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OPINION PAPER

Vitamin D: do we get enough?

A discussion between vitamin D experts in order to make a step towards the harmonisation of dietary reference intakes for vitamin D across Europe

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Abstract
Summary On September 29, 2011, acknowledged experts in the field of vitamin D, mainly European, were brought together in order to discuss the recent scientific advances in relation to vitamin D: the current requirements and associations with various health outcomes. In this article, the discussions resulting from the meeting are summarized.
Introduction Several groups at risk for developing vitamin D insufficiency have been identified. Accordingly, reviews indicate that a significant percentage of the population

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worldwide have serum 25-hydroxyvitamin D levels below 50 nmol/l. In addition to the role of vitamin D in bone health, recent studies suggest that it may play a pivotal role in other systems, e.g., the cardiovascular system, pancreas, muscle, immune system and brain. Most evidence, however, is obtained from observational studies and yet inconclusive.

Methods To exchange and broaden knowledge on the requirements for vitamin D and its effect on various health outcomes, a workshop entitled "Vitamin D Expert Meeting: Do we get enough?", was organized.

Results Despite low vitamin D levels worldwide, consensus on the definition of deficiency is not yet reached. In order to define cut-off points for vitamin D whilst taking into account extraskeletal health effects, randomized controlled trials in these fields are warranted. The experts do emphasize that there is evidence to suggest an important role for vitamin D in the maintenance of optimal bone health at all ages and that vitamin D supplementation, in most studies co-administered with calcium, reduces fracture risk in the senior population.

Conclusion To reach a serum 25-hydroxyvitamin D level of 50 nmol/l older adults aged ≥65 years are therefore recommended to meet a mean daily vitamin D intake of 20 μg (800 IU), which is best achieved with a supplement.

Keywords Bone · Cognition · Diabetes · Muscle · Requirements · Vitamin D

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Introduction

Studies from all over the world clearly report that an inadequate vitamin D status is a global issue, both in the developed as well as in the developing world. Individuals at risk for vitamin D deficiency are infants, young children, veiled women, persons with a coloured skin, older adults and persons who live at high latitudes [1, 2]. In some studies, 40 % up to 100 % of the elderly have been diagnosed with an insufficient 25(OH)D status [2, 3]. In hip fracture patients aged ≥ 65 years, 80 % appeared to have 25(OH)D levels below 50 nmol/l. Less than 5 % reached a serum levels of 75 nmol/l, considered by some as optimal fracture reduction [4, 5].

Vitamin D is best known for its role in calcium metabolism and bone health, but recent studies suggest a much broader role of vitamin D [6]. Evidence from clinical trials among older adults suggests a benefit of vitamin D supplementation on both musculoskeletal function and fall prevention, but evidence is inconclusive (reviewed in [7–9]). Vitamin D has also been suggested to be associated with glucose and fat metabolism, cognitive functioning, immune function, cancer and cardiovascular disease (CVD) (reviewed in [2, 10–15]). In addition, two meta-analysis of prospective cohort studies showed that lower 25(OH)D levels were associated with a higher mortality risk [16, 17].On the other hand, Zittermann and colleagues [16] do mention that two of the studies included in their meta-analyses suggest that overabundant 25(OH)D levels may increase mortality risk.

Although vitamin D can be obtained from food, its main source is not the diet. In fact, nutritional sources are rare and largely limited to fatty fish such as salmon. Vitamin D is synthesized in the skin when ultraviolet-B (UV-B) radiation targets the skin at a wavelength between 290 and 315 nm. However, at latitudes above 33° (all of Europe), UV-B radiation is only effective during the summer months. The effectiveness of UV-B depends furthermore on the time of the day. During summer, early morning and late afternoon UV-B radiation is also not strong enough to activate vitamin D production. Furthermore, the production of vitamin D in the skin decreases with age [18]. Skin protection, which is broadly practiced, may further reduce skin production of vitamin D [19]. Accordingly, studies suggest that in many countries 25(OH)D levels are below 50 nmol/l, especially during the winter months (summarized in [1, 8]). Consensus on the optimal dietary intakes is, however, not yet reached (Table 1) [8, 20–24]. Doets et al. [25] summarized the current recommended vitamin D intakes across Europe and showed that there is a large variation, e.g., the recommendation for Russian men ≥70 years, last updated in 1991, is set at 2.5 μg/day, whereas this is 15 μg/day in Iceland and Spain, which were updated in 2006 and 2007, respectively.

