

Benefit–risk assessment of vitamin D supplementation

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Received: 23 September 2009 / Accepted: 26 October 2009 / Published online: 3 December 2009

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Abstract

Summary Current intake recommendations of 200 to 600 IU vitamin D per day may be insufficient for important disease outcomes reduced by vitamin D.

Introduction This study assessed the benefit of higher-dose and higher achieved 25-hydroxyvitamin D levels [25(OH)D] versus any associated risk.

Methods and results Based on double-blind randomized control trials (RCTs), eight for falls ($n=2426$) and 12 for non-vertebral fractures ($n=42,279$), there was a significant

dose–response relationship between higher-dose and higher achieved 25(OH)D and greater fall and fracture prevention. Optimal benefits were observed at the highest dose tested to date for 700 to 1000 IU vitamin D per day or mean 25(OH)D between 75 and 110 nmol/l (30–44 ng/ml). Prospective cohort data on cardiovascular health and colorectal cancer prevention suggested increased benefits with the highest categories of 25(OH)D evaluated (median between 75 and 110 nmol/l). In 25 RCTs, mean serum calcium levels were not related to oral vitamin D up to 100,000 IU per day or achieved 25(OH)D up to 643 nmol/l. Mean levels of 75 to 110 nmol/l were reached in most RCTs with 1,800 to 4,000 IU vitamin D per day without risk.

Conclusion Our analysis suggests that mean serum 25(OH)D levels of about 75 to 110 nmol/l provide optimal benefits for all investigated endpoints without increasing health risks. These levels can be best obtained with oral doses in the range of 1,800 to 4,000 IU vitamin D per day; further work is needed, including subject and environment factors, to better define the doses that will achieve optimal blood levels in the large majority of the population.

Funding Heike Bischoff-Ferrari is supported by a Swiss National Foundation Professorship Grant (PP00B-114864). This project was supported by an investigator-initiated and unrestricted grant provided by DSM and by a Centre Grant of the University of Zurich and the Town of Zurich (Centre on Aging and Mobility).

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Keyword Falls · Fractures · Hypercalcemia ·
Recommendations · Risk · Vitamin D

Introduction

Voluminous data suggest that higher 25-hydroxyvitamin D [25(OH)D] serum concentrations are advantageous for chronic disease prevention. At present, strong evidence for causality is available for fracture [1] and fall endpoints [2], while promising epidemiologic and mechanistic studies suggest a key role of vitamin D in the preservation of cardiovascular health [3–6] and the prevention of cancer [7]

and other common chronic diseases [8]. However, benefits of vitamin D on falls, fractures, cardiovascular health, and cancer prevention that have been observed with higher 25(OH)D levels cannot be achieved in the large majority of individuals following current recommendations for vitamin D intake. The current adequate intake (AI) for vitamin D, as defined by the US Institute of Medicine (IOM), of 200 IU per day for adults up to 50 years of age (5 µg), 400 IU per day for adults between age 51 and 70 years (10 µg), and 600 IU per day for those aged 70 years and over (15 µg) will achieve a serum 25(OH)D level of up to 50 or 60 nmol/l for 2/3 of adults.

This review draws together recent work by the authors and others on the benefits and risks of higher achieved 25(OH)D levels beyond 60 nmol/l to provide guidance in current efforts to define dose recommendations for vitamin D in the absence of large randomized trials for non-skeletal endpoints. We first examined double-blind randomized control trial (RCT) data for fall and fracture prevention, as well as mean serum calcium levels by dose and achieved 25(OH)D levels. Specifically, we assessed a dose–response relationship for these endpoints with established causality to explore whether the benefit of higher vitamin D dose and higher 25(OH)D levels is accompanied by an increase in risk of hypercalcemia. Additionally, we assessed whether there were single case reports of hypercalcemia or nephrolithiasis from the same RCTs.

We also evaluated dose–response relationships for non-skeletal outcomes of public health significance, including cardiovascular disease and cancer, especially colorectal cancer, in the context of case reports of hypercalcemia and documented 25(OH)D levels. Our overarching goal was to determine the optimal 25(OH)D level and vitamin D intake that correspond to optimal health without risk of adverse effects.

Methods

In this review, we summarize evidence for optimal serum 25(OH)D levels with respect to benefit and risk. The established benefits of higher vitamin D dose and higher achieved serum 25(OH)D levels were reduction in falls and fractures as summarized in two 2009 meta-analyses of double-blind RCTs [1, 2]. The established risk of higher intake of vitamin D or higher achieved serum 25(OH)D level that we evaluated in the same RCTs and any available RCTs of vitamin D supplementation and reported 25(OH)D status was hypercalcemia, evaluated as mean serum calcium level. We also examined case reports of hypercalcemia or nephrolithiasis in these trials.

Additionally, we review benefits of vitamin D with the strongest evidence today from prospective epidemiological

studies that are supported by strong mechanistic evidence, specifically reduction of cardiovascular disease (incident hypertension and cardiovascular mortality) and colorectal cancer. Weaker evidence of a beneficial effect of vitamin D exists for other diseases, including multiple sclerosis [9], tuberculosis [10], insulin resistance [11, 12], other cancers [13–16], osteoarthritis [17, 18], and prevalent hypertension [19–21], but these are not considered here. For the assessment of risk in observational studies, we include data on serum calcium levels with any reported 25(OH)D level from case reports of vitamin D intoxication.

The risk assessment method used is a slight modification of the Institute of Medicine's tolerable upper intake level (UL) method, as applied in a previous risk assessment on vitamin D by some of the current authors [22]. Our procedure uses the UL protocol exactly, except for a conservative selection of data so that no further correction for uncertainty is required [23]. Details of the entire literature up to that time were described in the previous risk assessment [22].

