REVIEW

Vitamin D testing and treatment: a narrative review of current evidence

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Abstract

Vitamin D testing and treatment is a subject of controversial scientific discussions, and it is challenging to navigate through the expanding vitamin D literature with heterogeneous and partially opposed opinions and recommendations. In this narrative review, we aim to provide an update on vitamin D guidelines and the current evidence on the role of vitamin D for human health with its subsequent implications for patient care and public health issues. Vitamin D is critical for bone and mineral metabolism, and it is established that vitamin D deficiency can cause rickets and osteomalacia. While many guidelines recommend target serum 25-hydroxyvitamin D (25[OH]D) concentrations of ≥50 nmol/L (20 ng/mL), the minimum consensus in the scientific community is that serum 25(OH)D concentrations below 25–30 nmol/L (10–12 ng/mL) must be prevented and treated. Using this latter threshold of serum 25(OH)D concentrations, it has been documented that there is a high worldwide prevalence of vitamin D deficiency that may require public health actions such as vitamin D food fortification. On the other hand, there is also reason for concern that an exploding rate of vitamin D testing and supplementation increases costs and might potentially be harmful. In the scientific debate on vitamin D, we should consider that nutrient trials differ from drug trials and that apart from the opposed positions regarding indications for vitamin D treatment we still have to better characterize the precise role of vitamin D for human health.

Introduction

Vitamin D is critical for bone and mineral metabolism and is effective in the prevention and treatment of rickets and osteomalacia (1, 2, 3, 4, 5). Given that vitamin D receptors (VDRs) are expressed in almost every tissue and cell, there have been numerous investigations on potential extra-skeletal effects of vitamin D (6, 7, 8, 9, 10, 11, 12, 13, 14). Epidemiological studies showed that low 25-hydroxyvitamin D (25[OH]D) concentrations are associated with various acute and chronic diseases, thus raising a high interest in vitamin D (15, 16). Randomized controlled trials (RCTs) have, however, largely failed to show significant effects of vitamin D supplementation on various health outcomes (17, 18, 19, 20). As a consequence, there are nowadays controversial scientific discussions

and heterogeneous approaches in clinical routine and in public health actions regarding vitamin D testing and treatment (17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28).

In this brief narrative review, we give an overview on clinical and nutritional vitamin D guidelines and summarize the current evidence on the role of vitamin D for human health with its subsequent implications for patient care and public health issues. We start with a brief introduction on vitamin D physiology and its clinical effects and summarize nutritional clinical vitamin D guidelines. Then, we provide some insights and guidance regarding vitamin D testing and supplementation, followed by a critical appraisal of vitamin D research. Finally, we present our conclusions with an outlook on future directions in the field of vitamin D.

Vitamin D physiology

Vitamin D was initially described as a substance that was able to cure rickets and was termed 'D' as it was the fourth in the sequence of vitamins discovered (29). The main two isoforms are vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol) that share a similar metabolism so that we will not differentiate between these isoforms unless otherwise stated. It has been roughly estimated that ultraviolet-B (UV-B)-induced production of vitamin D in the skin accounts for about 80% of vitamin D supply, whereas dietary intake (e.g. fish, eggs or vitamin D-fortified food) plays usually only a minor role (30). The vitamin D supply from different sources is of course subject to significant variation based on genetic, environmental and lifestyle factors (30, 31, 32, 33). Classification of vitamin D status is based on serum 25(OH)D that is mainly derived from hydroxylation of vitamin D in the liver. Compared to vitamin D, 25(OH)D has a much higher serum concentration and a longer half-life (about 3 weeks versus 1 day) and is therefore considered the best parameter to indicate vitamin D supply from all different sources. 1,25-dihydroxyvitamin D (1,25[OH]2D) is the so-called active vitamin D hormone or calcitriol that has the highest affinity to the almost ubiquitously expressed VDR. Serum concentrations of 1,25(OH)2D are mainly derived from renal hydroxylation of 25(OH)D and are rather dependent on regulators of mineral metabolism (e.g. parathyroid hormone (PTH), phosphate or fibroblast growth factor-23 (FGF-23)) or kidney function, than on substrate availability of 25(OH) D, so that they do not well reflect vitamin D supply. In the circulation, vitamin D metabolites are mainly bound to vitamin D-binding protein (DBP) and to a lesser extent to albumin and lipoproteins with only a small fraction (less than 1%) circulating in its unbound (free) form (34). Although some tissues can take up DBP-bound vitamin D metabolites by the megalin–cubilin system, most cells seem to be dependent on free vitamin D metabolites that diffuse through the cell membrane to get access to the intracellularly located VDR. Therefore, measurements of free 25(OH)D might be useful in special conditions with significantly altered DBP levels (e.g. pregnancy, liver cirrhosis or hormonal contraceptive intake), but more data are needed to clarify the clinical significance of free 25(OH)D (34, 35). Vitamin D catabolism is initiated by 24-hydroxylation of vitamin D metabolites that are finally excreted in the bile and urine. For a more detailed description of vitamin D metabolism, we refer the reader to other excellent reviews (1, 6, 14, 22) (Fig. 1).