Circulating 25(OH)D has the longest half-life (3–6 weeks) of vitamin D metabolites and represents both sunshine and

Table 1 Overview of vitamin D recommendations

	Children 0–1 year	Children 1–2 years	Children 2–3 years	Children 4–10 years	Children 11–18 years	19–50 years	51–60 years	61–70 years	>70 years	Pregnant/lactating (>18 years)
Institute of Medicine (IOM)[a]	10	15	15	15	15	15	15	15	20	15
Endocrine Society[b]	10 (10–25)	15 (15–25)	15 (15–25)	15 (15–25)	15 (15–25)	15 (37.5–50)	15 (37.5–50)	15 (37.5–50)	20 (37.5–50)	20 (37.5–50)
DACH[c]	10	20	20	20	20	20	20	20	20	20
Health Council of the Netherlands[d]	10	10	10	10	10	10	10	10	20*	10
Belgian Health Council[a]	10	10	10	10	10–15	10–15	10–15	10–15	15	20
Nordic Dietary Recommendations[e]	10	10	7.5	7.5	7.5	7.5	7.5	10	10	7.5

All values are presented in μg/day

[a] RDA

[b] Daily requirement Endocrine Society for healthy subjects (line 1). Between brackets: recommendations of the Endocrine Society for subgroups at risk for vitamin D deficiency (line 2). Recommendations are mainly based on lower quality evidence, therefore they should be considered as suggestions for patient care

[c] German, Austrian and Swiss vitamin D recommendations (AI). With exception to the recommendations for young children, recommendations are for persons with an inadequate endogenous vitamin D synthesis

[d] AI for persons with inadequate endogenous vitamin D synthesis (* indicates recommended daily intake [RI])

[e] Recommended daily intake (RI)

dietary sources and can therefore be considered to be the best biomarker of vitamin D status. Although there is no unanimity yet on the optimal levels of serum 25(OH)D, current evidence discussed by the Institute of Medicine (IOM) suggests a serum 25(OH)D level above 50 nmol/l as being sufficient [8]. Guidelines as provided by the International Osteoporosis Foundation (IOF) [26] and Endocrine Society (ES) [22] suggest that for optimal fracture prevention at older age a threshold of 75 nmol/l is desirable.

Meeting

To exchange the new scientific insights on vitamin D and the resulting implications for requirements of vitamin D, considering vitamin D's broader effect on human health, a conference entitled "Vitamin D Expert Meeting: Do we get enough?" was held on September 29, 2011, in Wageningen. Acknowledged experts in the field of vitamin D were brought together in order to discuss the recent scientific advances in the field. This expert meeting was organized by Wageningen University and Research Centre in close collaboration with DSM. Invitations were primarily sent to European experts. Attendees were selected according to their specialisation/health outcome and their availability at the time of the meeting. The IOM was invited to take the US's reflections on board. The program included presentations about the Dietary Reference Intake (DRI) in North America by CJG, global vitamin D status by ES, insights from epidemiological studies by EH, the possible relation with various metabolic processes and diseases by HAB-F, EJMF, DJL, and LCPGMdG, and the interaction between diet, sunlight and 25(OH)D by SL-N. Furthermore, the question "How to close the gap" was addressed by RB. Sessions were chaired by RB and EJMF.

The DRI for vitamin D for North America

In November 2010, the IOM presented the revised DRIs for calcium and vitamin D, which were last updated in 1997 [8]. Recently, the ES published their views on the treatment and prevention of vitamin D deficiency [22]. When compared to the recommendations as set by the IOM, the ES advocates higher intake levels in pregnant and lactating women, persons with obesity and those using specific medications. According to one of the workshop participants, screening all the individuals 'at risk' according to the ES guidelines would involve about 50 million individuals, just in the USA alone. During the meeting an overview of the similarities and differences of the two reports was given and inconsistencies were discussed. For instance, the IOM focussed its conclusions on randomized controlled trials (RCTs) and

considers 25(OH)D levels above 50 nmol/l to be sufficient for more than 97.5 % of the population. Based on the effects of vitamin D on fracture and fall reduction, serum PTH and pathologic osteoid formation the ES advocates for a level of 75 nmol/l.

The individual effect of vitamin D on fracture risk is difficult to assess, as most fracture trials that gave a higher dose vitamin D (20 μg) also provided calcium supplements. Of three double-blind placebo-controlled trials that provided vitamin D alone, one that gave 2,500 μg in a 4-monthly interval for 5 years showed significant fracture reduction [27], one at the same dose level annually (12,500 μg) suggested an increased fracture risk [28] and one that gave 7,500 μg intramuscularly showed no benefit regarding fracture risk [29]. In one meta-analysis of double-blind RCTs, the authors compared at the higher intake level (>10 μg/day) the main effect of vitamin D to the combination of vitamin D plus calcium compared to placebo, and found that both pooled effects showed significant non-vertebral fracture reduction of 20 % [30].

