REVIEW ARTICLE

Vitamin D deficiency 2.0: an update on the current status worldwide

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Abstract

Vitamin D testing and the use of vitamin D supplements have increased substantially in recent years. Currently, the role of vitamin D supplementation, and the optimal vitamin D dose and status, is a subject of debate, because large interventional studies have been unable to show a clear benefit (in mostly vitamin D replete populations). This may be attributed to limitations in trial design, as most studies did not meet the basic requirements of a nutrient intervention study, including vitamin D-replete populations, too small sample sizes, and inconsistent intervention methods regarding dose and metabolites. Vitamin D deficiency (serum 25-hydroxyvitamin D [25(OH)D] < 50 nmol/L or 20 ng/ml) is associated with unfavorable skeletal outcomes, including fractures and bone loss. A 25(OH)D level of >50 nmol/L or 20 ng/ml is, therefore, the primary treatment goal, although some data suggest a benefit for a higher threshold. Severe vitamin D deficiency with a 25(OH)D concentration below <30 nmol/L (or 12 ng/ml) dramatically increases the risk of excess mortality, infections, and many other diseases, and should be avoided whenever possible. The data on a benefit for mortality and prevention of infections, at least in severely deficient individuals, appear convincing. Vitamin D is clearly not a panacea, and is most likely efficient only in deficiency. Given its rare side effects and its relatively wide safety margin, it may be an important, inexpensive, and safe adjuvant therapy for many diseases, but future large and well-designed studies should evaluate this further. A worldwide public health intervention that includes vitamin D supplementation in certain risk groups, and systematic vitamin D food fortification to avoid severe vitamin D deficiency, would appear to be important. In this narrative review, the current international literature on vitamin D deficiency, its relevance, and therapeutic options is discussed.

Introduction

Vitamin D testing has exponentially increased in recent years [1]. The definition and relevance of vitamin D deficiency are still under debate. Recent large observational data have suggested that ~40% of Europeans are vitamin D deficient, and 13% are severely deficient [2]. The relevance of this widespread deficiency and necessity for supplementation has been questioned [3]. Certainly, vitamin D is not a panacea. Because more often than not, trials have included non-deficient individuals, it is not surprising that interventional trials have usually not been able to find a benefit of vitamin D supplementation on clinical outcomes. This was also reflected in meta-analyses on the topic that

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were carried out with poor methodological standards [4]. Consequently, many authors have dismissed a role of vitamin D on important clinical outcomes, and suggested that vitamin D may be more an associative than a causal factor in acute and chronic disease.

On the other hand, a low vitamin D status is emerging as a very common condition worldwide, and several studies from basic science to clinical applications have highlighted a strong association with chronic diseases, as well as acute conditions. Moreover, the large amount of observational data currently available are also accompanied by pathophysiological associations of vitamin D with energy homeostasis, and regulation of the immune and endocrine systems [5].

Recent negative interventional trials may be biased by substantial methodological and study design errors, making it impossible to show the potential contributing role of vitamin D supplementation in a deficient population. Typically, most studies have missed important prerequisites for a nutrient intervention trial: the absence of the problem to be solved—vitamin D deficiency, often ridiculously small sample sizes, and varying interventional regimes regarding dose and metabolite. Even the recent very large trials did not exclusively include deficient populations [6–8]. Moreover, interventional regimes have used a one-size-fits-all approach without taking into account individual differences in BMI and vitamin D metabolism.

Methods

Articles were individually retrieved up to October 2019 by search in PubMed (MEDLINE). Studies were excluded if they were not in English. Across the last few decades, vitamin D-related research/publications have dramatically increased. Therefore, we decided to focus on the largest, most relevant, and most recent studies that are now in this version of the review.

All authors supplied a first draft paper on a specific topic. All papers were then exchanged and discussed among authors by e-mail.

Definition of vitamin D deficiency

Serum 25(OH)D is considered to be the best marker for assessing vitamin D status, and reliably reflects the free fractions of the vitamin D metabolites, despite the fact that, in theory, the bioavailable fractions may be more clinically informative [9, 10]. A range of below 75 nmol/L (or 30 ng/ml) of serum/plasma 25(OH)D concentration is considered vitamin D deficiency by most authors [11, 12]. A cutoff of <25 or <30 nmol/L (or 10/12 ng/ml) increases the risk of osteomalacia and nutritional rickets dramatically, and therefore is considered to determine severe vitamin D

Table 1 Risk groups for vitamin D deficiency including high-risk medications.

Risk group	Medication
Chronic disease, particularly kidney, heart, and liver failure, in particular transplant candidates and recipients	Several antiretroviral medications
Gastrointestinal diseases including Crohn's disease, inflammatory bowel disease, and malabsorption syndromes	Antifungals, e.g., ketoconazole
Granuloma-forming disorders including sarcoidosis and tuberculosis	Several antiseizure medications
Hospitalized individuals, especially ICU patients	Cholestyramine
Hyper- and hypoparathyroidism	Glucocorticoids
Obese children and adults, particularly after bariatric surgery	Rifampicin
Older adults with a history of falls and/or fractures, osteoporosis	
Oncologic patients	
Pregnant and lactating women, preparing for pregnancy	
Reduced UV-B exposure or effectiveness (shift workers, immobilized patients, chronic neuropsychiatric disease, dressing habits, burn and skin cancer survivors, and nonwhite persons)	
Respiratory diseases including COPD, asthma, and cystic fibrosis	

deficiency [13–16]. The clinical practice guidelines of the Endocrine Society Task Force on Vitamin D [12] have defined a cutoff level of 50 nmol/L as vitamin D deficient. Furthermore, different societies and expert bodies have defined 50 nmol/L as "vitamin D requirement of nearly all normal healthy persons," by using bone health as the main basis. For example, a cutoff level of 50 nmol/L is recommended by the Institute of Medicine (IOM, USA) in their "Dietary Reference Intakes". Vitamin D levels of <30 nmol/L (or 12 ng/ml) should likely be prevented with a public health approach [17]. There are many large and relevant risk groups for vitamin D deficiency (Table 1).