The benefit and risk that occur with increases in 25(OH)D concentration were placed in context with each other graphically using trend-plots for each selected endpoint (decreased risk of falls and non-vertebral fractures) at different doses of vitamin D and achieved 25(OH)D levels. Given the limitations of using mean achieved serum calcium levels reported as a risk endpoint in trials of vitamin D supplementation, we also used individual serum calcium values in published case reports of hypercalcemia alleging vitamin D intoxication to compare with the prospective cohort data relating 25(OH)D concentrations to risks of cardiovascular disease and colorectal cancer.

Results

Benefit and risk data from RCTs

Benefit of higher 25(OH)D levels on non-vertebral fracture prevention

In a recent meta-analysis, the efficacy of oral supplemental vitamin D in preventing non-vertebral and hip fractures among older individuals was examined (age 65+ years) [1]. The analysis included 12 double-blind RCTs for non-vertebral fractures ($n=42,279$; [1, 2, 24–32]) and eight RCTs for hip fractures ($n=40,886$; [24, 25, 29, 30, 32–35]) comparing oral vitamin D with or without calcium with calcium or placebo. The pooled relative risk (RR) was 0.86 (95% CI, 0.77–0.96) for prevention of non-vertebral fractures and 0.91 (95% CI, 0.78–1.05) for the prevention of hip fractures but with significant heterogeneity for both endpoints. Including all trials, anti-fracture efficacy

increased significantly with higher-dose and higher achieved blood 25(OH)D levels for any non-vertebral fractures and hip fractures separately. Consistently pooling trials with a higher received dose of more than 400 IU per day (received dose of 482–770 IU per day) resolved heterogeneity and resulted in fracture reduction, while the lower received dose (340–380 IU per day) did not reduce fracture risk. For the higher doses, the pooled RR was 0.80 (95% CI, 0.72–0.89; $n=33,265$ persons from nine trials) for non-vertebral fractures and 0.82 (95% CI, 0.69–0.97; $n=31,872$ from five trials) for hip fractures. The higher doses reduced non-vertebral fractures significantly in community-dwelling (–29%) and institutionalized older individuals (–15%), and its effects were independent of additional calcium supplementation. Non-vertebral fracture prevention started with achieved 25(OH)D levels of at least 75 nmol/l in the treatment group. From left to right, Fig. 1a indicates increased anti-fracture efficacy with higher dose and Fig. 1b with higher achieved 25(OH)D levels in the treatment group [meta-regression analyses by dose, $p=0.003$; by achieved 25(OH)D level, $p=0.04$; these values are based on 12 trials for dose and ten trials with measured 25(OH)D levels]. From Fig. 1a optimal fracture prevention occurred in trials with achieved mean 25(OH)D levels of approximately 75 to 110 nmol/l.

This threshold of optimal non-vertebral fracture prevention is supported by a large cross-sectional and population-based study that showed a positive dose–response association between higher 25(OH)D levels and hip bone density both in younger and older adults [36]. In the regression plots, higher serum 25(OH)D levels were associated with higher hip bone density throughout the reference range of 22.5 to 94 nmol/l in all subgroups by age and ethnicity. In younger whites and younger Mexican Americans, higher 25(OH)D levels were associated with higher hip bone density even beyond 100 nmol/l.

Benefit of higher 25(OH)D levels on fall prevention

In another meta-analysis, the efficacy of oral supplemental vitamin D in preventing falls among older individuals (age 65+years) was examined [2]. Only double-blind RCTs with prospective fall assessment were considered (falls were assessed as a primary or secondary endpoint, authors stated how falls were defined and assessed, and falls were assessed over the whole trial period). The analysis included eight double-blind RCTs ($n=2426$; [31, 37–43]) comparing oral vitamin D with or without calcium with calcium or placebo. The pooled RR was 0.87 (95% CI, 0.77–0.99) for prevention of falls but with significant heterogeneity (Q-test, $p=0.05$). Heterogeneity was observed for dose of vitamin D (low-dose, <700 IU per day versus higher-dose, 700 to 1000 IU per day; $p=0.02$) and achieved 25(OH)D

level (<60 nmol/l versus ≥ 60 nmol/l; $p=0.005$). Higher-dose supplemental vitamin D reduced fall risk by 19% (pooled RR=0.81; 95% CI, 0.71–0.92; $n=1921$ from seven trials). Falls were not reduced by low-dose supplemental vitamin D (pooled RR=1.10, 95% CI, 0.89–1.35 from two trials) or by achieved serum 25(OH)D concentrations less than 60 nmol/l (pooled RR=1.35, 95% CI, 0.98–1.84). Fall prevention increased with higher dose (Fig. 2a) and with higher achieved 25(OH)D levels in the treatment group (Fig. 2b). Similar to non-vertebral fracture prevention described above, optimal fall prevention appeared to occur in trials with achieved mean 25(OH)D levels of approximately 75 to 100 nmol/l (see Fig. 2b).

This threshold of optimal fall prevention is supported by a large cross-sectional and population-based study that showed a dose–response association between higher 25(OH)D levels and better lower extremity function in older adults [44]. For both tests (8-foot walk, repeated sit-to-stand), performance speed continued to increase throughout the reference range of 25(OH)D (22.5 to 94 nmol/l) with most of the improvement occurring in 25(OH)D levels going from 22.5 to approximately 60 nmol/l. Further improvement was seen in the range of 60–94 nmol, but the magnitude was less dramatic.

