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Review

Vitamin D: Current Guidelines and Future Outlook

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Abstract. *Vitamin D is of public health interest because its deficiency is common and is associated with musculoskeletal diseases, as well as extraskeletal diseases, such as cancer, cardiovascular diseases, and infections. Several health authorities have reviewed the existing literature and published nutritional vitamin D guidelines for the general population. There was a wide consensus that serum 25-hydroxyvitamin D [25(OH)D] concentration should be used to assess vitamin D status and intake, and that musculoskeletal, and not extraskeletal, effects of vitamin D should be the basis for nutritional vitamin D guidelines. Recommended target levels for 25(OH)D range from 25 to 50 nmol/l (10 to 20 ng/ml), corresponding to a vitamin D intake of 400 to 800 International Units (10 to 20 μg) per day. It is of concern that significant sections of the general population do not meet these recommended vitamin D levels. This definitely requires action from a public health perspective.*

Vitamin D is historically known as a substance that can prevent and cure rickets, a disease that is characterized by mineralisation deficits of the bones, *i.e.* of the growth plates (1, 2). In general, vitamin D is considered to be critical for bone and mineral metabolism and thus for musculoskeletal health (2, 3). Moreover, low vitamin D levels have also been associated with several extra-skeletal diseases such as cancer, infections and cardiovascular diseases, suggesting a wide role of vitamin D in human health (2-5). While a low vitamin D level is, thus, clearly an indicator of a poor health status, it is still largely unclear whether and to what extent vitamin D may be effective for the prevention and treatment of several extraskeletal diseases (6, 7). In light of the scientific controversy on potential effects of vitamin D and a high worldwide prevalence of low vitamin D levels, several health authorities have published nutritional vitamin D guidelines within the past few years (8-10).

In this brief narrative review, we aim to provide a focussed overview, critical discussion, and future outlook of nutritional vitamin D guidelines for the general population, thereby excluding guidelines intended for patient populations. After a brief introduction on vitamin D metabolism, we outline some common basic steps in the development of nutritional vitamin D guidelines. We then summarise the recommendations of existing vitamin D guidelines before critically discussing them. Finally, we provide a future outlook for vitamin D in public health, with a particular focus on the potential implications of some recently finished and ongoing randomized controlled trials (RCTs) on vitamin D.

Vitamin D Metabolism

The major source for vitamin D is endogenous synthesis in the skin, where ultraviolet-B from sunlight induces the conversion of 7-dehydrocholesterol, a liver-derived vitamin D precursor, to vitamin D (11). Nutritional sources of vitamin D such as fatty fish, mushrooms and eggs, usually play only a minor role

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as a source of vitamin D, while the contribution of storage and release of vitamin D and its metabolites from tissue stores, such as the adipose tissue, is still largely unclear. Vitamin D has two main isoforms, *i.e.* vitamin D_3 (cholecalciferol), the endogenous (human) and animal-derived form, and vitamin D_2 (ergocalciferol), the plant-derived form. As these two isoforms generally share the same pathways of metabolism and since a discussion on potential differences between these two isoforms is beyond the scope of this review, we refer to vitamin D throughout without further differentiating between vitamin D_2 and D_3. The main circulating vitamin D form, 25-hydroxyvitamin D [25(OH)D], is generated by hydroxylation of vitamin D in the liver. 25(OH)D is then further hydroxylated to 1,25-dihydroxyvitamin D [1,25(OH)D], the so-called active vitamin D hormone, in the kidneys. In addition, several extra-renal tissues also actively metabolize vitamin D and are also, for example, able to convert 25(OH)D to 1,25(OH)2D at local tissue level (11). The biological effects of 1,25(OH)2D are mediated by binding to the almost ubiquitously expressed vitamin D receptor (VDR), resulting in the regulation of hundreds of genes (11). Thus, 1,25(OH)2D functions like a classic steroid hormone with vitamin D-binding protein (DBP) being the main transport protein for vitamin D metabolites in the circulation. Catabolism of vitamin D metabolites is initiated by 24-hydroxylation to form biologically less active metabolites that are finally excreted *via* the bile and urine.

Development of Nutritional Vitamin D Guidelines

Recommendations for dietary vitamin D requirements [called dietary reference intakes (DRI) or dietary reference values (DRV)] are generally based on pre-defined processes such as the risk assessment framework approach that aim to address key questions/topics that are essential to develop nutritional vitamin D guidelines (12-16). A very simplified outline of the usual key steps required to develop nutritional vitamin D guidelines for the general population is given below.

