Consensus Statement on Vitamin D Status Assessment and Supplementation: Whys, Whens, and Hows

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Vitamin D Metabolism and Mechanism of Action

Metabolism

Vitamin D3 is produced in the skin from 7-dehydrocholesterol (7-DHC), while both vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol) can be present in the diet.

Vitamin D2 and D3 are hydroxylated first in the liver (and other tissues) to 25-hydroxyvitamin D (25(OH)D) and then in the kidney (and other tissues) to 1,25 dihydroxyvitamin D (1,25(OH)2D).

Both 25(OH)D and 1,25(OH)2D are subsequently metabolized to their 24 hydroxy forms.

Vitamin D Metabolism and Mechanism of Action

Vitamin D is highly lipophilic and bound to protein carriers that help maintain stable serum levels.

The half-life of serum 25(OH)D is 2 to 3 weeks, and that of the more water-soluble 1,25(OH)2D is approximately 5 to 8 hours.

The majority of circulating 25(OH)D, including its metabolites, are bound tightly by vitamin D binding protein (DBP) and more loosely bound by albumin.

Vitamin D Metabolism and Mechanism of Action

❑7-Dehydrocholesterol reductase

Although the production of vitamin D from 7-DHC under the influence of sunlight (UVB) is a nonenzymatic step, the production of 7-DHC is not. DHCR7 converts 7-DHC to cholesterol, so its activity dictates how much 7-DHC is available for vitamin D production.

Inactivating mutations of DHCR7 result in Smith-Lemli-Opitz syndrome, a developmental disorder.

AMPK (adenosine monophosphate–activated protein kinase C) and protein kinase A are potent **inhibitors** of DHCR7.

Vitamin D Metabolism and Mechanism of Action

25-Hydroxylases

The liver is the major source of 25(OH)D production from vitamin D. However, numerous enzymes within both mitochondria and microsomes have 25-hydroxylase activity.

ınitial studies suggested that CYP27A1, a mitochondrial enzyme was the major 25-hydroxylase. Current data support CYP2R1 as the major 25-hydroxylase, at least in the liver (and testes), where it resides in the microsomal compartment.

Five functional mutations in CYP2R1 have been described so far. Although these mutations result in little or no 25-hydroxylase activity in vitro, individuals maintain normal or even high 1,25(OH)2D levels. Such data suggest that, CYP2R1 could not be the only enzyme with 25-hydroxylase activity.

Vitamin D Metabolism and Mechanism of Action

Aatsinki et al found that a high-fat diet that induced obesity and type 2 diabetes (T2D), both **decreased** the hepatic messenger RNA and protein concentration of CYP2R1.

Thus, the concept that the low levels of 25(OH)D in obesity and the limited response to vitamin D supplementation in these individuals are somehow related to increased storage of vitamin D in fat is still controversial and needs further investigation.

Vitamin D Metabolism and Mechanism of Action

- **CYP27B1—the 25-hydroxyvitamin D–1α-hydroxylase**

Unlike the 25-hydroxylases, there is only a single 25(OH) D-1α-hydroxylase, CYP27B1.

The kidney is the main source of circulating 1,25(OH)2D, but many tissues, including the epidermis and other epithelial tissues, bone, placenta, and immune system cells, also express CYP27B1. The product, 1,25(OH)2D, likely has paracrine or autocrine actions.

Vitamin D Metabolism and Mechanism of Action

In the kidney, CYP27B1 is regulated primarily by parathyroid hormone (PTH) and insulin-like growth factor-1, which **stimulate** it, as well as by fibroblast growth factor 23 (FGF23) and 1,25(OH)2D itself, which **inhibit** it.

In nonrenal tissues cells, such as keratinocytes and macrophages, cytokines, such as, interferon-gamma (IFN-γ), tumor growth factor alpha (TNFα), and transforming growth factor beta1 (TGFβ1) are the major **inducers** of CYP27B1.

In peripheral blood mononuclear cells, interleukin (IL)-1, IL-2, and IL-15 also **stimulate** CYP27B1 activity, whereas IL-4 is **suppressive**.

Thus, the induction of CYP27B1 in these extrarenal tissues is by cytokines, and the failure of CYP27B1 in these tissues to respond to the increased circulating levels of 1,25(OH)2D and calcium account for the hypercalcemia often found in granulomatous diseases, such as sarcoidosis and lymphomas.

Vitamin D Metabolism and Mechanism of Action

- **CYP24A1 and CYP3A—the 25-hydroxyvitamin D–24(23) hydroxylases**

These are the catabolic enzymes of vitamin D metabolism, with both 25(OH)D and 1,25(OH)2D as their substrates.

CYP24A1 is the dominant 24-hydroxylase in most tissues, but CYP3A4 likely plays a role in the liver and intestine, where it is highly expressed. Both enzymes have 24-hydroxylase and 23-hydroxylase activity.

Vitamin D Metabolism and Mechanism of Action

Both enzymes are induced by 1,25(OH)2D—and CYP24A1 is induced by 25(OH)D as well—and the induction of CYP3A4 seems to be at least as great as that for CYP24A1 in the intestine.

CYP24A1 is under the control of 1,25(OH)2D and FGF23 (both **stimulatory**) and calcium. 5α-Dihydrotestosterone, via the progesterone receptor, has also been reported to stimulate CYP24A1.

Vitamin D Metabolism and Mechanism of Action

Inactivating mutations in CYP24A1 are now recognized as a major cause of **idiopathic infantile hypercalcemia,** a syndrome marked by severe hypercalcemia, hypercalciuria, and nephrocalcinosis, decreased PTH, low 24,25(OH)2D, and inappropriately normal to high 1,25(OH)2D.

Although initially identified in children, more recent case reports indicate that the diagnosis may not be made until adulthood, generally following a condition of increased 1,25(OH)2D production like pregnancy. Such adults generally present with early-onset nephrolithiasis and/or nephrocalcinosis.

Vitamin D Metabolism and Mechanism of Action

CYP3A4 mutations or drug-induced excess CYP3A4 activity have recently been linked to vitamin D deficiency and vitamin D–dependent rickets type 3, with affected individuals demonstrating greatly accelerated inactivation of vitamin D metabolites. This represents a novel mechanism for vitamin D deficiency.

Vitamin D Metabolism and Mechanism of Action

Mechanism of Action

The VDR is critical for most of the actions of vitamin D, with 1,25(OH)2D as its major ligand. VDR is a transcription factor found in nearly all cells. Vitamin D affects many cellular processes via the VDR, with one of the most important being the regulation of intestinal calcium absorption.