Prevalence of vitamin D deficiency worldwide

Prevalence rates of severe vitamin D deficiency, defined as 25(OH)D <30 nmol/L (or 12 ng/ml), of 5.9% (US) [18], 7.4% (Canada) [19], and 13% (Europe) [2] have been reported. Estimates of the prevalence of 25(OH)D levels <50 nmol/L (or 20 ng/ml) have been reported as 24% (US), 37% (Canada), and 40% (Europe) [2, 17–19]. This may vary by age, with lower levels in childhood and the elderly [17], and also ethnicity in different regions, for example, European Caucasians show lower rates of vitamin D deficiency compared with nonwhite individuals [2, 17].

Worldwide, many countries report very high prevalences of low vitamin D status. 25(OH)D levels <30 nmol/L (or 12 ng/ml) in >20% of the population are common in India, Tunisia, Pakistan, and Afghanistan. For example, it has been estimated that 490 million individuals are vitamin D deficient in India [2, 17].

Specific categories of patients have a very high prevalence of vitamin D deficiency. Often, they are characterized by an insufficiency or failure of organs involved in vitamin D metabolism. Patients with chronic renal failure and on hemodialysis, renal transplant recipients affected with liver disease or after liver transplantation may have a prevalence of vitamin D deficiency ranging from 85 to 99% [20–22].

Vitamin D deficiency in critical illness

Similarly, critically ill patients have a very high prevalence of vitamin D deficiency, and low vitamin D levels are clearly associated with greater illness severity, morbidity, and mortality in both adult and pediatric intensive care unit (ICU) patients, as well as medical and surgical ICUs [23]. However, as in most other populations, the most important question remains unanswered: whether low vitamin D is an innocent bystander, simply reflecting greater disease severity, or represents an independent and modifiable risk factor amenable to rapid normalization through loading dose supplementation [24, 25].

The question is meaningful, since in this subgroup of patients, many factors contribute to low levels: hemodilution, reduced production and conversion by the liver, reduced synthesis of vitamin D-binding protein, higher consumption during the acute phase of disease and systemic inflammation, and increased tissue demand and enhanced catabolism of metabolites. More data are emerging from basic science about the immediate and late effects of vitamin D supplementation on endocrine, autocrine, and paracrine and genomic targets.

Vitamin D replacement

Metabolites

It cannot be emphasized enough that various vitamin D metabolites with a very different efficacy, half-life, and risk of toxicity exist. This is discussed in detail in "Vitamin D supplementation: cholecalciferol, calcifediol and calcitriol" by Reinold Vieth et al. in this special issue.

Interval, target level, and dose

For some time, bolus dosing was en vogue because it was thought to be interesting for practical reasons. With the exception of critical care, bolus doses with long dosing intervals are not used. They are no longer recommended because of the higher risk of adverse effects (falls and fractures) associated with them [26]. Moreover, the 2017 individual patient data meta-analysis by Martineau et al. showed a clear benefit for vitamin D on acute respiratory infection when daily or weekly dosing was used, but not with longer dosing intervals [16]. In the intensive care, however, a typical daily dose is inefficient, and an upfront loading dose (followed by a daily dose) is necessary to improve vitamin D levels rapidly [27].

It is also important to note that different dosing regimes may have different effects on clinical outcomes. Because a daily dose leads to stable availability of various vitamin D metabolites, this could be an important explanation for many of the negative vitamin D intervention trials [28].

To maintain optimal vitamin D status, use of vitamin D supplementation is often required, as sunlight exposure and dietary intake alone is usually insufficient in most individuals [29–31]. Currently, there is no international consensus on the optimal level for vitamin D supplementation. Recommendations differ in many countries, and range from 400 to 2000 IU daily [11]. A safe and commonly available dose of 25 μg of vitamin D3 (1000 IU) raises 25-hydroxyvitamin D [25(OH)D] serum level by 15–25 nmol/L on average (over weeks/months) [32, 33]; it should be noted that there is a nonlinear response of serum 25(OH)D, with a steeper rise with <1 IU/day of vitamin D, and a more flattened response with >1 IU/day. This is evidenced by several studies in all age groups [11, 34].

By using the above-mentioned recommended vitamin D supplementation levels, there is no need to monitor serum or urinary calcium or renal function [35, 36]. There is no international consensus on the safe upper level for vitamin D supplementation. While the upper daily limit given by the Endocrine Society is 10,000 IU [12], the IOM and The European Food and Safety Authority recommend staying below 4000 IU/day (100 μg) [37, 38]. Most countries have prudently set the safe upper level at 50 μg daily (2000 IU) for adults [35]. However, this level was set despite the availability of adequate studies of dose–response relationships or toxicity. There is no convincing evidence that daily intakes of up to 125 μg (5000 IU) elicit severe adverse effects [39]. It has been reported that an intake of 1250 μg (50,000 IU) once every 2 weeks for several years, equivalent to 89.3 μg (3571 IU) daily, did not cause hypercalcemia or other evidence of hypervitaminosis D [40]. Small studies showed that even a daily consumption of up to 250 μg (10,000 IU) of vitamin D over long periods did not cause adverse effects in healthy adults [32, 33], though some studies revealed a negative impact on bone mineral density by using high-dose vitamin D supplementation of 10,000 IU/day [11]. Nevertheless, supplementation of

>10,000 IU of vitamin D is rarely necessary in clinical practice.

As there is no evidence that increasing the recommended daily dose of vitamin D supplementation up to 50 µg (2000 IU) would cause severe side effects in the general population, and considering that 20 µg (800 IU) is the lowest dose consistently associated with a bone benefit, it seems reasonable to recommend a daily dose of 20–50 µg (800–2000 IU) (levels 2–4 evidence, grades B–D recommendation) [39]. In general, a daily vitamin D of 800 IU appears to be sufficient to achieve a target 25(OH)D level of at least 50 nmol/L (or 20 ng/mL) in most healthy individuals, whereas 2000 IU is sufficient to achieve a level of at least 75 nmol/L (or 30 ng/mL).

Some data suggest that a higher 25(OH)D level than 50 nmol/L (or 20 ng/mL) may be required for optimal risk reduction for various endpoints [41–44].