Levels of 25(OH)D in relation to change in mean serum calcium levels and hypercalcemia in controlled trials

We included the published 22 RCTs involving an oral dose (either D2 or D3) of greater than or equal to 1,800 IU per day (or the equivalent in weekly, monthly, bolus doses, etc...) and in which both mean serum calcium and serum 25(OH)D were reported [45–66]. The reason for this cutoff stems from the purpose of conducting a risk assessment for doses close to or greater than the IOM identification of 2,000 IU as the tolerable UL. In addition, in Fig. 1a, b, we plotted mean serum calcium levels from five double-blind RCTs that reported serum calcium levels after vitamin D supplementation along with the fall and fracture endpoints [29, 34, 38, 43, 67]. The vitamin D doses in these five trials ranged from 400 to 800 IU vitamin D per day. In Fig. 1a, b, a total of 28 data points for mean calcium levels are depicted (two data points stem from one trial for the report by type of dwelling [45]). In Fig. 1a, b, we drew a trend line based on this series of mean serum calcium levels. The horizontal trend line indicates that mean serum calcium levels did not increase with higher doses of vitamin D up to 100,000 IU per day (Fig. 1a) or with higher achieved 25(OH)D levels up to 643 nmol/l (Fig. 1b). The one trial with 100,000 IU dose of vitamin D per day had a very short duration of 4 days, while the other trials ran for at least one half-life of vitamin D, which is 3 to 6 weeks. We address treatment duration in more detail later in the Results section. Notably, in none of the trials was there a shift of

mean serum calcium levels above the normal physiologic range (>2.6 mmol/l) with vitamin D treatment. However, in the Honkanen et al. trial depicted in Fig. 1a, b, there was an increase in mean serum calcium levels above 2.6 mmol/l in the institutionalized control group receiving calcium supplementation without vitamin D [45]. Not shown in Fig. 1 is one controlled trial with a report of increased mean calcium levels above 2.6 mmol/l as the trial did not measure 25(OH)D levels: the Narang et al. 1984 trial randomized 30 healthy adults to 0, 400, 800, 1,200, 2,400, and 3,800 IU per day for 90 days and observed a significant increase in mean serum calcium levels in the two highest dose groups (2.62 and 2.82 mmol/l, respectively) [68]. The limitations of the Narang study include the location and population studied (India), the small sample size ($n=5$ per group), and failure to measure serum 25(OH)D levels. Finally, the finding of a significant increase in mean serum calcium levels at these doses has not been replicated in any subsequent published RCT.

For reports of single cases of hypercalcemia, two RCTs of the 28 RCTs identified and depicted in Fig. 1a, b reported single cases where serum calcium levels rose above the normal range (>2.6 mmol/l): (1) Talwar et al. 2007 with a daily dose of 2,000 IU plus 1,500 mg calcium supplementation in healthy black women treated for 12 months [48]; and (2) Maalouf et al. 2008 with a daily dose of 2,000 IU vitamin D in healthy Lebanese adolescents treated for 12 months [47]. In the Talwar study, six isolated incidents of mild hypercalcemia occurred in eight clinical visits over 3 years in 208 women. The authors report that all six cases of hypercalcemia resolved on the repeat fasting sample. In the Maalouf study, hypercalcemia ranging from 2.7 to 2.77 mmol/l was described in seven of 340 adolescents, five cases in the placebo group, one with 1,400 IU vitamin D per week (equivalent to 400 IU per day), and one with 14,000 IU vitamin D per week (equivalent to 2,000 IU per day).

Of all controlled trials with vitamin D, an increased incidence of nephrolithiasis occurred only in the very large Women's Health Initiative (WHI) trial (involving 400 IU vitamin D plus 1,000 mg of calcium per day) [24].

We also identified ten uncontrolled trials with oral vitamin D supplementation at doses of at least 1,800 IU per day and reported serum calcium levels after treatment [69–77]. Of these, two reported an increase in mean serum calcium levels above the normal range or single cases with hypercalcemia: (1) Tucci et al. reported a mean serum calcium level that exceeded 2.6 mmol/l at baseline and after administration of 7,120 IU vitamin D per day in adult primary hyperparathyroidism patients [74]. Mean serum calcium levels were 2.73 mmol/l at baseline and after treatment; however, the authors also reported of two patients in whom serum calcium levels rose from 2.8 to