A main assumption underlying virtually all vitamin D guidelines is that 'total' serum 25(OH)D can be used as a biomarker of vitamin D status in general, and of vitamin D intake under conditions of minimal or no ultraviolet-B (sunlight) exposure. This assumption is made being aware of the relatively high inter-laboratory and inter-assay variability of 25(OH)D measurements, and in view of the accumulating evidence on the role of DBP and its impact on the 'free' and 'bioavailable' (*i.e.* free and albumin-bound) 25(OH)D concentrations (17, 18). Another assumption is that dietary requirements for other potentially interacting nutrients (such as calcium) are met.

The central question for guideline panels is whether there is sufficient evidence to claim a causal relationship between vitamin D status and certain health outcomes. For this aim, systematic evidence-based reviews (SEBR) are conducted to assess the relationship of vitamin D status and vitamin D interventions with skeletal and extra-skeletal health outcomes. Importantly, different study types, including cross-sectional and prospective observational studies, and not only RCTs or meta-analyses of RCTs, are considered in these SEBR. DRI or DRV for vitamin D are only released if existing evidence is considered sufficient in terms of a cause and effect relationship between vitamin D and certain health outcomes.

Following the identification of such a cause and effect relationship, the guideline panel aims to characterize a dose–response curve. Importantly, dose–response relationships between vitamin D intakes and health outcomes cannot be reliably calculated due to insufficient evidence; therefore serum 25(OH)D, as a biomarker of vitamin D intake, is usually used. This key process in determining the 25(OH)D and health outcome relationship results in the formulation of certain 'target' 25(OH)D concentrations, including the estimated average requirements (EAR), *i.e.* the 25(OH)D level at the estimated median requirement, and the recommended dietary allowance (RDA), *i.e.* the 25(OH)D level that meets or exceeds the vitamin D requirements of 97.5% of the population. If the standard deviation (SD) of the EAR is known, the RDA is set as the EAR plus twice the SD. Alternatively, the RDA can be estimated as 1.2 times the EAR if the data about variability in requirements are insufficient. If the EAR cannot be defined due to insufficient evidence, adequate intakes (AI) are recommended instead of RDAs. Although guideline panels perform extensive reviews of the literature, the final decision for setting the EAR/RDA/AI is usually not based on a specific statistical analysis, but rather on a panel decision taking into account the systematically reviewed whole body of literature.

After setting the 25(OH)D levels for the EAR/RDA/AI, the guideline panel aims to calculate the vitamin D intake required to achieve these desired 25(OH)D levels. For this aim, meta-regression analysis is performed on the achieved serum 25(OH)D according to total vitamin D intake. For this meta-regression analysis, conditions of minimal to no sunshine exposure are assumed so that *e.g.* only vitamin D RCTs performed during winter season at northern latitudes in Europe and Antarctica are used to calculate the dose–response relationship between vitamin D intake and serum 25(OH)D. The resulting regression curve on vitamin D intake and serum 25(OH)D shows the mean responses and the 95% confidence intervals (CI) around the mean response. It is critical for data interpretation and understanding that the 95% CI of this meta-regression analysis does not mean that 95% of the population will lie within this 95% CI, but rather that this 95% CI reflects the uncertainty about the position of the regression line. Some guidelines also calculate so-called 95% prediction intervals (PI) that allow for an approximation for the estimation of the requirements of 95%

of individuals in the overall population (19). Importantly, almost all nutritional vitamin D guidelines assume conditions of minimal or no sun exposure and acknowledge that the dietary vitamin D requirements may be lower or even be zero in the presence of dermal vitamin D synthesis.

In addition to EAR/RDA/AI, guideline panels also set the tolerable upper intake level that is 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 upper limit, the potential risk of adverse effects may increase" (15).

Overview of Vitamin D Guidelines

An excellent general overview of nutritional guidelines for vitamin D has been published (10). In general, recommended daily doses for vitamin D have significantly increased over the past 10 years. Many old guidelines recommended a daily vitamin D intake of 400 International Units (IU) (40 IU are equivalent to 1 μg) per day because this approximates to the vitamin D content of one teaspoon of cod-liver oil that was historically observed to be sufficient to prevent rickets (10, 20).

