Vitamin D:
effects on muscle function, falls and fractures

Clinical studies evaluating the effects of vitamin D alone or in combination with calcium on physical function, falls and fractures have been inconsistent. Vitamin D has, however, been the focus of much orthopaedic, trauma and endocrine research. Playing a central role in muscle and bone metabolism, some studies on Vitamin D therapies offer the tantalising suggestion of a reduction in falls and fractures simply with vitamin D supplementation. We review the background and evidence behind vitamin D.

THE PRODUCTION OF VITAMIN D

Vitamin D deficiency is a well recognised global health problem caused mainly by insufficient exposure to sunlight. It is estimated that one billion people have vitamin D deficiency or insufficiency worldwide,[1] and it is particularly prevalent among the elderly.[2] Vitamin D exists in two forms – cholecalciferol (D3) and ergocalciferol (D2). Ergocalciferol is obtained from yeast and plants. Cholecalciferol is 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 cholecalciferol (80% to 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-dihydroxyvitamin D ((1,25(OH)2D) or calcitriol), which is the biologically- active form of vitamin D (Fig. 1).

The 1-alpha hydroxylation can also occur in a multitude of other tissues (extra renal tissue, Fig. 1), generating locally active vitamin D, which leads to auto and /or paracrine effects. The principal measured index of vitamin D status is the serum 25OHD concentration, with a half-life of about three weeks, as compared with the biologically active form 1,25(OH)2D which has a half-life of only four to six hours.[4]

DIAGNOSTIC DEFINITION

Vitamin D status is assessed by measuring blood levels of 25OHD. The Institute of Medicine (IOM) considers that the recommended daily allowance for vitamin D should lead to a serum 25OHD level of at least 50 nmol/L and that individuals below that level should receive vitamin D supplementation.[5,6] In parallel, both the US Endocrine Society[7] and the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO)[8] recommend higher treatment targets (≥ 70 nmol/L to 75 nmol/L) for health benefits. The recently published National Osteoporosis Society UK guidance recommends 25OHD > 50 nmol/L for those at high risk of fragility fractures.[9]

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, is well recognised, however, increasingly the relationship between vitamin D deficiency and other conditions has been identified (Table I).[10]

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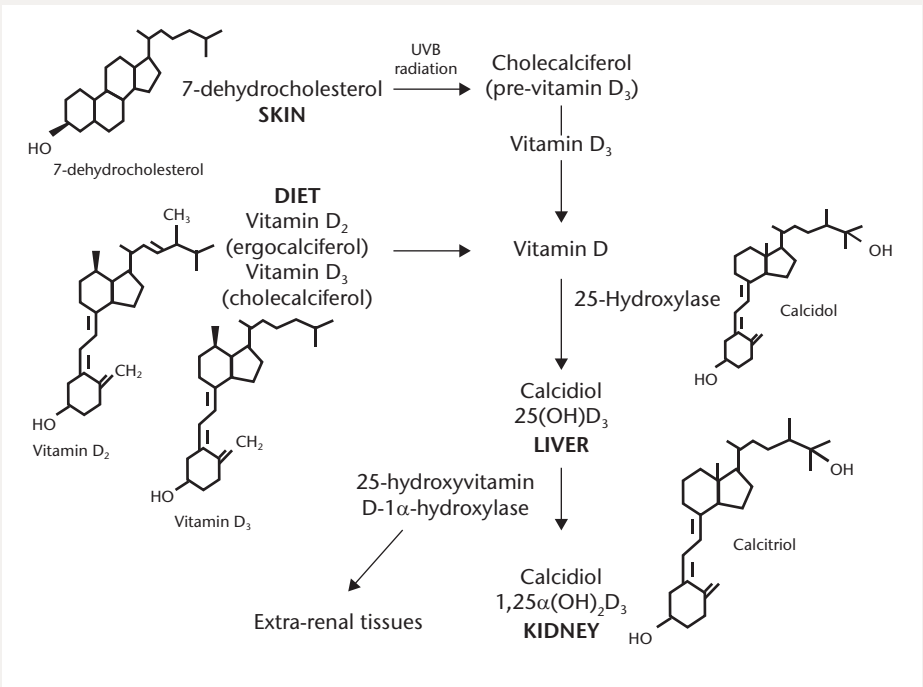

Fig. 1 Vitamin D metabolism (adapted from Dirks-Naylor 2011).[3] Metabolism of vitamin D from dietary intake and the skin precursor, 7-dehydrocholesterol by UV radiation to pre-vitamin D, and its subsequent hydroxylation in the liver and kidney to its active form.