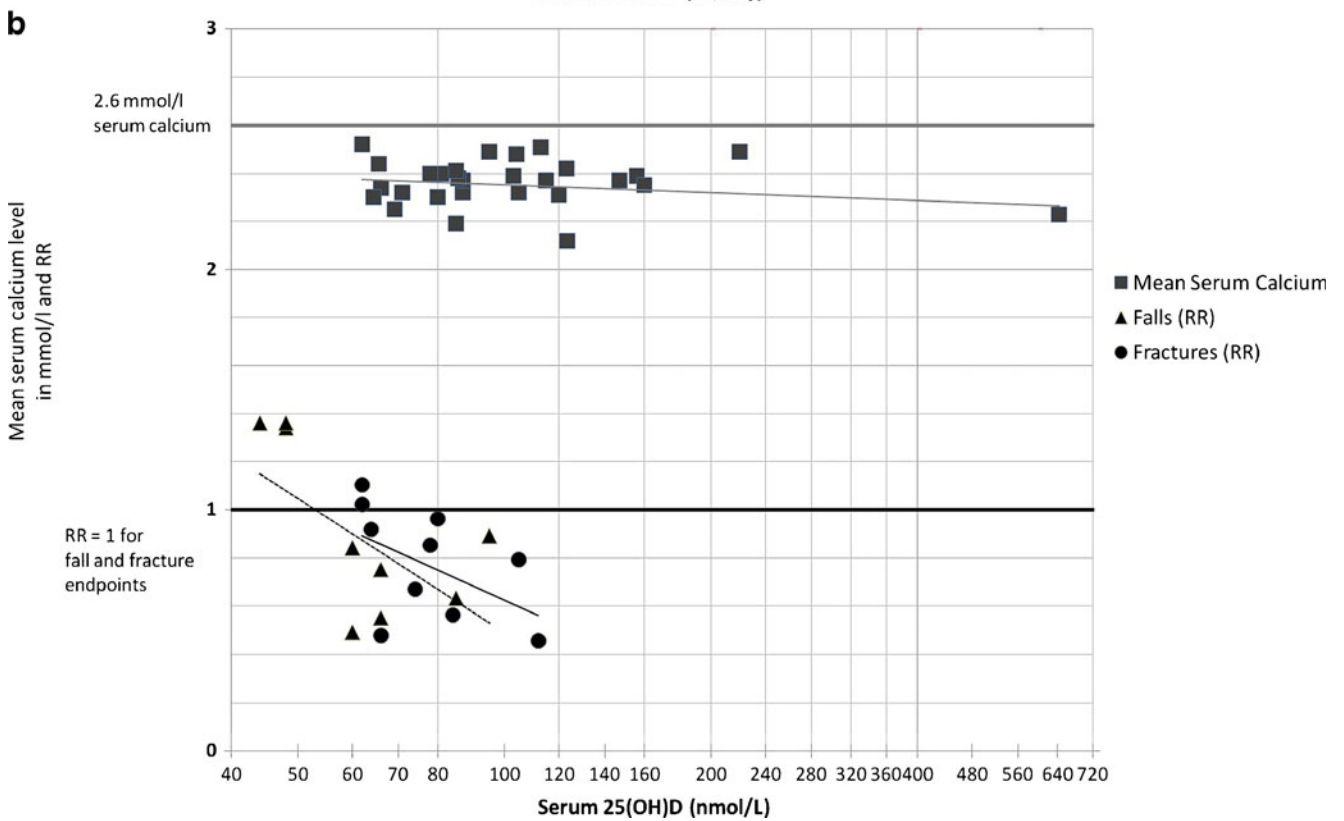
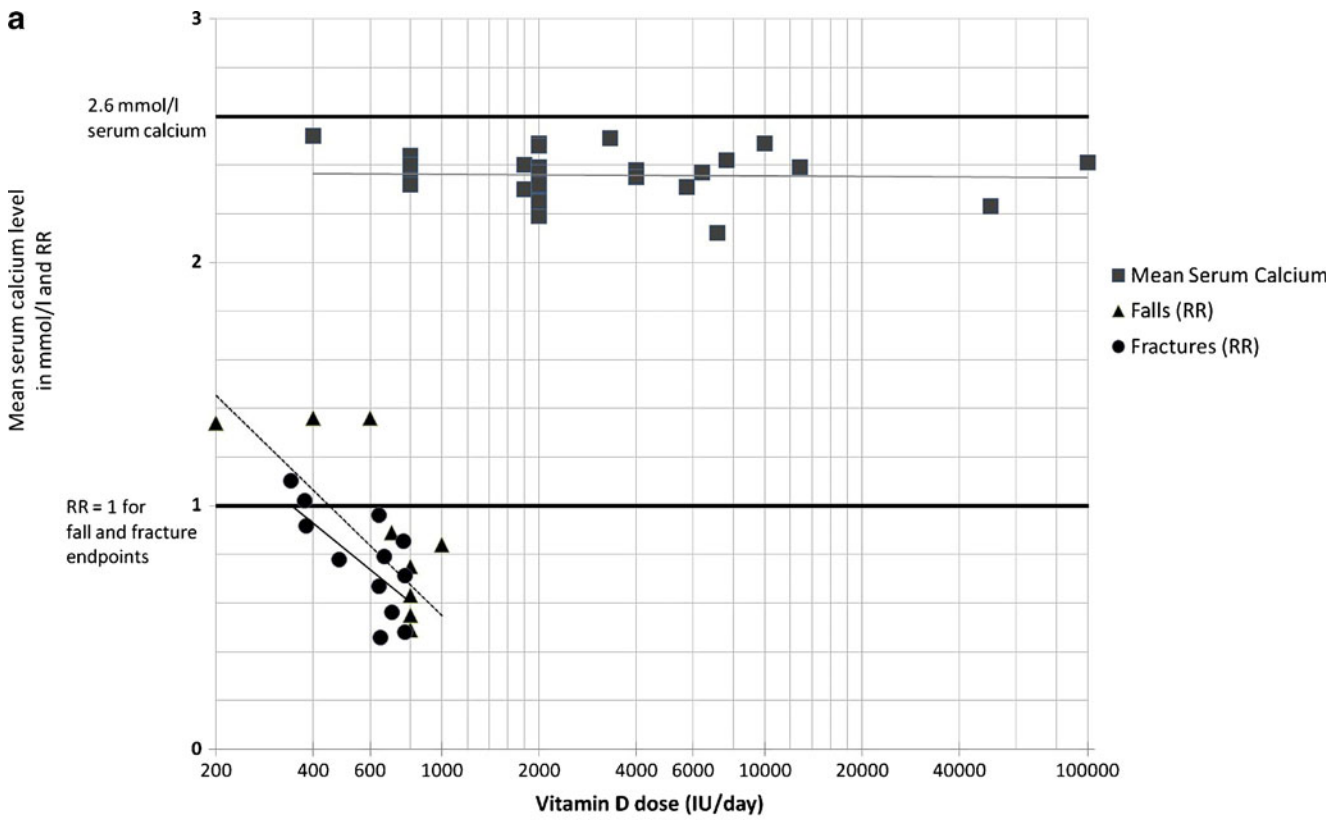
Fig. 1 Evidence from controlled RCTs. Trend-plots on benefit (fall and non-vertebral fracture prevention) and risk (mean achieved serum calcium levels) by dose of vitamin D and achieved 25(OH)D levels. **a** By dose of vitamin D. **b** By achieved 25(OH)D level. *Black circles* represent relative risks (RRs) from 12 double-blind RCTs on vitamin D supplementation and non-vertebral fracture risk as summarized in a 2009 meta-analysis (Bischoff-Ferrari et al.; *Archives of Internal Medicine* 2009 [1]). Trend line is based on series of effect sizes (*circles*). For any non-vertebral fractures, anti-fracture efficacy increased significantly with higher received dose [meta-regression: $\text{Beta}=-0.0007$; $p=0.003$; (**a**)] and higher achieved 25-hydroxyvitamin D levels [meta-regression: $\text{Beta}=-0.005$; $p=0.04$; (**b**)]. *Black triangles* represent relative risks (RRs) from eight double-blind RCTs on vitamin D supplementation and fall risk as summarized in a 2009 meta-analysis (Bischoff-Ferrari et al.; in press *British Medical Journal* [2]). Trend line is based on series of effect sizes (*triangles*). A meta-regression, which included 2,426 individuals from eight RCTs, indicated a significant inverse relationship between higher treatment dose and the risk of sustaining at least one fall [Beta-estimate for dose, 700 IU or higher compared with less= -0.337 ; $p=0.02$; (**a**)]. A meta-regression, which included 1,447 individuals from six RCTs with reported 25(OH)D levels, indicated a significant inverse relationship between higher achieved 25(OH)D level in the treatment group and the risk of sustaining at least one fall [Beta-estimate for a 25(OH)D of 60 nmol/l or higher compared with lower= -0.586 ; $p=0.005$; (**b**)]. *Gray squares* represent mean calcium levels in the treatment group from 25 vitamin D supplementation trials (28 data points; one trial with separate report from community-dwelling and hospitalized older individuals [45]). Trend line is based on series of mean serum calcium levels (*gray squares*). The doses of vitamin D applied in these trials ranged from 400 to 100,000 IU vitamin D per day. There was flat trend line for mean serum calcium levels with higher dose of vitamin D (Fig. 1a) and higher achieved 25-hydroxyvitamin D levels (Fig. 1b)

