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Review

Vitamin D in Preventive Medicine

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Abstract. *The global burden of vitamin D deficiency is of great concern for public health. Meta-analyses of randomized controlled trials (RCTs) have shown that vitamin D supplementation reduces fractures, falls, and mortality. These findings are, however, not universally accepted and there exists certain controversy regarding the potential benefits of vitamin D. Whereas vitamin D might also be relevant for extra-skeletal diseases such as cancer, cardiovascular diseases, or infections, the recommended Dietary Reference Intakes (DRI) are solely based on skeletal effects. The Recommended Dietary Allowance (RDA) range from 600 to 800 international units (IU) of vitamin D per day, corresponding to a 25-hydroxyvitamin D level of 20 ng/mL (50 nmol/L). Consequently, there exists a substantial gap between the RDA and the actual high prevalence of vitamin D deficiency in general populations, particularly among the elderly. Therefore, achieving the RDA will require additional efforts including food fortification, vitamin D supplementation and health campaigns.*

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Vitamin D deficiency is a well-recognized cause of rickets, which is characterized by impaired bone mineralization resulting in skeletal deformities (1-3). Apart from malnutrition, in particular, low sunlight exposure with the consequence of vitamin D deficiency has been a major contributor to the high prevalence of rickets during the past centuries (1). Prior to the discovery of vitamin D by McCollum in 1922, it had been documented that sunlight or ultraviolet-B (UV-B) exposure, which is required for vitamin D synthesis in the skin, was effective for the prevention and treatment of rickets (1). Nutrition is a minor source of vitamin D, and it has been widely established that babies and infants are supplemented with vitamin D for the purpose of rickets prevention (1-3). As sufficient calcium supply is required for physiological skeletal mineralization, it is clear that the effects of vitamin D on calcium absorption in the gut and calcium re-absorption in the kidneys are essential for bone and skeletal health. While in the past, rickets has been a major public health burden, nowadays it is observed that adults, especially with advancing age, are prone to vitamin D deficiency and may subsequently develop osteomalacia (4, 5). Similar to rickets, this disease is characterized by bone mineralization defects

of the adult skeleton leading to clinical signs such as bone pain and muscle weakness (4, 5).

In recent years, our perception of vitamin D has fundamentally changed from a substance that is "only" relevant for bone and mineral diseases, to a substance that might be critical for many extra-skeletal diseases and overall well-being (6-8). This can be attributed to the fact that vitamin D receptors (VDR) have been identified in almost every human cell and that VDR activation has been shown to regulate hundreds of genes (8). Hence, vitamin D can be characterized as a pro-hormone with a unique metabolism in which it is hydroxylated to its major circulating metabolite 25-hydroyvitamin D (25[OH]D) in the liver, and is later converted to 1,25-dihydroxyvitamin D (1,25[OH]2D), the so called active vitamin D hormone calcitriol (8). Serum calcitriol is predominantly produced in the kidneys but many extra-renal cells are also capable of converting 25(OH)D to 1,25(OH)2D on a local level. Stimulated by many publications linking vitamin D deficiency to several chronic diseases there is currently an ongoing debate regarding the potential role of vitamin D in preventive medicine (9-11).

In this narrative review, we set-out to provide a brief overview on the existing evidence of vitamin D and common chronic diseases relevant to the public health setting. Specifically, we focused on the most recent developments and meta-analyses, while outlining the recommended Dietary Reference Intakes (DRI) for vitamin D in the context of the actual prevalence of vitamin D deficiency, as well as the possible approaches on how vitamin D status could be further improved on an individual and population level. Finally, we discuss the ongoing vitamin D trials and present our conclusions on the available knowledge regarding vitamin D in preventive medicine.

