

Vitamin D, falls and fractures

In their analysis of RCTs and observational studies, AHRQ-Ottawa reported that the association between serum 25OHD and falls or physical performance was inconsistent, but rated the evidence overall as fair. A meta-analysis carried out by the Tufts team found no evidence of a vitamin D treatment having an effect on the reduction or prevention of falls in elderly people. This contrasts with the earlier meta-analyses by Bischoff-Ferrari^{21;22}, the limitations of which were discussed in the IOM report¹⁸. The overall conclusion of the IOM was that observational data provided some support for a link between vitamin D status and physical performance and that RCTs suggest that vitamin D supplementation of at least 800 IU/day, with or without calcium, may be beneficial for physical performance.

Meta-analyses of RCTs investigating the effect of vitamin D supplementation on fractures indicate that combined calcium and vitamin D supplementation modestly decrease the risk of hip and other non-vertebral fractures, while vitamin D alone is ineffective^{23;24}. AHRQ-Tufts concluded that combined vitamin D and calcium supplementation decreased fracture risk in institutionalised older people, but the effect in community-dwelling older people was inconsistent.

The problem in interpreting the results of RCTs on the 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, serum 25OHD 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 fractures²⁵.

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- i Evidence is sufficient to determine the effects on health outcomes, but the strength of the evidence is limited by the number, quality or consistency of the individual studies, the generalisability to routine practice, or the indirect nature of the evidence on health outcomes.
 - ii Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.

Summary

After considering the data from the systematic reviews from AHRQ-Ottawa and AHRQ-Tufts, the IOM developed a schematic representation of the relationship between vitamin D exposure as measured by serum 25OHD and integrated bone health outcomes (Figure 1). Furthermore, they suggested that a serum 25OHD 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 serum 25OHD < 30 nmol/L, but suggested that some people are potentially at risk of inadequacy when serum 25OHD is 30–50 nmol/L. Although a serum 25OHD of 30–50 nmol/L has been termed ‘vitamin D insufficiency’, this may be misleading as half the people with a serum 25OHD in this range have adequate vitamin D status. The IOM also suggested that practically everyone is sufficient in vitamin D when serum 25OHD > 50 nmol/L.

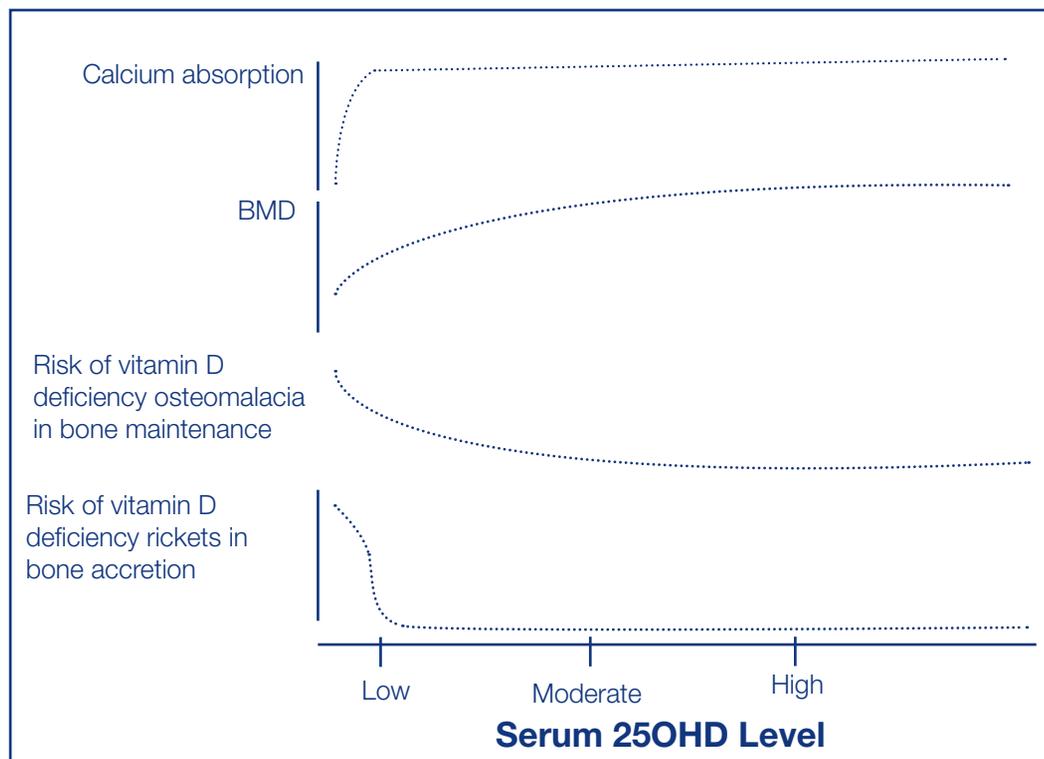


Figure 1 The relationship between vitamin D exposure as measured by serum 25OHD and integrated bone health outcomes¹⁸. (Adapted from an IOM schematic representation.)