3.03 mmol/l and from 2.83 to 3.05 mmol/l, respectively. (2) Restorff et al. reported of two single cases of mild hypercalcemia (2.69 mmol/l) at 3 months and normal levels at 6 months in one small uncontrolled trial of 33 elderly rheumatology patients with severe vitamin D deficiency treated with a single oral dose of 300,000 IU vitamin D3 [76].

The other remaining clinical trials we identified (both controlled and uncontrolled) did not assess serum calcium and/or serum 25(OH)D [30, 78–81]. In some instances, serum calcium was assessed, but only the observation of a lack of hypercalcemia or no significant change in serum calcium was reported [82–89]. Vitamin D daily (or equivalent) oral doses ranged in these trials from 2,000–300,000 IU.

Benefit and risk data from observational data

Data from epidemiologic studies on the RR of incident hypertension [4], all-cause [90], cardiovascular [90] mortality, and colorectal cancer [91] based on categories of median 25-hydroxyvitamin D levels are presented in Fig. 2. For all-cause and cardiovascular mortality, we included a population-based prospective cohort study (National Health and Nutrition Survey III) controlling for age, sex, race/ethnicity, season of blood-draw, income, region, body mass



index, physical activity, smoking status, cigarette pack years, asthma, chronic obstructive pulmonary disease, and renal function in community-dwelling individuals age 65 years and older [90]. Consistent findings have been

reported from a large cohort of patients undergoing angiography [3] and a second report within the National Health and Nutrition Survey III including younger individuals age 20 years and older [92], which confirmed an