In a recent ontology analysis, 11 031 putative VDR target genes were identified:

- 43% → metabolism
- 19% → cell and tissue morphology
- 10% → cell junction and adhesion
- 10% → differentiation and development
- 9% → angiogenesis
- 5% → epithelial to mesenchymal transition

Vitamin D Metabolism and Mechanism of Action

Furthermore, VDR can regulate various microRNAs (miRNAs) and long noncoding RNAs involving the expression of numerous proteins directly or indirectly.

Although most of the actions of VDR involve its role as a transcription factor within the nucleus, the VDR has also been shown to have nongenomic actions via its location in the plasma membrane and perhaps even in mitochondria.

Vitamin D Metabolism and Mechanism of Action

Regulation

The regulation of VDR expression is cell specific. For example, 1,25(OH)2D regulates VDR expression in bone cells but not in the intestine.

Many factors in addition to 1,25(OH)2D regulate VDR expression, including growth factors, insulin, as well as PTH, glucocorticoids, estrogen, and retinoic acid.

Calcium upregulates VDR expression in the parathyroid gland, presumably through its calcium-sensing receptor.

Vitamin D Metabolism and Mechanism of Action

- **Genomic actions**

human genome contains more than 23 000 VDR binding sites, most of which are cell specific.

The VDR binding sites can be thousands of bases away from the transcription start site (TSS) of the genes they regulate, and genes generally have multiple VDR binding sites, the activity of which may vary in different cells and species.

Assessment of Vitamin D Status

To date, total serum 25(OH)D, the sum of 25(OH)D3 and 25(OH)D2, is the accepted biomarker of vitamin D status.
Based on observational studies, mostly using traditional radioimmunoassay measurements, vitamin D guidelines issued by major organizations worldwide recommend optimal 25(OH)D levels to be in the range of 50 to 75 nmol/L (20-30 ng/mL). However, optimal levels are still debated for several reasons:

1. Lack of assay standardization
2. What is meant optimal 25(OH)D level, for whom and for what
3. Clinical prospective vs public health prospective (It is important to differentiate between screening, that is, a public health approach undertaken in the general populations, and testing, that is, targeted testing of high-risk individuals in the clinical setting.)

Screening and Testing for Vitamin D Status

❑ Screening in the general population—public health approach

Levels of 25(OH)D in the general population depending on several factors:

- Season → at the end of winter or in early spring would increase the detection of low 25(OH)D levels in the general population
- Latitude
- Cultural factors leading to reduced UVB light exposure
- Skin pigmentation
- Body mass index (BMI)
- Sex & Age
- Level of physical exercise
- Food fortification with vitamin D or use of vitamin D supplements
- Genetic factors such as gene polymorphisms

Screening and Testing for Vitamin D Status

Screening for optimal vitamin D status in the general population should be avoided as it is not informative and has a considerable economic burden.

Several characteristics and pathological conditions in the general population could place individuals at risk for severe deficits, These populations should be recognized.

Populations at risk of vitamin D deficiency

- ❑ Housebound people
- Disabled people
- Institutionalized people

- ❑ People working long hours indoors
- Office workers
- Factory or warehouse workers
- Taxi drivers
- Night-shift workers

- ❑ People with dark skin

- ❑ Low levels of physical activity

- ❑ People with a debilitating/chronic disease
- Diabetes
- Chronic kidney disease
- Gastrointestinal malabsorptive syndromes
- Parathyroid disorders
- Liver diseases

- ❑ Obesity—in particular those with highest levels of waist circumference

- ❑ Patients after bariatric surgery

- ❑ People taking medications increasing vitamin D catabolism:
- Phenobarbitone
- Carbamazepine
- Dexamethasone
- Rifampicin
- Nifedipine
- Spironolactone
- Ritonavir
- Cyproterone acetate

- ❑ Babies of vitamin D-deficient mothers

Endocrine Society2024

- **Indications for 25(OH)D measurement (candidate for screening):**

Rickets
Osteomalacia
Osteoporosis
Chronic kidney disease
Hepatic failure
Malabsorption syndromes
  Cystic fibrosis
  Inflammatory bowel disease
  Crohn's disease
  Bariatric surgery
  Radiation enteritis
Hyperparathyroidism
Medications
  Antiseizure medications
  Glucocorticoids
  AIDS medications
  Antifungals, e.g. ketoconazole
  Cholestyramine
African–American and Hispanic children and adults
Pregnant and lactating women
Older adults with history of falls
Older adults with history of nontraumatic fractures
Obese children and adults (BMI 30 kg/m^2)
Granuloma-forming disorders
  Sarcoidosis
  Tuberculosis
  Histoplasmosis
  Coccidiomycosis
  Berylliosis
Some lymphomas

Screening and Testing for Vitamin D Status

Paradoxically, listing situations where it may be reasonable to measure 25(OH)D accounts for most people. This would again result in overtesting with high costs for the health care system. Rather than testing in situations where it would be reasonable to, it would be better to test only in situations that actually warrant it. It comes down to the providers' judgment in first recognizing these high-risk individuals and then deciding to confirm with a measurement of 25(OH)D.

Methods: Assays, Thresholds, and Standardization

Assay standardization remains a major challenge to interpreting data from various studies evaluating vitamin D and its metabolites and analogues

The measurements could be obtained by either antibody-based methods (chemiluminescent or immunoenzymatic) or by liquid chromatography–mass spectrometry (LC-MS or LC-MS/MS), with the latter giving more consistent and accurate results.

The laboratory should define the reference values considering the method used for analyzing the molecule(s).

The unit of measure (molar or mass) should be clearly indicated. The mol/L unit should be preferred as the SI standard unit; alternatively, both mol/L and ng/mL should be reported.

Assessment of Other Vitamin D Forms and Main Metabolites

For circulating 25(OH)D, it is estimated that approximately 85% to 90% is bound by DBP and 10% to 15% by albumin; therefore, free 25(OH)D levels are estimated to be less than 1% of the total and can vary according to DBP and albumin polymorphisms and binding affinity.

In normal populations, total and free 25(OH)D, as well as free and calculated 25(OH) D, are correlated (~60%-70% in healthy individuals), and there is no clear evidence for a need to measure free metabolites in healthy individuals and many clinical settings.

However, this may not hold true in conditions affecting DBP such as pregnancy, cirrhosis, acute illness, conditions that may affect the affinity of DBP or albumin to its ligands, and even in aging nursing home residents, for whom the free concentration is a better assessment than the total.

Assessment of Other Vitamin D Forms and Main Metabolites

Measurement of 1,25(OH)2D may contribute to the diagnosis of conditions with **low calcitriol levels**, such as 1α-hydroxylase deficiency, or those associated with **high 1,25(OH)2D levels**, such as hereditary vitamin D–resistant rickets, granulomatous conditions (sarcoidosis and tuberculosis), and the hypophosphatemic syndromes.

