Optimizing the management of your patients' vitamin D deficiency

The value of vitamin D testing

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Life needs answers

Vitamin D deficiency

Vitamin D deficiency is highly prevalent, particularly in the elderly and people with osteoporosis.[1,2]

Epidemiology

A high prevalence of vitamin D deficiency has been documented in many studies worldwide irrespective of age, health status or latitude.[1] However, vitamin D deficiency is particularly common in elderly populations, where osteoporosis is a frequent comorbidity (Table 1, Figure 1).[1,2] Clinical consequences of vitamin D deficiency in this population include an increased risk of falls[3] and fractures.[4,5] Clinical risk factors for vitamin D deficiency include decreased intake, principally due to limited sunlight exposure, and abnormalities in gastrointestinal, kidney and liver function.[2] Sufficient sunlight exposure is essential for maintaining adequate vitamin D levels, thus, features of 'modern living,' such as clothing habits, reduced time spent outdoors and the use of sunscreen, predispose individuals to vitamin D deficiency.[2] Factors influencing vitamin D status are shown in Table 2.[6]

Patient population	Vitamin D deficiency (% patients)
Nursing home or housebound residents, mean age 81 years	25–50%
Elderly ambulatory women, aged > 80 years	44%
Women with osteoporosis, aged 70–79 years	30%
Patients with hip fractures, mean age 77 years	23%
African American women, aged 15–49 years	42%
Adult hospitalized patients, mean age 62 years	57%

Table 1: Prevalence of vitamin D deficiency in commonly encountered clinical patient populations in the USA.[2]

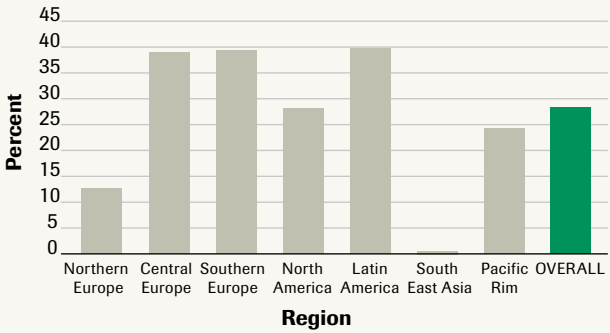

Figure 1: Prevalence of 25(OH) vitamin D < 20 ng/mL among 7,564 postmenopausal women with osteoporosis aged 31–80 years, by region.[1]

A number of biological and environmental factors combine to influence vitamin D status.[6]

Table 2: Factors influencing vitamin D status.[6]

Factors influencing vitamin D status
Synthesis of vitamin D from sunlight
Exposure to ultraviolet radiation
• Latitude
• Season
• Use of sunscreen
• Clothing
Skin
• Pigmentation
• Temperature
• Scarring e.g. burns
• Age
Bioavailability of vitamin D
Gastrointestinal malabsorption of vitamin D
• Celiac disease
• Biliary obstruction
• Chronic pancreatitis
• Liver failure
• Cystic fibrosis
• Crohn's disease
• Gastric bypass
• Bile acid-binding medication (e.g. colestyramine, colestipol)
Obesity
Enzyme activity
• 1-α-hydroxylase: Serum phosphorus, Parathyroid hormone, Genetic mutations
• 25-hydroxylase: Concentration of 25(OH) vitamin D
• Cytochrome P450 enzymes (CYP24, CYP3A4): Medications (phenobarbital, phenytoin, carbamazepine, rifampicin, antiretrovirals)
Other factors
Kidney disease
• Chronic kidney disease
• Nephrotic syndrome
Liver disease
• Cholestatic liver disease
• Parenchymal liver disease
• Hepatic failure
Granulomatous disorders and malignancies
• Sarcoidosis, tuberculosis, fungal granulomas, berylliosis
• Certain tumors (tumor-induced osteomalacia)

Vitamin D plays a crucial role in calcium and bone metabolism.[6]

Biological role of vitamin D

Vitamin D has been recognized as a vital component in bone metabolism and bone health since it was discovered almost a century ago. 1,25 $(OH)_2$ vitamin D, the only active form of vitamin D, plays a crucial role in calcium and bone metabolism by increasing bone turnover, increasing intestinal calcium absorption and decreasing parathyroid hormone (PTH) secretion (Figure 2).[4,6] In addition, vitamin D plays an important role in skeletal muscle function.[4,5,7] It is now thought that a combination of bone and muscle effects contribute to increased risk of falls and fractures associated with vitamin D deficiency.[5,8]