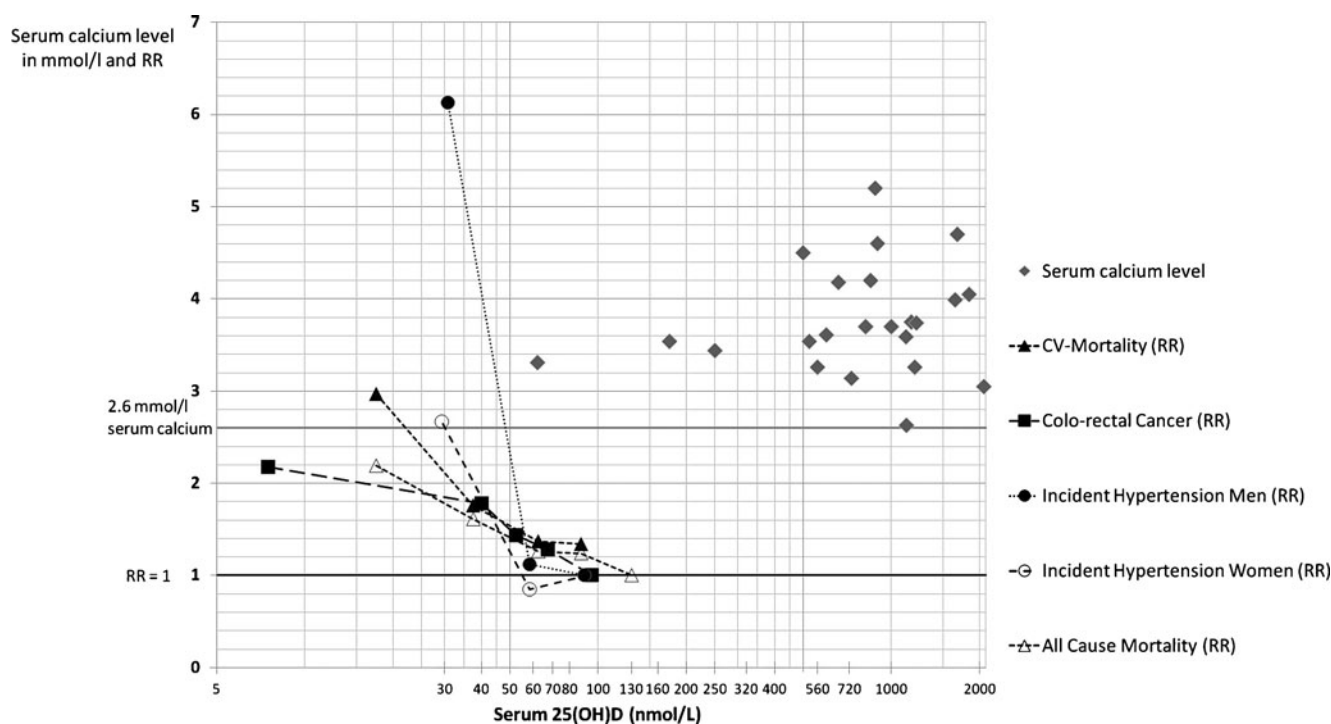


Fig. 2 Trend-plots on benefit from observational studies (cardiovascular disease prevention and colorectal cancer prevention) and risk (case reports of hypercalcemia) by achieved 25(OH)D level. *Dashed lines* relate to data from epidemiologic studies on the RR of incident hypertension [4], all-cause [90], cardiovascular [90], mortality, and colorectal cancer [91] based on categories of median 25-hydroxyvitamin D levels. For colorectal cancer, we included a quantitative meta-analysis of five studies [91]. Based on this summary of non-skeletal endpoints of

public health significance, there was a dose–response of better health status with higher median 25(OH)D levels. By visual inspection, the desirable median serum 25(OH)D level to be achieved for all endpoints was approximately 100 nmol/l. The *solid gray diamonds* relate to 24 case reports of hypercalcemia with corresponding 25(OH)D levels. Twenty-two of 24 cases of hypercalcemia were reported at 25(OH)D levels beyond 240 nmol/l 25(OH)D

optimal 25(OH)D range of 100 to 120 nmol/l for all-cause mortality.

For colorectal cancer, we included a quantitative meta-analysis of five studies [91]. For all non-skeletal endpoints of public health significance illustrated in Fig. 2, there was a dose–response of better health status with higher median 25(OH)D levels. By visual inspection, the desirable median serum 25(OH)D level to be achieved for all non-skeletal endpoints included in this report was approximately 100 nmol/l.

The solid gray diamonds in Fig. 2 relate to 24 case reports of hypercalcemia allegedly from vitamin D intoxication with corresponding 25(OH)D levels [93–115]. Only two out of 24 cases with hypercalcemia were reported at 25(OH)D levels below 240 nmol/l 25(OH)D [93, 110], one of which involved an 85-year-old woman who reported consuming 400 IU/d vitamin D and had a 25(OH)D of 62 nmol/l [93], the other in a newly arrived international 10-month-old adoptee [110]. These appear to be aberrant cases which have not been replicated in the literature. Extending to a cutoff of 400 nmol/l 25(OH)D, a third case with hypercalcemia occurred with 25(OH)D levels of 250 nmol/l. The third case occurred in a 77-year-old

woman with primary hyperparathyroidism who received 50,000 IU D2 daily instead of weekly for 2 years with a 25(OH)D level of 250 nmol/l [96]. All other cases of hypercalcemia ($n=21$) were reported at 25(OH)D levels of 525 to 2070 nmol/l, clearly outside a target range of 75 to 110 nmol/l for optimal health illustrated in Figs. 1b and 2. There are also case reports in the published literature describing individual circumstances where extremely high vitamin D doses have been claimed (ranging from 50,000 IU to 150,000 IU per day vitamin D2 or D3), verified by correspondingly high serum 25(OH)D values (ranging from 107 to 1126 nmol/l), but serum calcium levels were reported to not exceed the threshold for hypercalcemia (2.6 mmol/l) [116] [98, 117].

Summary of serum 25(OH)D response to oral vitamin D

In summary, the data for fall and fracture prevention as well as epidemiologic data on preservation of cardiovascular health, general mortality and colorectal cancer prevention suggest that serum 25(OH)D levels close to 100 nmol/l are desirable and carry no risk of hypercalcemia, as evidenced by controlled trials. Figure 3 illustrates 25(OH)D response

to vitamin D doses between 200 to 1,000 IU per day in fall and fracture trials and 1,800 IU to 7,600 IU from other RCTs included in Fig. 1a, b. With a supplement equal to the AI for young adults of 400 IU per day, data from three large RCTs achieved a mean increase in 25(OH)D levels to 56.7 nmol/l (range, 44 to 64 nmol/l) after a mean treatment duration of 653 days leaving more than 50% of individuals below the desirable target range of at least 75 nmol/l for fall and fracture reduction and with very limited chances to reach an optimal range close to 100 nmol/l. With a supplement of 800 IU vitamin D per day, a recommendation 200 IU higher than the highest of the AI values for the oldest segment of the population, tested in nine RCTs for a mean duration of 697 days resulted in a mean increase in 25(OH)D levels to 75 nmol/l (range, 60 to 105 nmol/l) after a mean treatment duration of 697 days (range, 56 to 1,680 days) leaving about 50% of individuals below the desirable target