One of the factors associated with fracture risk is PTH, as it stimulates calcium release from bone. Low 25(OH)D levels have been shown to increase PTH secretion by the parathyroid glands, whereas PTH synthesis is suppressed when low 25(OH)D levels are restored. A recent literature review of 70 papers showed that several studies did not identify a ceiling effect for serum PTH with increasing vitamin D levels. Serum 25(OH)D levels varied, however, from 25 to 125 nmol/l, and therefore no specific upper limit could be specified [31].

One large cross-sectional study investigated bone mineral density (BMD) as an endpoint for bone health with respect to 25(OH)D status in both younger and older adults and suggested a positive correlation between 25(OH)D levels and hip BMD with optimal levels occurring between 75 and 100 nmol/l [32]. On the other hand, intervention studies showed little increase in BMD in vitamin D-replete participants [33].

Global vitamin D status — the map

Vitamin D insufficiency appears to be a common health issue all over the world. Therefore, a global map of 25(OH)D status in the different regions of the world has been launched (2012) by DSM, in partnership with the IOF [34]. During this meeting preliminary results of an European map illustrating the 25(OH)D status within different European countries was presented (Fig. 1). A literature study resulted in a selection of 80 peer-reviewed papers. A paper was considered eligible when it contained information on 25(OH)D — a sensitive marker of vitamin D status — either in a representative population based study or in a representative specific age group such as postmenopausal women or the elderly. For the general population mean 25(OH)D levels between 50 and 75 nmol/l were observed in Norway, France and Corsica, whereas in the Netherlands, Germany, Switzerland, Finland and Estonia the serum 25(OH)D levels were in the range of 25–50 nmol/l, revealing insufficiency. These values are below those recommended by the IOM. Data on postmenopausal women were only available of residents of the UK and Spain, showing average levels of 50–75 nmol/l. Mapping of the 25(OH)D status of elderly showed that elderly people appear to be at a higher risk for low 25(OH)D levels across Europe.

Vitamin D and health

Insights from epidemiological studies

Interest in the possible health benefits of vitamin D is rapidly growing and has led to an increasing number of papers on the possible association of 25(OH)D with several non-skeletal health outcomes. The results of meta-analyses performed within various epidemiological cohort studies were presented. It is clear that environmental factors such as sunlight induced synthesis, oily fish and supplement intake are of importance, however, also genetic make-up has been shown to affect 25(OH)D status. Meta-analyses by the Sunlight Consortium demonstrated a 2.5 increased risk of hypovitaminosis D for individuals in the top compared to lowest quartile based on the polymorphisms of a number of genes of the vitamin D pathway, namely those coding the vitamin D binding protein (GC), 25-hydroxylase (CYP2R1) and an enzyme involved in the metabolism of 7-dehydrocholesterol (DHCR7), which is a precursor of vitamin D [35]. Epidemiological studies have provided support for an association between perinatal vitamin D supplementation and the later risk of type 1 diabetes [36], with recent genetic studies suggesting a causal relation [37]. Analyses from epidemiological cohort studies such as the 1958 British Birth Cohort, suggest a link between 25(OH)D status and a wide range of outcomes including the metabolic syndrome [38], lung function and respiratory infections [39]; however, whether these associations are causal has yet to be demonstrated. Recent published data of an RCT in 182 patients with chronic obstructive pulmonary disease (COPD) showed no effect on vitamin D in the entire cohort, whereas COPD exacerbations were significantly reduced with vitamin D supplementation in patients with baseline 25(OH)D levels below 25 mmol/l [40].

Falls — evidence from intervention studies

Most evidence suggesting a favourable effect of vitamin D is related to bone health. Therefore, also the latest studies on