Table I. Vitamin D deficiency and associated conditions

Vitamin D deficiency	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

Another important relationship to the orthopaedic surgeon is that between vitamin D and muscle function. Vitamin D deficiency leads to weakness of the proximal muscle groups, affecting weight-bearing antigravity muscles of the lower limb necessary for postural balance and walking. Patients usually complain of symptoms such as 'heaviness in the legs', tiring easily, and difficulty in climbing stairs or rising from a chair.[11,12] Functionally, the result is slower walking speed, prolonged sit-to-stand time, lower quadriceps strength[13] and an increased risk of falls and fall-related fractures.[14,15] In addition to muscle weakness, falls involve neural responses, which are also influenced by vitamin D status.[16] Furthermore, vitamin D deficiency is associated with secondary hyperparathyroidism[17] as well as hypophosphataemia,[18] which also leads to muscle weakness.

CELLULAR EFFECTS OF VITAMIN D

Histopathologically, vitamin D deficiency leads to atrophy of the type II muscle fibres.[19] Birge and Haddad[20] were the first to show that 25OHD directly influences muscle phosphate metabolism in the diaphragms of vitamin D-deficient rats. The vitamin D receptor (VDR) is expressed in the cell nuclei of human muscle cells[21,22] and vitamin D has been shown to affect muscle cell contractility.[23] The number of VDRs decreases with age, which may contribute to the observed reduction in muscle strength with ageing. The effects of vitamin D on muscle cells are further supported by muscle biopsy and electrophysiological studies. Low vitamin D levels have been shown to cause an abnormal pattern with reduced motor unit potential duration, a decrease in amplitude and an increase in polyphasicity, without concomitant signs of denervation.[24] Treatment with vitamin D leads to reversal of muscle atrophy, including an increase in both the number and cross-sectional area of the fibres.[25,26]

Vitamin D acts directly through genomic[27-29] and non-genomic mechanisms[30,31] (Fig. 2).

Genomic effects are initiated by the binding of vitamin D to the vitamin D receptor (VDR), which results in changes in gene transcription. Non-genomic effects of vitamin D are rapid and mediated by the membrane-bound VDR, and it is these effects which have been shown to be primarily related to muscle. The evidence for this is strengthened further by the generation of the VDR knockout mice model. In the study by Endo *et al*[33] which was designed to investigate the physiological roles of vitamin D in skeletal muscle development, they examined skeletal muscle in VDR gene-deleted mice. They found that each muscle fibre was small and variable in size although overall myocyte differentiation occurred normally and the effects were independent of secondary metabolic changes such as hypocalcaemia and hypophosphataemia.

EFFECTS ON PHYSICAL FUNCTION, FALLS AND FRACTURES

Clinical studies evaluating the effects of vitamin D alone, or in combination with calcium, on physical function, falls and fractures have given inconsistent results. In a recent systematic review,[34] 16 randomised controlled trials (RCTs) evaluating the effects of vitamin D on muscle function were reviewed. Half of the studies showed a beneficial effect in terms of improved muscle strength,[35,36] reduced body sway,[37] an improved timed up-and-go test,[36,37] increased 12-minute gait speed[37] and improved aggregated measure of physical abilities.[38,39] Hand grip strength, which is commonly used to measure muscle function in clinical research, has also been shown to respond to vitamin D supplementation in observational studies,[40,41] but no effect has been seen in RCTs. This observation supports the hypothesis that vitamin D primarily affects the proximal muscles, causing proximal myopathy in the state of severe deficiency. The overall conclusion of the IOM was that observational data provide 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.