Toxicity

The use of vitamin D supplementation has increased substantially. Growing awareness of vitamin D in the general population, and over-the-counter vitamin D with partially very high doses, include the risk for uncontrolled use and exogenous hypervitaminosis D, resulting in high concentrations of serum 25(OH)D or free 1,25-dihydroxyvitamin D [1,25(OH)$_2$D], leading to hypercalciuria and finally hypercalcemia [45]. Reports of vitamin D overdose are rare in the literature. Serum 25(OH)D usually exceeds 375 nmol/l (or 150 ng/ml), and factors such as high-calcium intake contribute to the risk of hypercalcemia [46]. However, there are also endogenous causes of hypervitaminosis D, such as increased production of 1,25(OH)$_2$D as part of granulomatous disorders or lymphomas [47]. Having a long half-life in the tissues, vitamin D accumulation due to excessive intake lasts up to 18 months [48], and may cause chronic toxic effects such as nephrocalcinosis following hypercalcemia and hypercalciuria [47].

Since the 1930s, public health officials in the United States and the United Kingdom have recommended routine fortification of foods like milk to prevent vitamin D deficiency and low vitamin D status, which was expected to be an effective public health strategy [46]. However, there was an increased incidence of hypercalcemia due to massive intakes of vitamin D from various food fortifications. In some cases, hypercalcemia was associated with drinking vitamin D-fortified milk, revealing a fortification of up to 232,565 IU instead of standard 400 IU/quart, and consequently, prohibition of milk fortification [49]. However, current evidence suggests that vitamin D fortification prevents deficiency safely and effectively [50, 51]. Feeding animals might represent an additional source of vitamin D without compromising product quality. For example, consumption of vitamin D-enriched eggs from hens fed with additional vitamin D3 resulted in a zero prevalence <25 nmol/L, while the control group showed an usual seasonal decline in winter with 22% being <25 nmol/L [52]. The rationale and guidance for systematic vitamin D food fortification, including a call for action, has recently been published by an expert group of vitamin D scientists.

Selected RCTs in recent years

Several very large randomized controlled trials have been or are being performed in recent years. They are summarized in Table 2 [53–63].

Effect size and basic statistical principles

Though it appears attractive to dismiss any relevant effect of vitamin D on all the conditions that have been studied in those partly very large trials in recent years, it must be considered that often the basic principles for optimal design of a nutrient intervention study were not fulfilled [64], e.g., measurement of vitamin D at baseline and choosing vitamin D deficiency as an inclusion criterion, using a meaningful intervention able to change vitamin D status, and verification of vitamin D status improvement by repeat measurement.

Moreover, even in the largest trials including thousands of individuals, the sample size was still too small when mostly individuals without vitamin D deficiency and a low baseline risk were included. By modeling future intervention trials, Brenner et al. reported that several hundreds of thousands of participants would be necessary to be able to show an effect on mortality [65].

On the other hand, even a very small effect may be useful for a substance with such an excellent safety profile and low cost, especially when considering a public health approach. However, to show a small, but meaningful benefit on important outcomes like mortality or infections, very large population samples are needed, but such trials are very costly and will likely be scant.

Important systematic reviews and meta-analyses

The association of vitamin D supplementation on a number of endpoints including mortality has been explored in more detail in the last few years. Selected relevant systematic reviews and meta-analyses are summarized in Table 3 [16, 66, 67].

Table 2 Recent important vitamin D intervention trials (ongoing and finished).