The Endocrine Society Task Force has recently published a clinical-practice guideline on the evaluation, prevention and treatment of vitamin D deficiency²⁶. This defined vitamin D deficiency as a serum 25OHD <50 nmol/L but advocated that 25OHD concentration should exceed 75 nmol/L, to maximise the effect of vitamin D on calcium, bone and muscle metabolism. Nevertheless, as highlighted by the IOM, a serum 25OHD between 40 and 50 nmol/L is sufficient for bone health in 50% of healthy people, so a concentration of <50 nmol/L should not necessarily be considered diagnostic of vitamin D deficiency, nor necessarily a threshold for intervention with supplementation.

In agreement with the IOM, we propose that the following vitamin D thresholds are adopted by UK practitioners in respect to bone health:

- **Serum 25OHD < 30 nmol/L is deficient.**
- **Serum 25OHD of 30–50 nmol/L may be inadequate in some people.**
- **Serum 25OHD > 50 nmol/L is sufficient for almost the whole population.**

We decided to adopt the IOM thresholds, as these are based on evidence from two systematic reviews commissioned by the IOM¹⁸⁻²⁰. Nevertheless, the basis of these thresholds has been questioned by some authors^{27,28}. They highlight a German autopsy study that appeared to show histomorphometric evidence of a mineralisation defect in some subjects with a *post-mortem* serum 25OHD concentration between 50 and 75 nmol/L²⁹, but the interpretation of this study was criticised in the IOM report and in a recent commentary³⁰. Although meta-analyses of the effects of vitamin D supplementation on falls and fractures by Bischoff-Ferrari et al suggest that serum 25OHD concentrations of 75–100 nmol/L are required for optimal benefit^{21,22,31}, the proportion of subjects with serum 25OHD measurements in the studies included in these meta-analyses was generally small. Furthermore, the meta-regression analysis used to examine the relationship between the level of serum 25OHD achieved and falls and fracture reduction was extensively criticised by the IOM.

How should we assess Vitamin D status?

Introduction

There are well over 40 identified metabolites of vitamin D³². 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 hours³³, this is relatively short compared to 25OHD, which has a half-life of 21–30 days^{34,35}. Therefore, measurement of 25OHD 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 hours³⁶⁻³⁹, and while 25OHD circulates in nmol/L concentrations 1,25(OH)₂D is present in pmol/L concentrations.

25OHD production is dependent on the 25 hydroxylation that takes place in the liver. This step is primarily dependent on the substrate concentration (vitamin D)^{40,41} 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 tissues⁴². It requires 25OHD 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 25OHD needs to decrease to around 10 nmol/L for 1,25(OH)₂D to decrease significantly⁴³. Measurement of PTH will reflect deficiency of 25OHD sufficient to alter calcium homeostasis, but changes in PTH are affected by many factors other than 25OHD and hyperparathyroidism is caused by many factors⁴⁴.

Biochemical assessment of Vitamin D status

There are several factors that need to be taken into account when measuring 25OHD, including the concentration of vitamin D binding protein (VDBP) and albumin binding of vitamin D in the plasma. 25OHD (calcidiol) circulates in the blood as both the plant/fungi-derived (dietary) 25OHD₂ and the sunlight-derived and animal-derived (diet) 25OHD₃. For most people, the majority (80–90%) of circulating 25OHD 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 25OHD comes from the diet.