Assessment of Other Vitamin D Forms and Main Metabolites

LC-MS/MS techniques make it now feasible to measure most of the circulating vitamin D metabolites.

Besides specific clinical situations, a few previous reports have also highlighted a potential role for vitamin D metabolites, in particular of the 24,25 to 25(OH)D ratio, in better-predicting fracture risk as compared to only 25(OH)D levels.

Assessment of Other Metabolites

- **Infantile hypercalcemia, type 1, caused by defects in CYP24A1**

Despite the name of the disease, infantile hypercalcemia, type 1 affects individuals throughout life, usually causing nephrolithiasis (unexplained 1,25(OH)2D-dependent hypercalcemia, hypercalciuria, kidney stones, and suppressed levels of PTH) .It is especially problematic in pregnant females due to the placental production of 1,25(OH)2D3, which cannot be efficiently metabolized.

The utility of measuring 24-hydroxylated forms, particularly the 25(OH)D to 24,25(OH)2D ratio, has been established as a useful screening tool by groups worldwide. Ratios are elevated from 5 to 25 in normal individuals to more than 80 in infantile hypercalcemia–affected individuals.

Assessment of Other Metabolites

- **Chronic kidney disease**

Many studies have documented a fall in serum 25(OH)D and 1,25(OH)2D with a decline in renal function.

.Patients and animal models with kidney disease both show changes in the levels of 24,25(OH)2D3 and 1,24,25(OH)3D3 with changes in glomerular filtration rates.

Assessment of Other Metabolites

- **Routine documentation of vitamin D metabolites in randomized controlled trials**

In most recent large RCTs, participants were monitored only for health effects and serum 25(OH)D levels.

JAMA study: used doses of up to 10 000 IU of vitamin D/day, monitored only 25(OH)D, and reported deleterious effects of the vitamin D on bone mineral density (BMD).

by reanalyzing the serum from participants in the study for the full vitamin D metabolome including 1,25(OH)2D3, 24,25(OH)2D3, and 1,24,25(OH)3D3, Burt and colleagues found that several vitamin D metabolites, including 1,24,25(OH)3D3 but not 1,25(OH)2D3, were elevated in individuals given the 10,000 IU of vitamin D/day dose, a fact that could explain the bone loss observed at high supplementation rates.

Clinical Outcomes of Vitamin D Deficiency

- **Skeletal Outcomes**
- **Extra skeletal Outcomes:**

  - Cancer
  - Cardiovascular risk
  - Respiratory effect
  - Autoimmune diseases
  - Diabetes
  - Mortality

Clinical Outcomes of Vitamin D Deficiency

❑ Skeletal Outcomes

Meta-analyses of clinical trials with vitamin D and calcium have demonstrated a decrease in hip and other fractures of around 10% in nursing home residents, whereas vitamin D alone was not effective.

As almost all effective trials used a calcium supplement in addition to vitamin D, the effect on BMD of vitamin D supplements alone is difficult to determine, but it is considered to be less than 1% , and high doses may even be harmful when administered to vitamin D–replete individuals.

Clinical Outcomes of Vitamin D Deficiency

❑ Cancer

No effects of vitamin D supplementation on cancer risk were observed in the large VITAL and ViDA trials, nor the FIND trial using daily dosing in older participants, nor on cancer mortality in the D-Health study, which used monthly dosing —in line with prior trials and MR results.

However, a subanalysis of the VITAL trial showed that vitamin D supplementation could have some minor benefits in individuals with normal BMI.

VD reduced metastatic or fatal cancers by 17%; strongest reduction in normal BMI

Clinical Outcomes of Vitamin D Deficiency

In addition, several independent trials have suggested, in post hoc analysis, the potential benefits of vitamin D supplementation on cancer mortality, especially when the follow-up is longer than 4 years.

A meta-analysis of RCTs suggested that vitamin D supplementation decreased cancer mortality (daily regimens in normal-weight individuals) .

Clinical Outcomes of Vitamin D Deficiency

- **Cardiovascular risk**

Convergent evidence from MR studies and RCTs suggests that vitamin D supplementation does not decrease the risk of cardiovascular disease (CVD), especially in vitamin D–replete adults.

This conclusion may also apply to those with vitamin D deficiency based on subgroup analyses of the ViDA and VITAL trials. However, both studies recruited very few participants with severe vitamin D deficiency , rendering these conclusions uncertain.

Clinical Outcomes of Vitamin D Deficiency

A detailed analysis of the ViDA trial found some modest benefits on central (but not peripheral) blood pressure.

VD lowered central blood pressure in deficient participants

The FIND trial failed to note a reduction in the number of major CV events, however, subsequent exploratory analyses revealed that high-dose vitamin D supplementation might result in benefits in atrial fibrillation prevention in older individuals, even in case of relatively high baseline 25(OH)D concentrations.

VD reduced atrial fibrillation risk by 27%-32%

Clinical Outcomes of Vitamin D Deficiency

In the D-Health trial, the overall rate of major CV—and especially the rate of myocardial infarction and coronary revascularization—was lower in the intervention group compared to the placebo group, although the absolute risk difference was small.

Clinical Outcomes of Vitamin D Deficiency

- **Respiratory effects**

Vitamin D is known to influence the immune system.

Serum 25(OH)D levels of less than 25 nmol/L are associated (observationally and genetically) with an increased risk of bacterial pneumonia.

A meta-analysis of 25 trials showed a small but significant decrease in the incidence of acute respiratory infections in the vitamin D group compared with the control group when baseline vitamin D status was poor (<25 nmol/L).

RCTs show that vitamin D supplementation can benefit infants, toddlers, and preschool children aged 0 to 5 years with a quicker recovery and fewer respiratory symptoms.

Clinical Outcomes of Vitamin D Deficiency

There is also consistent evidence for an association between low 25(OH)D levels and poor COVID-19 outcomes, although the evidence supporting a beneficial effect of vitamin D supplementation in decreasing the risk of COVID-19 complications is conflicting.

An MR study found no evidence that vitamin D is protective against SARS-CoV-2 infection or COVID-19 severity.

However, a meta- analysis of several observational studies comprising almost 2 million adults suggests that inadequate vitamin D status increases susceptibility to COVID-19 and severe COVID-19, while the association with mortality was less robust.

Clinical Outcomes of Vitamin D Deficiency

Furthermore, low 25(OH)D levels were also recently associated with an increased risk for long COVID occurrence.

However, a phase 3 RCT found no effect of vitamin D supplementation on the risk of developing long COVID after an episode of COVID-19.

Also, deficient vitamin D status was recently reported to be associated with a reduced long-term immune response to the anti–COVID-19 vaccination.

