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ORIGINAL RESEARCH

Is High Dose Vitamin D Harmful?

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Abstract With the potential to minimize the risk of many chronic diseases and the apparent biochemical safety of ingesting doses of oral vitamin D several-fold higher than the current recommended intakes, recent research has focussed on supplementing individuals with intermittent, high-dose vitamin D. However, two recent randomized controlled trials (RCTs) both using annual high-dose vitamin D reported an increase, rather than a decrease, in the primary outcome of fractures. This review summarises the results from studies that have used intermittent, high doses of vitamin D, with particular attention to those finding evidence of adverse effects. Results from observational, population-based studies with evidence of a U- or J-shaped curve are also presented as these findings suggest an increased risk in those with the highest serum 25D levels. Speculative mechanisms are discussed and biochemical results from studies using high-dose vitamin D are also presented. Emerging evidence from both observational studies and RCTs suggests there should be a degree of caution about recommending high serum 25D concentrations for the entire population. Furthermore, benefit of the higher doses commonly used in clinical practice on falls risk reduction needs to be demonstrated. The safety of loading doses of vitamin D should be demonstrated before these regimens become recommended as routine clinical practice. The current dilemma of defining vitamin D insufficiency and identifying safe and efficacious repletion regimens needs to be resolved.

Keywords Steroid hormones · Vitamin D · Osteoporosis · Fractures · Age · Aging

The need for vitamin D supplementation has evolved because it is widely recognized that a significant proportion of many populations has inadequate vitamin D status [1]. Serum 25-hydroxyvitamin D (25[OH]D) levels of 25 nmol/L or less are considered "deficient," while the definition of "insufficiency" varies, with some experts regarding less than 50 nmol/L as the cut-off [2] and others considering less than 75 nmol/L as "insufficient" [3–5]. "Insufficient" in this review refers to 25(OH)D levels in the range 25–50 nmol/L, "intermittent" dosing refers to at least 1-week dosing intervals, and "high dose" refers to an intermittent bolus dose of at least 20,000 IU or a daily dose of 4,000 IU. Although the risk of many chronic disorders may be reduced by an upward shift in the community's vitamin D status, daily dosing has proven to be problematic, particularly for older people, the group most likely to directly benefit from an improvement in vitamin D status [6]. Many randomized trials have reported poor compliance with daily regimens [7]. Furthermore, some people require substantial doses of vitamin D to achieve serum 25(OH)D levels within the target range [8, 9]. An intermittent, larger dose of vitamin D reduces this compliance issue in a simple and cost-effective manner and reduces the likelihood that the target group will remain below the threshold of 25(OH)D regarded as "insufficient," although significant controversy exists regarding what level of serum 25(OH)D

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is "sufficient" [3, 10–12]. Both the public and practitioners want to make informed decisions regarding both the target level of 25(OH)D to optimize health and the appropriate dosing regimen to achieve this target level.

According to current evidence from biochemical, observational, and randomized controlled trials (RCTs), serum 25(OH)D levels of at least 50 nmol/L are required for normalization of PTH levels, to minimize the risk of osteomalacia, and for optimal bone and muscle function [2, 13, 14], with many experts regarding 75 nmol/L as the threshold for optimal bone health [12, 15–17]. The skeletal consequences of 25(OH)D insufficiency include secondary hyperparathyroidism, increased bone turnover and bone loss, and increased risk of low-trauma fractures. From a skeletal perspective, evidence from RCTs suggests that vitamin D may be considered a threshold nutrient with little bone benefit observed at levels of 25(OH)D above that at which parathyroid hormone (PTH) is normalized [2]. However, molecular studies have demonstrated that vitamin D plays a role in cell differentiation, function, and survival [18, 19]. Adequate calcium intake is imperative to gain optimal benefit from improving vitamin D status in those with insufficient 25(OH)D levels. The relative contributions of vitamin D and calcium to reducing fracture risk remain unclear [20], and improving calcium intake is also associated with suppression of PTH levels [21, 22]. Observational studies have shown a decreased risk of many disorders, including certain types of cancer, mental disorders, cardiovascular disease, and skin and autoimmune disorders, associated with serum 25(OH)D levels greater than 70–80 nmol/L [9, 12, 16]. It has therefore been argued that 25(OH)D levels should be in the range of 70–100 nmol/L to maximize these nonskeletal benefits.

With the potential to minimize the risk of many chronic diseases and the apparent safety of ingesting doses of oral vitamin D severalfold higher than the current recommended intakes, recent research has focused on supplementing individuals with intermittent, high-dose vitamin D. There is an urgent need to determine the efficacy and safety of these regimens. Using biochemical parameters of safety, particularly plasma and urine calcium, there are numerous studies reporting that a single oral dose of 300,000–600,000 IU of D_2/D_3 rapidly enhances serum 25(OH)D and reduces PTH in people with deficiency [23–25]. Although dosing intervals of greater than 2–3 months and/or intermittent bolus doses (>200,000 IU) are not regarded as physiological [26], such an approach offers a realistic and pragmatic public health measure to target at-risk populations and addresses the emerging public health issue of widespread vitamin D insufficiency [6, 27].