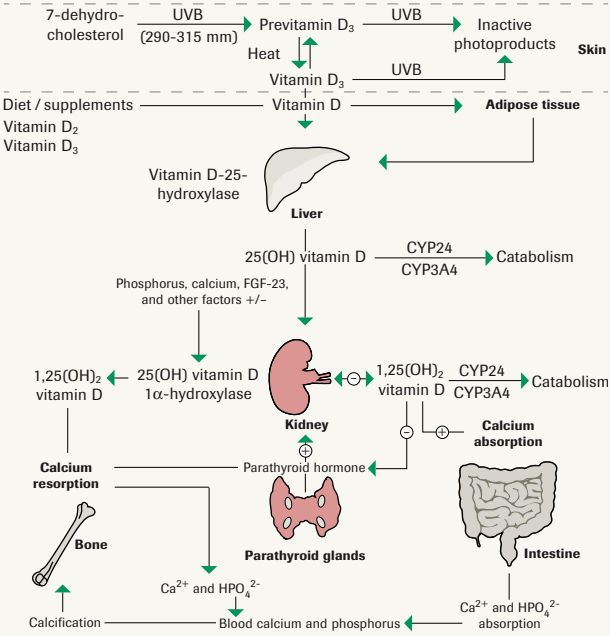

Figure 2: Vitamin D metabolism and effects.[4] Ca^{2+}: calcium; FGF-23: fibroblast growth factor 23; HPO_4^{2-}: phosphorus; UVB: ultraviolet B.

Clinical benefits of vitamin D supplementation

Vitamin D supplementation improves muscle strength, balance and mobility in the elderly.[9–12]

Supplementation with high-dose vitamin D has been shown to improve muscle strength, balance and mobility in elderly people with impaired muscle function.[9-11] The effect of vitamin D supplementation on muscle strength and mobility in elderly women (aged 70–90 years) was assessed in a 1-year, population-based, double-blind, randomized, controlled trial (RCT).[9] A total of 302 community-dwelling women with vitamin D deficiency were randomized to receive either vitamin D_2 (1,000 IU/day) plus calcium citrate (1 g/day) or calcium citrate (1 g/day) plus placebo. In those with baseline values in the lowest tertile of strength, vitamin D improved muscle strength (hip extensors 22.6%, hip adductors 13.5% [Table 3]). Mobility (timed up and go test was significantly improved in those with impaired mobility at baseline (17.5%, $p < 0.05$ [Fig. 3]).[9]

In addition, a meta-analysis of data from RCTs in elderly men and women aged ≥ 60 years demonstrated that vitamin D supplementation (800–1,000 IU/day) reduced postural sway ($p = 0.04$), improved mobility (TUAG, $p = 0.03$) and increased lower extremity strength ($p = 0.04$).[10] In a 16-week, double-blind, placebo controlled trial in elderly men and women (aged ≥ 70 years) with vitamin D deficiency, vitamin D supplementation (8,400 IU/week) significantly ($p = 0.047$) improved balance in a subgroup of patients who had a high level of mediolateral body sway at baseline.[11]

Tertile of strength (kg)	Mean (Standard Error) % difference in change (vitamin D vs placebo)
Hip extensor	
Lowest	22.6 % (9.5 %)*
Middle	-3.8 % (5.9 %)
Highest	-1.1 % (5.1 %)
Hip adductor	
Lowest	13.5 % (6.7 %)*
Middle	-6.8 % (4.5 %)
Highest	-0.2 % (4.2 %)

*Values are mean (standard error), *p < 0.05.*
Extensor: low = ≤11 kg, medium = 12-15 kg, high = ≥16 kg
Adductor: low = ≤12 kg, medium = 13-16 kg, high = ≥17 kg

Table 3: Supplementation with high-dose vitamin D (1,000 IU/day) improves muscle strength in elderly women with vitamin D deficiency and impaired muscle strength.[9]