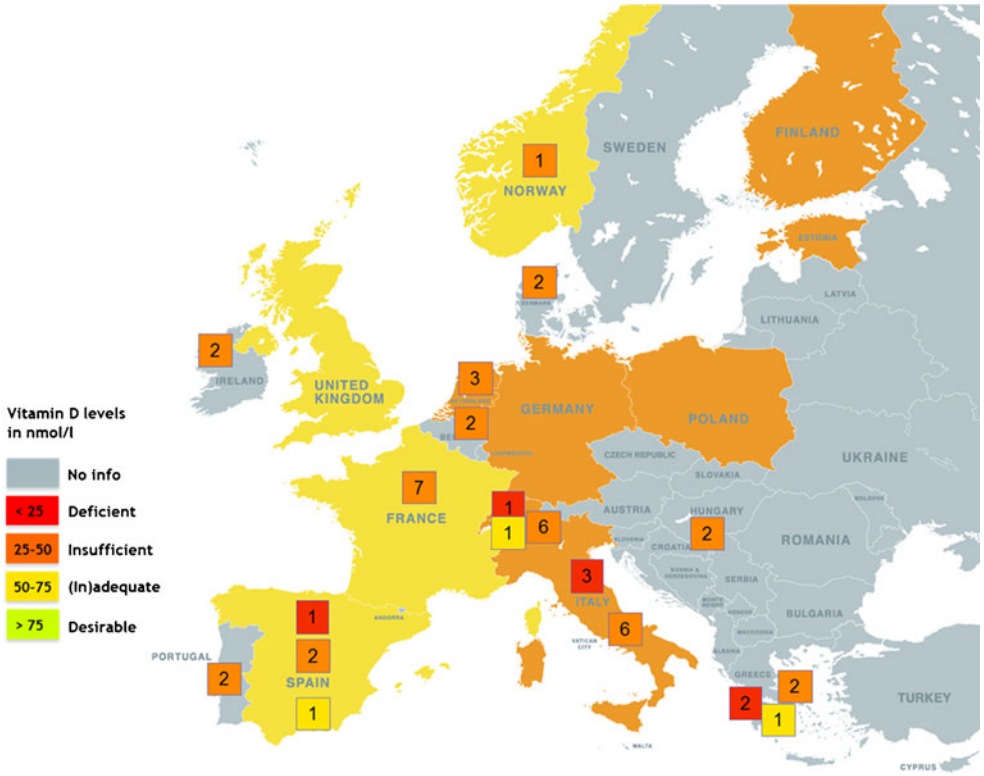

Fig. 1 Vitamin D status in Europe. Based on representative data (full coloured countries) and smaller studies in elderly (number displayed in square). References available as supplementary material

the possible relation of vitamin D with fall rate and fracture risk were presented during the meeting. Currently, there is disagreement regarding the interpretation of the scientific evidence on vitamin D and falls. Bischoff-Ferrari et al. [7] state that scientific evidence clearly supports the use of vitamin D in the prevention of falling. However, the IOM strongly disagrees with this point of view. According to the IOM [41], the inclusion procedure of the meta-analyses of eight double-blind RCTs (n=2,426) as performed by Bischoff-Ferrari and colleagues [7] was questionable, the statistical analyses were incorrect and data were inappropriately presented. Bischoff-Ferrari and colleagues [42] did not agree on the incorrect inclusion of RCTs, but did reanalyse the data in order to account for the stochastic dependencies (correlations) between the corresponding risk ratios in the multiple dosing trial by Broe et al. [43] and found a reduction in the odds of falling overall for dose of <17.5 μg versus 17.5–25 μg/day, OR 0.73 (95 % confidence interval (CI) 0.62–0.87). The IOM re-analysed the data of this meta-analysis [8] and concluded that there is lack of sufficiently strong evidence for the formulation of DRIs for vitamin D regarding fall prevention, according to their final meta-regression of RCTs showing relative risks (RRs) of 0.95 (95 % CI 0.89–1.02) per 2.5 μg/day increase in vitamin D intake [8]. One of the included RCTs even shows an increased fall rate among community-dwelling women aged ≥70 years receiving a single dose of 12,500 μg cholecalciferol annually for 3–5 years when compared to the placebo group, RR 1.15 with 95 % CI 1.02–1.30 [28]. Also, Glendenning et al. [44] observed in their 9-month trial that 28.9 % of the post-menopausal women, assigned to 3,750 μg cholecalciferol every 3 months, experienced at least one fall, whereas this was 26.7 % in the placebo group. This difference was, however, not significant (OR 1.06 with 95 % CI 0.75–1.49) [44]. A double-blind RCT on vitamin D supplementation and falls with sufficient power may help to solve this disagreement.