Clinical Outcomes of Vitamin D Deficiency

Vitamin D supplementation also seems effective in safely and substantially reducing the rate of moderate/severe acute exacerbations of chronic obstructive pulmonary disease in patients with baseline 25(OH)D levels less than 25 nmol/L—but not in those with higher levels.

A meta-analysis, conversely, found no role for vitamin D supplementation in improving expiratory lung function.

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Clinical Outcomes of Vitamin D Deficiency

Regarding asthma:

In a meta analysis of 955 patients ,with asthma needed systematic steroids, there was an overall reduction in exacerbations.

A subgroup analysis of those with 25(OH) vitD less than 10 ng/ml ,increased effect of vitamin D in reducing exacerbation was seen (RR 0.33,95% CI, 0.11-0.98 P=0.045).

A post hoc analysis of a New Zealand cardiovascular study (ViDA) with 5110 participants in 775 participants those with COPD and asthma no Signiant difference in exacerbations between placebo and VD was found, However in the 60 participants with serum 25(OH)vitDless than 10 ng/ml exacerbations occurred 7% on vitamin D compared with 70% on placebo($P<0.005$).

Clinical Outcomes of Vitamin D Deficiency

- **Autoimmune diseases**

immune system is downregulated by 1,25(OH)2D in animal models. Thus, vitamin D deficiency might predispose to autoimmune diseases. Observational studies have suggested this effect might apply to humans.

The VITAL RCT showed that vitamin D supplementation (2000 IU daily) decreased the risk of autoimmune diseases, especially rheumatoid arthritis and polymyalgia rheumatica.

VD reduced autoimmune diseases by 22%

At least 8 large MR studies all agree that genetically predicted lower 25(OH) D levels increased the risk of developing multiple sclerosis either during adolescence or adulthood.

Clinical Outcomes of Vitamin D Deficiency

❑ Diabetes

Despite observational studies consistently confirming lower serum 25(OH)D concentrations in patients with T2D or metabolic syndrome, most MR studies have not supported these conclusions.

In a small subgroup of individuals with obesity and prediabetes, supplementation provided some modest benefit, albeit lower than lifestyle modifications or metformin.

Of note, daily vitamin D supplementation (4000 IU) in the large D2d trial did not retard the progression of prediabetes into T2D.

A post hoc and meta-analysis, however, suggested a possible beneficial effect in individuals with vitamin D deficiency (<30 nmol/L) at baseline or in participants who were able to achieve consistently high (≥100 nmol/L) serum 25(OH)D levels.

Clinical Outcomes of Vitamin D Deficiency

Furthermore, analysis of the combined results of the D2d (US), Tromsø (Norway), and DPVD (Japan) RCTs—which were specifically designed and conducted to test whether vitamin D reduces the risk of diabetes in adults with prediabetes—showed that vitamin D supplementation reduced the risk of developing T2D in people with prediabetes not selected for vitamin D deficiency.

An updated individual participant data meta-analysis of the same trials showed that vitamin D reduced the risk of progression from prediabetes to diabetes by 15%. Also, vitamin D increased the likelihood of regression to normal glucose regulation by 30%, with no evidence of risk.

Clinical Outcomes of Vitamin D Deficiency

In additional analyses, participants in the vitamin D group who maintained intratrial blood 25(OH)D of 50 ng/mL or greater (≥125 nmol/L) had a 76% risk reduction in new-onset diabetes compared to those who maintained blood 25(OH)D of 20 to 29 ng/mL (50-75 nmol/L).

The evidence from large-scale MR studies and RCTs is convergent and does not support vitamin D supplementation to prevent T2D in the general population. However, vitamin D supplementation benefits those with prediabetes and a predisposition to T2D, especially those with vitamin D deficiency

Clinical Outcomes of Vitamin D Deficiency

Mortality

Observational data have repeatedly linked poor vitamin D status with increased mortality.

A Cochrane meta-analysis of 56 randomized trials including almost 100 000 participants, of whom were women older than 70 years, revealed that vitamin D, administered over 4 years, decreased mortality; this effect was seen in 38 trials of vitamin D3, but not with other forms of vitamin D.

A newer meta- analysis of 52 RCTs, including more than 75 000 individuals, concluded that vitamin D (either vitamin D3 or D2) supplementation did not change mortality compared with no supplementation. Again, subanalyses found that vitamin D3 (instead of D2) supplementation tended to reduce mortality.

Clinical Outcomes of Vitamin D Deficiency

The positive but small effect of vitamin D on mortality was confirmed by a recent umbrella review of observational, randomized, and MR studies.

In conclusion, if vitamin D supplementation benefits extraskeletal health outcomes and major diseases, it is likely to have some effects on mortality, especially in older adults with poor vitamin D status, but not in younger, replete individuals.

Clinical Outcomes of Vitamin D Deficiency

- **Summary of Vitamin D Deficiency-associated Clinical Outcomes**

When it comes to vitamin D, it is advisable to “giveth to those who needeth”.In fact, the benefit-to-risk ratio for vitamin D depends on the target population and medical condition.

Nonetheless, RCTs, MR studies, and metanalyses suggest a link between vitamin D status with the immune system and diabetes, as well as fleeting effects on some CV events and some benefits on mortality risk when vitamin D3 is used.

Vitamin D Supplementation

Dosing Regimens

Cholecalciferol and other formulations such as ergocalciferol, eldecalcitol, calcifediol, etc are available in a pill. It is expressed as µg or IU (where 10 µg is 400 IU).

Daily doses are generally preferred when vitamin D replacement is considered necessary.

The effect of a given dose on changing blood 25(OH)D varies considerably from person to person due to many factors, such as body weight, absorption, diet, degree of adiposity, CYP2R1 activity, DBP.

Vitamin D Supplementation

The recommended dietary allowance for vitamin D by the National Academy of Medicine is set at 400 to 800 IU per day, and the tolerable upper intake level at 4000 IU per day.

Infants and children have different upper tolerance limits compared to adults.

To maintain a desirable 25(OH)D concentration, the 2010 IOM guidelines recommend 600 IU/d (15 μg) for children, adolescents, and adults, and 400 IU/d (10 μg) for infants.

ES guidelines recommend 400 to 1000 IU/day (10-25 μg) for infants aged up to 1 year and 600 to 1000 IU/day (15-25 μg) for children older than 1 year to treat and prevent vitamin D deficiency.

Vitamin D Supplementation

Obese and overweight individuals requiring 2.6 and 1.47 times higher supplementation, respectively.

ES guidelines suggesting that the vitamin D dosage for obese people is “three times” greater than the recommended dose for individuals with normal body weight.