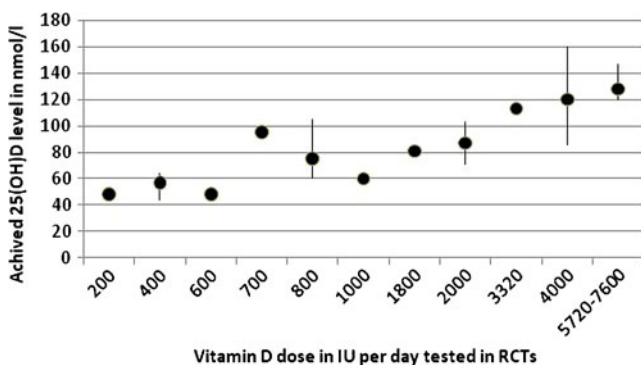


Fig. 3 Dose of vitamin D and achieved 25(OH)D levels based on RCTs with a duration of at least 4 weeks. **a** Lower-dose trials (double-blind fall and fracture RCTs). This *graph* summarizes data from identified RCTs (as illustrated in Fig. 1) with oral doses of vitamin D of less than 10,000 IU vitamin D per day and a treatment duration of at least 4 weeks. *Dots* either represent the mean 25(OH)D level from a single trial or the mean and the range of several trials. There were three RCTs with 400 IU vitamin D per day with a mean increase in 25(OH)D levels to 56.7 nmol/l (range, 44 to 64 nmol/l) after a mean treatment duration of 653 days (range, 140 to 1148 days). The trial with 700 IU vitamin D and achieved mean serum levels close to 100 nmol/l may be an outlier due to the high starting levels documented in the trial (84 nmol/l in men and 72 nmol/l in women age 65 years and older[26]). There were nine RCTs for 800 IU per day with a mean increase in 25(OH)D levels to 75 nmol/l (range, 60 to 105 nmol/l) after a mean treatment duration of 697 days (range, 56 to 1,680 days). There were seven RCTs with 2,000 IU vitamin D per day with a mean increase in 25(OH)D levels to 87 nmol/l (range, 71 to 103 nmol/l) after a mean treatment duration of 146 days (range, 42 to 365 days). There were three RCTs for 4,000 IU per day with a mean increase in 25(OH)D levels to 120 nmol/l (range, 85.5 to 160 nmol/l) after a mean treatment duration of 168 days (range, 56 to 365 days), and there were four trials with a treatment dose between 5,720 and 7,600 IU vitamin D per day with a mean increase in 25(OH)D levels to 128 nmol/l (range, 120–147 nmol/l). From this summary of available dose–response data from RCTs, most trials among healthy younger and older adults reached a mean value in the target range of 75 to 110 nmol/l with 1,800 IU to 4,000 IU vitamin D3 per day treated for at least 42 days

range of at least 75 nmol/l for fall and fracture reduction and a small chance to reach an optimal range close to 100 nmol/l. Most healthy younger and older adults reached the target range of 75 to 110 nmol/l with 1,800 IU to 4,000 IU vitamin D3 per day treated for at least 42 days.

Discussion

Recommendations for consumption of a nutrient are a function of the tolerable UL and the recommended dietary allowances (RDA) or for some nutrients the AI. For vitamin D, the necessary evidentiary basis for a RDA (i.e., the mean requirement and an estimate of variance) could not be identified by the IOM in 1997, and, instead, an AI was identified [118]. The AI is an estimated average intake by a group or groups of healthy people and may not reflect the intake needed to achieve a specific health outcome. In order to assess whether a higher vitamin D intake resulting in higher achieved 25(OH)D level is desirable and safe, we performed a dose–response evaluation bringing together data on benefits and risks of higher doses and higher achieved 25(OH)D levels.

Based on endpoints with established causality from double-blind RCTs as well as epidemiologic data on cardiovascular health (incident hypertension, general mortality, and cardiovascular mortality) and colorectal cancer prevention, our review suggests that the target range of 25(OH)D level for these benefits is not accompanied by increased risk of hypercalcemia. Notably, all endpoints evaluated for dose–response with higher 25(OH)D levels point to a similar target range of at least 75 nmol/l and better approximately 100 nmol/l.

Based on our benefit assessment, the current intake recommendations for vitamin D using the AI are insufficient to bring a majority of individuals up to at least 75 nmol/l 25(OH)D and close to 100 nmol/l. Revising recommendations towards a higher dose of vitamin D thus needs an assessment of risk with vitamin D supplementation doses that may bring most of the population into the target range of 75 to 110 nmol/l. This 25(OH)D range was reached in most trials with 1,800 to 4,000 IU vitamin D per day. Likely, individuals who start with lower 25(OH)D levels will need a supplementation dose at the higher end of this range [59, 119]. Most vulnerable to low vitamin D levels are elderly [120, 121], individuals living in northern latitudes with prolonged winters and thus low UVB exposure [122, 123], obese individuals [124], and African Americans of all ages [36, 125, 126].

In our current risk assessment, hypercalcemia was chosen as the critical effect, the adverse effect occurring at the lowest intake. There were no increases in mean calcium levels with higher vitamin D intakes tested in

controlled trials up to 100,000 IU per day. For single cases of hypercalcemia from RCTs, there were cases of mild hypercalcemia from two of 28 studies, which resolved on repeating fasting samples in one study [48] and were more frequent in the placebo group in the second study [47].

When we extend our assessment of risk to include case reports of hypercalcemia and associated 25(OH)D levels, hypercalcemia occurred in 22 of 24 cases beyond 240 nmol/l 25(OH)D. Of the two cases that occurred at serum levels below 240 nmol/l 25(OH)D, one case involved an 85-year-old woman who reported consuming 400 IU/d vitamin D and had a 25(OH)D of 62 nmol/l [93]. The other was described in a newly arrived adoptee with unknown vitamin D exposure [110]. Notably, 21 of 24 cases of hypercalcemia occurred with 25(OH)D levels beyond 400 nmol/l.

The only RCT that documented an increased risk of nephrolithiasis was the WHI, which tested 400 IU vitamin D in combination with 1,000 mg of calcium (hazard ratio, 1.17; 95% confidence interval, 1.02 to 1.34) [24]. Whether this was the only trial large enough to detect a small risk of nephrolithiasis with vitamin D supplementation or whether this was caused by the substantial calcium supplement intake taken in combination with the vitamin D and/or the additional calcium and vitamin D supplements taken by the majority of participants outside the study protocol in the WHI trial is unclear. However, the low-dose vitamin D used in the WHI argues against a causal role of the increased risk of nephrolithiasis. Based on epidemiologic data, a higher vitamin D intake was not independently associated with nephrolithiasis in one large cohort [127] consistent with findings from a recent study of 18 healthy postmenopausal women with vitamin D deficiency where vitamin D supplementation did not increase urinary calcium excretion [128]. On the other hand, calcium supplementation was associated with a 20% increased risk of nephrolithiasis in the Nurses' Health Study I [129], although not in a cohort of younger women [129]. Overall, the data are insufficient to identify nephrolithiasis as the critical effect.