Clinical effects of vitamin D

Physiologic effects of vitamin D and its metabolites are mainly exerted by binding to the VDR with subsequent downstream regulation of hundreds of genes, but there are also non-genomic rapid effects including a direct stabilizing effect on the endothelium (1, 36). Vitamin D has a critical role in the regulation of calcium and phosphate metabolism by effects on the intestine, bone and the kidneys. Breaking it down to a simple concept, an adequate vitamin D status is required to maintain normal calcium and phosphate levels and prevents secondary hyperparathyroidism. In this context, vitamin D is particularly important for optimal intestinal calcium absorption and exerts major effects on bone by maintaining mineral homeostasis but also by direct pleiotropic effects on bone cells (37, 38). Historically, the discovery of vitamin D was essential for the successful prevention and treatment of epidemic rickets in the early 20th century (39). This was achieved by increasing the vitamin D supply to the general population by public health actions such as intake of cod liver oil, UV radiation, vitamin D food fortification and, finally, also vitamin D supplementation (39). Nutritional rickets is characterized by bone deformities (Fig. 2) as a result of reduced apoptosis of hypertrophic chondrocytes in the growth plate and reduced mineralization (2, 3, 4, 5, 39). Additional symptoms are muscle weakness and developmental delay, and in severe cases, rickets may be fatal due to life-threatening heart failure and cardiac arrest (2, 3, 4, 5, 39). While vitamin D deficiency can cause rickets in bones with
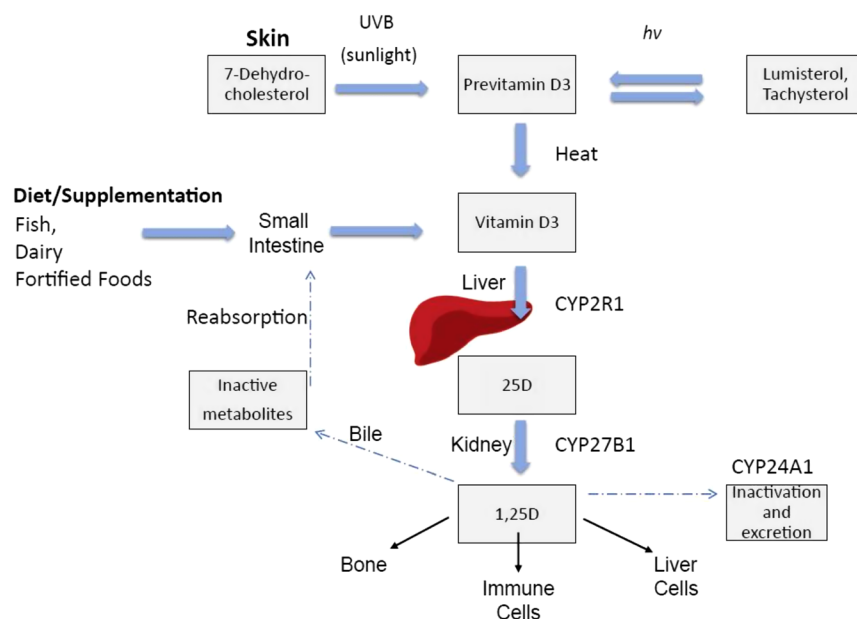
Figure 1
Vitamin D endogenous synthesis and metabolism. Endogenous vitamin D synthesis occurs primarily through sunlight exposure which produces pre-vitamin D3. It is hydroxylated in the liver and then in the kidney, producing 1,25D (1,25 dihydroxyvitamin D), the physiologically active form of vitamin D which acts in target sites in bone and immune cells, as well as liver cells. Abbreviations: CYP (cytochrome P450), UV-B (ultraviolet-B), hν (denotes photochemical reaction). Reproduced from Keane *et al*. (14) under the terms of the CC Attribution 4.0 International (CC BY 4.0) licence.

open growth plates, osteomalacia constitutes defective mineralization of existing bone leading to reduced bone stiffness and is frequently associated with bone pain and muscle weakness (4, 40). Treatment of nutritional rickets and osteomalacia with vitamin D plus calcium is associated with great improvements of bone mineral density (BMD), but data from RCTs and meta-analyses on vitamin D supplementation in unselected populations show either no or only slight increases in BMD (41, 42, 43, 44, 45). In subgroup analyses of RCTs, it has been documented that moderate improvements of BMD by vitamin D supplementation may be restricted to individuals with 25(OH)D serum concentrations ≤30 nmol/L (multiply by 2.496 to convert ng/mL to nmol/L) with no significant effect at higher 25(OH)D levels (43, 44). On the other hand, vitamin D deficiency is not necessarily associated with rickets or osteomalacia, suggesting that other factors such as those related to phosphate and calcium homeostasis play a role and apparently determine the individual sensitivity to detrimental effects of vitamin D deficiency. Regarding the effects of vitamin D supplementation on falls and fractures, the current meta-analyses of RCTs draw inconsistent conclusions with either a neutral or a small beneficial effect (46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57). Beyond methodological issues of meta-analyses, these inconsistent results may be attributed to the fact that only sensitive persons may significantly benefit, for example, those with low 25(OH)D receiving an adequate dose of vitamin D and those at high fracture/fall risk such as institutionalized individuals (46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57).

Beyond musculoskeletal effects, several studies investigated the potential extra-skeletal actions of vitamin D. Cell culture and animal studies as well as observational data support the hypothesis that vitamin D is critical for a variety of common diseases including for example, cardiovascular, autoimmune, and neurological diseases, infections, pregnancy complications and cancer (1, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20). By contrast, RCTs have largely shown no effect of vitamin D supplementation on nonskeletal health outcomes (7, 17, 18, 19, 20, 58, 59, 60, 61, 62, 63, 64, 65, 66). Nevertheless, some meta-analyses of RCTs documented beneficial vitamin D effects on certain health outcomes such as respiratory tract infections, asthma exacerbations, some pregnancy outcomes and mortality (67, 68, 69, 70, 71, 72). These data should, however, be interpreted with caution due to some limitations such as heterogeneity, different sources of potential bias, data quality of original trials and partially small effect sizes.