Life stage group	IOM recommendations				Committee recommendations for patients at risk for vitamin D deficiency	
	AI	EAR	RDA	UL	Daily requirement	UL
Infants						
0 to 6 months	400 IU (10 μg)			1,000 IU (25 μg)	400–1,000 IU	2,000 IU
6 to 12 months	400 IU (10 μg)			1,500 IU (38 μg)	400–1,000 IU	2,000 IU
Children						
1–3 yr		400 IU (10 μg)	600 IU (15 μg)	2,500 IU (63 μg)	600–1,000 IU	4,000 IU
4–8 yr		400 IU (10 μg)	600 IU (15 μg)	3,000 IU (75 μg)	600–1,000 IU	4,000 IU
Males						
9–13 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	600–1,000 IU	4,000 IU
14–18 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	600–1,000 IU	4,000 IU
19–30 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
31–50 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
51–70 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
>70 yr		400 IU (10 μg)	800 IU (20 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
Females						
9–13 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	600–1,000 IU	4,000 IU
14–18 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	600–1,000 IU	4,000 IU
19–30 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
31–50 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
51–70 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
>70 yr		400 IU (10 μg)	800 IU (20 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
Pregnancy						
14–18 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	600–1,000 IU	4,000 IU
19–30 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
31–50 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
Lactation[a]						
14–18 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	600–1,000 IU	4,000 IU
19–30 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU
31–50 yr		400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000 IU	10,000 IU

AI, Adequate intake; EAR, estimated average requirement; UL, tolerable upper intake level.

[a] Mother's requirement, 4,000–6,000 IU/d (mother's intake for infant's requirement if infant is not receiving 400 IU/d).

Vitamin D Supplementation

- **Daily supplementation**

In a recent RCT comparing 3 different dosing regimens in vitamin D–deficient participants with similar total end-of-study cumulative doses (D3 daily 10 000 IU 8 weeks, then 1000 IU for 4 weeks; 50 000 IU weekly for 12 weeks; and 100 000 IU every 2 weeks for 12 weeks), the group receiving the daily supplementation was the quickest to reach sufficiency (<2 weeks, although receiving a higher cumulative dose in the first 8 weeks when compared to the other 2 arms) and reached the highest serum 25(OH)D levels.

The greater 25(OH)D exposure of daily regimens could be due to lower activation of the 24-hydroxylase enzyme (CYP24A1).

Vitamin D Supplementation

Greater 25(OH)D exposure and lesser 24-hydroxylase activity might be the rationale behind the potential extraskeletal benefits of cholecalciferol supplementation:

- Reduction in cancer mortality
- Reduction in advanced cancers (metastatic or fatal), especially among those with normal BMI
- Reduction of relapse or death in digestive-tract cancers
- Prevention of autoimmune diseases
- Prevention of acute respiratory infections

Vitamin D Supplementation

- **Weekly and monthly regimens**

As compared with a daily regimen, a bolus dose is associated with a higher 24,25(OH)2D level and a higher 24,25(OH)2D to 25(OH)D ratio.

Monthly regimens have been tested in several large trials with multiple outcomes. Compared to a placebo, 100 000 IU monthly did not influence the risk of CVD, falls, fracture, or cancer, and lung or arterial functions in vitamin D–replete individuals.

In the D-Health trial, 60 000 IU monthly did not influence all-cause mortality but was associated with a higher risk of falls in those with a BMI of less than 25.

This observation was in agreement with another trial in which a higher percentage of fallers was detected with 60 000 IU/month compared to 24 000 IU/month over 1 year.

Vitamin D Supplementation

Overall, trials with weekly or monthly vitamin D supplementation regimens did not show significant effects on clinical variables.

Currently, there is no evidence of a superiority in the benefit/risk ratio of weekly or monthly vitamin D regimens over daily supplementation.

Vitamin D Supplementation

- **Longer intervals**

Although one study using high doses with prolonged intervals (100 000 IU every 4 months) administered to community- dwelling adults older than 50 years found a reduction in fractures, other similar studies (500 000 IU every year/150 000 IU every 3 months) did not show a reduction in hip/vertebral/nonvertebral/total fracture incidence.

Regarding the relation between long-term intervals of vitamin D administration and CVD risk, falls, and fracture outcomes in older and community-dwelling people, in a systematic review with meta-analysis, Barbarawi et al did not find significant results favoring vitamin D intervention (100 000 IU every 4 months /500000 IU yearly) in preventing falls, fractures, or CVDs.

Vitamin D Supplementation

- **Summary of Vitamin D Dosing Regimens**

In conclusion, one of the major justifications for longer intervals with high doses in vitamin D administration, to address low compliance with more frequent regimens, is controversial.

The rationale gains support in children and adolescents rather than in older individuals.

Cited meta-analyses underscored the point that there is no evidence of efficacy in intermittent high-dose and longer intervals of vitamin D administration in reducing fracture rate, falls, CV events, or infectious diseases.

An increase in falls in older individuals has been observed with large, intermittent dosing.

Routes of Administration

Oral supplementation of cholecalciferol is the most commonly used approach. It is effective, simple, and generally safe. Therefore, it is the preferred way to supplement vitamin D.

However, sometimes, the parenteral route may be a better method for improving vitamin D status than oral administration of vitamin D, particularly in situations like intestinal malabsorption.

Interestingly, a new transdermal route of vitamin D administration is being proposed but data is not enough.

Routes of Administration

- **Oral administration**

Cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2) are fat-soluble vitamins that are absorbed in the small intestine. Because they are lipophilic compounds, their absorption is similar to the absorption of lipids.

On average, about 80% of vitamin D is absorbed, but the variation in absorption can be large (55%-99%).Taking vitamin D supplements with a fat-containing meal may improve vitamin D absorption.

Routes of Administration

Cholecalciferol and ergocalciferol are both rapidly absorbed,and the plasma levels peak after about 24 hours of ingestion.

Absorption into the enterocytes of the intestinal wallis a passive process in pharmacological doses and active transport seems to occur especially with dietary doses of vitamin D.

From the enterocytes, vitamin D is exported in chylomicrons by the lymphatic route.

Routes of Administration

Bariatric surgery and intestinal malabsorption syndromes that reduce fat absorption, such as inflammatory bowel diseases, cystic fibrosis, and severe cholestasis, can also reduce vitamin D absorption.

However, intestinal malabsorption does not seem to affect the absorption of calcidiol as much, most likely because calcidiol is more water soluble, thus not requiring bile salts for absorption, and because calcidiol is absorbed by the portal route instead of the lymphatic route.

Routes of Administration

As cholesterol transporters are involved in vitamin D absorption, factors that interfere with cholesterol absorption could also affect vitamin D absorption.