Vitamin D, Fractures and Falls

Beyond rickets and osteomalacia, vitamin D is currently a recommended standard treatment for patients with osteoporosis (12). In an individual patient data meta-analysis of randomized controlled trials (RCTs) it was demonstrated that a supplemental vitamin D dose of approximately 800 to 2000 International Units (IU) per day (1 IU is equivalent to 0.025 μg vitamin D) was effective in reducing the incidence of any non-vertebral and hip fractures (13). Nevertheless, whether fracture prevention by vitamin D supplementation is modified by the prevailing vitamin D status, nutritional vitamin D intake, calcium intake, or age is still largely unclear. In addition, it should be noted that not all meta-analyses investigating this issue reached the conclusion that vitamin D supplementation significantly reduces the risk of fractures (14, 15). While most vitamin D RCTs were performed in older individuals, the question arises of whether vitamin D should also be advocated for primary fracture prevention in younger as well as non-institutionalized persons. In this context, the U.S. Preventive Services Task Force (USPSTF) argues against daily vitamin D and calcium supplementation for primary prevention of fractures in non-institutionalized postmenopausal women (15). This is in line with a meta-analysis indicating that there was no significant impact of vitamin D supplementation on bone mineral density (BMD) (16). It must, however, be stressed that older individuals are more prone to vitamin D deficiency, osteomalacia, and fractures, and several experts conclude that the current evidence justifies the recommendation of a vitamin D intake, at best with a supplement, of 800 IU per day for those above the age of 65 years (17).

Vitamin D deficiency, particularly in the setting of osteomalacia, has also been associated with muscle weakness. Various meta-analyses of RCTs have, therefore, addressed the question as to whether vitamin D supplementation diminishes the risk of falls in older individuals, albeit, those studies have not consistently displayed a significant effect (18-22). It has been proposed that a disparity in the inclusion criteria of studies and data extraction might, in part, explain the heterogeneous findings on vitamin D and falls (19).

At present, there exist much more systematic reviews and meta-analyses than original RCTs on vitamin D, fractures and falls (19). In general, current literature suggests that vitamin D supplementation may reduce non-vertebral fractures with, in our opinion, an effect on falls that is probable but still needs to be further studied (23). Of concern, however, is the disparity in conclusions reported among overlapping meta-analyses. Solving this crucial issue in the field of vitamin D will be one of the numerous major tasks that need to be accounted for in coming years (19).

Vitamin D and Cancer

The present story of vitamin D and cancer was preceded by observations in the first half of the 20th century, proposing that higher sunlight (UV) exposure was associated with reduced cancer mortality (24, 25). As UV exposure is required for vitamin D production in the skin, it has been postulated by Garland and Garland in 1980 that vitamin D could protect against cancer (26). Their hypothesis was based on the observation that colorectal cancer deaths were inversely associated with solar radiation (26). Several further etiological studies confirmed that mortality due to various cancer sites was significantly reduced in regions with high UV exposure (27). Thus, while UV exposure is well-known to augment the risk of skin cancer, VDR activation does comprise of some beneficial effects towards skin cancer to the point that vitamin D deficiency is perhaps an issue that shouldn't be overlooked in such patients (28). To this end, various molecular effects of VDR activation protect against the initiation and progression

of cancer (29, 30). In epidemiological studies, it has been documented that low 25(OH)D levels are associated with increased risk of many different cancer sites (31-33). It has become particularly evident that patients already diagnosed with cancer have a significantly reduced survival if they are vitamin D-deficient (31-34). In spite of this, data derived from RCTs on vitamin D supplementation and cancer incidence as well as mortality are sparse and have largely failed to show any beneficial impact of vitamin D on cancer incidence and mortality (35). Nonetheless, it is worth mentioning that two recent meta-analyses of RCTs demonstrated that vitamin D supplementation is associated with modest, though statistically significant reduction in overall cancer mortality (36-38). Due to high drop-outs of the analyzed studies along with other limitations of the data, it is however still not completely clear whether vitamin D supplementation is actually reducing cancer mortality (38).

Vitamin D and Extra-skeletal Diseases

Vitamin D deficiency has been identified as an independent risk factor for many chronic diseases including, beyond cancer and musculoskeletal diseases, also cardiovascular and cerebrovascular diseases, infections, autoimmune diseases and neurological diseases such as dementia (6-11, 22, 39-41). The current evidence for vitamin D and these extra-skeletal diseases has been well-reviewed elsewhere (6-11, 22, 39-41). In an "umbrella review" of published reviews and meta-analyses regarding vitamin D and multiple health outcomes it was concluded that "highly-convincing evidence of a clear role of vitamin D does not exist for any outcome, but associations with a selection of outcomes are probable" (22). In detail, probable associations with vitamin D concentrations were found for birth weight, dental caries in children, maternal vitamin D concentrations at term, and parathyroid hormone (PTH) concentrations in dialysis patients (22). By contrast, a meta-analysis on cardiovascular effects of vitamin D concluded that vitamin D supplementation might protect against heart failure (42). Thus, a clinically-significant cardiovascular protective effect of vitamin D should not be ruled-out. This notion is also supported by recent data suggesting that vitamin D might lower blood pressure which is considered one of the main factors for global disease burden and premature mortality (43-45). Although the current evidence is insufficient to state that vitamin D protects against any of these suggested extra-skeletal diseases, we cannot rule-out the possibility that forthcoming studies will provide evidence for the extra-skeletal benefits regarding vitamin D.