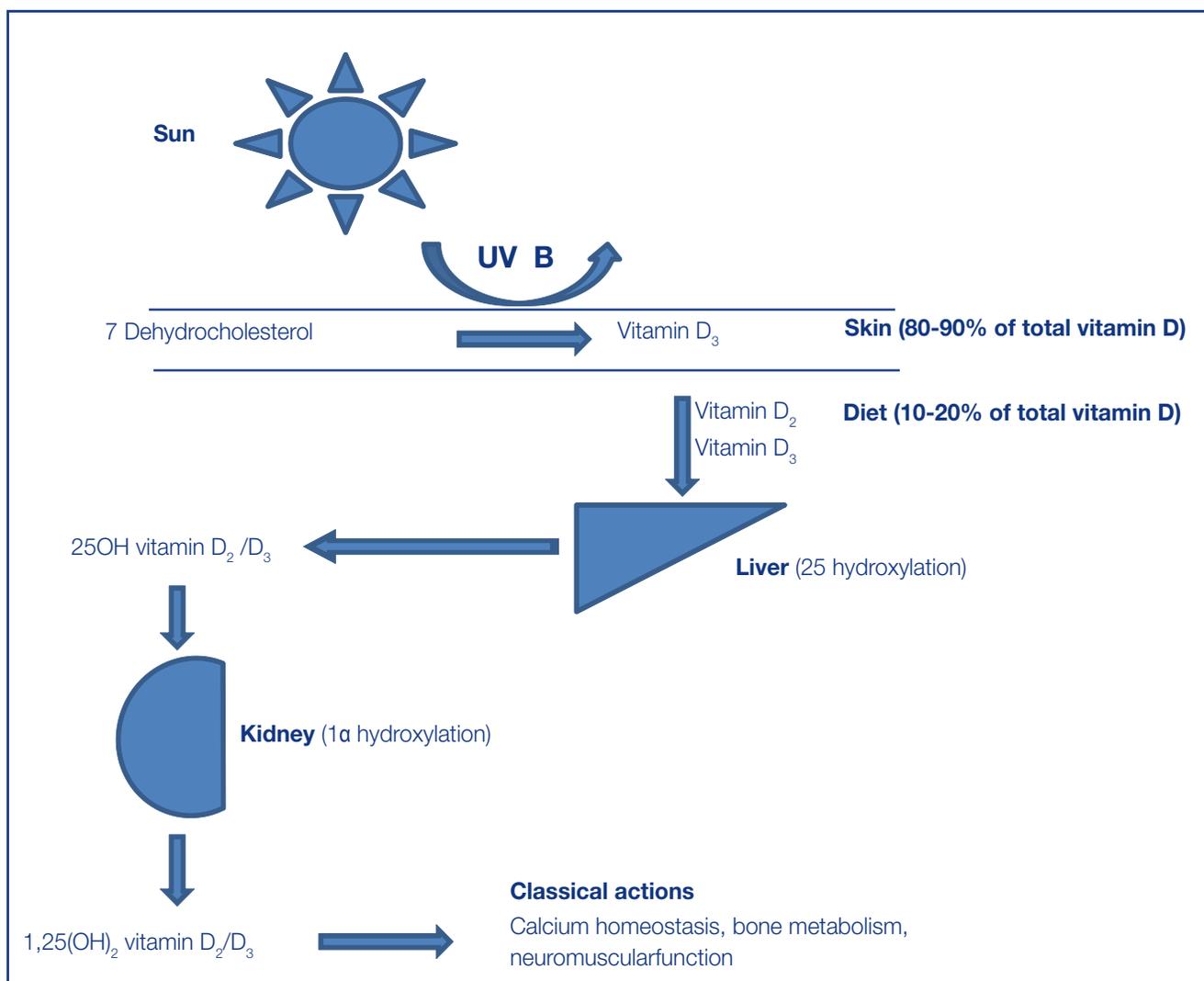


Figure 2 Metabolism of vitamin D (adapted from⁷⁷)

The main methods available to estimate 25OHD are immunoassay, or 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 25OHD. Immunoassays do not necessarily identify all vitamin D₂. However, 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 25OHD₂ 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 synthesised by babies and younger children but has also been detected in adult populations⁴⁵.

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 serum 25OHD is the best way of estimating vitamin D status.
- The assay used should have the ability to recognise all forms of 25OHD (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 25OHD.
- Some laboratories restrict 25OHD measurements to patients in whom there has been shown to be an abnormality in adjusted serum 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, where there are clinical grounds for suspecting vitamin D deficiency, 25OHD should 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 serum 25OHD for unclear clinical indications, resulting in large numbers of tests. The recommendations presented here provide a rational approach to 25OHD testing. Good-practice principles should always be adopted when considering testing for 25OHD. These include being able to justify that the result will affect clinical management, being aware that the relationship between the patients' symptoms and 25OHD 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.