Nowadays, the Institute of Medicine (IOM) report on vitamin D and calcium released in 2010 is considered the benchmark for recent vitamin D guidelines for developing DRV/DRI (21, 22). The IOM concluded that the evidence on skeletal, but not on non-skeletal health outcomes, was sufficient to provide a sound scientific basis for vitamin D intake requirements. The IOM report selected outcomes such as calcium absorption, bone mineral density, osteomalacia and rickets. Risk of adverse consequences with reference to these outcomes increases below a 25(OH)D level of of 30 nmol/l (divide by 2.496 to convert to ng/ml), whereas there seems to be no additional benefit of a 25(OH)D level higher than 50 nmol/l. Concentrations of 25(OH)D of between 30 and 50 nmol/l are a grey zone in which the median vitamin D requirement may lie. Therefore, the IOM report set the EAR at 400 IU per day, corresponding to a 25(OH)D level of 40 nmol/l, and recommends an RDA for vitamin D of 600 IU per day for those aged 1-70 years and 800 IU per day for older individuals, corresponding to a 25(OH)D level of 50 nmol/l. The higher RDA for older individuals was explained by, amongst other reasons, a higher uncertainty of the available evidence for some age-related characteristics such as a higher fracture risk, and by RCT data supporting the efficacy of 800 IU per day for reduction of fracture risk. Due to limited evidence, an AI of 400 IU of vitamin D per day was set for the ages of 0 to 12 months. The upper limit for daily vitamin D intake was set at 1,000 IU for those aged 0 to 6 months, 1,500 IU for 6 to 12 months, 2,500 IU for ages 1 to 3 years, 3,000 IU for ages 4 to 8 years, and 4000 IU for individuals aged 9 years and older.

The European Food Safety Authority (EFSA) released dietary reference values for vitamin D in 2016 and considered, in line with the IOM report, a serum 25(OH)D level of 50 nmol/l as a suitable target (23). The AIs for daily vitamin D intakes were set at 600 IU for individuals aged 1 year and older, and at 400 IU for infants aged 7 to 11 months. Evidence was considered insufficient for setting AI in the first half-year of life, but it was noted that 400 IU per day are considered adequate for the majority of infants at this age (19). The upper limits for daily vitamin D intake set by the EFSA are 1000 IU in the first year of life, 2000 IU for 1 to 10 years, and 4000 IU for ages 11 years and older (23).

While we consider the IOM and the EFSA reports as the main nutritional vitamin D guidelines for the general population, we briefly touch a few aspects of other reports in this area and refer to other publications regarding a detailed list of all available guidelines (10). In 2012, the Nutrition Societies in Germany, Austria and Switzerland (DACH) published new reference values for vitamin D and considered a serum 25(OH)D level of 50 nmol/l or higher as an indicator of optimal vitamin D status (24). To achieve this level, a daily vitamin D intake of 800 IU per day for ages 1 year and older was recommended based on Irish RCTs by Cashman *et al*., who reported that a daily vitamin D intake of 800 IU per day is sufficient to achieve a 25(OH)D level of at least 50 nmol/l in about 90% to 95% of the Irish population (24, 25). In the first year of life, 400 IU of vitamin D were recommended (24). In the UK, the Scientific Advisory Committee on Nutrition (SACN) concluded that serum concentrations of 25(OH)D levels should not fall below 25 nmol/l at any time of the year in order to preserve musculoskeletal health (26). To achieve this, the SACN report recommends a reference nutrient intake, *i.e*. the amount of vitamin D that is likely to meet the needs of 97.5% of the population, of 400 IU of vitamin D per day for individuals aged 4 years or older. Data were considered insufficient for younger children but a "safe intake" of 340 to 400 IU per day has been recommended for ages 0 to <1 year, and of 400 IU per day for ages 1 up to <4 years. Several other nutritional vitamin D guidelines have been published, with the vast majority recommending target levels for 25(OH)D in the range of 25 to 50 nmol/l corresponding to vitamin D intakes ranging from 400 to 800 IU per day (10). In this context, we also want to stress that we restrict our review to nutritional vitamin D guidelines for the general population and we do not list or discuss vitamin D guidelines for patient populations, nor certain expert recommendations in this field (27-29).

Comment on Vitamin D Guidelines

It is beyond the scope of this review to address specific potential limitations of the above-mentioned nutritional vitamin D guidelines, but it should be acknowledged that the IOM report has been the subject of intensive discussion (8,

30, 31). In particular, the interpretation of a post-mortem bone biopsy study by Priemel *et al.* on the relationship between 25(OH)D and signs of osteomalacia has caused much controversy, as published elsewhere (8, 30, 31). Anyway, we greatly appreciate the guideline panels for their work and simply want to comment on some aspects that are, in our opinion, of relevance with reference to the above mentioned DRI.

The huge gap between recommended DRI for vitamin D and the actual high prevalence of vitamin D deficiency in the general population is of major concern (9, 32, 33). This definitely requires action from public health authorities to improve the vitamin D status in the general population in order to meet the dietary vitamin D requirements (34, 35). In particular vitamin D fortification of food, but also a combination of different approaches, is required to address the public health problem of vitamin D deficiency (34, 35). If health authorities are not seriously willing to address this issue, it may cause a significant public health burden. It should, however, also be stressed that it is important to avoid potential oversupplementation with vitamin D in the general population, although it seems logical that many individuals will start to take vitamin D supplements on a regular basis as long as health authorities release guidelines but do not initiate actions to meet the dietary vitamin D requirements (36). Interestingly, in the US, the daily vitamin D supplement use of ≥1,000 IU (with 95% CI) increased from 0.3% (0.1-0.5%) in 1999-2000, to 18.2% (16.0-20.7%) in 2013-2014 (36).