Fractures — evidence from intervention studies

To date, several meta-analyses have been published on vitamin D supplementation and fracture risk, using different inclusion criteria [8, 30, 45–49]. In the latest meta-analysis of pooled participant-level data of 11 RCTs on oral vitamin D supplementation and fracture prevention, Bischoff-Ferrari and colleagues conclude their paper as follows: "High–dose vitamin D supplementation (≥20 μg daily) was somewhat favourable in the prevention of hip fracture and any non-vertebral fracture in persons 65 years of age or older". The authors do mention, however, that all trials with vitamin D dosages ≥20 μg daily also supplemented calcium and that therefore the effect of an actual vitamin D intake ranging from 19.8 to 25 μg/day without additional calcium could not be assessed [49]. Tang and colleagues reviewed evidence of calcium use and calcium in combination with vitamin D on fracture risk by including 17 trials, showing a significant risk reduction, RR 0.88 (95 % CI 0.83–0.95) [48]. Separate analyses of the trials which supplemented calcium only and those supplementing calcium in

combination with vitamin D shows that there is only a small and non-significant difference between the two. The authors postulate that this may be because the vitamin D dosages used — 800 IU or lower — were not high enough to be effective in reducing fracture risk. A meta-analysis performed by the US Department of Health and Human Services (UDHHS), including ten double-blinded and three open-design trials (n=58,712), investigated the effect of vitamin D supplementation on total fracture risk among postmenopausal women and men aged ≥50 years and did not find a significant fracture reduction (pooled OR=0.90 with 95 % CI 0.81–1.02) [46]. The authors suggested that the benefit of vitamin D may depend on additional calcium and may be primarily seen in institutionalized individuals, which is consistent with the meta-analysis of Boonen and colleagues [45]. Moreover, in the DIPART Study, including seven RCTs in which vitamin D or vitamin D in combination with calcium was used to prevent fractures, hazard ratios (HR) of 1.01 (95 % CI 0.92–1.12) and 0.92 (95 % CI 0.86–0.99) were found for analyses including any fracture, respectively [47]. Subgroup analyses within the analysis by the UDHHS, including four trials reporting 25(OH)D concentrations >74 nmol/l at the end of the study, showed a statistically significant decreased fracture risk for participants reaching those levels [46]. These results are consistent with the outcomes of the more recent meta-analysis [30], which included 12 double-blind RCTs for non-vertebral fractures (n=42,279) and eight RCTs for hip fractures (n=40,886). Significant heterogeneity for received dose of vitamin D and achieved level of 25-hydroxyvitamin D in the treatment group for hip and any non-vertebral fractures was found [30]. No fracture reduction was observed for a received dose of 10 μg or less per day or achieved 25-hydroxyvitamin D levels of less than 74 nmol/l. Conversely, a higher received dose of 12–19 μg supplemental vitamin D per day reduced non-vertebral fractures by 20 % (pooled RR=0.80 with 95 % CI 0.72–0.89; n=33,265 from nine trials) and hip fractures by 18 % (pooled RR=0.82 with 95 % CI 0.69–0.97; n=31,872 from five trials). The IOM confirms a significant fracture reduction among those that reach at least 75 nmol/l in the treatment group, however, the IOM questions this finding as different assays were used to measure 25(OH)D levels with uncertain accuracy [8, 50, 51]. However, in an earlier meta-analysis of double-blind RCTs, Bischoff-Ferrari et al. [52] argue that despite interlaboratory differences there would still be a similar trend between higher 25(OH)D and fracture reduction. The aforementioned differences in interpretation and other methodological differences between studies have resulted in the current discussion on optimal vitamin D levels [49, 53–57].

Physical performance

Human muscle tissue is also a potential target organ for vitamin D action [58]. Clinical findings in vitamin D deficiency-associated myopathy include proximal muscle weakness, diffuse muscle pain, and gait impairments such as waddling way of walking [59]. Double-blind RCTs demonstrated that 20 μg/day vitamin D_3 resulted in a 4–11 % gain in lower extremity strength or function [60, 61], an 9 % up to 28 % improvement in body sway in adults age 65 years and older after 2–12 months of treatment [61, 62] and in an up to 72 % reduction in the rate of falls [43]. In fact, it has been suggested that the benefit of vitamin D on fracture risk may be mediated by the effect on muscle strength and fall prevention [63]. Extending to trials among individuals with a lower risk of vitamin D deficiency and including open design trials, a meta-analysis by Stockton et al. [64] identified 17 RCTs that tested any form of vitamin D treatment and documented a muscle strength related endpoint. The authors suggested that based on their pooled findings, vitamin D may not improve grip strength, but a benefit of vitamin D treatment on lower extremity strength could not be excluded among individuals with 25(OH)D starting levels of >25 nmol/l. In addition, the authors report a significant benefit among two studies with participants that started with 25(OH)D levels <25 nmol/l [64]. Muir and Montero-Odasso[9] also conducted a review of RCTs on the effect of vitamin D supplementation on physical performance and showed an effect on strength and balance, but not gait. One of the issues addressed by the authors is the possibility of selection bias [9]. The authors speculate that RCTs which excluded persons with specific medical conditions may have resulted in the attenuation of a probable relationship, as the persons with these specific conditions may be the ones experiencing the greatest benefit of supplementation with vitamin D [9]. Mechanistic studies show several pathways through which vitamin D may stimulate muscle mass and muscle strength, including amongst others the promotion of muscle cell proliferation and growth and an increase in the diameter and the percentage of type II muscle fibres [58]. Moreover, a genomic pathway has been postulated via binding with the vitamin D receptor (VDR) in muscle resulting in de novo protein synthesis [65, 66]. However, a recent publication questions the presence of VDR in muscle tissue since the receptor could not be located in this study while using a highly specific antibody [67].