The issue of vascular calcification in persons on renal dialysis has also been addressed in detail in the 2007 risk assessment and is not addressed in this review [22]. However, reports in the literature continue to be restricted to extremely high doses of vitamin D₃ or administration of the active hormonal form, 1,25(OH)₂D₃ and/or related analogues, and most of these reports are in animals, not humans. There continues to be no credible evidence to support the notion that oral vitamin D doses up to and even exceeding 10,000 IU per day are associated with vascular calcification in humans, including dialysis patients, and there is no basis for identifying vascular calcification as the critical effect.

There are several limitations to the evaluation of dose–response relationship through a trend–plot approach using

mean serum calcium levels after treatment in trials that also report 25(OH)D levels. This approach may miss single cases of hypercalcemia. To address this problem, we also assessed the report of hypercalcemia in all available controlled trials without evidence of an increased risk with higher achieved 25(OH)D levels up to 640 nmol/l or a daily dose of 100,000 IU vitamin D from controlled trials. Also, in theory, a direct comparison of the benefit and risk resulting from consumption of vitamin D would require a common metric. As an indicator of risk, we used increases in mean or individual case serum calcium level (a continuous variable, within the range permitted by physiological controls), while the benefit was assessed with the endpoints fall and fracture prevention, as well as endpoints of cardiovascular health and colorectal cancer prevention (categorical outcomes for individuals with population effects identified as relative risk). General limitations to this assessment of benefit and risk of vitamin D are that our findings may not be generalizable to particularly vulnerable subgroups of the population, such as patients of high age in critical care or those with hypersensitivity to vitamin D (e.g., sarcoidosis), as high-dose vitamin D trials are either ongoing or have not been performed in such populations. Also, we used the equivalent daily dose of vitamin D for intermittent dosing of weekly or monthly applications, which may overestimate the per day dose to some degree [130]. However, the benefit and risk assessment from RCTs is similar if achieved 25(OH)D levels are plotted instead of dose. Finally, we have selected observational data on the benefit of vitamin D, which may largely, but not fully represent the available literature.

The IOM established a UL for vitamin D based on hypercalcemia as the critical effect, and two studies have been cited as a matter of concern by the IOM, (1) the trial by Honkanen et al. included in our risk assessment and (2) the trial by Narang et al. not included in our risk assessment as 25(OH)D levels were not available. Notably, in the trial by Honkanen et al. the hypercalcemia observed is not relevant to the risk assessment of vitamin D because it occurred in the institutionalized control group with a mean serum 25(OH)D concentration of 10.4 nmol/l [45]. Both groups of hospitalized and community-dwelling older adults showed no increase in serum calcium levels with 1,800 IU vitamin D per day. The trial of Narang et al. [68] that IOM relied upon to identify a no observed adverse effect level of 2,400 IU vitamin D per day and establish a UL of 2,000 IU per day is now considered unreliable because several other more recent clinical trials included in our risk analysis have failed to confirm the occurrence of hypercalcemia at intakes of up to more than ten-fold those used in that study [118]. Consequently, the 2007 risk assessment concluded that the UL could be safely adjusted upward to 10,000 IU [22]. Nonetheless, in general, the

causal relationship between excessive vitamin D intake and hypercalcemia is well-established [22] but the dose that will result in this critical effect is higher than any used in the RCTs and prospective cohort studies that have been reported. Thus, the flat-line relationship of serum calcium to the other parameters in Fig. 1a, b does not contradict the identification of hypercalcemia as the critical effect for excess vitamin D; it indicates only that the effect must occur at higher 25(OH)D concentrations and with higher oral intakes of vitamin D.

As calcium absorption is improved with higher serum 25(OH)D levels [131, 132], future studies may need to evaluate whether current calcium intake recommendations with higher doses of vitamin D beyond 2,000 IU per day are safe or require downward adjustment [131]. If dietary calcium is a threshold nutrient, as suggested by Dr. Heaney [119], then that threshold for optimal calcium absorption may be at a lower calcium intake when vitamin D status is adequate. Regarding relevant endpoints, a downward adjustment of calcium intake recommendations is supported by the recent meta-analysis on non-vertebral fracture prevention where fracture prevention at a vitamin D dose greater than 480 IU per day was independent of additional calcium supplementation. Also, two recent epidemiologic studies suggested that both PTH suppression [132] and hip bone density [133] may only depend on a higher calcium intake if serum 25-hydroxyvitamin D levels are very low.

Summary

In this analysis, we examined benefits (reductions in fractures and falls) and risks (hypercalcemia) as a function of vitamin D intake and serum concentrations of 25(OH)D in randomized trials. We also used non-randomized evidence to evaluate the levels of 25(OH)D at which benefits (reductions in colorectal cancer and cardiovascular disease) and risks (hypercalcemia and nephrolithiasis) are observed. We found no pattern of evidence to suggest that risks are elevated within the ranges of serum 25(OH)D or oral vitamin intake related to increased benefits (75–110 nmol/l). Instead, the reliable evidence that excess vitamin D can cause hypercalcemia in generally healthy adults comes from daily intakes of vitamin D greater than 100,000 IU or serum 25(OH)D exceeding 240 nmol/L, which are far higher than those necessary to achieve the benefits. The evidence from randomized trials suggests that the dose of vitamin D supplement needed to bring the large majority of persons to the range of optimal serum 25(OH)D may be in the range of 1,800 to 4,000 IU per day. Further work is needed, taking into account subject and environment factors, to better define the doses that will achieve the optimal blood levels in the large majority of the population.

Conflicts of interest None.

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