Of particular interest is the association between vitamin D status and cancer, with several observational studies showing an inverse association between serum 25(OH)D concentrations and cancer incidence as well as mortality (73, 74, 75, 76, 77). Meta-analyses of RCTs largely report a moderate, yet significant reduction in cancer mortality by vitamin D supplementation (19, 20, 65, 72). Vitamin D effects on cancer were also evaluated in the VITamin D and OmegA-3 TriaL (VITAL), a RCT in 25,871 older participants in the United States who were randomized to 50 µg (1 µg equals 40 international units (IU)) of vitamin D daily or placebo (78). After a median

Figure 2
Three children with rickets (reproduced, with permission, from Wellcome Library, London. Wellcome Images images@wellcome.ac.uk http://wellcomeimages.org; Three children with rickets; anon., Friends' Relief Mission, Vienna XII, n.d.; Photograph circa 1920–1930; reproduced under the terms of the CC Attribution 4.0 International (CC BY 4.0) licence).

follow-up time of 5.3 years, the hazard ratios (with 95% confidence intervals (95% CI)) were 0.83 (0.67–1.02) for death from cancer, 1.02 (0.79–1.31) for breast cancer, 0.88 (0.72–1.07) for prostate cancer, and 1.09 (0.73–1.62) for colorectal cancer. In analyses excluding 1 year and 2 years of follow-up, neither of which was pre-specified, the hazard ratios (95% CI) for death from cancer were 0.79 (0.63–0.99) and 0.75 (0.59–0.96), respectively. Furthermore, in a subgroup analysis of study participants with a BMI below 25 kg/m^2, cancer mortality was significantly reduced by vitamin D supplementation with a hazard ratio (95% CI) of 0.76 (0.63–0.90). In the entire study cohort, the mean ± standard deviation serum 25(OH)D concentration at baseline was 77 ± 25 nmol/L, and follow-up measurements in a subgroup of participants after 1 year indicated an increase in serum 25(OH)D concentrations in the treatment group of 30 nmol/L. The findings from the VITAL trial support a potential beneficial effect of vitamin D supplementation on cancer mortality, but they do not confirm the reductions in cancer incidence such as those for breast cancer that would have been expected from previous observational studies (73, 74, 75, 76, 77, 78).

Vitamin D guidelines

Several vitamin D guidelines and guidance papers have been published with heterogeneous and partially opposed opinions and recommendations regarding vitamin D requirements (79, 80, 81, 82, 83, 84). To avoid confusion and misinterpretations, it is essential to differentiate nutritional vitamin D guidelines targeted for the general population from clinical vitamin D guidelines intended for patients care.

Nutritional vitamin D guidelines use the terms dietary reference intakes (DRIs) or dietary reference values (DRVs) to describe the distribution of dietary vitamin D requirements in the population (84). Understanding of DRV/DRI in terms of their definition (Table 1), the process of their development, as well as their intended implications is essential for their use as public health policy instruments (84, 85). For deeper insights into these issues we refer the reader to other excellent publications, but we wish to briefly describe some of the key aspects of DRV/DRI (84, 85). A critical point regarding vitamin D requirements is that they are currently mainly based on musculoskeletal outcomes for which serum 25(OH)D concentrations have been used to characterize the dose–response relationship. As part of this process, the Institute of Medicine (IOM) in North America has defined target serum 25(OH)D concentrations at the estimated average requirement (EAR) and at the recommended dietary allowance (RDA) that should meet the vitamin D requirements in 50 and 97.5% of the population, respectively (86). The EAR and the RDA for vitamin D, that is, the dietary intakes of vitamin D to achieve the 'EAR-like' and 'RDA-like' serum 25(OH)D concentrations, were then calculated according to meta-regression analyses of 'winter' vitamin D RCTs. Winter RCTs were chosen because DRV/DRI apply to conditions with minimal or no sunlight exposure with consequently hardly any UV-B-induced endogenous vitamin D synthesis in the skin. Major health agencies have used similar approaches, and the resulting DRV/DRI for vitamin D are listed in Tables 2 and 3 (86, 87, 88, 89, 90, 91). While the RDA is traditionally adopted for planning intakes of individuals, as it meets the vitamin D requirements of 97.5% of individuals within a population, it must be differentiated

Table 1 Definitions for the constituent dietary reference intakes and dietary reference values (reproduced from Cashman ([85](#)) under the terms of the CC Attribution 4.0 International (CC BY 4.0) licence).

Institute of Medicine's *Dietary Reference Intakes*	European Food Safety Authority's *Dietary Reference Values*
Estimated average requirement (EAR): The average daily nutrient intake level that is estimated to meet the requirements of half of the healthy individuals in a particular life stage and gender group	*Average requirement (AR):* The level of (nutrient) intake estimated to satisfy the physiological requirement or metabolic demand, as defined by the specified criterion for adequacy for that nutrient, in half of the people in a population group, given a normal distribution of requirement
Recommended dietary allowance (RDA): The average daily dietary intake level that is sufficient to meet the nutrient requirements of nearly all (97.5 percent) healthy individuals in a particular life stage and gender group	*Population reference intake (PRI)*: The level of (nutrient) intake that is adequate for virtually all people in a population group. On the assumption that the individual requirements for a nutrient are normally distributed within a population and the inter-individual variation is known, the PRI is calculated on the basis of the AR plus twice its standard deviation (s.d.). This will meet the requirements of 97.5% of the individuals in the population
Adequate intake (AI): The recommended average daily intake level of a nutrient based on observed or experimentally determined approximations or estimates of intakes that are assumed to be adequate for a group (or groups) of apparently healthy people; used when the RDA cannot be determined	*Adequate intake (AI):* The value estimated when a PRI cannot be established because an AR cannot be determined. An AI is the average observed or experimentally determined approximations or estimates of nutrient intake by a population group (or groups) of apparently healthy people that is assumed to be adequate
Tolerable upper intake level (UL): The highest average daily nutrient intake level that is likely to pose no risk of adverse health effects to almost all individuals in the general population. As intake increases above the UL, the potential risk of adverse effects may increase	*Tolerable upper intake level (UL):* The maximum level of total chronic daily intake of a nutrient (from all sources) judged to be unlikely to pose a risk of adverse health effects to humans