However, ezetimibe, an inhibitor of cholesterol transport, does not seem to affect vitamin D absorption despite the reduction in cholesterol absorption. There is also no strong evidence that phytosterols, plant sterols used to inhibit cholesterol absorption, impair vitamin D absorption.

In contrast, there is some evidence that drugs used to reduce intestinal fat absorption, such as orlistat and olestra, may also reduce vitamin D absorption.

Vitamin D Supplementation

Vitamin D supplements are available in different vehicles, such as oil-containing gel capsules, oily drops, and hard powder tablets.

Vitamin D may be better absorbed from a powder-based vehicle than from an oil-based vehicle in cases of intestinal fat malabsorption, such as in cystic fibrosis.

Vitamin D Supplementation

- **Parenteral administration**

Parenteral administration of intermittent vitamin D boluses may be indicated in patients with hypovitaminosis D who are not suitable for oral intake or with intestinal malabsorptive diseases, including inflammatory bowel disease, celiac disease, pancreatic insufficiency, short-bowel syndrome, and post bariatric surgery.

Vitamin D Supplementation

Intramuscular cholecalciferol may be the preferred form of vitamin D to be used in these clinical settings.

In fact, it has been shown that cholecalciferol was able to reach higher serum 25(OH)D levels more rapidly than ergocalciferol when both vitamin D forms were administered as a single large intramuscular dose (300 000 UI) in adult or older patients with hypovitaminosis D.

Vitamin D Supplementation

Moreover, in the study by Romagnoli et al, 2 months after administration of this large, intramuscular cholecalciferol dose, serum 25(OH)D levels were higher than those obtained after the same oral dose. Therefore, intermittent intramuscular cholecalciferol could be useful in clinical conditions when rapid correction of hypovitaminosis D is unnecessary and for long-term maintenance of adequate serum vitamin D levels, as in some older patients, to improve their adherence to vitamin D supplementation. However, safety concerns limit the clinical use of intermittent, excessive vitamin D doses.

In fact, large intramuscular boluses (300 000 IU) induce unwanted effects such as an increase in falls and fracture events or enhance bone turnover. There is a consensus to administer vitamin D boluses not higher than 100 000 IU.

Different Forms of Vitamin D Supplementation

The main supplemental oral forms of vitamin D are cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2). Both are readily available without a prescription. Cholecalciferol is the most used form of supplemental vitamin D.

Calcidiol (calcifediol, 25(OH)D), the inactive vitamin D metabolite produced in the liver, and other vitamin D analogues, such as calcitriol (1,25(OH)2D, the physiologically active form of vitamin D) and alfacalcidol (1-hydroxyvitamin D), are used as prescription medicines in some conditions.

Different Forms of Vitamin D Supplementation

- **Ergocalciferol**

Ergocalciferol does exist in nature (mainly in plants and fungi).

The 2 forms of vitamin D, cholecalciferol (D3) and ergocalciferol (D2), are often used interchangeably as supplementation or treatment of vitamin D deficiency however, multiple studies and meta-analyses comparing the effect of D2 and D3 on circulating 25(OH)D concentration have found cholecalciferol to be superior.

Challenges to 25(OH)D measurement are widely recognized. The presence of 2 circulating 25(OH)D forms, 25(OH)D3 and 25(OH)D2, adds additional challenges, notably for automated immunoassays. Importantly, it is possible that the antibodies used in immunoassays may not detect 25(OH)D2 and 25(OH)D3 equally, and the proprietary approach to releasing 25(OH)D from DBP may not liberate the 2 forms equally.

Different Forms of Vitamin D Supplementation

In addition to assay issues, widespread use of intermittent high- dose ergocalciferol (“bolus” therapy) appears to alter vitamin D metabolism, with increased 24-hydroxylase activity.

To summarize, vitamins D2 and D3 are not equivalent in raising circulating 25(OH)D, and bolus dosing may have adverse effects on vitamin D metabolism and clinical outcomes.

As such, it is to be expected that calls for the use of only cholecalciferol and avoidance of ergocalciferol have been and continue to be published with recent osteoporosis-treatment guidance advising cholecalciferol over ergocalciferol.

Different Forms of Vitamin D Supplementation

- **Calcifediol**

Calcifediol is the intermediate metabolite between cholecalciferol and calcitriol. Several pharmacokinetic studies have demonstrated its hydrophilic properties, leading to higher solubility in organic solvents, less sequestration in adipose tissue, smaller distribution volume, and shorter half-life when compared to cholecalciferol.

By virtue of its hydrophilic properties, calcifediol is readily absorbed via the venous portal system and thus quickly increases circulating concentrations of 25(OH)D3.

Different Forms of Vitamin D Supplementation

In contrast to cholecalciferol, which is mostly stored in fat tissue, 25(OH)D tends to be more evenly distributed throughout the body (20% in muscle, 30% in circulation, 35% in fat, and 15% elsewhere).

The administered dose will generally lead to predictable 25(OH)D levels and effective PTH suppression.

In cases of toxicity, this form of vitamin D is easier to manage than cholecalciferol.

Different Forms of Vitamin D Supplementation

The clinical situations that make use of calcifediol attractive are:

- Obesity
- Malabsorption syndromes
- Hepatic failure
- Patients with inactivating mutations of genes encoding CYP2R1 (the principal enzyme that is responsible for vitamin D 25-hydroxylation)
- Patients taking drugs that could influence the activity of cytochrome enzymes (ie, antiretroviral or antitubercular)
- Situations in which quick attainment of vitamin D sufficiency is desirable

Different Forms of Vitamin D Supplementation

Calcifediol was shown to have the same bioavailability in healthy adults with differing BMI and adults with intestinal malabsorption compared to controls.

New extended-release calcifediol formulations are more effective than cholecalciferol in raising serum 25(OH)D levels even in overweight nondialytic CKD patients with secondary hyperparathyroidism.

Different Forms of Vitamin D Supplementation

- **Calcitriol**

Calcitriol is the active hormonal form of vitamin D and the natural VDR ligand. It promotes active intestinal calcium absorption and suppresses PTH secretion.

Calcitriol has a short half-life of around 5 to 8 hours; therefore, it should be administered daily (or with intermittent regimens) and sometimes in lower doses distributed over a 24-hour period.

Calcitriol increases the activity of CYP24A1, which stimulates the degradation of 25(OH)D. This results in serum 25(OH)D not being useful as a marker of adequate vitamin D supplementation.

Different Forms of Vitamin D Supplementation

Moreover, some studies have reported a more significant incidence of adverse events such as hypercalcemia and hypercalciuria. Thus, there is a need to monitor serum and urine calcium and phosphate.