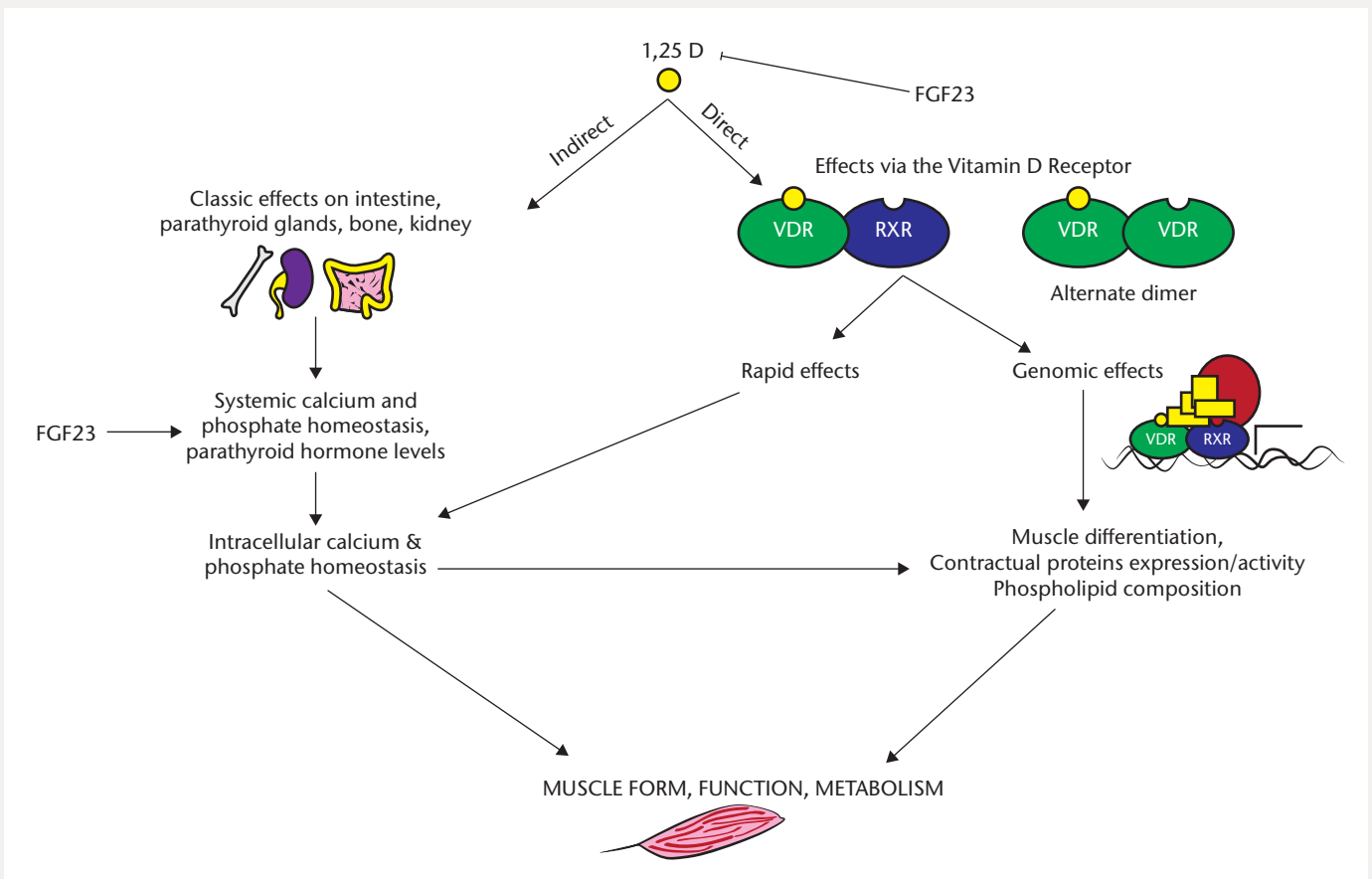

Fig. 2 Genomic and non-genomic effects of vitamin D on muscle (adapted from Girgis 2013).[32]