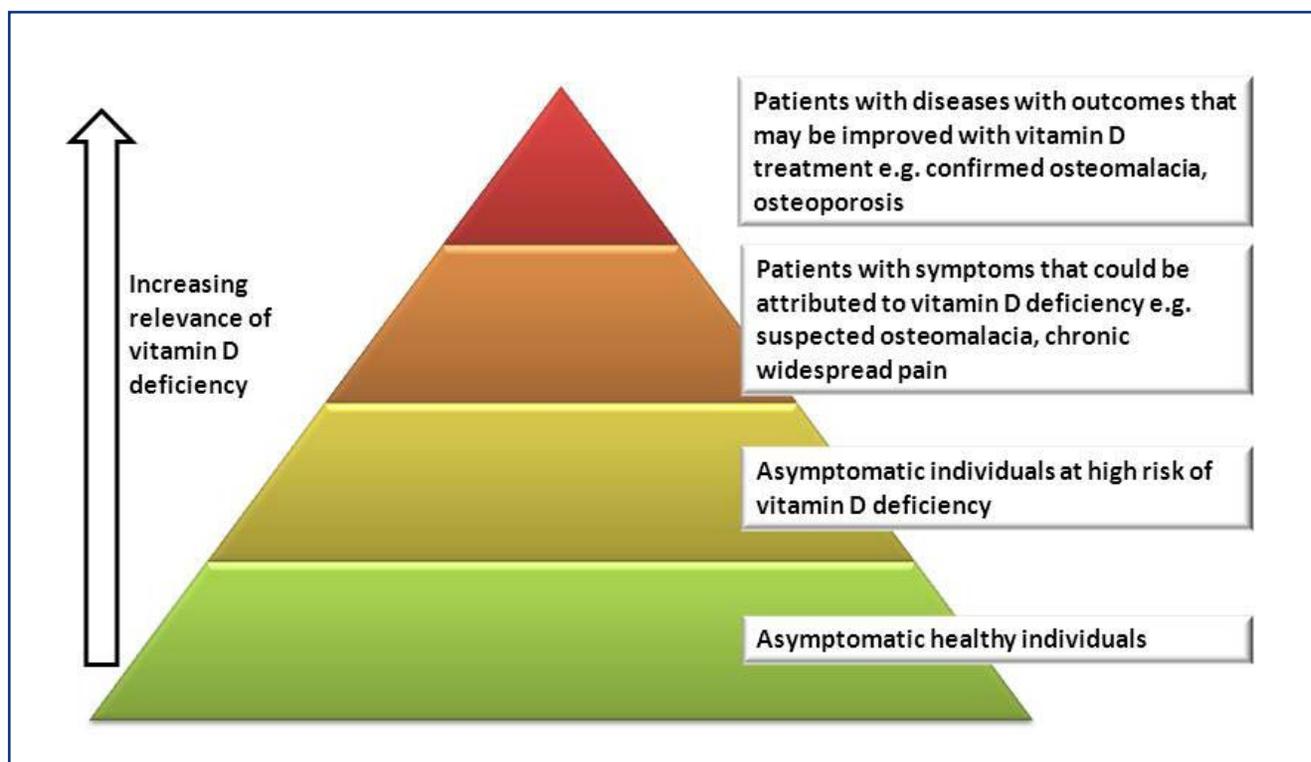


Figure 3 Schematic representation that helps to define broad groups for clinical consideration and decision making.

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), to avoid the development of hypocalcaemia. Nevertheless, routine 25OHD testing may be 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 serum 25OHD level is causal or a surrogate marker (e.g. of poor nutrition or a lack of outdoor

activity). Nonetheless, if patients are suspected of having symptoms caused by osteomalacia, or have chronic widespread pain^{46,47}, a case can be made to measure serum 25OHD 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 25OHD. These individuals are more likely to be vitamin D-deficient and current UK guidance from the Department of Health recommends that these individuals have a higher intake of vitamin D (see box below).

Recommendation:

Do not routinely test 25OHD levels in these groups.

Department of Health Guidanceⁱⁱⁱ

Adult groups at risk of vitamin D deficiency:

- all pregnant and breastfeeding women, especially teenagers and young women
- 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:

- All pregnant and breastfeeding women should take a daily supplement containing 10 µg (400 IU) of vitamin D, to ensure the mother's requirements for vitamin D are met and to build adequate foetal stores for early infancy.
- 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.