between the individual and the population perspective. When taking care of an individual, the RDA is the intake target for this individual, but in terms of public health actions, the goal is not, and should not be, to assure that 97.5% of the population exceeds the RDA equivalent serum concentration, that is, 50 nmol/L when using the IOM RDA. Shifting the population vitamin D intake distribution to the point at which 97.5% of the population exceed the RDA like serum 25(OH)D concentration would consequently shift the higher end of the intake distribution toward potentially harmful levels ([84, 92](#)). In this context, it should also be noted that the RDA was calculated based on meta-regression analyses indicating that the lower end of the 95% CI for the median intake is ≥50 nmol/L, that is, we can be sure that at least 50% of the individuals will achieve ≥50 nmol/L at an RDA vitamin D intake. Such conventional meta-regression analyses using aggregate (group) data are suitable for establishing EARs as they well indicate mean responses and CI around these mean responses. They are not ideal for calculating RDAs, because they do not adequately capture between-individual variability as it can be done using regression analyses based on individual participant data (IPD) ([84, 85](#)). Using the same dataset for different statistical approaches, it has been documented in IPD analyses that a vitamin D intake of about 30 µg (1200 IU) per day is required to achieve a serum 25(OH)D concentration of ≥50 nmol/L in 97.5% of the population, whereas 12.7 µg (508 IU) per day were calculated according to the use of the lower end of the 95% CI of the mean response using aggregate data ([84, 85](#)). Such statistical considerations are crucial for the understanding and dealing with DRV/DRI. A simplified summary of nutritional guidelines is that target serum 25(OH)D concentrations range from ≥25 to ≥50 nmol/L corresponding to a daily vitamin D intake of 10–20 µg (400–800 IU). General populations around the world generally fail to meet these vitamin D intakes and target serum 25(OH)D concentrations pointing to the need for public health actions such as systematic vitamin D food fortification ([93, 94, 95, 96, 97, 98](#)). In Europe, for example, serum 25(OH)D concentrations <30 nmol/L and <50 nmol/L are reported in 13.0 and 40.4% of the general population, respectively ([93](#)). Therefore, some countries have already introduced systematic vitamin D food fortification to improve vitamin D intakes in the general population ([99, 100, 101, 102, 103](#)). While systematic vitamin D food fortification in countries such as the United States or Canada has improved vitamin D status in the general population, further actions have to be taken to optimize their food fortification approaches ([80](#)). In Finland, however, systematic vitamin D food fortification was highly effective by reducing the prevalence of individuals with serum 25(OH)D concentrations <30 nmol/L below 1% ([99](#)).

Table 2 Dietary reference values (DRV)/dietary reference intakes (DRI) for vitamin D (reproduced from Pilz *et al*. (81) under the terms of the CC Attribution 4.0 International (CC BY 4.0) licence).

Country (health authority)	United States and Canada (IOM)		Europe (EFSA)	Germany, Austria and Switzerland (DACH)	UK (SACN)	Nordic European countries (NORDEN)
DRV/DRI Target 25(OH)D in nmol/L	EAR 40	RDA 50	AI 50	AI 50	RNI 25	RI 50
Age group	Vitamin D intakes in µg (international units, IU) per day (1 µg = 40 IU)					
0–6 months	10 (400)			10 (400)	8.5–10 (300–400)	
7–12 months	10 (400)		10 (400)	10 (400)	8.5–10 (300–400)	10 (400)
1–3 years	10 (400)	15 (600)	15 (600)	20 (800)	10 (400)	10 (400)
4–6 years	10 (400)	15 (600)	15 (600)	20 (800)	10 (400)	10 (400)
7–8 years	10 (400)	15 (600)	15 (600)	20 (800)	10 (400)	10 (400)
9–10 years	10 (400)	15 (600)	15 (600)	20 (800)	10 (400)	10 (400)
11–14 years	10 (400)	15 (600)	15 (600)	20 (800)	10 (400)	10 (400)
15–17 years	10 (400)	15 (600)	15 (600)	20 (800)	10 (400)	10 (400)
18–69 years	10 (400)	15 (600)	15 (600)	20 (800)	10 (400)	10 (400)
70–74 years	10 (400)	20 (600)	15 (600)	20 (800)	10 (400)	10 (400)
75 years and older	10 (400)	20 (600)	15 (600)	20 (800)	10 (400)	20 (800)
Pregnancy	10 (400)	15 (600)	15 (600)	20 (800)	10 (400)	10 (400)
Lactation	10 (400)	15 (600)	15 (600)	20 (800)	10 (400)	10 (400)

IOM, Institute of Medicine; EFSA, European Food Safety Authority; DACH, Germany, Austria and Switzerland; SACN, Scientific Advisory Committee on Nutrition; EAR, Estimated Average Requirement; RDA, Recommended Dietary Allowance; AI, Adequate Intake; RNI, Reference; Nutrient Intake; RI, Recommended Intake; 25(OH)D, 25-hydroxyvitamin D.