Insulin resistance and type 2 diabetes

Based on association studies, it has been suggested that there is a possible role for vitamin D in the regulation of glucose and insulin levels [68–71]. VDRs and 1-α-hydroxylase have been identified in the pancreatic β-cell. Via its ability to regulate calcium fluxes, vitamin D may furthermore influence insulin release as well as insulin action. Moreover, by affecting cytokine production, vitamin D may play a beneficial role in β-cell survival and insulin

sensitivity. The evidence up to now shows that although animal studies and several epidemiological cohort studies point towards a protective effect of 25(OH)D on the development of type 2 diabetes [72], RCTs have not yet provided convincing evidence [12]. Mitri and colleagues [12] discuss that results of observational studies have to be interpreted with caution as they are limited by the possibility of residual confounding and reverse causation. Moreover, studies often rely on only one 25(OH)D measurement, while 25(OH)D fluctuates during the year [12]. The authors also speculate about the inconclusive data from trials. RCTs were often small, not specifically designed to assess the effect of vitamin D on glucose outcomes and used relatively low dosages. Furthermore, it is difficult to account for exposure to other sources of vitamin D, e.g. UV radiation and oral intake via foods [12].

Cognitive functioning and dementia

A growing body of evidence implicates low serum 25(OH)D levels in the pathogenesis of neurological diseases including multiple sclerosis [13] and stroke [73]. Low 25(OH)D levels are also associated with prevalent cognitive impairment and dementia as reviewed by Balion et al. [11]. For example, in elderly adults in the Health Survey for England who were severely vitamin D deficient (<25 nmol/l) an almost three times increased odds of cognitive impairment was observed when compared to those who were vitamin D sufficient (>75 nmol/l) [74]. Similarly, severely deficient US elders in the NHANES were almost four times more likely to be cognitively impaired than those with a sufficient vitamin D status (OR=3.9 with 95 % CI 1.5–10.4) [75]. However, cross-sectional studies are unable to exclude the possibility that such associations are a result of disease progression rather than being causal. Animal and in vitro experiments suggest that vitamin D is neuroprotective through several mechanisms including vasoprotection and amyloid phagocytosis and clearance [76, 77]. Two large prospective studies go some way to establish the temporal relationship with cognitive decline. The risk of cognitive decline, as assessed with the Mini Mental State Examination (MMSE) was 60 % higher in elderly Italian adults in the InCHIANTI study who are severely deficient when compared with those with sufficient levels [78]. After adjustment for age, site and season of blood drawn, an OR of 1.41 (95 % CI 0.61–3.28) for cognitive decline was observed when Slinin and colleagues [79] compared elderly US men in the Osteoporotic Fractures in Men Study in the lowest quartile (<50 nmol/l) with those in the highest quartile (>74 nmol/l); however, the association was not significant. Future neuroimaging studies and randomized trials are needed to provide further information about the underlying mechanisms and the efficacy of vitamin D supplements in combating dementia.