Title	Methods	Intervention	Objectives/primary endpoint	Results	Comment
VITAL Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease. By Manson et al. [7, 53]	RCT, two-by-two factorial design	Vitamin D3 (cholecalciferol) at a dose of 2000 IU/day and marine n−3 (also called omega-3) fatty acids at a dose of 1 g/day.	Composite endpoint of incidence of invasive cancer or cardiovascular events among men 50 years of age or older and women 55 years of age or older.	During a median follow-up of 5.3 years, cancer was diagnosed in 1617 participants (793 in the vitamin D group and 824 in the placebo group; hazard ratio, 0.96; 95% confidence interval [CI], 0.88–1.06; $P = 0.47$). A major cardiovascular event occurred in 805 participants (396 in the vitamin D group and 409 in the placebo group; hazard ratio, 0.97; 95% CI, 0.85–1.12; $P = 0.69$) Supplementation with vitamin D did not result in a lower incidence of invasive cancer or cardiovascular events than placebo ($n = 25871$).	Only 1 in 8 had 25OHD <20 ng/ml! Placebo group was allowed to take 800 IU/day.
VIDA overview of results from the Vitamin D Assessment (ViDA) study. By Scragg [54, 55]	RCT	Vitamin D3 (2.5 mg or 100,000 IU) or placebo softgel oral capsules, mailed monthly to participants' homes, with two capsules sent in the first mail-out post-randomization (i.e., 200,000 IU bolus, or placebo), followed 1 month later (and thereafter monthly) with 100,000 IU vitamin D3 or placebo capsules.	Evaluate the efficacy of monthly vitamin D supplementation in reducing the incidence of a range of acute and chronic diseases and intermediate outcomes.	No effect of vitamin D on the cumulative incidence of CVD which occurred in 11.8% of the vitamin D group and 11.5% of placebo, yielding a hazard ratio of 1.02 (95% CI 0.87–1.20). No effect of vitamin D on the incidence of falls, with 51.7% in the vitamin D group and 52.7% in the placebo group reporting at least one fall, giving an adjusted hazard ratio for falls of 0.98 (95% CI 0.92–1.06). No effect of vitamin D on the incidence of fractures, which were observed in 6% of participants in the vitamin D arm and 5% in the placebo arm. The adjusted hazard ratio of fracture was 1.15 (95% CI 0.92–1.45) for vitamin D compared with placebo. In 328 incident cancer cases were identified, with the cumulative incidence being 6.5% in the vitamin D group and 6.4% in the placebo group. The adjusted hazard ratio was 1.01 (95% CI 0.81–1.25). No significant lung function improvements (vitamin D vs. placebo) in the total sample, vitamin D-deficient participants or asthma/COPD participants. no beneficial effects on arterial function.No beneficial effect of vitamin D supplementation on incidence of cardiovascular disease, falls, non-vertebral fractures and all cancer ($n = 5110$).	beneficial effects from vitamin D supplementation for lung function among ever smokers (especially if vitamin D deficient).
DO-HEALTH Vitamin D3-Omega-3-Home Exercise-Healthy Ageing and Longevity Trial. By Bischoff-Ferrari [56]	Interventional study	Simple home exercise program three times a week and to take regular supplements of vitamin D and/or Omega-3 fatty acids and/or placebo.	Fracture risk, cognitive function, blood pressure, lower extremity function, and rate of infection. Further key endpoints include rate of falls, joint health (osteoarthritis), sarcopenia, frailty, oral and dental health, glucose metabolism and diabetes, major cardiovascular events, maintenance of autonomy, and quality of life.	Instead of the planned 3000 patients, 1078 patients were included with a baseline 25-hydroxyvitamin D level <20 ng/ml or 50 nmol/l. The 90-day mortality was 23.5% in the vitamin D group (125 of 531 patients) and 20.6% in the placebo group (109 of 528 patients) (difference, 2.9 percentage points; 95% CI, −2.1 to 7.9; $P = 0.26$). There were no clinically important differences between the groups with respect to secondary clinical, physiological, or safety end points.	No results available.
FIND Finnish Vitamin D Trial. By Tuomainen et al. [57]	RCT	3 groups with 6000 in each, with daily supplementation of either: (1) 40 μg/day (1600 IU) of vitamin D3, (2) 80 μg/day (3200 IU) of vitamin D3, or (3) placebo.	Cardiovascular disease [Time Frame: 5 years] CVD incidence in Vitamin D arms vs. placebo arm. Cancer [Time Frame: 5 years] Cancer incidence in Vitamin D arms vs.placebo arm.	Recruitment completed. ($n = 2495$). Last update on https://clinicaltrials.gov, October 2018 Blood samples were collected for assessment of effect modification by baseline 25-hydroxyvitamin D, as well as for future ancillary studies of genetic/biochemical hypotheses.	No results available.
AMATERASU Effect of Vitamin D Supplementation on Relapse-Free Survival Among Patients With Digestive Tract Cancers; The AMATERASU Randomized Clinical Trial. By Urashima et al. (2019)	RCT	Oral supplemental capsules of vitamin D (2000 IU/day); or placebo.	Relapse or death in patients with digestive tract cancers overall and in subgroups stratified by 25-hydroxyvitamin D (25[OH]D) levels.	Relapse or death occurred in 50 patients (20%) randomized to vitamin D and 43 patients (26%) randomized to placebo. Death occurred in 37 (15%) in the vitamin D group and 25 (15%) in the placebo group. The 5-year relapse-free survival was 77% with vitamin D vs. 69% with placebo (hazard ratio [HR] for relapse or death, 0.76; 95% CI, 0.50–1.14; $P = 0.18$). The 5-year overall survival in the vitamin D vs. placebo groups was 82% vs. 81% (HR for death, 0.95; 95% CI, 0.57–1.57; $P = 0.83$). Among patients with digestive tract cancer, vitamin D supplementation, compared with placebo, did not result in significant improvement in relapse-free survival at 5 years ($n = 166$).	

Table 2 (continued)

Title	Methods	Intervention	Objectives/primary endpoint	Results	Comment
VIDAL Vitamin D and Longevity (VIDAL) Trial: Randomized Feasibility Study. By Peto et al. [58]	RCT	100,000 IU monthly (average 3300 IU/day) of oral vitamin D3 or double-blind placebo control or 100,000 IU monthly (average 3300 IU/day) of oral vitamin D3 or open control.	Overall mortality in men and women aged 65–84.	Results not available (planned $n = 375$) ($n = 1615$).	Bolus dose has been shown to be problematic, especially at intervals longer than 1 week.
VDOP The Vitamin D in Older People. By Schoenmakers et al. (2013) [59]	RCT	Monthly oral dosing with 12,000 IU, 24,000 IU or 48,000 IU of vitamin D3.	Plasma 25OHD concentration required to maintain bone health and to develop a set of biochemical markers that reflects the effect of vitamin D on bone.	Results not available (planned $n = 375$).	None.
D2D Vitamin D Supplementation and Prevention of Type 2 Diabetes. Pittas et al. [6]	RCT	4000 IU/day of vitamin D3 or placebo.	New-onset diabetes trial design was event-driven, with a target number of diabetes events of 508.	After a median follow-up of 2.5 years, the primary outcome of diabetes occurred in 293 participants in the vitamin D group and 323 in the placebo group (9.39 and 10.66 events per 100 person-years, respectively). The hazard ratio for vitamin D as compared with placebo was 0.88 (95% confidence interval, 0.75–1.04; $P = 0.12$). Among persons at high risk for type 2 diabetes not selected for vitamin D insufficiency, vitamin D3 supplementation at a dose of 4000 IU per day did not result in a significantly lower risk of diabetes than placebo ($n = 2423$).	Inclusion regardless of the baseline serum 25-hydroxyvitamin D level! (27.7 ng/ml at baseline in the vitamin D and 28.2 ng/ml in the placebo group!).
SUNSHINE Effect of High-Dose vs. Standard-Dose Vitamin D3 Supplementation on Progression-Free Survival Among Patients With Advanced or Metastatic Colorectal Cancer. By Kimmie et al. [60]	RCT	mFOLFOX6 plus bevacizumab chemotherapy every 2 weeks and either high-dose vitamin D3 ($n = 69$) or standard-dose vitamin D3 ($n = 70$) daily until disease progression, intolerable toxicity, or withdrawal of consent.	Progression-free survival (PFS) in patients with advanced or metastatic colorectal cancer.	The median progression-free survival for high-dose vitamin D3 was 13.0 months (95% CI, 10.1–14.7; 49 PFS events) vs. 11.0 months (95% CI, 9.5–14.0; 62 PFS events) for standard-dose vitamin D3 (log-rank $P = 0.07$); multivariable hazard ratio for PFS or death was 0.64 (1-sided 95% CI, 0–0.90; $P = 0.02$). There were no significant differences between high-dose and standard-dose vitamin D3 for tumor ORR (58% vs. 63%, respectively). Among patients with metastatic CRC, addition of high-dose vitamin D3, vs. standard-dose vitamin D3, to standard chemotherapy resulted in a difference in median PFS that was not statistically significant, but with a significantly improved supportive hazard ratio. ($n = 139$).	
Effect of Higher vs. Standard Dosage of Vitamin D3 Supplementation on Bone Strength and Infection in Healthy Infants A Randomized Clinical Trial. By Rosendahl et al. [61]	RCT	400 or 1200 IU of vitamin D3 daily from age 2 weeks to 24 months.	Bone strength and incidence of parent-reported infections at 24 months.	We found no differences between groups in bone strength measures, including bone mineral content (mean difference, 0.4 mg/mm; 95% CI, −0.8 to 1.6), mineral density (mean difference, 2.9 mg/cm3; 95% CI, −8.3 to 14.2), cross-sectional area (mean difference, −0.9 mm2; 95% CI, −5.0 to 3.2), or polar moment of inertia (mean difference, −66.0 mm4, 95% CI, −274.3 to 142.3). Bone strength measurements for total bone and cortical bone did not differ between groups. No differences of infection between groups (incidence rate ratio [IRR], 1.00; 95% CI, 0.93–1.06) A vitamin D3 supplemental dose of up to 1200 IU in infants did not lead to increased bone strength or to decreased infection incidence. Daily supplementation with 400 IU vitamin D3 seems adequate in maintaining vitamin D sufficiency in children younger than 2 years ($n = 975$).	These findings imply that a daily dose of 1200 IU of vitamin D3 in this age group is safe, but even 400 IU will maintain vitamin D sufficiency in most children.
Effect of Monthly, High-Dose, Long-Term Vitamin D Supplementation on Central Blood Pressure Parameters: A Randomized Controlled Trial Substudy. By Sluyter et al. [62]	RCT substudy	Vitamin D3 200,000 IU (initial dose) followed 1 month later by monthly 100,000-IU doses ($n = 256$) or (2) placebo monthly ($n = 261$).	Effects of monthly, high-dose, long-term (≥1-year) vitamin D supplementation on central blood pressure (BP).	Mean depersonalized 25-hydroxyvitamin D increased from 66 nmol/L (SD: 24) at baseline to 122 nmol/L (SD: 42) at follow-up in the vitamin D group, with no change in the placebo group. Monthly, high-dose, 1-year vitamin D supplementation lowered central BP parameters among adults with vitamin D deficiency but not in the total sample ($n = 517$).	Benefit of vitamin D only among adults with vitamin D deficiency but not in the total sample. Largely replete population Bolus dose.

