

## CLINICAL GUIDELINE

# National Osteoporosis Society Vitamin D Guideline Summary

TERRY J. ASPRAY<sup>1,2</sup>, CLAIRE BOWRING<sup>3</sup>, WILLIAM FRASER<sup>4</sup>, NEIL GITTOES<sup>5</sup>, M. KASSIM JAVAID<sup>6</sup>, HELEN MACDONALD<sup>7</sup>, SANJEEV PATEL<sup>8</sup>, PETER SELBY<sup>9</sup>, NUTTAN TANNA<sup>10</sup>, ROGER M. FRANCIS<sup>2</sup>

<sup>1</sup>The Bone Clinic, Musculoskeletal Unit, Freeman Hospital, Newcastle upon Tyne, UK

<sup>2</sup>Institute for Ageing and Health, Newcastle University, Newcastle upon Tyne, UK

<sup>3</sup>National Osteoporosis Society, Bath BA2 0PJ, UK

<sup>4</sup>Norwich Medical School, University of East Anglia, Norwich NR4 7TJ, UK

<sup>5</sup>Department of Medicine, University Hospitals Birmingham, Birmingham B15 2TH, UK

<sup>6</sup>NIHR BRU, NDORMS, University of Oxford, Nuffield Orthopaedic Centre, OXFORD, OX3 7HE, UK

<sup>7</sup>Musculoskeletal Research, University of Aberdeen, Aberdeen AB25 2ZD, UK

<sup>8</sup>Department of Rheumatology, Epsom & St Helier University Hospital, Carshalton, Surrey SM5 3AA, UK

<sup>9</sup>Department of Medicine, Manchester Royal Infirmary, Oxford Road, Manchester, UK

<sup>10</sup>Women's Services & Arthritis Centre, N W London Hospitals NHS Trust, Harrow, Middlesex, UK

Address correspondence to: Terry J. Aspray. Tel: (+44) 01912 336161; Fax: (+44) 01912 231159. Email: t.j.aspray@newcastle.ac.uk

---

## Abstract

The National Osteoporosis Society (NOS) published its document, Vitamin D and Bone Health: A Practical Clinical Guideline for Patient Management, in 2013 as a practical clinical guideline on the management of vitamin D deficiency in adult patients with, or at risk of developing, bone disease. There has been no clear consensus in the UK on vitamin D deficiency its assessment and treatment, and clinical practice is inconsistent. This guideline is aimed at clinicians, including doctors, nurses and dieticians. It recommends the measurement of serum 25 (OH) vitamin D (25OHD) to estimate vitamin D status in the following clinical scenarios: bone diseases that may be improved with vitamin D treatment; bone diseases, prior to specific treatment where correcting vitamin D deficiency is appropriate; musculoskeletal symptoms that could be attributed to vitamin D deficiency. The guideline also states that routine vitamin D testing is unnecessary where vitamin D supplementation with an oral antiresorptive treatment is already planned and sets the following serum 25OHD thresholds: <30 nmol/l is deficient; 30–50 nmol/l may be inadequate in some people; >50 nmol/l is sufficient for almost the whole population.

For treatment, oral vitamin D3 is recommended with fixed loading doses of oral vitamin D3 followed by regular maintenance therapy when rapid correction of vitamin D deficiency is required, although loading doses are not necessary where correction of deficiency is less urgent or when co-prescribing with an oral antiresorptive agent. For monitoring, serum calcium (adjusted for albumin) should be checked 1 month after completing a loading regimen, or after starting vitamin D supplementation, in case primary hyperparathyroidism has been unmasked. However, 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 guideline focuses on bone health as, although there are numerous putative effects of vitamin D on immunity modulation, cancer prevention and the risks of cardiovascular disease and multiple sclerosis, there remains considerable debate about the evaluation of extraskelatal factors and optimal vitamin D status in these circumstances.

**Keywords:** *vitamin D deficiency, muscle and vitamin D, vitamin D deficiency threshold, vitamin D testing older people, osteomalacia*

---

## Background

Vitamin D is important for the maintenance of bone health and may have a potential role in the prevention of non-skeletal disorders such as cardiovascular, neoplastic and metabolic disease, although there remains a paucity of evidence from randomised clinical trials [1]. However, there is no universal consensus on the criteria for an optimal vitamin D status. Vitamin D deficiency is common in the UK, particularly in older people [2] and as awareness has increased that it may contribute to the development of metabolic bone disease, osteomalacia, osteoporosis and result in increased rates of falls and fractures, there has been a dramatic increase in measurement of serum 25 hydroxyvitamin D (25OHD).