Because of these safety and clinical practicality issues, there is consensus that calcitriol use should be limited to:

- hormone replacement for patients with limited/absent renal tubular 1-α-hydroxylase activity (vitamin D–resistant rickets type 1)
- X-linked hypophosphatemic rickets
- chronic hypoparathyroidism
- moderate-to- severe kidney failure when calcitriol production is impaired or to suppress excessive PTH secretion

Different Forms of Vitamin D Supplementation

However, as calcitriol use is associated with frequent hypercalcemia, its use could be replaced by analogues with less calcemic activity approved for use in patients with secondary hyperparathyroidism in renal failure, in particular maxacalcitol (22-oxa-1,25(OH)2D3) and falecalcitriol (1,25(OH)2-26,27-F6-D3), which are currently available in Japan, and paricalcitol (19-nor-1,25(OH)2D2) and doxercalciferol (1α(OH)D2), available in the United States.

Different Forms of Vitamin D Supplementation

In conclusion, calcitriol is not suitable for supplementation or nutritional fortification and, guidelines suggest that vitamin D supplementation is advised in patients with chronic hypoparathyroidism, chronic kidney failure, and low vitamin D status in addition to receiving therapeutic doses of calcitriol.

Vitamin D Safety and Monitoring

- **Vitamin D toxicity**

VDT prevalence is unknown, but it is rare due to the wide therapeutic index of vitamin D.

VDT is defined by a biochemical phenotype with markedly elevated calcifediol concentrations (>150 ng/mL or >375 nmol/L).

Signs and symptoms of VDT are related primarily to hypercalcemia, with complications encompassing adverse events in the CV, renal, gastrointestinal, neurological, and musculoskeletal systems.

Vitamin D Safety and Monitoring

In healthy individuals, hypervitaminosis D is usually defined as “exogenous” as it develops after uncontrolled use of megadoses of vitamin D or its metabolites or analogues.

On the other hand, excessive production of calcitriol in granulomatous disorders, lymphomas, and idiopathic infantile hypercalcemia results in “endogenous” hypervitaminosis D.

Calcitriol levels may be in the normal reference range or even reduced in exogenous VDT while elevated in endogenous VDT. PTH levels can be very low or undetectable.

Vitamin D Safety and Monitoring

Exogenous factors that interact with VDT risk include dosage, calcium in the diet or as a supplement, vitamin D intake with the diet, social status (ie, neglected patients), artificial UV light treatment sessions, quantity of supplement use, and time of exposure.

Endogenous risk factors comprise age, sex, vitamin D status, hypersensitivity syndromes, and the pharmacogenetics of the vitamin D response and metabolism. This is why there is no clear cutoff above which VDT occurs and below which it does not.

Vitamin D Safety and Monitoring

❑ Monitoring vitamin D status during treatment

Regarding vitamin D supplementations, there is limited evidence for when to monitor response to therapy or toxicity.

Van Groningen et al calculated that the cholecalciferol loading dose required to reach the serum 25(OH)D target level of 75 nmol/L can be calculated as dose (IU) = **40 × [75 – serum 25(OH) D] × body weight.**

Cholecalciferol can maintain physiological 25(OH)D serum levels above 30 ng/mL (75 nmol/L) but below 50 ng/mL (125 nmol/L) for a long time, regardless of whether the dosage given is daily or intermittent.

Routine monitoring of 25(OH)D levels is generally unnecessary for patients on long-term maintenance vitamin D doses of up to at least 2000 IU/day.

Vitamin D Safety and Monitoring

Retesting after 8 to 12 weeks from the start of supplementation may be appropriate when poor compliance is suspected, in case of symptoms suggestive of vitamin D deficiency, and for patients at risk of persistent 25(OH)D level below 30 ng/mL (75 nmol/L):

- hospitalized individuals
- people in whom vitamin D therapy uncovers subclinical primary hyperparathyroidism
- obese individuals
- Individuals undergoing bariatric surgery
- Individuals who use of certain concomitant medications (eg, anticonvulsant medications, glucocorticoids)
- Patients with malabsorption, including inflammatory bowel disease and celiac disease.

For patients on potent antiresorptive agents (eg, denosumab or zoledronic acid), vitamin D levels should be checked annually per protocol.

THANK YOU FOR YOUR ATTENTION

Conclusions

Vitamin D metabolism involves a different extensive panel of enzymes

The VDR has been demonstrated to act as a key role transcription factor in most cells and can regulate a plethora of genes.

Assessing a distinctive pattern of noncanonical vitamin D metabolites may allow us to better characterize different pathological conditions related to vitamin D metabolism that do not depend only on reduced solar exposure or vitamin D diet intake.

Conclusions

Another critical issue is the lack of an accepted laboratory test assay standardization, and this prevents a proper interpretation of data reported by different studies

Thus, 25(OH)D laboratory assays should be monitored in their performance through external quality assessment plans providing target reference values from standardized measurement procedures.

More recently, the interest in the putative extraskeletal effects of vitamin D have resulted in several clinical trials addressing vitamin D's influence on cancer and CV risk, respiratory effects, autoimmune diseases, diabetes, and mortality.

Conclusions

their null results were mainly related to the enrollment of vitamin D–replete adults in whom benefit would be unlikely and the inhomogeneous methodologies in vitamin D supplementation with different forms, metabolites, and doses.

Indeed, subsequent secondary analyses have progressively shown that vitamin D might be useful in reducing cancer incidence and mortality in the long term, in reducing autoimmune diseases and CV events (in particular central arterial hypertension, myocardial infarction, and atrial fibrillation) occurrence, and the development of diabetes from prediabetes forms.

Conclusions

Oral administration is the preferred route

Cholecalciferol remains the preferred choice, and it is generally safe, requiring less strict monitoring.

No need to monitoring serum 25(OH)D in the healthy population.

Characteristics and results of the most recent and largest randomized controlled trials on vitamin D supplementation

Study	Participants (n)	Age (mean ± SD), y	Sex (% of women)	Mean BMI	Ethnicity*a* (% White ethnicity)	Basal Serum 25(OH)D, ng/mL	Final Serum 25(OH)D, ng/mL	Dose used	Follow-up, y	Primary outcome(s)	Conclusions and comments
VITAL	25871	67 ± 7	51	28	71	30.8 ± 10	42 ± 10	2000 IU/d + omega-3 1 g/d	5.3	Invasive cancers and major CV events	End point not met, but reduction in total cancer mortality when excluding first 1-2 y of follow-up
										Incidence of metastatic or fatal cancer	VD reduced metastatic or fatal cancers by 17%; strongest reduction in normal BMI
										Two or more falls and falls resulting in a doctor or hospital visit	End point not met
										All incident autoimmune diseases	VD reduced autoimmune diseases by 22%
										Incident total, nonvertebral, and hip	End point not met; enrolled individuals were generally