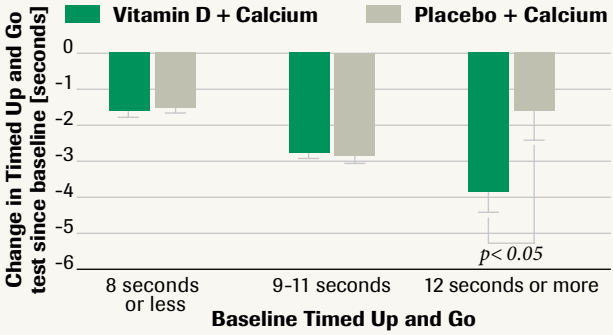

Figure 3: Supplementation with high-dose vitamin D (1,000 IU/day) improves mobility in elderly women with vitamin D deficiency and impaired mobility.[9]

High-dose vitamin D supplementation, in combination with calcium, significantly reduces the risk of falls in the elderly.[12–16]

Prevention of falls

High-dose vitamin D supplementation (≥ 700 IU/day), in combination with calcium, effectively reduces the risk of falling in elderly people (> 63 years).[12–15] Supplementation with high-dose vitamin D reduces the number of fall incidents,[12–15] the number of people who fall,[12,13] the number of people with multiple falls[14,16] and the number of falls that require medical attention.[16] The reductions in the risk of falling have been demonstrated in community-dwelling elderly people[12,15] and in inhabitants of nursing homes.[13,14,15] A key factor in management of vitamin D deficiency is long-term maintenance dosing once the patient's 25(OH)D level is in the optimal range.[2] Adherence to a daily dose of at least 800 to 2,000 IU is required to avoid recurrence of vitamin D deficiency.[2]

In a study of 242 men and women (aged ≥ 70 years) with serum 25(OH) vitamin D levels below 31 ng/mL, supplementation with vitamin D (800 IU/day) and calcium (1,000 mg/day) reduced the number of people with first falls after 20 months by 39% compared with calcium alone ($p < 0.01$) (Figure 4).[12]

In a meta-analysis of seven RCTs in men and women over 65 years of age, vitamin D supplementation (≥ 700 IU/day, $n = 1{,}921$) reduced the number of falls by 19%.[15] Furthermore, the analysis demonstrated that the higher the achieved level of 25(OH) vitamin D, the more pronounced the reduction in fall incidents. With 25(OH) vitamin D levels > 24 ng/mL there was a significant reduction (23%) in falls whereas no significant effect was observed with 25(OH) vitamin D levels < 24 ng/mL.[15]

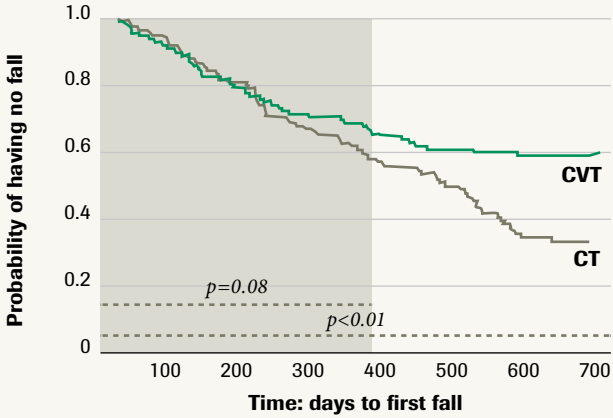

Figure 4: The probability of having a fall is significantly lower with calcium (1,000 mg/day) + vitamin D (800 IU/day) [CVT] compared with calcium alone (1,000 mg/day) [CT] in men and women aged ≥ 70 years.[12]

High-dose vitamin D supplementation significantly reduces the risk of non-vertebral and hip fractures in the elderly and in postmenopausal women.[17,18]

Prevention of fractures

A meta-analysis of double-blind RCTs demonstrated that high-dose vitamin D supplementation (482-770 IU/day) significantly reduced the risk of hip and nonvertebral fractures in elderly men and women (≥ 65 years) by approximately 20%.[17] The relative risk (RR) [95% confidence interval, CI] was 0.80 [0.72–0.89] ($n = 33,265$ individuals from 9 trials) for nonvertebral fractures and 0.82 [0.69–0.97] ($n = 31,872$ individuals from 5 trials) for hip fractures (Figure 5). High-dose vitamin D supplementation reduced the risk of nonvertebral fractures in community-dwelling and institutionalized older individuals by 29% and 15% respectively, and the effects were independent of additional calcium supplementation. Hip fracture reduction was significant among community-dwelling individuals (21%) and among institutionalized individuals receiving cholecalciferol (28%).
In addition, the analysis found that the reduction in fracture risk increased with the 25(OH) vitamin D level achieved (Figure 6).[17]