Table 2 (continued)

Title	Methods	Intervention	Objectives/primary endpoint	Results	Comment
VITDAL-ICU Effect of high-dose vitamin D3 on hospital length of stay in critically ill patients with vitamin D deficiency: the VITdAL-ICU randomized clinical trial. By Amrein et al. [112]	RCT	Patients with vitamin D deficiency (≤20 ng/mL) assigned to receive either vitamin D3 or a placebo.	Vitamin D3 or placebo was given orally or via nasogastric tube once at a dose of 540,000 IU followed by monthly maintenance doses of 90,000 IU for 5 months.	Length of hospital stay was not significantly different between groups (20.1 days [IQR, 11.1–33.3] for vitamin D3 vs. 19.3 days [IQR, 11.1–34.9] for placebo; $P = 0.98$). Hospital mortality and 6-month mortality were also not significantly different (hospital mortality: 28.3% [95% CI, 22.6–34.5%] for vitamin D3 vs. 35.3% [95% CI, 29.2–41.7%] for placebo; hazard ratio [HR], 0.81 [95% CI, 0.58–1.11]; $P = 0.18$; 6-month mortality: 35.0% [95% CI, 29.0–41.5%] for vitamin D3 vs. 42.9% [95% CI, 36.5–49.4%] for placebo; HR, 0.78 [95% CI, 0.58–1.04]; $P = 0.09$). ($n = 475$).	
VIOLET Vitamin D to Improve Outcomes by Leveraging Early Treatment. By PETAL Network [111]	RCT	Single dose of 540,000 IU of vitamin D3 vs. Placebo.	Patients with vitamin D deficiency (levels <20 ng/mL) and at high risk for ARDS and 90-day mortality.	Results not available (planned $n = 3000$, actual ca. 1400). Last update on https://clinicaltrials.gov September 2019.	Stopped prematurely at the first interim analysis (ca. $n = 1400$). One loading dose only, no follow-up medication, and primary endpoint 90-day mortality Substantially less severely ill population compared with previous ICU studies.
VITDALIZE Effect of High-dose Vitamin D3 on 28-day Mortality in Adult Critically Ill Patients (VITDALIZE). By Amrein et al. (Protocol in BMJ Open NOV 2019) [113]	RCT	Oral dose of vitamin D3 (540,000 IU loading followed by 4000 IU daily for 3 months) or placebo.	28-day mortality in adult critically ill patients with severe vitamin D deficiency (≤12 ng/ml or undetectable).	Recruitment ongoing (planned=2400).	Including only patients with severe vitamin D deficiency (≤12 ng/ml or undetectable).

NA not applicable, *RCT* randomized controlled trial, *IU* International units, *CVD* cardiovascular disease

Table 3 Selected important systematic reviews and meta-analyses.