ⁱⁱⁱ Vitamin D – advice on supplements for at risk groups. Letter from the Chief Medical Officers for the United Kingdom. [accessed 29 06 12] http://www.dh.gov.uk/en/Publicationsandstatistics/Lettersandcirculars/Dearcolleagueletters/DH_132509

Asymptomatic healthy individuals

The use of serum 25OHD 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 screening⁴⁸. Although vitamin D deficiency is highly prevalent, universal screening of asymptomatic populations is not recommended.



Who do we treat?

In those patients where 25OHD is tested (discussed in the previous section: ‘Who should be tested for vitamin D deficiency?’), the results should be acted upon as follows:

- Serum 25OHD < 30 nmol/L: treatment recommended.
- Serum 25OHD 30–50 nmol/L: treatment is advised 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
 - conditions associated with malabsorption.
- Serum 25OHD > 50 nmol/L: provide reassurance and give advice on maintaining adequate vitamin D levels through safe sunlight exposure and diet.

How do we treat vitamin D deficiency?

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 regime 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 D₃⁴⁹⁻⁵¹ and lower tissue bioavailability⁵², especially after intermittent bolus dosing⁵³. In light of this controversy and the inconsistent availability of various formulations, 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 25OHD₂, 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 bioavailability⁵⁴, slower onset of repletion⁵¹ 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 25OHD varies not only according to external factors such as exposure to sunlight (UVB) and diet but also by patient characteristics, including genetic factors⁵⁵ as well as body composition^{56;57}. These patient characteristics may also influence the subsequent pharmacokinetics and pharmacodynamics of vitamin D supplementation⁵⁸.

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 dose⁵⁹ 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 effective⁶⁰ but that when different dosing regimens are consistently delivered they have equal biochemical efficacy⁶¹.

The evidence for lower-dose daily dosing is based primarily on the clinical trial studies for drugs used to treat osteoporosis⁶². 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 studies⁶³.



Furthermore, most studies have focused on short-term therapy and the risks and benefits of longer-term, higher-dose, intermittent therapy have not been established.

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.

In the past it was advocated that a single large dose (300,000 IU or higher) of vitamin D (Stosstherapie) 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 elderly⁷⁸. However, more recently it has been suggested that large doses of vitamin D given intermittently are ineffective⁶⁴ and might actually increase fracture risk⁶⁵.

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.

Recommendations:

- 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), the recommended treatment regimen is based on fixed loading doses followed by regular maintenance therapy.
- 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.

Calcium supplementation

The use of calcium supplements at doses between 400 and 800 mg is associated with poor persistence⁶³ and efficacy⁶⁶. It has been suggested that there may be adverse cardiovascular outcomes associated with combination therapy, but this requires further clarification^{67;68}. However, it is reassuring to note that a recent 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 alone⁶⁹

Recommendations:

- 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>).
- If patients with osteoporosis are found to not be reliably or regularly consuming at least 700 mg calcium per day, titrated supplementation with either calcium-only supplements or calcium and vitamin D combined supplements is recommended.



Example regimens

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), the recommended treatment regimen is based on fixed loading doses followed by regular maintenance therapy.

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 capsules, one given weekly for 6 weeks (300,000 IU)
- 20,000 IU capsules, two given weekly for 7 weeks (280,000 IU)
- 800 IU capsules, five a day given for 10 weeks (280,000 IU).

The following should be borne in mind:

- Supplements should be taken with food to aid absorption.
- Calcium/vitamin D combinations should not be used as sources of vitamin D for the above regimens, given the resulting high dosing of calcium.

2) Maintenance regimens may be considered 1 month after loading with doses equivalent to 800 to 2000 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

It is well known that vitamin D treatment can unmask previously undiagnosed primary hyperparathyroidism⁷⁰. It is important that the clinician is aware of this. Although the dosing regimen is unlikely to result in toxicity, it should be recognised that certain groups may be at increased risk of this or adverse side effects and they should be monitored. This is usually done by measuring adjusted serum 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 25OHD 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 25OHD levels, the results are more consistent: a daily supplement of 20 to 25 µg (800 to 1000 IU) calciferol will cause an increase in 25OHD of 24 to 29 nmol/L. Most of these studies have suggested that a new steady-state 25OHD level is reached by about 3 months. While this is in line with what would be expected given the elimination half-life of 25OHD, a more recent study has found that the steady-state levels are not obtained until after 6 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 3 months treatment must be given and it may be more prudent to wait until 6 months have passed.