Characteristics and results of the most recent and largest randomized controlled trials on vitamin D supplementation

Study	Participants (n)	Age (mean ± SD), y	Sex (% of women)	Mean BMI	Ethnicity *a* (% White ethnicity)	Basal Serum 25(OH)D, ng/mL	Final Serum 25(OH)D, ng/mL	Dose used	Follow-up, y	Primary outcome(s)	Conclusions and comments
D-Health	21 315	69.3	46	28	96.5%	31 ± 10*d*	46 ± 12	60 000 IU/mo	5.7	All-cause mortality	End point not met; VD increased cancer risk when first 2 y of follow-up were excluded
										Risk of falling	End point not met; VD increased risk when BMI <25, but not when BMI ≥25
										Major CV events	End point not met; VD might reduce CV events (small absolute risk difference and CI consistent with null finding); VD reduced myocardial infarction by 19%

Characteristics and results of the most recent and largest randomized controlled trials on vitamin D supplementation

Study	Participants (n)	Age (mean ± SD), y	Sex (% of women)	Mean BMI	Ethnicity *a* (% White ethnicity)	Basal Serum 25(OH)D, ng/mL	Final Serum 25(OH)D, ng/mL	Dose used	Follow-up, y	Primary outcome(s)	Conclusions and comments
ViDA	5110	66 ± 8	58	29 ± 5.1	83	27 ± 9[e]	54 ± 16	200 000 IU + 100 000 IU/mo	3.3	Incident CVD and death Fractures and falls Cancer incidence and mortality	End point not met; in one substudy, VD lowered central blood pressure in deficient participants End point not met End point not met; daily or weekly dosing for longer period may require further study

Characteristics and results of the most recent and largest randomized controlled trials on vitamin D supplementation

Study	Participants (n)	Age (mean ± SD), y	Sex (% of women)	Mean BMI	Ethnicity *a* (% White ethnicity)	Basal Serum 25(OH)D, ng/mL	Final Serum 25(OH)D, ng/mL	Dose used	Follow-up, y	Primary outcome(s)	Conclusions and comments
FIND	2495	685	43	27 ± 4	100	30 ± 7	40 ± 9 (1600 IU/d arm) 48 ± 9 (3200 IU/d arm)	1600 or 3200 IU/d	4.3	Incident major CVD and invasive cancer Atrial fibrillation risk	End point not met; study failure possibly due to sufficient VD status in most participants at baseline VD reduced atrial fibrillation risk by 27%-32%

Characteristics and results of the most recent and largest randomized controlled trials on vitamin D supplementation

Study	Participants (n)	Age (mean ± SD), y	Sex (% of women)	Mean BMI	Ethnicity *a* (% White ethnicity)	Basal Serum 25(OH)D, ng/mL	Final Serum 25(OH)D, ng/mL	Dose used	Follow-up, y	Primary outcome(s)	Conclusions and comments
D2d	2423	60 ± 10	45	32 ± 5	67	28 ± 10	54 ± 15	4000 IU/d	2.5	T2D in adults with prediabetes Development of T2D according to intratrial serum 25(OH)D level	End point not met VD resulting in 25(OH)D level ≥100 nmol/L reduces risk of T2D

Vitamin D form	Circulating half-life	Features	When to use it
Cholecalciferol (vitamin D3)	Around 1 day (longer functional half-life in correlation with its slow release from the adipose tissue)	• Native form of human- and animal-produced vitamin D • Lipophilic, stored in fat and released on need • Useful in clinical practice as it renders possible intermittent administration regimes • Wide safety range thanks to the predicted mechanisms regulating its hydroxylation	Most clinical situations where a vitamin D deficiency must be addressed (see below for exceptions)

Vitamin D form	Circulating half-life	Features	When to use it
Ergocalciferol (vitamin D2)	Around 2 days	• Inferior to cholecalciferol in increasing 25(OH)D serum levels • Risk of over- or under-estimation of total 25(OH)D in the presence of substantial amounts of 25(OH)D2 with subsequent risk of vitamin D toxicity in case of dose increments • Widely prescribed in the USA in high doses (50,000 IU) • High doses alter vitamin D metabolism, increasing 24 hydroxylase activity	Most clinical situations where a vitamin D deficiency must be addressed (see below for exceptions)

Vitamin D form	Circulating half-life	Features	When to use it
Calcifediol(25(OH)D)	2-3 weeks	• Hydrophilic, thus higher solubility in organic solvents, less sequestration in adipose tissue, smaller distribution volume and shorter half-life compared to cholecalciferol • Fast increase in 25(OH)D serum levels along with PTH suppression • Easier to manage than cholecalciferol in case of toxicity • More efficient internalization in cells expressing the megalin-cubilin system	Malabsorption syndromes, obesity, CYP2R1 dysfunction, or in situations in which a quick attainment of vitamin D sufficiency is desirable

Vitamin D form	Circulating half-life	Features	When to use it
Calcitriol (1,25(OH)2D)	5-8 hours	• Promotes active intestinal calcium absorption and suppresses PTH secretion • Increases the activity of the CYP24A1, which stimulates the degradation of 25(OH)D • Risk of hypercalcemia and hypercalciuria • To be administered daily or in lower doses distributed over a 24-hour period	As a hormone replacement for patients with limited/absent renal tubular 1--hydroxylase activity; vitamin D resistant rickets type 1, X-linked hypophosphataemic rickets, chronic hypoparathyroidism, as an alternative to the use of the native missing hormone PTH, and moderate-to-severe kidney failure Consider replacing it with analogs with less calcemic activity (maxacalcitol; falecalcitriol; paricalcitol; doxercalciferol)

Abbreviations:

1,25(OH)2D, 1,25 dihydroxyvitamin D; 7-DHC, 7-dehydrocholesterol; 25(OH)D, 25-hydroxyvitamin D; BMD, bone mineral density; BMI, body mass index; CDC, Centers for Disease Control and Prevention; CKD, chronic kidney disease; CVD, cardiovascular disease; DBP, vitamin D binding protein; ES, Endocrine Society; HAT, histone acetyltransferase activity; HDAC, histone deacetylase activity; ICU, intensive care unit; IL, interleukin; IOM, Institute of Medicine; LC-MS, liquid chromatography–mass spectrometry; miRNA, microRNA; MR, mendelian randomization; OR, odds ratio; PTH, parathyroid hormone; RCT, randomized controlled trial; SRC, steroid hormone receptor coactivator; T2D, type 2 diabetes; TSS, transcription start site; UVB, sunlight; VDR, vitamin D receptor; VDSP, Vitamin D Standardization Program; vitamin D2, ergocalciferol; vitamin D3, cholecalciferol; VDT, vitamin D toxicity.