Adverse health effects

There is little or no data on toxicity of high doses of vitamin D for more than 1 year. A safe upper intake of 250 μg (10,000 IU/day) based only on serum calcium data is described in the most recently published benefit–risk assessment by Bischoff-Ferrari et al. [80]. In 2010, the IOM applied a safety factor of 2.5 and defined a safe upper limit of 100 μg [8]. A recent cross-sectional post-mortem bone histology study showed no pathologic accumulation of osteoid in a mixed German population of men and women with serum 25(OH)D levels above 75 nmol/l, although in 97.5 % of the cases abnormal osteoid was only present below 50 nmol/l. On the other hand, a reasonable proportion of those with 25(OH)D levels below 25 nmol/l also appeared to have normal bone mineralization, suggesting that it is not possible to directly extrapolate these results to the individual level [81]. Care has to be taken with regard to calcium intake, as a too high calcium intake may increase CVD risk [82]. Gallagher and colleagues observed hypercalciuria in 30 percent of women treated with vitamin D and a calcium intake of 1,260 mg/day [83]. Moreover, an increased prevalence of nephrolithiasis was observed in the Women's Health Initiative, in which participants were assigned to 10 μg of vitamin D in combination with 1,000 mg of calcium during on average 7 years [84]. At this moment, evidence for an adverse effect of high serum 25(OH)D levels is inadequate, possible adverse interactions with high calcium intakes may require further attention.

Diet, sunlight and 25(OH)D

The interaction between diet and sunlight exposure on 25(OH)D, functional markers of calcium metabolism and bone health has been investigated in Asian and Caucasian women living in Surrey, Southern England, participating in the D-FINES (Vitamin D, Food Intake, Nutrition and Exposure to Sunlight) Study. Comparing D-FINES data with data of women living in Aberdeen, North England, Macdonald and colleagues [85] showed that during the winter period, the average 25(OH)D levels were 10 nmol/l lower compared to those living at lower latitudes [85]. Although there was three times as much rainfall in the summer of 2007, when compared to the summer of 2005 and 2006, spring 25(OH)D levels in 2008 were not significantly affected. Caucasian women had consistently higher serum 25(OH)D levels than Asian women. Premenopausal status was associated with a 6 nmol/l higher serum 25(OH)D level when compared to postmenopausal status. Vitamin D intake levels were on average 2–3 μg/day and did not differ between the two ethnic groups. None of the Asian women was using vitamin D supplements at the start of the study and also exposure to sunlight appeared to be lower when compared to Caucasian women.

As vitamin D2 and D3, the two calciferols, display different affinities for the vitamin D binding protein, food fortification with either vitamin D2 or D3 may differently affect 25(OH)D status. Studies in the 1930s did not point towards a distinction, but a recent trial comparing large doses of vitamin D2 versus vitamin D3 at 1,250 μg per week for 12 weeks does suggest that vitamin D3 supplementation results in a higher increase of 25(OH)D over time [86]. Using smaller doses of D2 and D3 (25 μg daily), no differences in serum 25(OH)D were shown after 12 weeks of supplementation [87]. Currently, the D2–D3 Study is conducted to further explore this dissimilarity between ergocalciferol and cholecalciferol. The study aims to compare the efficiency of 15 μg/day of both calciferols, determine whether there is a difference in effect of the calciferol when carried by either solid or fluid foods and disentangle potential underlying mechanisms. Based on aforementioned results it was suggested that dietary vitamin D intakes in the UK may be too low to significantly affect 25(OH)D status. As vitamin D only occurs in a small range of foods, food fortification may be one of the methods to increase dietary vitamin D intakes. Supplementation may, however, be necessary in specific populations like Asian people which are at an increased risk for developing vitamin D deficiency. In future research it may be interesting to address the question whether there is a metabolic adaptation of populations accustomed to low 25(OH)D status during specific periods of the year.

How to close the gap — outlook for Europe

The meeting was concluded with a short overview of the current evidence of vitamin D recommendations and its effect on skeletal health and beyond. The main discussion among vitamin D researchers was related to the optimal 25(OH)D concentrations; do we aim for either levels above 50 nmol/l or levels above 75 nmol/l? The implications are that meeting a level of 50 nmol/l requires about 15–20 μg daily (600–800 IU), whereas meeting a level of 75 nmol/l requires 40–50 μg (1,600–2,000 IU) daily [83]. Before reaching a consensus on the optimal DRIs, participants of the meeting decided that the postulated DRIs should preferably be based on RCTs and had to be applicable to the general population. For those at an increased risk for developing inadequate 25(OH)D levels a more specific advice had to be formulated. Lastly, recommendations should preferably be harmonized across Europe. Subsequently, the experts concluded that up to now for most health outcomes, except bone health and risk reduction of falls (EFSA claim), there is insufficient evidence with regard to the optimum 25(OH)D level or vitamin D intake. When summarizing the evidence several aspects have to be taken into account. First of all, most RCT examining the effect of vitamin D on bone health and fall prevention co-administered calcium. The individual effect of vitamin D is therefore difficult to assess. Secondly, in vitamin D supplementation trials it is difficult to account for difference in UV radiation, which may disturb the relations studied. Thirdly, most human studies on vitamin D and health outcomes beyond bone health were observational, using either cross-sectional or longitudinal data. Therefore, the possibility of reverse causation and residual confounding cannot be excluded. Fourthly, evidence from in vitro and molecular studies have to be read with caution as they often link 1,25(OH)D levels with specific target tissues [88], while 1,25(OH)D is not the optimal biomarker for vitamin D and showing a low correlation with 25(OH)D [89]. Finally, pooling and comparing studies is difficult due to the lack of standardization of 25(OH)D assays [90]. Most assays used today are able to distinguish between high and low vitamin D levels, however there may be quite some variation when looking at the absolute levels.