Title	Methode	Intervention	Objectives/primary endpoint	Results	Conclusion	Comment
Association between vitamin D supplementation and mortality: systematic review and meta-analysis. By Zhang et al. [3]	Systematic review	Randomized controlled trials comparing vitamin D supplementation with a placebo or no treatment for mortality were included.	To investigate whether vitamin D supplementation is associated with lower mortality in adults.	52 trials with a total of 75,454 participants were identified. Vitamin D supplementation was not associated with all-cause mortality (RR 0.98, 95% CI 0.95–1.02), cardiovascular mortality (RR 0.98, 95%CI 0.88 to 1.08), or non- cancer, non-cardiovascular mortality (RR 1.05, 95% CI 0.93 to 1.18). Vitamin D supplementation statistically significantly reduced the risk of cancer death (RR 0.84, 95% CI 0.74 to 0.95). In subgroup analyses, all-cause mortality was significantly lower in trials with vitamin D3 supplementation than in trials with vitamin D2 supplementation (P for interaction = 0.04).	Vitamin D supplementation alone was not associated with all-cause mortality in adults compared with placebo or no treatment. Vitamin D supplementation reduced the risk of cancer death by 16%. Additional large clinical studies are needed to determine whether vitamin D3 supplementation is associated with lower all-cause mortality.	
Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. By Martineau et al. [16]	Systematic review	Randomized, double-blind, placebo-controlled trials of supplementation with vitamin D3 or vitamin D2 of any duration were eligible for inclusion if they had been approved by a research ethics committee, and if data on the incidence of acute respiratory tract infection were collected prospectively and prespecified as an efficacy outcome.	To assess the overall effect of vitamin D supplementation on risk of acute respiratory tract infection.	25 eligible randomized controlled trials (total 11,321 participants, aged 0–95 years) were identified. Vitamin D supplementation reduced the risk of acute respiratory tract infection among all participants (OR 0.88, 95% CI 0.81–0.96; P for heterogeneity <0.001). The best effects could be shown at daily or weekly vitamin D without additional bolus doses (OR 0.81, 95% CI 0.72 to 0.91), but not in those receiving one or more bolus doses (OR 0.97, 95% CI 0.86 to 1.10). The protective effects were stronger in those with baseline 25-hydroxyvitamin D levels <25 nmol/L (OR 0.30, 95% CI 0.17– 0.53) than in those with baseline 25-hydroxyvitamin D levels ≥25 nmol/L (OR 0.75, 95% CI 0.60–0.95).	Vitamin D supplementation was safe and it protected against acute respiratory tract infection overall. Patients who were very vitamin D deficient and those not receiving bolus doses experienced the most benefit.	Patients who were severely vitamin D deficient and those not receiving bolus doses experienced the most benefit.
Vitamin D and vitamin D analogs for preventing fractures in post-menopausal women and older men. By Avenell et al. [66]	Systematic review	Randomized or quasi-randomized trials that compared vitamin D or related compounds, alone or with calcium, against placebo, no intervention or calcium alone, and that reported fracture outcomes in older people. The primary outcome was hip fracture.	To determine the effects of vitamin D or related compounds, with or without calcium, for preventing fractures in post-menopausal women and older men.	In total, 53 trials with a total of 91,791 participants were included. A high-quality evidence was found that vitamin D alone is unlikely to be effective in preventing hip fracture (11 trials, 27,693 participants; RR 1.12, 95% CI 0.98–1.29) or any new fracture (15 trials, 28,271 participants; RR 1.03, 95% CI 0.96–1.11). Also a high-quality evidence was shown that vitamin D plus calcium results in a small reduction in hip fracture risk (9 trials, 49,853 participants; RR 0.84, 95% CI 0.74–0.96; p = 0.01). Also a high- quality evidence was found that vitamin D plus calcium reduces the risk of any type of fracture (10 trials, 49,976 participants; RR 0.95, 95% CI 0.90– 0.99). Mortality was not adversely affected by either vitamin D or vitamin D plus calcium.	Vitamin D alone is unlikely to prevent fractures in the doses and formulations tested so far in older people. Supplements of vitamin D and calcium may prevent hip or any type of fracture. There was a small but significant increase in gastrointestinal symptoms and renal disease associated with vitamin D and calcium. This review found that there was no increased risk of death from taking calcium and vitamin D.	In high-risk populations (residents in institutions with an estimated 54 hip fractures per 1000 per year), this equates to nine fewer hip fractures per 1000 older adults per year (95% CI 2– 14).

Table 3 (continued)

Title	Methode	Intervention	Objectives/primary endpoint	Results	Conclusion	Comment
Vitamin D supplementation for chronic liver diseases in adults. By Bjelakovic et al. [67]	Systematic review	Randomized clinical trials that compared vitamin D at any dose, duration, and route of administration vs. placebo or no intervention in adults with chronic liver diseases.	Assess the beneficial and harmful effects of vitamin D supplementation in people with chronic liver diseases.	supplementation (29 trials, 71,032 participants, RR 0.97, 95% CI 0.93–1.01). In total, 15 randomized clinical trials with 1034 participants were included. Participants in six trials had baseline 25-hydroxyvitamin D levels at or above vitamin D adequacy (20 ng/mL), while participants in the remaining nine trials were vitamin D insufficient (<20 ng/mL). The effect of vitamin D on all-cause mortality at the end of follow-up is uncertain because the results were imprecise (Peto OR 0.70, 95% CI 0.09–5.38). The effect of vitamin D on liver-related mortality, and on serious adverse events such as hypercalcemia, myocardial infarction, and thyroiditis, is uncertain because the results were imprecise.	Authors are uncertain as to whether vitamin D supplements in the form of vitamin D3, vitamin D2, 1,25-dihydroxyvitamin D, or 25-dihydroxyvitamin D have important effect on all-cause mortality, liver-related mortality, or on serious or non-serious adverse events because the results were imprecise. There is no evidence on the effect of vitamin D supplementation on liver-related morbidity and health-related quality of life.	Only few trials with an insufficient number of participants, high risk of bias with significant intertrial heterogeneity.

Selected target organs, conditions, and endpoints

Mortality

Vitamin D deficiency has been strongly associated with various health outcomes, including all-cause mortality [68]. A 2014 Cochrane meta-analysis showed a relevant and significant lower all-cause mortality of ~7% and cancer mortality of ~13% in patients who received vitamin D3 [69]. The results of a meta-analysis by using individual participant data conducted by Gaksch et al., analyzing almost 17,000 individuals, showed a strong association between low 25(OH)D and increased risk of all-cause mortality [70]. Using a Mendelian randomization with genetic variants in the vitamin D synthesis pathway, the analysis of Aspelund et al. supports a causal relationship between vitamin D deficiency and increased all-cause mortality. However, despite a cohort of >10,000 participants, it was still too underpowered to confirm a causal relationship [71].

Lung

The effect of vitamin D on the lungs has a strong rationale, demonstrated by basic science, due to its immunomodulant, anti-inflammatory, and anti-infective role that has been highlighted in patients with community-acquired infections, acute respiratory failure, as well as in lung transplantation recipients (this is a very specific model for severe infective and inflammatory lung disease) [21].