The guideline was developed by a group of clinicians and scientists with expertise in vitamin D, metabolic bone disease and osteoporosis. The group used the most up-to-date synthesis of the evidence presented in the Institute of Medicine (IOM) report in 2010 [3], supplemented by literature reviews to identify papers published subsequently. In response to clinical need, the National Osteoporosis Society has developed a practical clinical guideline on the management of vitamin D deficiency in adult patients with, or at risk of developing, bone disease. There has been a proliferation of conflicting guidance, for example, recommending target serum 25(OH)D >72.5 nmol/l [4], and there is inconsistent practice across the UK with regard to the clinical management of vitamin D status [4–8]. This guideline will help clinicians, including doctors, nurses, dietitians and other practising clinicians, to focus on issues which have hitherto caused confusion among patients and health-care professionals:

- the indications for measuring serum 25OHD;
- how to interpret the results and
- strategies for the correction of vitamin D deficiency.

This guideline does not address the management of vitamin D deficiency in childhood, in pregnancy or in patients with severe chronic kidney disease (CKD stages 4–5). It is a guideline of treatment and not public health recommendations.

## Methods

The IOM report from 2010 is the most recent comprehensive review of vitamin D status [3], which itself sought evidence from two systematic reviews, addressing ten *Key Questions*, from the Agency for Healthcare Research and Quality (AHRQ), based in Tufts University and Ottawa. Robust methodologies of systematic evidence-based review were used [9, 10], which assessed study design and quality of publications, using a Jadad score, which evaluated documentation of randomisation, blinding and concealment of allocation.

The questions addressed by the AHRQ relevant to this guideline comprise

- ‘Are specific circulating concentrations of 25OHD associated with bone health outcomes in: ... women of

reproductive age [and] elderly men and postmenopausal women?’

- ‘Do food fortification, sun exposure, and/or vitamin D supplementation affect circulating concentrations of 25 (OH)D?’
- ‘What is the evidence regarding the effect of supplemental doses of vitamin D on bone mineral density and fracture or fall risk and does this vary with age groups, ethnicity, body mass index, or geography?’
- ‘Does intake of vitamin D above current reference intakes lead to toxicities (e.g. hypercalcemia, hypercalciuria, and calcification of soft tissue or major organs)?’
- ‘What is the association between serum 25(OH)D concentrations or calcium balance and clinical outcomes?’
- ‘What is the effect of vitamin D or combined vitamin D and calcium intakes on serum 25(OH)D concentrations?’

## Recommendations

The recommendations are summarised below, numbered from one to nine for convenience, followed by a brief summary of their potential impact on practice and any particular areas of uncertainty.

- (1) Measurement of serum 25OHD is the best way of estimating vitamin D status.

Serum 25OHD should be measured to evaluate vitamin D status, which is in keeping with standard clinical practice. It is the logical metabolite for assessment, believed to reflect medium term levels of substrate for vitamin D metabolism. The guideline covers a little more technical detail on the preferred 25OHD assay methodology, including the need to use a method which measures both vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol) [11]. The *gold standard* assay method is tandem mass spectrometry which is generally used as a research tool but the importance of quality control on laboratory methods is also stressed. Alternative assays relevant to evaluating vitamin D status, such as serum 1,25 (OH)<sub>2</sub> vitamin D, parathyroid hormone or markers of bone turnover, may complement the assessment but are not routinely recommended; and serum calcium is important where severe vitamin D deficiency or toxicity are likely.

- (2) 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 and
- patients with musculoskeletal symptoms that could be attributed to vitamin D deficiency.

- (3) 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.

With regard to assessing vitamin D status in clinical practice focusing on musculoskeletal health, for known or suspected osteomalacia or vitamin D-deficiency-associated myopathy, it is appropriate to measure serum 25OHD. It is also appropriate to measure serum 25OHD where prevalent deficiency is likely to have an effect on co-prescribed medication. However, there is weak evidence to support this practice and routine measurements cannot be justified when vitamin D (with or without calcium) supplement will be co-prescribed, for example, in asymptomatic patients receiving oral bisphosphonates.