Vitamin D and Mortality

Most, but not all, epidemiological studies involving the general population as well as patients suffering from heart disease, chronic kidney disease, liver failure, diabetes mellitus or metabolic syndrome, as well as nursing home residents identified low 25(OH)D concentrations to be an independent risk factor for mortality (46-54). This has been confirmed in a few meta-analyses in general populations as well as in patients suffering from chronic kidney disease (55-58). Of note, the association between 25(OH)D and mortality shows a U- or a reverse J-shaped curve (59, 60). In a meta-analysis by Zittermann *et al*. the lowest mortality risk was observed at 25(OH)D concentrations ranging from 30 to 35 ng/mL (75 to 87.5 nmol/L) (55). Mortality risk was by trend higher at 25(OHD levels above 35 ng/mL (87.5 nmol/L) but it was neither statistically significantly increased nor do we have, at present, sufficient data to judge on the relationship between 25(OH)D and mortality at concentrations above approximately 45 to 50 ng/mL (112.5 to 125 nmol/L).

In addition to these observational data it has turned-out in meta-analyses of RCTs that vitamin D3 supplementation reduces overall mortality (14, 37, 58, 61). In a Cochrane meta-analysis, Bjelakovic *et al*. reported that 150 individuals would need to be treated over five years in order to prevent one additional death (37). Although this finding was statistically significant it must be noted that due to incomplete follow-up data of the analyzed RCTs and some other limitations it is still not entirely clear whether this reflects a true effect (14, 37, 58, 61). Nevertheless, a reduction in mortality on the background of vitamin D supplementation according to meta-analyses of RCTs provides a strong rationale in favour of the benefits and safety of vitamin D.

Dietary Reference Intakes of Vitamin D

In 2010, the Institute of Medicine (IOM) updated the recommendations for the intake of vitamin D and calcium (62). After an extensive review, it was concluded that the beneficial effects of vitamin D on skeletal health are a sufficient basis for intake recommendations whereas it was also noted that the evidence for any non-skeletal effect of vitamin D is still insufficient and remains inconclusive. In detail, the Recommended Dietary Allowances (RDAs) for vitamin D that should cover the requirements of ≥97.5% of the general population are: 600 IU per day for ages 1-70 years, and 800 IU per day for ages 71 year and older (62). This should correspond to a serum 25(OH)D level of at least 20 ng/mL (50 nmol/L), as calculated by regression analyses using data from vitamin D intervention studies performed in the winter season (62, 63). Similar levels have been recommended in other countries and by other leading health authorities (63-66). Importantly, the RDAs have been calculated for individuals with minimal or no sunlight exposure, which is *e.g*. the case in nothern Europe during

winter season because UV-B exposure during winter months at these latitudes is too weak for a sufficient endogenous vitamin D production in the skin (62).

Prevalence of Vitamin D Deficiency and Current Vitamin D Intakes

When examining the prevalence of vitamin D deficiency it has to be acknowledged that there exists no universal cut-off. According to the IOM report, a 25(OH)D level of 20 ng/mL (50 nmol/L) would meet the requirement of 97.5% of the population, whereas levels of 16 ng/mL (40 nmol/L) would meet the requirements of 50% of the general population (average requirement), and levels below 12 ng/mL (30 nmol/L) indicate risk of vitamin D deficiency (62). A lot of scientific discussion has taken place on whether 30 ng/mL (75 nmol/L) should be set as the standard threshold level of 25(OH)D sufficiency rather than 20 ng/mL (50 nmol/L). Nevertheless, there is wide agreement that it is a reasonable goal to prevent and treat 25(OH)D levels below 20 ng/mL (50 nmol/L). When discussing recommendations for certain 25(OH)D concentrations it must be underlined that some recommendations such as the IOM report are for the general population whereas other guidelines such as the Endocrine Society clinical practice guideline are for patient care (21, 62).