In another meta-analysis of RCTs, high-dose vitamin D supplementation (> 700 IU/day), in combination with calcium, significantly reduced the risk of nonvertebral

and hip fractures in postmenopausal women by 17.0% and 29.1% respectively.[18] RR [95% CI] was 0.77 [0.63–0.93, 4 studies] for nonvertebral fractures and 0.70 [0.53–0.90, 5 studies] for hip fractures.[18]

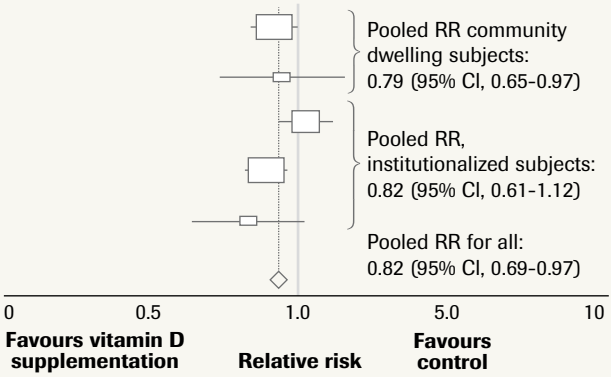

Figure 5: A meta-analysis of double-blind RCTs demonstrated that high-dose vitamin D supplementation (600–800 IU/day) reduces the risk of hip fractures in elderly men and women (≥ 65 years).[17]

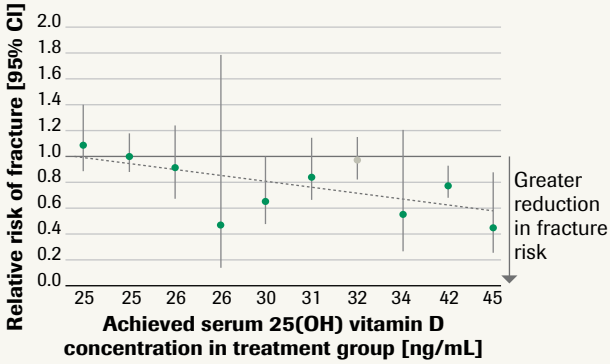

Figure 6: The reduction in non-vertebral fracture risk following high-dose vitamin D supplementation (482–770 IU/day) increases with the level of 25(OH) vitamin D achieved.[17] *Each data point along the X-axis represents an individual trial.*

• *trials with cholecalciferol (D_3)* • *trial with ergocalciferol (D_2)*
..... *trend line through the point estimates of all trials.*[17]

Vitamin D measurement

Due to large interindividual variability, measurement of 25(OH) vitamin D is necessary, both before and during supplementation, to ensure optimal levels are reached.[19–23]

Clinical rationale

Measurement of 25(OH) vitamin D, before and during supplementation, is necessary for effective patient management.[19-23] Indeed, standard supplementation, in the absence of 25(OH) vitamin D measurement, can result in unnecessary polypharmacy for some elderly patients[19] as well as to the under-treatment of severe deficiencies.[20]

The need for accurate measurement of vitamin D levels during follow-up is related to the substantial interindividual variation in 25(OH) vitamin D serum levels post-supplementation (Figure 7).[21–23] Potential factors influencing vitamin D levels are listed in Table 4. However, interindividual variation has also been shown to remain after correction for body weight and baseline vitamin D levels.[21] Moreover, in a RCT in 60 community-dwelling women aged ≥ 65 years, 37% of the participants receiving vitamin D supplementation remained deficient in vitamin D after 6 months (Table 5).[21] These data highlight that one post-supplementation measurement may not be sufficient; further testing may enable the physician to adjust dosage and also ascertain patient compliance.

Given the large variations in vitamin D metabolism[21–23] and response,[21] alongside the documented dose-dependent

effect both of received and achieved dose,[17] effective measurement and monitoring of vitamin D has the potential to improve dose individualization and encourage compliance with therapy.