(4) In agreement with the IOM, we propose that the following vitamin D thresholds for serum 25OHD are adopted by UK practitioners in respect to bone health

- less than 30 nmol/l is deficient;
- 30–50 nmol/l may be inadequate in some people and
- greater than 50 nmol/l is sufficient.

There is no universal consensus on the level of serum 25OHD which constitutes *sufficiency*. However, in line with the IOM review, the guideline supports a serum 25OHD threshold of 30 nmol/l for deficiency and a potential for deficiency between 30 and 50 nmol/l. These thresholds correspond to an increased risk of osteomalacia for the former and secondary hyperparathyroidism for the latter. This is a very contentious area, as thresholds as high as 75 nmol/l have been recommended by some, but the evidence to support this is weak [12].

(5) Oral vitamin D3 is the treatment of choice in vitamin D deficiency.

With regard to treatment, oral vitamin D as cholecalciferol (D3) rather than ergocalciferol (D2) is recommended, based on evidence from meta-analysis on serum 25OHD levels achieved [13]. However, it is recognized that vitamin D2 may be preferred by vegetarians and others whose religious and cultural beliefs would rather avoid vitamin D from animal origin, and that much of the clinical evidence for treating osteomalacia has been from studies using vitamin D2.

(6) Where rapid correction of vitamin D deficiency is required, such as for symptomatic disease or before treatment with a potent antiresorptive agent (e.g. zoledronate or denosumab) the recommended treatment regimen is based on:

- A fixed loading regimen to provide a total of ~300 000 IU vitamin D, given either as separate weekly or daily doses over 6–10 weeks
- Followed by maintenance therapy comprising vitamin D in doses equivalent to 800–2,000 IU daily (occasionally up to 4,000 IU daily), given either daily or intermittently at higher doses.

(7) 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.

It is common practice (and recommended in a previous clinical review in the *BMJ* [14]) to give large loading doses to patients with vitamin D deficiency. However, there is no available evidence with clinical outcomes that giving *loading* doses in excess of 600 000 IU of vitamin D3 has any beneficial effect, in the absence of clinical osteomalacia. Indeed, a number of studies using bolus dosing of 300,000–600,000 IU of vitamin D2 or vitamin D3 have shown a paradoxical increased rate of adverse events, including falls and fractures [15–17]. Hence, the guideline recommends *loading* doses of vitamin D3 only for symptomatic disease or for patients at an increased risk of hypocalcaemia, about to receive potent antiresorptive medication.

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

(9) 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.

Measurement of serum calcium (adjusted for serum albumin) is recommended, where *loading* doses of vitamin D3 have been given, but monitoring of serum 25OHD is not recommended, except in circumstances where malabsorption is likely.

## Overcoming barriers

It is important that the context for this guideline is clear: these recommendations relate to optimising vitamin D status for patients' musculoskeletal health. Vitamin D status may also be relevant to other health factors such as immunomodulation, cardiovascular disease, diabetes mellitus and multiple sclerosis, where target serum 25OHD levels >50 nmol/l have been recommended. However, there is no consistent evidence that vitamin D supplementation is beneficial using clinical non-musculoskeletal outcomes [3, 9, 10]. Alternative international guidelines [4, 12], with a tendency to target serum 25OHD at >75 nmol/l, are likely to continue to confuse matters. Secondly, this is a clinical guideline focusing on who and how to assess and treat for vitamin D deficiency. It is not aimed at influencing public health policy or defining a target for vitamin D *sufficiency* at a population level, which is within the remit of the Department of Health Scientific Advisory Committee on Nutrition (SACN), who are currently reviewing the dietary reference values for vitamin D. In short, in order to overcome potential barriers, we have already ensured support from key stake holders (including the British Geriatrics Society, Society for Endocrinology, Primary Care Rheumatology Society, Royal Pharmaceutical Society and Royal College of Nursing) and would recommend that these guidelines are adopted by NHS trusts, Clinical Commissioning

Groups and Health Boards in the UK. We look forward to the SACN report but do not anticipate that it will alter this guideline's recommendations significantly.