Recommendation:

- Routine monitoring of serum 25OHD is unnecessary but may be appropriate in patients with symptomatic vitamin D deficiency or malabsorption and where poor compliance with medication is suspected

Based on the pharmacokinetics of 25OHD, assessment of adjusted serum calcium levels within 1 month after the administration of the last loading dose should be undertaken to detect those with primary hyperparathyroidism. The presence of hypercalcaemia should lead to cessation of further vitamin D supplementation prior to investigation of the hypercalcaemia.

Recommendation:

- Adjusted serum calcium should be checked 1 month after completing the loading regimen or after starting vitamin D supplementation in case primary hyperparathyroidism has been unmasked.

Vitamin D toxicity

Overt vitamin D toxicity manifests itself through chronic hypercalcaemia. It is rarely seen unless the vitamin D dose is very high, either through inappropriate high-dose treatment or accidental overdosing⁷¹. 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/day) and duration (months to years). They concluded that vitamin D below 10,000 IU/day is not usually associated with toxicity, whereas doses equal to or above 50,000 IU/day for several weeks or months are frequently associated with toxicity, including documented hypercalcaemia. Although the IOM report states that

toxicity as defined by hypercalcaemia is not seen with a 25OHD below 500 nmol/L, there are cases where serious symptoms have been associated with 25OHD. The European Food Safety Authority (EFSA) has recently reviewed evidence and concluded that an upper limit of 4000 IU (100 µg) a day is safe for adults and children over 11 years of age ⁷². Less severe symptoms include hypercalciuria and renal stones. There is weak evidence for other adverse events (mortality, cancer) but these are unlikely to be a problem when the aim is to correct vitamin D deficiency. Studies that have shown a reverse-J-shaped curve for the relationship between mortality and 25(OH)D show a beneficial effect as 25OHD concentrations increase to 30 nmol/L, with lowest mortality at 50 nmol/L and then increased risk above 75 nmol/L ¹⁸. Yearly high-dose vitamin D is ineffective and may cause increased risk of fracture ⁶⁵.

Hypercalcaemia

High intakes of either vitamin D₂ or vitamin D₃ can cause toxicity through hypercalcaemia. The high serum 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 D₃ ¹⁸. Patients with granulomatous disease are at risk of hypercalcaemia because of increased 1α-hydroxylase activity (which converts 25OHD to active 1,25(OH)₂D). Toxicity has been reported during vitamin D treatment of tuberculosis and in patients with active sarcoidosis ⁷³. Specialist advice should be sought before starting these patients on vitamin D therapy.

In normal subjects, overall higher serum calcium concentrations were seen with vitamin D treatment at 2400 IU per day and 3800 IU per day compared to the lower doses tested, but only in the higher dose group (3800 IU per day) did this exceed normal limits (10 mg/dL, 2.63 mmol/L) ⁷¹.

Hypercalciuria and renal stones

There was an increased incidence of renal stones in the Women's Health Initiative study ⁷⁴ in those who were taking vitamin D with calcium supplements. Previous observational studies have shown that there is increased risk of renal stones with supplemental calcium intake, whereas dietary calcium intake may protect against this ^{75;76}. There is no strong evidence that correcting vitamin D deficiency with vitamin D alone will increase the risk of renal stones. However patients with active nephrolithiasis should be managed on a case by case basis.



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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 should 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.
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 ineffective⁶⁴ or associated with higher rates of falls and fractures⁶⁵. In the absence of further studies, such single-loading-dose strategies are not recommended.

Example regimens:

1. Loading regimes 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 capsules, one given weekly for 6 weeks (300,000 IU)
 - 20,000 IU capsules, two given weekly for 7 weeks (280,000 IU)
 - 800 IU capsules, five a day given for 10 weeks (280,000 IU).

The following should be borne in mind:

- Supplements should be taken with food to aid absorption.
 - Calcium/vitamin D combinations should not be used as sources of vitamin D for the above regimens, given the resulting high dosing of calcium.
2. Maintenance regimens may be considered 1 month after loading with doses equivalent to 800 to 2000 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 IM injection or orally
- use of activated vitamin D preparations (calcitriol and alfacalcidol).

Monitoring:

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



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