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EDITORIAL

Understanding vitamin D deficiency

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The production of vitamin D

Vitamin D deficiency is a global health problem caused mainly by insufficient exposure to sunlight. It is estimated that 1 billion people have vitamin D deficiency or insufficiency worldwide [1], particularly prevalent among elderly people [2]. Vitamin D exists in two forms—D2 (ergocalciferol), which is obtained from yeast and plants and D3 (cholecalciferol), obtained from the diet through the ingestion of vitamin D containing products (fatty fish and eggs), vitamin D fortified milk or margarine and /or the use of multivitamins. However, the primary source of vitamin D3 (80–90% of the body stores) is via ultraviolet irradiation of the precursor molecule 7-dehydrocholesterol in the skin. Vitamin D (D2 and D3) are then subsequently hydroxylated in the liver by 25-hydroxylase to produce 25-hydroxyvitamin D (25OHD). 25OHD is then further hydroxylated in the kidney by the 1-alpha hydroxylase to form 1,25-di25OHD ($1,25(OH)_2D$) or calcitriol), which is the biologically active form of vitamin D. The 1-alpha hydroxylation can also occur in a multitude of other tissues, generating locally active vitamin D, which leads to auto and /or paracrine effects. The principal index of vitamin D status is the serum 25OHD concentration, with a half-life of ~3 weeks, when compared with the biologically active form $1,25(OH)_2D$ which has a half-life of only 4–6 h [3].

Measurement of vitamin D

25OHD levels are measured in ng/ml or nmol/l (1 ng/ml is equivalent to 2.5 nmol/l). However, several technical problems should be recognised when measuring vitamin D levels:

- There are two main types of assays used for measuring 25OHD-the immune-based assay (commonly used in clinical practice) and the chromatography-based assay (commonly considered the gold standard for research). The utilisation of different methods among laboratories obviously leads to a great variability in test results. This has therefore led to the recent introduction of the standard reference material for vitamin D by the National Institute of Standards and Technology in the USA [4].
- Total circulating 25OHD is the sum of 25OHD2 and 25OHD3, but not all the immunoassays used in clinical practice are able to detect 25OHD2, which can lead to underestimation of 25OHD levels.
- Potential confounders of 25OHD measurement may be present, which can falsely elevate 25OHD, such as other vitamin D metabolites, which are relatively abundant and can account from 2 to 20% of the 25OHD measured.

The function of vitamin D

The vitamin D endocrine system plays a primary role in the maintenance of extracellular fluid calcium concentration. The association between vitamin D deficiency and bone disease, such as rickets, osteomalacia and osteoporosis are well recognised; however, increasingly the relationship between vitamin D deficiency and other conditions have been identified, Table 1 [5].

In the elderly falls are a major problem, leading to significant morbidity, increased mortality and substantial consumption of healthcare resources. Vitamin D deficiency is associated with muscle weakness predominantly of the proximal muscle groups. This leads to slower walking speed, prolonged sit-to-stand time, lower quadriceps strength [6], poor Short Physical Performance Battery (SPPB) scores and a higher rate of falls [7]. These observational findings have been confirmed by intervention studies with daily dosing of vitamin D from 800 to 1000 IU per day associated with a

Table 1. Vitamin D deficiency and associated conditions

Cardiovascular	Cardiovascular disease, aortic dilatation, orthostatic hypotension
Respiratory	Bronchiectasis, asthma, cystic fibrosis, bronchiolitis, obstructive sleep apnoea
Gastrointestinal	Inflammatory bowel disease, chronic hepatitis, liver cirrhosis, pancreatitis
Neurological	Multiple sclerosis, myasthenia gravis, meningomyelocele, depression
Musculoskeletal	Muscle weakness, osteoarthritis, rheumatoid arthritis, juvenile arthritis
Metabolic	Metabolic syndrome, diabetes mellitus, diabetic nephropathy, infertility (male), chronic kidney disease
Cancer	Breast, colorectal, ovarian, lung, prostate
Skin	Psoriasis, systemic lupus erythematosus, eczema

20– 30% reduction in falls rate and significant improvements in body sway [8]. Vitamin D status has also been shown to be critical in the response to physical fitness training in the community-dwelling elderly [9]. Significant increases in lower limb power and other measures of fitness were demonstrable in those with replete (>67.5 nmol/l) concentrations of 25OHD, with no improvement in those with concentrations of <47.5 nmol/l. The recent Cochrane analysis found that vitamin D supplementation in care home residents reduced the rate of falls by 27% [rate ratio, 0.63 (95% CI: 0.46, 0.86); 5 trials, 4603 participants] [10].