## Key points

- Measurement of serum 25OHD is the best way of estimating vitamin D status.
- Vitamin D thresholds in respect to bone health are:
  - 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, fixed loading doses of oral vitamin D3 followed by regular maintenance therapy is recommended.
- Vitamin D therapy (without loading doses) is recommended where correction of deficiency is less urgent or when co-prescribing with an oral antiresorptive agent.
- Adjusted serum calcium should be checked at 1 month after completing a loading regimen or after starting vitamin D.

## References

1. Rosen CJ, Adams JS, Bikle DD *et al.* The non-skeletal effects of vitamin D: an endocrine society scientific statement. *Endocr Rev* 2012; 33: 456–92. doi:10.1210/er.2012-1000.
2. Hirani V, Primatesta P. Vitamin D concentrations among people aged 65 years and over living in private households and institutions in England: population survey. *Age Ageing* 2005; 34: 485–91. doi:10.1093/ageing/afi153.
3. Ross AC, Institute of Medicine (U. S.). Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. *DRI, Dietary Reference Intakes : Calcium, Vitamin D*. Washington, DC: National Academies Press, 2011.
4. Holick MF, Binkley NC, Bischoff-Ferrari HA *et al.* Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society clinical practice guideline. *J Clin Endocrinol Metabol* 2011; 96: 1911–30.
5. Tangpricha V, Kelly A, Stephenson A *et al.* An update on the screening, diagnosis, management, and treatment of vitamin D deficiency in individuals with cystic fibrosis: evidence-based recommendations from the Cystic Fibrosis Foundation. *J Clin Endocrinol Metabol* 2012; 97: 1082–93. doi:10.1210/jc.2011-3050.
6. Perez-Lopez FR, Brincat M, Erel CT *et al.* EMAS position statement: vitamin D and postmenopausal health. *Maturitas* 2012; 71: 83–8. doi:10.1016/j.maturitas. 2011.11.002.
7. Adami S, Romagnoli E, Carnevale V *et al.* Guidelines on prevention and treatment of vitamin D deficiency. *Reumatismo* 2011; 63: 129–47. doi:10.4081/reumatismo. 2011.129.
8. Kulie T, Groff A, Redmer J *et al.* Vitamin D: an evidence-based review. *J Am Board Family Med* 2009; 22: 698–706. doi:10.3122/jabfm.2009.06.090037.
9. Cranney A. Effectiveness and Safety of Vitamin D in Relation to Bone Health. Rockville, MD: U.S. Dept. of Health and Human Services, Public Health Service, Agency for Healthcare Research and Quality, 2007.
10. Chung M, Balk EM, Brendel M *et al.* Vitamin D and calcium: a systematic review of health outcomes. Evidence report/technology assessment. *Evid Rep Technol Assess (Full Rep)*. 2009; 183: 1–420.
11. Fraser WD, Milan AM. Vitamin D assays: past and present debates, difficulties, and developments. *Calcif Tissue Int* 2013; 92: 118–27. doi:10.1007/s00223-012-9693-3.
12. Vieth R. Why the minimum desirable serum 25-hydroxyvitamin D level should be 75 nmol/l (30 ng/ml). *Best Practice Res: Clin Endocrinol Metabol* 2011; 25: 681–91.
13. Tripkovic L, Lambert H, Hart K *et al.* Comparison of vitamin D2 and vitamin D3 supplementation in raising serum 25-hydroxyvitamin D status: a systematic review and meta-analysis. *Am J Clin Nutr* 2012; 95: 1357–64. doi:10.3945/ajcn.111.031070.
14. Pearce SH, Cheetham TD. Diagnosis and management of vitamin D deficiency. *BMJ* 2010; 340: b5664. doi:10.1136/bmj.b5664.
15. Sanders KM, Stuart AL, Williamson EJ *et al.* Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *JAMA* 2010; 303: 1815–22. doi:10.1001/jama.2010.594.
16. Law M, Withers H, Morris J *et al.* Vitamin D supplementation and the prevention of fractures and falls: results of a randomised trial in elderly people in residential accommodation. *Age Ageing* 2006; 35: 482–6. doi:10.1093/ageing/afj080.
17. Smith H, Anderson F, Raphael H *et al.* Effect of annual intramuscular vitamin D on fracture risk in elderly men and women—a population-based, randomized, double-blind, placebo-controlled trial. *Rheumatology (Oxford)* 2007; 46: 1852–7. doi: 10.1093/rheumatology/kem240.

Received 27 May 2014; accepted in revised form 27 May 2014