However, two recent RCTs, both using annual high-dose vitamin D, reported an increase, rather than a decrease, in the primary outcome of falls [27] and fractures [27, 28]. These findings highlight the need for a better understanding of different dosing regimens before pragmatic, population-based interventions are implemented. This review summarizes results from studies that have used intermittent, high doses of vitamin D, with particular attention to those finding evidence of adverse effects. Results from observational, population-based studies with evidence of a *U*- or *J*-shaped curve are also presented as these findings suggest an increased risk in those with the highest serum 25(OH)D levels. We do not attempt to present a comprehensive, systematic review of the extensive number of observational and intervention studies reporting the health benefits of improving vitamin D status in adults with insufficient status [7, 29–32] or to present a "balanced" view of the potential risk/benefit ratio of vitamin D supplementation.

Biochemical Outcomes of Single, Large Doses of Vitamin D

The immediate concern of hypervitaminosis D is hypercalciuria and hypercalcemia [2]. However, a large therapeutic window exists for vitamin D–related hypercalcemia, which has not been reported at serum 25(OH)D levels below 220 nmol/L and generally not reported below 500 nmol/L [2]. Based on these biochemical parameters, Vieth and colleagues [17] conducted a 6-month safety and efficacy study and concluded that consumption of more than 4,000 IU/day causes no harm and effectively raises 25(OH)D levels to "high-normal" concentrations (<140 nmol/L) in practically all adults. The 2011 Institute of Medicine report on dietary intake of vitamin D recommended an upper limit of 4,000 IU/day, although it also stated that up to 10,000 IU/day is safe [33].

Of the studies included in this review, the cases of hypercalcemia and/or hypercalciuria are few and their incidence in the randomized trials is rarely different from that observed in the placebo group (Table 1). The study by Grimnes and colleagues [34], where one group was given 6,500 IU/day and another was given 400 IU/day, reported a significant difference between groups in serum ionized calcium at 12 months. In another trial, two of 33 patients receiving a single bolus dose of 300,000 IU vitamin D_3 had mild hypercalcemia [35]. Participants in this study were older, recruited from a rheumatology clinic, and likely to have reduced kidney function compared with other trial participants who were, on average, younger (Table 1). However, some of the larger trials did not specifically investigate for hypercalcemia or hypercalciuria (Table 1).

A 1995 review of the safety and effectiveness of different regimes of vitamin D supplementation in the elderly suggested that daily low-dose supplementation is the regimen of choice for prevention of hypovitaminosis D but

Table 1 Biochemical outcomes of studies using intermittent high-dose vitamin D

Reference	Dosing regimen			Serum 25(OH)D profile					
	Vitamin D_2 or D_3	Dose (IU) oral or IM	Regimen for dosing	25(OH)D at baseline	Peak 25(OH)D	Time point at peak 25(OH)D	25(OH)D end of study	Time point end of study	Assay for 25(OH)D
Diamond et al. [25]	D_3	600,000	IM, single bolus	32 ± 8	114 ± 35	4 months	73 ± 13	12 months	RIA IDS
Bacon et al. [24]	D_3	3 groups: (1) 500,000 (2) 500,000 ± 50,000/month (3) 50,000	Oral: (1) single bolus (2) bolus ± monthly (3) monthly	58 ± 25	130 (SD not given)	1 month	69 ± 5 Group 1, 91 ± 4 Group 2, 80 ± 5 Group 3	9 months	RIA DiaSorin
Premaor et al. [70]	D_3	300,000 group 1, 800 group 2	Oral: ±500calcium daily; group 1: single bolus group 2: daily	27 ± 15	80 in single-bolus dose group 48 in daily dose (SD not given)	1-month peak in bolus group, 2-month peak in daily group	30	9 months	LIAISON Chemiluminescence DiaSorin
Ilahi et al. [47]	D_3	100,000	Oral: single bolus	68 ± 19	105 ± 23	Day 9	74 ± 10	4 months	RIA IDS
Smith et al. [28]	D_2	300,000	IM: once a year	57 ± 24	Reported 21 % increase but only the 36 % increase in 1,25(OH)D was significantly different	4 months	N/A: by 9 months postdose 25(OH)D but not 1,25(OH)D "drifted toward basal values"	3 years	RIA Nicholls
Sanders et al. [27]	D_3	500,000	Oral: once a year	49 (IQR 40–63)	120	1 month	74 ± 20	3–5 years	RIA DiaSorin
Cipriani et al. [23]	D_3	600,000	Oral: single bolus	40 ± 16	190	Day 3	156 ± 65	30 days	RIA DiaSorin
Rossini et al. [48]	D_3	600,000 300,000 100,000	Oral: single bolus	60 ± 17	167 ± 43 in 600,000 IU group	Day 3	88 ± 14	Day 90	ELISA IDS
Von Restorff et al. [35]	D_3	300,000	Oral: single bolus	15 ± 6	81 ± 30	3 months	69 ± 18	6 months	RIA DiaSorin
Pekkarinen et al. [71]	D_3	97,333 group 1, 800 group 2	Oral: all had 1 g calcium/day, group 1: 4-monthly dose, group 2: daily dose	55 (range 17–84)	72 in 4-monthly group, 78 in daily dose group	10 months in 4-monthly group, 3 months in daily group	74 in 4-monthly group, 62 in daily dose group	12 months	HPLC