Vitamin D supplementation reveals direct anti-inflammatory properties in the lungs. This is due to local inhibition of nuclear factor-κB and mitogen-activated protein kinase activity, reducing the secretion of inflammatory cytokines and chemokines involved in the lung inflammatory process and extravascular leaking, such as interleukin (IL)-1β, IL-6, and IL-8. This, in turn, also influences the number of inflammatory cells infiltrating the interstitial space [72]. Moreover, $1,25(OH)_2D$ is also implicated in the reduction of oxidative stress by inhibiting anti-protease activity, and acting on the nuclear factor erythroid-related factor 2, a transcriptional regulator of most antioxidant genes. Moreover, vitamin D acts with well-known anti-infectious properties by increasing proliferation of monocytes to macrophages (acting as a fine-tuner of the innate and adaptive immunity), and determining a transcriptional upregulation of cathelicidin also in the airway epithelial cells. Finally, $1,25(OH)_2D$ inhibits the expression of several metalloproteinases in airway smooth-muscle cells and alveolar macrophages, thus being involved in the tissue remodeling pathway by regulating the process of bronchial airway muscle activation and extracellular matrix deposition

by fibroblasts. All these complex pathways, partially modified by vitamin D, warrant supplementation in patients with respiratory disease. Significant benefits have already been shown in adults and children with asthma, and for the prevention of respiratory tract infections, particularly in severe vitamin D deficiency.

Sepsis

Sepsis, a complication of severe infection, is characterized by signs of systemic inflammation expressed with failure of organs often remote from the site of the initial infection. Septic patients have high mortality and lower circulating levels of vitamin D. The interest in vitamin D for infection has risen after the recognition of the expression of the vitamin D receptor, ubiquitous in cells of the innate and adaptive immune system. Vitamin D is an important link between Toll-like receptor activation and antibacterial responses. The in vivo supplementation of a high dose of cholecalciferol (400.000 IU as a single bolus) in the early stage of sepsis and septic shock has been shown able to safely and rapidly increase the level of vitamin D, as well as the circulating level of cathelicidin, a vitamin D-dependent endogenous anti-microbial and endotoxin-binding peptide largely found in human neutrophils [73]. These findings were corroborated by the significant reduction of IL-1β and IL-6, which play important roles in the early inflammatory response.

Organ transplantation recipients

Several studies have highlighted that lower 25(OH)D levels are associated with prolonged hospitalization and mortality, also in the postsurgical setting. Given its wide immuno-biological effects, vitamin D has been frequently considered a potential modulating factor after solid organ (and stem cell) transplantation (mainly liver, kidney, and lung). The transplantation recipient population is particularly prone to infections, mainly in the early stage after transplantation, due to immunomodulation/chronic immunosuppressive therapy and to long-term bone dysfunction. The recipients of solid organ transplantation are, by definition, vitamin D insufficient for manifold reasons, including limited sunlight exposure, limited physical activity, reduced dietary intake of vitamin D in food, as well as liver and kidney dysfunction according to their main disease. As an example, in liver transplantation recipients (a group of patients with very low vitamin D levels), osteoporosis has a high prevalence, with a large decline in bone mineral density in the first year after transplantation. Moreover, a negative association between low vitamin D levels and graft function, as well as a role of vitamin D in reducing the recurrence of hepatitis C virus infection, has been demonstrated. Several interventional trials on vitamin D supplementation in lung and kidney recipients are ongoing under the hypothesis that vitamin D supplementation may contribute to reducing the occurrence of rejection by it immunomodulating action.

Pregnancy

In 2019, two Cochrane analyses on vitamin D and pregnancy were published. They suggested that vitamin D supplementation may reduce gestational diabetes, low birthweight, and preeclampsia, but a higher than currently recommended dose appeared to have no additional benefit except for possible further reduction of gestational diabetes [74, 75]. However, several studies in recent years have highlighted that women are at high risk for vitamin D deficiency, and this is associated with adverse pregnancy outcomes, including preeclampsia and gestational diabetes [76–80]. It has been demonstrated that vitamin D supplementation is able to reduce adverse pregnancy outcomes when a higher level is achieved, with an increasing efficacy when the target level is raised from 20 to 40 ng/mL or 50 ng/mL. Interestingly, the maximum change is achieved 6–8 weeks after initiating the treatment, likely exerting the genomic actions of vitamin D [81–83]. Three major adverse pregnancy outcomes appear to improve with vitamin D supplementation: a 60% reduction in preeclampsia, a 50% reduction in gestational diabetes, and a 40% reduction in preterm delivery [84]. These data are consistent with previous work on the topic [82]. Moreover, following the genomic and epigenetic effects of vitamin D supplementation, vitamin D deficiency during pregnancy also seems able to induce specific genomic pathways relevant to autoimmune disease in childhood and later in life [85, 86]. The placenta can convert 25(OH)D to the active form 1,25(OH)$_2$D, similarly to the kidneys; therefore, more basic research should shed light in the future on the specific vitamin D metabolism during pregnancy [85]. The FDA has recently approved the statement "Pregnant women who have higher serum vitamin D levels have a decreased risk of preterm birth."

Taking into account the recent literature, vitamin D deficiency is associated with worse outcomes during pregnancy, and at least 400–600 IU of daily vitamin D supplementation is reasonable for women with a vitamin D level <40 ng/mL, with higher required doses in more severe deficiency.