In systematic reviews, it turned-out that a significant proportion of individuals in general populations has 25(OH)D concentrations below 20 ng/mL (50 nmol/L) (67, 68). For instance, in one systematic review on worldwide vitamin D status comprising 195 studies with 168,000 individuals, more than one-third (37.3 %) of the studies' mean 25(OH)D values were below 20 ng/mL (50 nmol/L) (66). Vitamin D intake including nutrition and supplements has also been assessed in many different countries (69-71). Notably, the intake from all vitamin D sources is in most general populations below 200 IU per day (5μg per day) and is thus far below the RDA (69-71).

When reporting on the prevalence of vitamin D deficiency it should be taken into consideration that the measurement of 25(OH)D is challenging and there exist significant assay and laboratory differences (72-75). This has led to approaches for the standardization of 25(OH)D measurements and the Vitamin D Standardization Program (VDSP) including the NIH Office of Dietary Supplements (ODS) in collaboration with the CDC National Center for Environmental Health (NCEH), the National Institute of Standards and Technology (NIST) and Ghent University is currently working on this (76, 77). Beyond the issue of standardization, there remain several knowledge gaps, such as the impact of the vitamin D binding protein (DBP) and some vitamin D metabolites such as the 3-epimer on the assessment of vitamin D status (77-79).

Prevention and Treatment of Vitamin D Deficiency

Developing strategies to prevent and treat vitamin D deficiency are extremely challenging, since the contribution of various vitamin D sources to circulating 25(OH)D levels remains, in large parts, unclear and there exists a significant modification by several environmental and individual characteristics (63, 64, 71, 80, 81). In most individuals, UV-B induced vitamin D synthesis in the skin is the major source for circulating 25(OH)D levels. This is well-reflected by the significant seasonal variation of 25(OH)D. Moreover, cutaneous vitamin D production as well as other sources, *i.e.* nutrition (*e.g.* fish or eggs), vitamin D supplements or mobilisation of stores from *e.g.* the adipose tissue, have a high variability. Metabolism and levels of 25(OH)D are also influenced by *e.g.* inflammation or other hormones including PTH and fibroblast-growth-factor-23 (FGF-23) (82, 83). Therefore, precise estimation of 25(OH)D status is hardly possible even after taking into account the dietary, lifestyle, and genetic determinants of vitamin D (84).

When examining the current vitamin D intake and 25(OH)D status in the general population, it is obvious that we have a huge gap between the RDA and the actual intake and levels of vitamin D. While there are ongoing investigations to extend our knowledge on vitamin D and its DRI, health professionals and health authorities have to deal with the present evidence and recommendations and have to take responsibilities for public health issues regarding vitamin D.

Countries such as the United States or Finland have already introduced vitamin D food fortification to improve the vitamin D status of the general population. Indeed, food fortification seems to be the best approach for improving vitamin D status on a population level (71). To this end, vitamin D supplementation appears to be a reasonable approach for individual improvement of vitamin D status when considering the care of patients or persons at high risk of vitamin D deficiency. Several expert panels contemplate the use of a general vitamin D supplementation as a worthy approach for preventing and treating vitamin D deficiency among at-risk populations, particularly among the elderly (17). This is supported by the fact that a vitamin dose according to the RDA of 600 to 800 IU vitamin D per day has a wide therapeutic window when considering the safe tolerable upper intake levels of 4000 IU per day, as suggested by the IOM and the EFSA (European Food and Safety Authority) (62, 85). In humans, vitamin D doses up to 10,000 IU per day have not been associated with significant adverse effects (86). A dose of 10,000 IU vitamin D per day is also approximately equivalent to the maximum endogenous vitamin D production in the skin, and there is no report on sunlight induced vitamin D intoxication. Acute vitamin D intoxication with hypercalcemia, acute renal

failure and calcifications does not occur until 25(OH)D levels rise above approximately 150 to 200 ng/mL (~375 to 500 nmol/L) (86). Considering that the dose response relationship between vitamin D intake and 25(OH)D concentration plateaus with higher amounts, it is only possible with extreme overdosing to achieve such toxic concentrations of 25(OH)D (87). It must however be acknowledged that only very few data are available on long-term effects of vitamin D above the safe tolerable upper intake levels of 4000 IU per day (88, 89). Regarding vitamin D supplement selection there is an ongoing debate as to whether supplementation of vitamin D3 is more effective compared to vitamin D2 in raising circulating 25(OH)D levels, though most experts advocate the use of vitamin D3 (90). The dose response relationship for increasing levels of 25(OH)D following vitamin D supplementation demonstrates a high variability and is dependent on several factors such as body weight, age, simultaneous calcium intake and basal 25(OH)D status, etc. (87, 91-93). As a crude estimate, supplementation of 1000 IU of vitamin D3 per day may increase 25(OH)D levels by approximately 10-20 ng/mL (25 to 50 nmol/L) (91-93). Importantly, re-measurements of 25(OH)D should not be performed prior to 3 months of commencing vitamin D supplementation since this is approximately the duration it takes to achieve a steady state for 25(OH)D. Interestingly, concomitant calcium intake, which may slightly increase cardiovascular events, seems to decrease the compliance of vitamin D supplementation (91, 94). A healthy and balanced diet is of course important, but almost nobody reaches a daily vitamin D intake of 600 to 800 IU by a normal western diet without food fortification and without supplements (63, 64, 70, 71).