A limitation of current vitamin D guidelines is that the meta-regression analyses for the dose–response relationship between vitamin D intake and serum 25(OH)D are based on aggregate data and not on individual participant data (IPD) (37-39). The point is that meta-regression analyses based on aggregate data cut the information down to aggregate data of study groups instead of using the complete individual data, so that only between-study variability but not between-individual variability was considered in existing vitamin D guidelines (37-39). To address this issue, Cashman *et al.* performed a meta-regression analysis from IPD of seven vitamin D RCTs during winter including 882 participants (39). The vitamin D intake requirement to achieve a 25(OH)D level of at least 50 nmol/l in ≥97.5% of the individuals was 560 IU vitamin D per day when the meta-regression analysis was based on the conventional aggregate data, whereas it was 1,040 IU of vitamin D per day when calculated by the IPD-based approach (39). Interestingly, a recent RCT on vitamin D performed in 201 women during winter in Germany fits these data well, as a similar vitamin D dose (*i.e.* 800 IU vitamin D per day plus nutritional vitamin D intake, which is usually between 100 to 200 IU per day) has been shown to fulfil the dietary vitamin D requirement (40). Therefore, IPD meta-analyses should be the preferred statistical approach when carrying out meta-analyses and generating dose–response curves for nutritional guidelines.

Future Outlook

While several nutritional vitamin D guidelines have been published within the past few years, future tasks include working on and implementing public health strategies (in particular mandatory vitamin D fortification of food) to meet the dietary vitamin D requirements in the general population. Initiatives such as the EU ODIN project (Food-based solutions for Optimal vitamin D Nutrition and health throughout the life cycle; FP7-KBBE-2013-7-single-stage; Grant agreement no: 613977) aim to address this issue and will hopefully make a difference to public health policies in the future (35). These efforts will hopefully lead to a wide introduction of vitamin D food fortification (35).

Knowledge on vitamin D effects is significantly increasing as many RCTs on vitamin D have just been published or will be finished soon (41-46). The large vitamin D RCTs on clinical endpoints published in 2017 have not shown beneficial effects of vitamin D (43, 44). These findings come as no surprise as these RCTs have several limitations, such as the inclusion of individuals regardless of their 25(OH)D status, thus ignoring the results of meta-analyses showing that the risk of adverse health outcomes such as mortality is only significantly increased at very low 25(OH)D levels (47, 48). Considering that the associations of 25(OH)D and some health outcomes display a U- or J-shaped relationship, the achieved 25(OH)D levels of the placebo and intervention groups of some recent RCTs do not meaningfully differ with regard to relative risks for *e.g.* mortality when plotting the two groups onto a 25(OH)D and mortality regression curve (43, 44, 47, 48). Further potential limitations of these vitamin D trials are low response rates and access to vitamin D supplements and laboratory tests for 25(OH)D (49). Another problem with these RCTs is that they evaluated relatively high doses of vitamin D and not the doses required to meet the DRI, that are much lower. This is of concern, in particular when considering that a higher vitamin D dose may even be worse compared to a lower dose, as shown in a RCT with respect to risk of falls (50). Moreover, findings such as those from the EVITA trial showing no beneficial effect of 3 years of vitamin D supplementation on mortality or other clinical endpoints in 400 heart failure patients with low 25(OH)D levels should be accepted and communicated as relatively clear results of no effect (45). Apart from this, it should be acknowledged that long-term RCTs are required to evaluate health outcomes such as cancer, multiple sclerosis or Alzheimer´s disease adequately, but such long-lasting trials would also increase the risk of withdrawal and low adherence (49). Besides RCTs, Mendelian randomization studies that

evaluate whether genetically determined variation in 25(OH)D is associated with health outcomes are also needed, as they enable us to study life-long exposure (49, 51, 52). To conclude this future outlook for vitamin D, we are of the opinion that the accurate interpretation of vitamin D trials and their translation into potential public health actions and information will be one of the major challenges in the near future, particularly in view of reports of negative, null and positive effects of vitamin D (45, 50, 52-58).

Conclusion

Nutritional vitamin D guidelines usually recommend target levels for 25(OH)D of 25 to 50 nmol/l, corresponding to vitamin D intakes ranging from 400 to 800 IU per day. The alarming fact that significant sections of the general population do not meet these dietary vitamin D recommendations requires action from a public health perspective. Finally, it will be a challenge to accurately interpret the findings of large RCTs on vitamin D and to further improve our knowledge on vitamin D effects, with a particular focus on severely vitamin D-deficient individuals and on Mendelian randomization studies.

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