Cancer

Vitamin D supplementation as a strategy for preventing cancer was considered, as results from several observational studies suggested an association between vitamin D deficiency and risk for several types of cancer [87]. It was

already assumed in 1980 that calcitriol could inhibit the growth of malignant melanoma cells [88]. Ecologic studies revealed a decreased cancer mortality in areas with greater sun exposure [11]. Over the decades, vitamin D and its anticancer action was investigated for various malignancies resulting in mixed findings [89]. Hence, the cancer-protective effect of vitamin D remained unclear. In 2014, two meta-analyses revealed no significant decrease in the incidence of cancer in association with vitamin D supplementation, but a significant reduction in the rate of death from cancer [90, 91]. However, as most of the data derive from observational studies, correlation does not imply causation. Investigating cancer incidence following vitamin D plus calcium supplementation, Lappe et al. revealed a non-, but nearly significant (hazard ratio 0.70; 95% CI 0.47–1.02) 30% risk reduction compared with placebo [92]. A recent large RCT using a daily dose of 2000 IU vitamin D3 conducted by Manson et al. [7], analyzing the incidence of cancer following vitamin D supplementation in over 25,000 participants, did not reveal a significant reduction neither of invasive cancer of any type nor in the rate of death from any cause. However, subgroup analyses revealed a significant lower cancer incidence in normal-weight individuals. Considering that the study was not adjusted for this comparison, this finding should be considered hypothesis-generating. An ongoing long-term RCT [93], investigating vitamin D supplementation and the incidence of cancer and precancerous lesions in a high-risk population (overweight adults with prediabetes), will provide further and important data on the causality.

Diabetes

Several studies demonstrated a link between 25(OH)D levels and diabetes, and revealed a higher frequency of vitamin D deficiency in patients with type 1 diabetes mellitus (T1DM) compared with healthy individuals [94–97]. Investigating prenatal vitamin D exposure of the fetus, a lower gestational 25(OH)D level [98] or avoiding vitamin D-fortified food [99] was significantly associated with higher risk of developing T1DM. In infancy, vitamin D supplementation [100] or vitamin D-fortified margarine [99] was shown to reduce the risk of developing type 1 diabetes mellitus. The effect of vitamin D supplementation on T1DM onset seems to be dependent on life stage. Supplementation between 7 and 12 months of age resulted in an almost twofold lower risk of developing T1DM compared with earlier supplementation [101]. In adolescents, many studies revealed no association between 25(OH)D level and onset of T1DM [102–104]. However, there is a clear effect of vitamin D in young adults, as low 25(OH)D levels were significantly associated with developing T1DM [105]. However, according to the available literature, the cause-

and-effect relationship is inconclusive. On the other hand, diabetes per se results in physiological changes too, such as increased renal elimination of vitamin D-binding protein compared with healthy individuals [106]. Therefore, the value of hypovitaminosis D as a trigger for developing T1DM remains unclear. Vitamin D deficiency was also shown to have a negative impact on insulin resistance [107]. Hence, a higher risk of developing type 2 diabetes mellitus (T2DM) in individuals with low 25(OH)D levels was assumed. However, vitamin D supplementation did overall not result in a lower risk of developing T2DM [6, 108]. In the recent D2D study by Pittas et al., vitamin D did not significantly reduce new onset of diabetes, but vitamin D deficiency was no inclusion criterion, and only a minority of included patients had a 25(OH)D level <50 nmol//L (or 20 ng/mL). Moreover, the hypothesized treatment effect used for the sample size calculation was relatively large (hazard ratio 0.75 for the vitamin D group). The actual hazard ratio for vitamin D as compared with placebo was 0.88 (95% confidence interval, 0.75–1.04; $P = 0.12$). Interestingly, the effect appeared to be stronger in patients with a BMI <30. However, a post hoc subgroup analysis of individuals with a 25(OH)D level below 12 ng/ml (30 nmol/l) revealed a significantly reduced risk of developing T2DM (hazard ratio 0.38; 95% CI, 0.18–0.80).

Musculoskeletal effects of vitamin D

The detrimental effects of vitamin D deficiency on the musculoskeletal system were the first visible mode of action that was attributed to vitamin D (i.e., rickets in children).

The necessity of an adequate vitamin D status for muscle and bone health is undebated, and therefore not discussed in detail in this review.

Vitamin D intoxication and hypersensitivity

Vitamin D intoxication is rare and usually only occurs at very high supplementation doses [109]. However, various mutations in vitamin D metabolizing enzymes that may lead to increased sensitivity to standard vitamin D supplementation or even endogenous vitamin D intoxication with hypercalcemia, hypercalciuria, and nephrocalcinosis/chronic renal insufficiency have been described [110]. Typically, these mutations affect CYP24A1, the enzyme that catabolizes 1,25OHD2 to the inactive metabolite 24,25OHD2. Therefore, a diagnosis can be made by using the ratio of 24,25:25 D and does not necessarily require genetic testing.

This condition has been termed idiopathic infantile hypercalcemia, but due to the greatly varying clinical phenotypes, patients may well become symptomatic only in

adulthood. Currently, no causal treatment is available, but avoidance of a high-calcium diet, UV-B exposure, and vitamin D or calcium supplements is advised.

The future

Vitamin D deficiency is highly prevalent, but the literature to support vitamin D supplementation is unsatisfactory to date. Unless major funding sources are used for vitamin D research, it appears sensible to focus on vitamin D-deficient populations with a high event rate. Vitamin D is clearly not a panacea, but may be an important, inexpensive, and safe adjuvant therapy for many diseases and stages of life, including pregnancy, childhood, and old age. Public health efforts to prevent severe vitamin D deficiency should therefore be further promoted.

In the critically ill setting, one large vitamin D supplementation trial has recently been published (VIOLET [111]) and one is still ongoing (NCT03096314 and NCT03188796). VIOLET randomized patients with 25 (OH)D levels below 50 nmol/L (or 20 ng/ml) "at risk for ARDS" to one single high dose of vitamin D3 (540,000 IU), and evaluated its effect on the primary outcome: 90-day mortality. It was prematurely stopped in mid-2018 after inclusion of ca. One-third of the patients originally planned, and no differences in mortality and secondary endpoints have been reported, with no differences in subgroup analyses and safety endpoints [111].

VITDALIZE is a European multicenter RCT, including severely vitamin D-deficient ICU patients with a 25 OH D level <30 nmol/L (or 12 ng/ml), and randomizes patients to a loading dose of oral/enteral vitamin D3 (540,000 IU) followed by 4000 IU daily for 90 days, with the primary outcome being 28-day mortality. Recruitment is ongoing in Austria and Belgium, should be expanded to other European countries in 2020, and will likely continue for a few more years.

Compliance with ethical standards

Conflict of interest KA has received speaker honoraria and an unrestricted grant from Fresenius Kabi. The other authors declare that they have no conflict of interest.

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