The muscle and vitamin D

Muscle atrophy, particularly of type II fibres, has been described histopathologically in vitamin D deficiency. Birge and Haddad [11], in the mid-1970s, were the first to show that 25OHD directly influences muscle phosphate metabolism in vitamin D-deficient rats. Since then, several studies have shown that vitamin D metabolites affect muscle cell metabolism through three main pathways:

- by mediating gene transcription;
- through rapid pathways not involving DNA synthesis;
- by the allelic variant of the vitamin D receptor (VDR).

Both in animal models and in humans, VDRs have been found in skeletal muscle cells that specifically bind 1,25 $(OH)_2D$. At the cell nucleus, this ligand receptor interaction is modulated by various transcription factors and biochemical processes, resulting in a final transcription complex. Vitamin D supplementation induces rapid changes in muscle cell calcium metabolism that cannot be explained by a slow genetic pathway. This is possible through the action of the VDR acting directly on the muscle cell membrane [12]. On binding, several secondary messenger pathways are activated, resulting in enhanced calcium uptake (within minutes), both through voltage-dependent calcium channels and calcium release-activated calcium channels. Muscle strength also appears to be influenced by the genotype of the VDR in the muscle cell and with the use of specific restriction endonucleases, several VDR polymorphisms have been identified [13].

The optimal level of vitamin D

In the last decade, there has been growing advocacy for achieving higher circulating levels of 25OHD than are necessary for maintenance of normocalcemia, in the hope that this has additional benefits for bone and non-bone health. In 2011, the governments of USA and Canada commissioned a report by the Institute of Medicine (IOM) [14] and concluded that:

- the estimated average vitamin D requirement from all dietary sources should be 10 μg (400 IU) daily in those with minimal sunlight exposure;
- a 25OHD level <30 nmol/l indicated risk of deficiency and 25OHD >50 nmol/l indicated sufficiency;
- 25OHD levels in excess of 125 nmol/l could be associated with harm.

The IOM considered that the recommended daily allowance for vitamin D should lead to serum 25OHD levels of at least 50 nmol/l and that individuals below that level should receive vitamin D supplementation. In contrast, the US Endocrine Society has recommended a higher treatment target (70 nmol/l) for health benefits and state that individuals <50 nmol/l should be considered as vitamin D deficient [15]. On the other hand, in fragile elderly subjects who are at an increased risk of falls and fracture, a minimal serum 25OHD level of 75 nmol/l is recommended by the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) [16].

National guidance on the management of vitamin D

Unsurprisingly, this has led to controversy and confusion in the management of vitamin D deficiency in adult patients with, or at risk of developing, bone disease in the UK. We therefore welcome, in this edition, an authoritative practical clinical guideline by the National Osteoporosis Society UK on the management of vitamin D deficiency. The guideline has been designed to help will clinicians, including doctors, nurses, dieticians and other practising clinicians containing key recommendations around

- best way of estimating vitamin D status;
- recommendations for vitamin D testing;
- threshold definitions for vitamin D deficiency;
- treatment of choice for vitamin D deficiency;
- guidance on rapid correction of vitamin D deficiency;
- guidance on maintenance therapy;
- guidance on monitoring blood tests.

In conclusion, vitamin D deficiency is a major health problem, with a plethora of conflicting guidance, and inconsistent clinical management across the UK. We welcome this authoritative guidance, which will help towards better care and management of their patients.

Key points

- The prevalence of vitamin D deficiency is high world-wide, particularly in the elderly.
- 25OHD is the best marker of vitamin D status and is defined as a 25OHD < 30 nmol/l.
- The primary role of vitamin D is the maintenance of extracellular fluid calcium concentrations, but more recently it has been associated with many other conditions.
- Vitamin D deficiency is associated with muscle weakness predominantly of the proximal muscle groups through both genomic and non-genomic pathways.
- Muscle weakness due to vitamin deficiency is reversible with vitamin D supplementation.
- Recent National guidance has been published on the management of vitamin D deficiency in adult patients with, or at risk of developing, bone disease in the UK.

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Conflicts of interest

O.S. has received honoraria from Eli Lilly, Takeda and Consilent Healthcare in the last 12 months.

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