Apart from nutritional guidelines on vitamin D requirements in the general population, there are also clinical vitamin D guidelines that aim to guide clinicians, when taking care of specific patient populations or individuals. A selection of these guidelines is presented in this paragraph. The 'Global Consensus Recommendation on Prevention and Management of Nutritional Rickets' recommends for the prevention of rickets the supplementation of 10 µg (400 IU) of vitamin D daily from birth to 12 months, and thereafter, vitamin D intakes through diet and supplements to meet the nutritional requirement according to the IOM report (i.e. 15–20 µg (600–800 IU) per day) (5). For treatment of nutritional rickets, the minimum recommended dose is 50 µg (2000 IU) of vitamin D per day for a minimum of 3 months plus oral calcium intake of 500 mg per day (5). Regarding vitamin D supplementation of osteoporosis patients, the recommendations are not fully consistent but 20 µg (800 IU) of vitamin D per day can be recommended in the general management of osteoporosis patients (104, 105, 106). Higher vitamin D intakes up to 50 µg (2000 IU) of vitamin D per day may also be used in specific patients but do not represent the common consensus of major osteoporosis guidelines (104, 105, 106). Some experts argue that in older individuals (aged ≥65 years), a general intake of a daily vitamin D supplement with 20 µg (800 IU)

Table 3 Tolerable upper intake levels for vitamin D (adapted from Pilz *et al*. (80) under the terms of the CC Attribution 4.0 International (CC BY 4.0) licence).

Country (health authority)	United States and Canada (IOM)	Europe (EFSA)
Age group	Vitamin D in µg (international units, IU) per day (1 µg = 40 IU)	
0–6 months	25 (1000)	25 (1000)
6–12 months	37.5 (1500)	35 (1400)*
1–3 years	62.5 (2500)	50 (2000)
4–8 years	75 (3000)	50 (2000)
9–10 years	100 (4000)	50 (2000)
11–17 years	100 (4000)	100 (4000)
18 years and older	100 (4000)	100 (4000)
Pregnancy	100 (4000)	100 (4000)
Lactation	100 (4000)	100 (4000)

EFSA, European Food Safety Authority; IOM, Institute of Medicine. *recently updated (180)

is a reasonable approach to ensure a sufficient vitamin D status (82). In patients with chronic kidney disease (CKD), it is suggested by the 'Kidney Disease: Improving Global Outcomes (KDIGO) 2017 Clinical Practice Guideline' that vitamin D deficiency and insufficiency be corrected by vitamin D supplementation using treatment strategies recommended for the general population (107). Parathyroid diseases also require particular attention regarding vitamin D status and represent an indication for measurement of serum 25(OH)D concentrations (108, 109, 110). Patients with primary hyperparathyroidism and 25(OH)D concentrations <50 nmol/L should be repleted with vitamin D doses (e.g. 15–25 µg (600–1000 IU) daily) aiming to bring 25(OH)D ≥50 nmol/L at a minimum, but a goal of 75 nmol/L also is reasonable (108). In primary hypoparathyroidism, it is also recommended to ensure a serum 25(OH)D concentration >50 nmol/L with a suggested supplemental vitamin D dose of 10–20 µg (400–800 IU) per day (109, 110). One major vitamin D guideline for patient care is the 'Endocrine Society Clinical Practice Guideline' for evaluation, treatment and prevention of vitamin D deficiency that supports the IOM recommendations for vitamin D intake to maximize bone health and muscle function in the general population (24). However, the 'Endocrine Society Clinical Practice Guideline' significantly differs from the IOM report as it is suggested to measure serum 25(OH)D concentrations in individuals at risk of vitamin D deficiency (Table 4). If vitamin D deficiency, classified as serum 25(OH)D <50 nmol/L, is detected in such individuals, it is recommended to supplement vitamin D to achieve serum 25(OH)D concentrations of at least 75 nmol/L. In detail, vitamin D-deficient adults should be treated with 1250 µg (50,000 IU) vitamin D once a week for 8 weeks or its equivalent of 150 µg (6000 IU) daily, followed by a maintenance dose of 37.5–50 µg (1500–2000 IU) daily. In obese patients, patients with malabsorption syndromes (in particular patients after bariatric surgery), and patients on medications affecting vitamin D metabolism, a higher dose (e.g. two to three times higher) is suggested to treat vitamin D deficiency. There has been an intensive scientific debate on the differences in the recommendations regarding vitamin D requirements from the IOM report and the Endocrine Society Clinical Practice guideline that is beyond the scope of this review (23, 24, 25, 26). In simple terms, the IOM report does not conclude that there is additional benefit of achieving serum 25(OH)D concentrations of 75 nmol/L when compared to 50 nmol/L. Furthermore, whether or which differences exist regarding vitamin D

Table 4 Indications for 25-hydroxyvitamin D measurements (candidates for screening) (reproduced, with permission, from Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Hassan Murad M & Weaver CM; Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline; *Journal of Clinical Endocrinology & Metabolism*; 2011; **96**(7) 1911–1930; by permission of Oxford University Press (24)).

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

requirements in general populations and in certain patient populations or at-risk individuals is an unresolved issue (23, 24, 25, 26).

Practical vitamin D testing and supplementation

There is a consensus that population-wide screening for vitamin D deficiency by measuring serum 25(OH)D concentrations in asymptomatic low-risk patients should not be done (111, 112, 113, 114). There is, however, no consensus on indications for 25(OH)D testing in patients at risk of vitamin D deficiency with suggested indications ranging from almost no testing to relatively wide testing according to the Endocrine Society Clinical Practice Guideline (Table 4). Making the long story short,