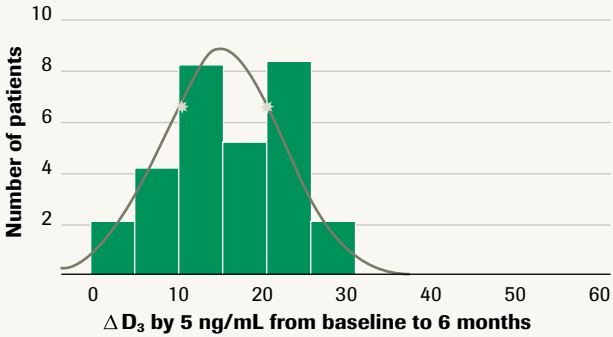

Figure 7: Substantial interindividual variation in serum levels of 25(OH) vitamin D following supplementation with vitamin D (1,000 IU/day).[21]

Factors that may influence post-supplementation serum level of 25(OH) vitamin D
Absorption rate
Adherence
Assay used
Body mass index
Dose/dosing frequency of supplementation
Endogenous vitamin D status (see table 2)
Pregnancy and lactation
Vitamin D baseline level
Vitamin D supplement type
Other medications

Table 4: Factors that may influence serum levels of 25(OH) vitamin D following supplementation.[2,8,21,23,24,26,27]

25(OH) vitamin D at 6 months, ng/mL	Patients % (n)
< 20	37% (10)
20-29.9	43% (13)
≥ 30	20% (6)

Table 5: Vitamin D deficiency persists in a high percentage of elderly women (≥ 65 years) despite high-dose vitamin D supplementation (1,000 IU/day).[21]

Expert opinion-based recommendations support the testing of high-risk groups in clinical practice at baseline and at 3 month intervals.[2,8,24]

Target groups – Expert recommendations

A number of recently published guidelines provide practical guidance on vitamin D measurement.[2,8,24,25,26] There is general consensus of expert opinion regarding the high-risk groups that would benefit from vitamin D testing (Table 6). Expert opinion is also generally similar for the recommended frequency of testing (baseline and at 3 months until a desirable level is achieved), although the precise target levels for serum 25(OH) vitamin D are a matter of debate (Figure 8).[2,8,24,25,26,28]

Furthermore, whilst serum $1,25(OH)_2D$ testing can provide useful information in selected patients (e.g. with acquired/inherited disorders of vitamin D and phosphate metabolism), the Endocrine Society Task Force guidelines recommend performing serum 25(OH) D testing in patients at risk of vitamin D deficiency.[26]

Recommended populations for vitamin D testing
Patients likely to have (or be at risk of) bone loss due to: • Osteoporosis or risk of osteoporosis[8,24,26,29] • Osteomalacia or rickets[8,26,29] • Fractures[2,26] • Older age and a recent fall[8,26,29] • Hyperparathyroidism[26,29]
Patients with decreased endogenous production of 25(OH)D, such as: • Institutionalized or homebound patients[8,24] • Individuals with decreased sunlight exposure or dark skin[2,24]
Patients with non-standard metabolism/catabolism of 25(OH)D due to: • Obesity in children and adults (BMI >30kg/m²)[8,26] • Pregnancy and lactation in women[8,26] • Corticosteroid treatment[8,26] • Malabsorption syndromes[2,24,26,29] • Hepatic failure[2,26] • Granulomatomas[26,29] • Chronic kidney disease and transplant recipients[2,8,26,29]

Table 6: Consensus of expert recommendations for target populations for vitamin D testing.[2,8,24,26,29]

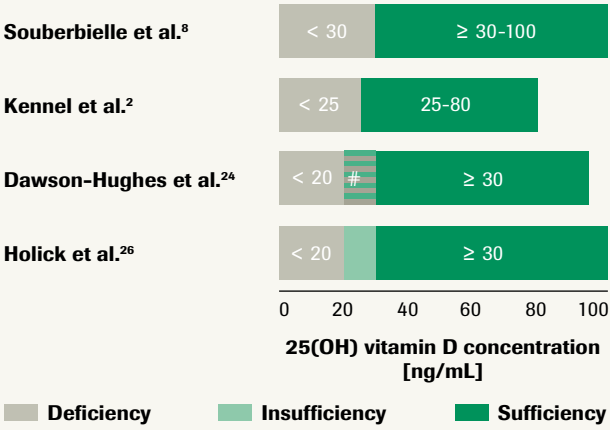

Figure 8: Expert recommendations for target levels of serum 25(OH) vitamin D. In this figure adaptation, vitamin D concentrations are expressed in ng/mL, where 1 ng/mL is equal to 2.496 nmol/L.[2,8,25,26]

#8 out of 10 of IOF Working Group agreed 30 ng/mL, remaining 2 felt target is 20-30 ng/mL

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