Infants and children

Critical analysis of the current scientific evidence shows that, in children, rickets is preventable by a dose of 10 μg/day, which is in consensus with the current guidelines for this target group in the US, UK, Belgium and the Netherlands. Therefore, the consensus dose for both infants and children was set at 10 μg/day. Difficulties in implementing these recommendations, however, include that more and more vitamin D-enriched products are sold.

Adults and elderly

Osteoporotic fracture risk has been shown to decrease with vitamin D intakes of 12–19 μg [30], in combination with an adequate calcium intake. Direct and indirect evidence indicates furthermore that 25(OH)D levels of ≥50 nmol/l are desired and not contraindicated with regard to other health outcomes, including the optimal functioning of the parathyroid glands/PTH secretion [91, 92], calcium metabolism [93, 94] and BMD [95–97]. Moreover, valid hypotheses based on preclinical data and in vitro studies have been raised for a role of vitamin D in the development of extra-skeletal diseases, including respiratory infections, tuberculosis, multiple sclerosis, cancer, diabetes and CVD. RCTs, however, are needed to verify these results. As supplementation of 15–20 μg/day has been shown to increase 25(OH)D levels to 50 nmol/l or higher and since there is, at present, insufficient evidence supporting an amplified beneficial role of vitamin D with 25(OH)D serum levels >50 nmol/l, the meeting considered a vitamin D intake of 20 μg/day to be sufficient in a population of healthy adults and elderly, which is in line with the recently published DACH recommendations [20]. To date, there is insufficient data on the

optimal 25(OH)D levels in order to achieve the maximum peak bone mass in adolescence and young adulthood, therefore no specific DRI was formulated for this age group. Issues remaining after the discussion were related to the safety level of intakes higher than 50 μg/day during a longer period, whether a higher dose of vitamin D eliminates the need for calcium supplements and how to implement and increase the compliance to current guidelines. In conclusion, there is evidence suggesting that vitamin D — besides its established role in bone health — may contribute to reduce the risk of a variety of chronic diseases to benefit human health, but more evidence is warranted. It is generally felt that in adults a daily intake of 20 μg vitamin D is a safe dose to assure an appropriate vitamin D status.

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Attendees Elske M Brouwer-Brolsma (Minutes secretary), Wageningen University, the Netherlands; Heike Annette Bischoff-Ferrari (Speaker), UniversitätsSpital Zurich, Switzerland; Roger Bouillon (Chair), Katholieke Universiteit Leuven; Edith JM Feskens (Chair), Wageningen University, the Netherlands; Chris J Gallagher (Speaker), Division of Endocrinology Creighton, United States of America; Elina Hypponen (Speaker), Institute of Child Health, United Kingdom; David J Llewellyn (Speaker), Institute of Biomedical and Clinical Sciences Peninsula College of Medicine and Dentistry University of Exeter Royal Devon and Exeter Hospital Barrack Road Exeter, United Kingdom; Elisabeth Stoecklin (Speaker), DSM Nutritional Products, Switserland; Susan Lanham-New (Speaker), University of Surrey, United Kingdom; Jutta Dierkes, University of Bergen, Norway; Arie K Kies, DSM Biotechnology Center, the Netherlands; Frans J Kok, Wageningen University, the Netherlands; Christel Lamberg-Allardt, University of Helsinki, Finland; Ulrich Moser, Switzerland; Henk van den Berg, the Netherlands; Stefan Pilz, Medical University of Graz, Austria; Wim H Saris, DSM Nutritional Products, the Netherlands; Natasja M van Schoor, VU University Medical Center, the Netherlands; Peter Weber, DSM Nutritional Products, Switzerland; Renger Witkamp, Wageningen University, the Netherlands; Armin Zittermann, Ruhr University Bochum, Germany; Lisette CPGM de Groot (Speaker), Wageningen University, the Netherlands.

Conflicts of interest None.

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