no study has shown the effectiveness of 25(OH)D screening in certain groups so that any recommendations regarding 25(OH)D testing have a relatively low evidence base and are mostly derived from expert opinions. A high suspicion or diagnosis of rickets or osteomalacia does definitely justify the measurement of serum 25(OH)D concentrations. As mentioned earlier, several guidelines and experts argue that serum 25(OH)D concentrations should be measured in patients with hyper- and hypoparathyroidism as well as in CKD patients (107, 108, 109, 110). Although serum 25(OH)D concentrations are widely measured in patients with osteoporosis, there is some controversy on whether such a testing should be done in all patients, just selected high-risk patients or not at all. While there is definitely uncertainty regarding precise indications for vitamin D testing in at-risk individuals, there is evidence available that an uncritical high use of serum 25(OH)D measurements is performed in clinical routine that significantly increases healthcare costs (112, 113, 114, 115). Clinicians should be aware that laboratory measurements of serum 25(OH)D have shown significant inter-assay and inter-laboratory differences leading to efforts for standardization and a pressure toward well-validated gold standard measurements by mass spectrometry (115). There is, of course, a seasonal variation in serum 25(OH)D concentrations with the highest levels at the end of summer and the lowest levels at the end of winter, but the tracking of serum 25(OH)D concentrations over time reveals that a single measurement of serum 25(OH)D at a given time point provides an estimate of future 25(OH)D levels (even if years apart) which is similar to the tracking of blood pressure or blood lipids (116).

Apart from testing issues and the uncertainty regarding target concentrations, it is crucial to be aware on the dose–response relationship of vitamin D intakes and serum 25(OH)D concentrations. It should be considered that the average nutritional vitamin D intake in the general population is typically below 5 µg (200 IU) per day (80, 98). Using data from vitamin D RCTs in winter, Cashman *et al.* have calculated in an IPD regression analysis that with an overall (diet plus supplements) vitamin D intake of 10 µg (400 IU) per day, the percentages of individuals with serum 25(OH)D concentrations ≥25, ≥30 and ≥50 nmol/L, would be 97.5, 95 and about 50%, respectively (84, 85). To ensure that 97.5% of the individuals would achieve serum 25(OH)D concentrations ≥50 nmol/L would require an overall vitamin D intake of approximately 30 µg (1200 IU) per day (84, 85). These estimates are, for example, supported by studies on food fortification in Finland

as well as by vitamin D RCTs showing that a vitamin D supplement with 20 µg (800 IU) per day is sufficient to achieve serum 25(OH)D concentrations ≥50 nmol/L in almost all participants (117, 118, 119). In pregnant women, it was calculated that a daily overall vitamin D intake of about 30 µg (1200 IU) ensured that almost all women had serum 25(OH)D concentrations ≥50 nmol/L and that cord 25(OH)D concentrations were >25 nmol/L in 99% and ≥30 nmol/L in 95% of the newborns (120).

Regarding the precise vitamin D intake serum 25(OH)D dose–response curve, there are slightly inconsistent results in the literature (88, 91). As a frequently quoted rough summary, it can be estimated that per intake of about 2.5 µg (100 IU) of vitamin D per day, the serum 25(OH)D concentrations may increase by about 2.5–5 nmol/L but with quite significant variability of such estimates in the literature (88, 91). Although not clearly established, there are data indicating that the dose–response curve is not linear and flattens at higher intakes (88, 91). Furthermore, several studies suggest that achieved increases in serum 25(OH)D are significantly higher in individuals with lower compared to higher baseline levels and are lower in persons with a higher BMI (88, 91). Although there is no clear recommendation to perform follow-up measurements of serum 25(OH)D after starting with a daily vitamin D supplement, it bears mentioning that re-measurements of serum 25(OH)D should not be done earlier than after 8 weeks on treatment because this is approximately the time required to reach a steady state (88, 91). Of note, some studies indicate that it may take even 12 weeks or longer to reach a steady state in serum 25(OH)D (121).

It should be noted that daily, weekly or monthly vitamin D dosing regimens can be used because they result in the same serum 25(OH)D concentrations (122, 123). Nevertheless, some experts recommend to prefer daily doses as vitamin D itself may be biologically relevant, but has only a half-life of about a day and because some RCTs on intermittent high-dose vitamin D supplementation have reported adverse effects such as increased falls and fractures (124, 125, 126, 127). In detail, an annual dose of 12,500 µg (500,000 IU) of vitamin D for 3–5 years in 2256 community-dwelling women aged 70 years or older resulted in an increased risk of fractures and falls with incident rate ratios (with 95% CI) compared to placebo of 1.15 (1.02–1.30; $P = 0.03$) and 1.26 (1.00–1.59; $P = 0.47$), respectively (124). Interestingly, *post hoc* analyses showed that increased risk of falls was exacerbated in the 3-month period following the annual vitamin D dose, with a similar trend for fractures (124). This also means that

risk was particularly increased during the period with the highest serum 25(OH)D concentrations during the year in the intervention group with a median concentration, 1 month after the annual dose, that was slightly higher than 120 nmol/L including 24% of the participants with levels ≥150 nmol/L (124). Importantly, another RCT over 1 year in 200 community-dwelling men and women aged 70 years and older with a prior fall reported that risk of falls was significantly increased in participants allocated to monthly doses of 1500 μg (60,000 IU) of vitamin D compared to monthly doses of 600 μg (24,000 IU) of vitamin D (mean number of falls per participant: 1.47 vs 0.94; $P=0.02$) (125). By contrast, other RCTs on intermittent high-dose vitamin D supplementation such as the Vitamin D Assessment (ViDA) Study in 5108 older individuals randomized to 2500 μg (100,000 IU) of vitamin D per month or placebo did not report on increased risk of fractures or falls (128, 129). In line with this, a recent meta-analysis on vitamin D supplementation and musculoskeletal health outcomes did not find differences for daily versus intermittent vitamin D doses (57). Interestingly, there are also data suggesting that there may be a U-shaped association of serum 25(OH)D and risk of falls (130). Anyway, we believe that some caution is warranted with intermittent high-dose vitamin D supplementation and with potential adverse effects of very high serum 25(OH)D concentrations.