With respect to Vitamin D's effect on falls, the recent meta-analysis commissioned by the Endocrine Society found that the odds ratio for falling in those randomised to vitamin D supplementation with or without calcium was 0.86 (95 % confidence interval (CI) 0.77 to 0.96), however, the quality of analysis was moderate given significant heterogeneity within the included studies.[42] A more recent review by Bolland et al[43] which identified 20 RCTs involving 29 535 participants repeated the analysis but with stricter inclusion criteria and utilising all available data from factorial and multi-arm studies. In this review, they found no effect of vitamin D on falls, whether used alone or in combination with calcium. Other subgroup analyses showed no influence on outcome of baseline 25OHD, 25OHD achieved, study duration, residential status, or whether falls were primary or secondary endpoints. The Cochrane analysis of trials in community-dwelling individuals similarly found no benefit unless trial subjects were preselected for vitamin D deficiency, where the risk ratio was 0.70 (95 % CI 0.56 to 0.87).[44] In care facilities, on the other hand, the Cochrane review by Cameron et al[45] found that vitamin D supplementation reduced the rate of falls (rate ratio, 0.63 (95 % CI 0.46 to 0.86); five trials, 4603 participants). Similar conclusions were drawn from the meta-analysis by Bischoff-Ferrari et al,[39] who showed that vitamin D in doses of > 700 IU per day reduced falls risk (RR, 0.81 (95 % CI 0.71 to 0.92); n = 1921 from seven trials), whereas lower doses did not. It seems likely, given these conflicting outcomes from well-conducted trials, that vitamin D supplementation does have an effect on likelihood of falls, but only in patients with initial deficiency. There would be a reasonable argument within the general orthopaedic setting for measuring and correcting vitamin D deficiency on patients admitted with falls.

The data on anti-fracture efficacy is perhaps the most conflicting. The Cochrane analysis of vitamin D and related vitamin D compounds for preventing fractures resulting from osteoporosis in older people by Avenell et al[46] concluded that vitamin D alone is unlikely to prevent fractures in the doses and formulations tested so far in older people, but supplements of vitamin D and calcium may prevent hip or any type of fracture. This is similar to the conclusions drawn from the DIPART-patient level pooled analysis of 68 500 patients from seven major vitamin D fracture trials conducted in the US and Europe.[47] By contrast, the meta-analysis by Bischoff-Ferrari et al[48] concluded that high-dose vitamin D supplementation (≥ 800 IU daily) was effective in the prevention of hip fracture and any non-vertebral fracture in persons 65 years of age or older. A more recent review by Lips et al,[49] evaluating 19 RCTs and 13 meta-analyses with vitamin D, either alone or in combination with vitamin D, showed a decrease in fracture incidence in seven RCTs, a neutral outcome in ten RCTs, and in two trials with yearly high-dose vitamin D, an increase in fracture incidence.[50,51] In three out of four well-powered trials that used the recommended doses of daily vitamin D of between 700 IU and 1000 IU, vitamin D supplementation did not significantly influence fracture risk. However, in one of these trials, a statistically significant fracture reduction was observed in care home residents with severe vitamin D deficiency, low calcium intake and good compliance.[52] Of the 13 meta-analyses, 11 showed a significant decrease in fracture incidence in the supplemented groups (analyses for vertebral fractures were negative in all cases). The review concluded that a vitamin D supplement of 800 IU per day in combination with calcium may decrease the incidence of non-vertebral fractures, especially in older people with a low-baseline vitamin D status, low calcium intake and showing good compliance.

KEY POINTS:

- The prevalence of vitamin D deficiency is high worldwide, particularly in the elderly
- 25 hydroxyvitamin D (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
- Vitamin D supplement of 800 IU per day in combination with calcium may decrease the incidence of non-vertebral fractures, especially in older people with a low-baseline vitamin D status and low calcium intake

CONFLICT OF INTEREST

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

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