Recommendations regarding sufficient sunlight exposure for increasing 25(OH)D levels reflect a double-edged dagger considering UV exposure as a well-accepted carcinogen (28). While there is ongoing discussion on this topic, some authors propose that the net effects of moderate UV exposure may be beneficial (28). It appears that short and frequent sun exposure is a reasonable approach for improving vitamin D status (28). Foremost, the recommended and required vitamin D levels can be achieved with much less intensive UV or sunlight exposure than that which causes an erythema or sunburn (*i.e.* a sub-erythemal dose) (28, 95-97). The dose of UV-B or sunlight exposure required for a sufficient vitamin D production depends on several factors such as latitude, daytime, skin pigmentation, and age, though exposing on most days about 20% of your skin for a few minutes in the noon sunshine in summer months is usually sufficient at latitudes such as *e.g.* Boston (95-97).

Obesity should also be considered since it has a significant impact on vitamin D status (98, 99). Deposition of vitamin D in various tissues, particularly the adipose tissue, seems to be one of the main factors why there is an inverse association between body weight and 25(OH)D. Some studies revealed that reducing body weight is effective in increasing 25(OH)D levels. Hence, besides the established beneficial effects, combating obesity should also be known in the lay public as something that brings more "sunshine vitamin" into your life. Campaigns for promoting a healthier lifestyle through outdoor exercise could lead to a "2 for 1", with participants obtaining sufficient sunlight exposure for simply being outdoors, while a reasonable amount of physical activity would be aimed at lowering the burden of obesity (100).

Ongoing Vitamin D Trials

Some large vitamin D RCTs in the general population are currently ongoing and should be completed in the years 2017 to 2020 (101, 102). The anticipated results from these trials will undeniably draw a new picture on the effects of vitamin D in preventive medicine. The efforts of these trials are greatly appreciated, but when looking back at the history of previous disappointing vitamin trials it becomes apparent that vitamin D will probably repeat the story of other vitamins such as vitamin E (103, 104). In our opinion, one major pitfall of the vitamin D RCTs is that they do not specifically enrol vitamin D deficient individuals, thus ignoring the U-shaped association between 25(OH)D and outcome with a significant increase in risk only at very low 25(OH)D levels. Additional limitations of ongoing vitamin D RCTs are that they allow vitamin D supplementation in the placebo group and use a fixed dose for everyone. It is therefore rather unlikely that these studies will demonstrate significant overall benefits of vitamin D supplementation (103). In light of these limitations, we strongly encourage further vitamin D RCTs including participants with very low 25(OH)D levels and with vitamin D doses to achieve optimal 25(OH)D levels as documented by previous meta-analyses of epidemiological studies.

Conclusion

It is widely accepted that vitamin D is essential for the maintenance of skeletal health and accumulating evidence suggests that vitamin D deficiency is an independent risk factor for various extra-skeletal diseases including cancer. Whether vitamin D is simply a marker of risk or has actually some beneficial effects on non-skeletal diseases remains to be elucidated. Therefore, current recommendations regarding preventive medicine should be based on skeletal effects of vitamin D. While RDAs have recently been published for vitamin D, it is also apparent that there is a huge gap between these recommendations and the genuine vitamin D intake and vitamin D status in the general population. Health professionals and public health authorities are, therefore, encouraged to place further emphasis on combating vitamin

D deficiency. Potential approaches include food fortification for the general population, vitamin D supplementation in at-risk individuals such as the elderly, and by advocating lifestyle modifications such as outdoor physical activity for the avoidance of obesity with careful and balanced sunlight exposure, and a healthy diet. Though, in addition, studies designed to determine the most optimal and efficient means in achieving a physiologic and healthy vitamin D status are urgently needed.

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