From a clinical perspective, vitamin D intoxication is characterized by hypercalcemia, which is preceded by hypercalciuria (80, 127). Hypercalcemia induced by vitamin D intoxication does, however, usually only occur at serum 25(OH)D concentrations above 375 nmol/L and is very rare (80, 127, 131). Nevertheless, in view of limited data on high serum 25(OH)D concentrations and some observational studies reporting U- or J-shaped curves on the association between serum 25(OH)D and outcomes such as mortality, the IOM report classified serum 25(OH)D concentrations greater than 125 nmol/L, if sustained, as potentially harmful (25). It has been argued that the increased risk at high serum 25(OH)D concentrations might have been partially attributed to patients with previous vitamin D deficiency who therefore received vitamin D supplements, but whenever discussing associations between serum 25(OH)D and outcome, it must be stressed that such data should be based on surveys with standardization of 25(OH)D measurements. Current meta-analyses of observational studies do not report on significantly elevated risk of adverse events at serum 25(OH)D concentrations higher than 125 nmol/L, so that it is still unclear which serum 25(OH)D concentrations should be used as a threshold level for vitamin D toxicity (132, 133). To get some deeper insights into the association of serum 25(OH)D concentrations and clinical outcomes such as mortality, we show the results of an IPD meta-analysis on standardized serum 25(OH)D concentrations in Fig. 3 (16). Importantly, in the VITAL trial, there were no safety concerns with regard to hypercalcemia, kidney stones or kidney failure with a daily supplementation of 50 μg (2000 IU) vitamin D (78).
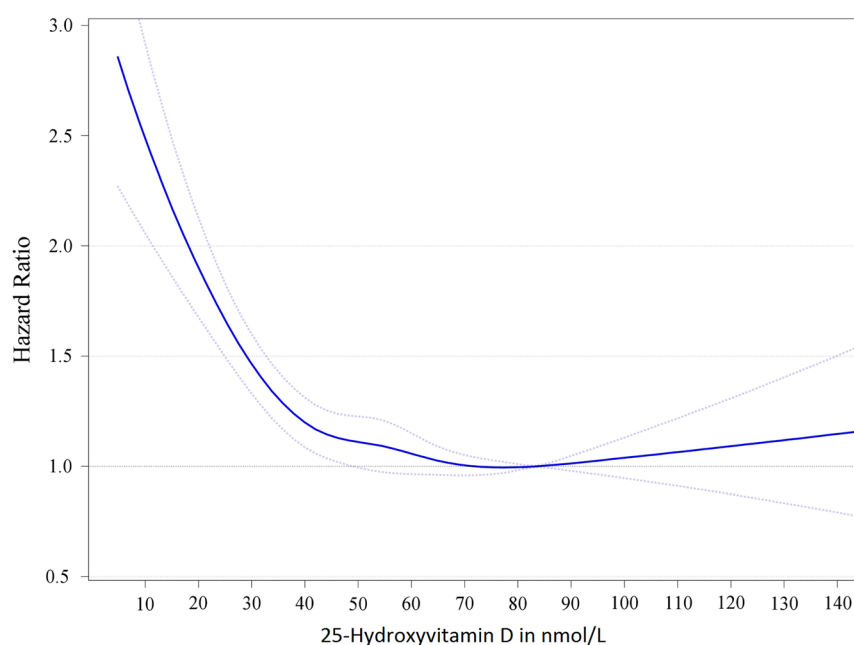

Figure 3
Dose–response trend of hazard ratios of death from all causes by standardized 25-hydroxyvitamin D. Dose–response trend of hazard ratios of all-cause mortality by standardized 25-hydroxyvitamin D were adjusted for age, sex, BMI and season of blood drawing concentrations. Hazard ratios (blue line with 95% confidence interval as the dotted blue lines) are referring to the 25-hydroxyvitamin D concentration of 83.4 nmol/L (i.e. the median 25-hydroxyvitamin D concentration for the group with 25-hydroxyvitamin D concentrations from 75 to 99.99 nmol/L). Reproduced from Gaksch *et al.* (16) under the terms of the CC0 1.0 Universal (CC0 1.0) Public Domain Dedication.

Apart from oral intake, vitamin D can also be administered intramuscularly with a similar, yet delayed, increase compared to oral intakes (134, 135, 136). Transdermal applications of vitamin D do also raise serum 25(OH)D, but more data on this topic are needed (137, 138). Apart from vitamin D, there are also 25(OH)D preparations available for treatment that are about 3.2–5-fold as effective as vitamin D in raising serum 25(OH)D concentrations (139, 140). Regarding vitamin D3 and D2, most experts argue to rather prefer vitamin D3, as it is the endogenous form that may be more potent in increasing serum 25(OH)D concentrations compared to vitamin D2 (141). The lower affinity to DBP of vitamin D2 metabolites compared to vitamin D3 metabolites may contribute to a more rapid clearance of vitamin D2 (142, 143, 144). Reviewing the current literature on this topic, Bouillon *et al.* concluded that vitamin D2 can be considered as a good analog of vitamin D3 rather than as being truly bioequivalent (144). As part of the discussion on optimal strategies for vitamin D supplementation, it should also be emphasized that a healthy lifestyle with moderate sunlight exposure, a healthy diet (including fish) and avoiding or treating obesity can also effectively increase serum 25(OH)D concentrations (145, 146, 147, 148, 149).

Critical appraisal of vitamin D research

Several vitamin D RCTs have been published and are currently ongoing that have or will substantially increase our knowledge on vitamin D. Robert Heaney and other scientists pointed out that the evidence-based medicine (EBM) guidelines, developed specifically for drugs, have been applied to nutrients and their trials without considering major differences between nutrients and drugs (150, 151, 152, 153, 154, 155, 156, 157). One key point is that the dose–response curve of nutrient intake and outcomes is generally not linear, and it requires an accurate interpretation and study design of nutrient trials considering this dose–response curve. Assessment of nutrient status at baseline and study end and aiming for a change in nutrient intake that is associated with a significant change in outcomes on the dose–response curve is important. RCTs including participants regardless of their prevailing vitamin D status or with high serum 25(OH)D concentrations may miss to report significant vitamin D effects in 'sensitive' populations such as vitamin D-deficient individuals (158, 159). It should appear logical that when even established treatments such as aspirin are not effective in terms of improved clinical outcomes when given to everyone in the population, vitamin D will also

fail and is not a 'wonder drug' (160). Unfortunately, many vitamin D RCTs have a similar study design as previous disappointing nutrient trials with no selection of sensitive (e.g. vitamin D deficient) individuals, and may, therefore likewise show no effect or might even be harmful (158, 159, 161). Subgroup analyses of vitamin D-deficient individuals, even if showing beneficial effects, will likewise not be widely accepted and will definitely not be able to compete with drug trials results that are not derived from unselected participants but rather from very large cohorts of carefully selected and 'sensitive' populations (158). Assessment of calcium intake is also crucial in vitamin D RCTs because it seems that individuals with a poor calcium intake may be more sensitive to adverse effects of vitamin D deficiency and vice versa.

It is important to point out that EBM is not exclusively based on RCTs but also on other study designs including, apart from classic observational studies, also Mendelian Randomization (MR) studies (157). These MR studies evaluate whether genetically determined serum 25(OH)D levels are associated with outcome and have the advantage over RCTs that they assess lifelong exposure (162, 163). While observational studies on vitamin D have been very useful to generate hypotheses that have to be further tested in RCTs or MR studies, they are definitely prone to bias or reverse causation as for example, DBP decreases due to critical illness thus consequently decreasing total serum 25(OH)D (164). It is also important to note that serum 25(OH)D concentrations in observational studies are mainly derived from sunlight-induced vitamin D synthesis in the skin, while interventional studies rather supplement vitamin D than increasing UV-induced vitamin D synthesis that may also exert vitamin D-independent effects on human health. Moreover, there are still several knowledge gaps regarding the role and regulation of DBP or regarding data on potential vitamin D toxicity at high serum 25(OH)D concentrations (164, 165, 166, 167). As an important task for future vitamin D research, Sempos *et al.* have proposed to develop an international 'Rickets Registry' based on standardized serum 25(OH)D and a standardized case definition of rickets (166).

Better education for professionals and the lay public is also required to reduce the overuse of high-dose vitamin D supplements (in particular doses that exceed the tolerable upper intake levels according to Table 3) in those who do not need it and to improve the underuse of vitamin D supplements in those individuals in whom it is indicated (168, 169, 170, 171, 172, 173). Infrequent use of vitamin D supplements in individuals with a low

socioeconomic status has to be considered (170, 171, 172, 173). Importantly, rickets is still a worldwide public health problem causing morbidity and mortality and is even increasing in Europe with immigrants from Middle East, Africa and Asia being at particularly high risk (174). Prevalence and incidence of vitamin D deficiency-associated nutritional rickets is difficult to assess due to incomplete reporting and inconsistent case definition, but even if conservative estimates of only a few single-digit cases per 100,000 is true, vitamin D-deficient rickets and the therewith associated infant deaths are preventable and require adequate public health actions (174, 175, 176, 177).

Conclusions

It is established that vitamin D deficiency can cause rickets and osteomalacia with a significant risk increase at serum 25(OH)D concentrations <25–30 nmol/L, pointing to the need for prevention and treatment of such low serum 25(OH)D concentrations on an individual and population level. Adequate vitamin D supplementation may also have moderate beneficial effects on BMD, fractures and falls. These effects seem to be only evident in vitamin D-sensitive populations, that is, in particular in those with serum 25(OH)D concentrations <30 nmol/L and older or at-risk individuals. Importantly, high calcium intake may partially compensate for reduced serum 25(OH)D concentrations. Meta-analyses of RCTs indicated that vitamin D supplementation may also reduce extra-skeletal outcomes such as infections, asthma exacerbations, pregnancy outcomes and mortality, but more data are required to clearly establish causality. Anyway, effect sizes on any of these outcomes, if truly present, are only small but may eventually be significant on a population level. Clinicians are confronted with an overwhelming testing and self-supplementation of vitamin D in the general population. It is therefore recommended that vitamin D testing should not be misused as a universal population-wide screening tool, but rather be applied only in selected individuals at high risk of vitamin D deficiency. Being aware of inconsistent guidelines and recommendations, we suggest that a reasonable approach for clinicians is to supplement vitamin D in those individuals with measured serum 25(OH)D <50 nmol/L and osteoporosis patients. A supplemental dose of 20 µg (800 IU) of vitamin D per day should be sufficient for almost all individuals to safely achieve serum 25(OH)D concentrations ≥50 nmol/L and to exert beneficial clinical effects according to some

dose–response analyses of RCTs (24, 49, 56). Even if following more conservative approaches, there is an imperative requirement for vitamin D treatment in individuals with serum 25(OH)D concentrations <25–30 nmol/L, a level that can be prevented by a supplemental vitamin D dose of 10 µg (400 IU) per day. We believe that upcoming large vitamin D RCTs will likewise not show significant beneficial effects as they did not target vitamin D-deficient or sensitive high-risk individuals, but will provide important safety data for relatively high doses of vitamin D supplementation in the general older population (158, 161, 178, 179).

Author contribution statement
All authors contributed to the drafting and critical review of this manuscript.

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