Table 1 continued

Reference	Dosing regimen			Serum 25(OH)D profile					
	Vitamin D_2 or D_3	Dose (IU) oral or IM	Regimen for dosing	25(OH)D at baseline	Peak 25(OH)D	Time point at peak 25(OH)D	25(OH)D end of study	Time point end of study	Assay for 25(OH)D
Trivedi et al. [46]	D_3	100,000	Oral: 4 monthly	N/A	N/A	N/A	74 nmol/L in vitamin D group 3 weeks postdose, 53 nmol/L in placebo group	4th year of 5-year study	Not stated
Giusti et al. [8]	D_3	300,000 group 1, 1,000 group 2	Oral: group 13-monthly, group 2: daily dose	23 ± 12	Both groups had ? higher 25(OH)D at 6 months compared to 3 months		58 ± 19 in 1,000 IU/day group 80 ± 30 in 300,000 months group mean ± SD IU/3	6 months	RIA DiaSorin
Jorde et al. [72]	D_3	3 groups: D_3 400,000 group 1, 20,000 group 2, placebo group 3	Oral: weekly dosing, all given calcium 500 mg/day	53 (range 11–112)	81 ± 30	3 months	Group 1: 112, group 2: 88, group 3: 50	12 months	Chemiluminescence Modular E170
Grimnes et al. [34]	D_3	6,500 group 1, 800 group 2	Oral: daily doses	71 ± 23	N/A	N/A	Group 1: 185 (34), group 2: 89 (17)	12 months	RIA DiaSorin
Vieth et al. [73]	D_3	4,000 group 1, 600 group 2	Oral: daily doses	48 ± 9 39 ± 9 (two recruitment periods)	112 ± 41 4,000 IU group, 79 ± 30 600 IU group	~6 months (winter)	N/A	≤15 months	RIA DiaSorin
Heaney et al. [37]	D_3	4 groups: placebo, 1,000, 5,000, 10,000	Oral:daily doses	70	200 in 10,000 IU group, 140 in 5,000 IU group (SD N/A)	120 days	Approximately the same as at 120 days	4 months	~IDS method
Law et al. [74]	D_2	100,000	Oral: 3 monthly	47 (35–102: 90th percentile)	82 (67–185) 5th/95th percentiles)	1 month	N/A	10 months	ELISA IDS
Aloia et al. [75]	D_3	4,000 (± 1,200 mg calcium)	Oral: daily doses	66 (24)	N/A	N/A	111 (30)	3 months	RIA DiaSorin

Table 1 continued

Reference	Participant characteristics			Outcomes		
	Number of participants	Age (years)	Gender	Primary outcome	Hypercalcemia reported (yes/no)	Proportion of hypercalcemia
Diamond et al. [25]	50	66, range 32–87	F, M	Serum 25(OH)D status	Yes	Mild hypercalcemia (<2.70 nmol/L) in 2/50, hyperparathyroidism in 1/50
Bacon et al. [24]	63	82 ± 7	F, M	Serum 25(OH)D and PTH and bone formation marker P1NP	Yes	0/63
Premaor et al. [70]	28	81 ± 9	F, M	Serum 25(OH)D and reversion of secondary hyperparathyroidism, higher bolus dose more effective in the short term	Yes	0/28
Ilahi et al. [47]	30	Range 61–84 group 1, 27–47 group 2	F, M	Serum 25(OH)D recommended dosing interval ≤2 months to ensure continuous 25(OH)D above baseline	Yes	0/30
Smith et al. [28]	43	79 (IQR 77–83)	F, M	Fractures combined F/M no difference between groups	No	N/A
Sanders et al. [27]	137 ($n = 75$ from vitamin D group and n = 58 placebo group)	76 (IQR 73–80)	F	Falls & fracture15 % increased falls and 26 % increased fractures in vitamin D groups	Yes Specifically assessed in subgroup only	0/137 with biochemistry, 0/2, 256 reported in entire group
Cipriani et al. [23]	48	36 ± 8 (range 25–56)	F, M	Serum 25(OH)D and calcium metabolism	Yes	0/48
Rossini et al. [48]	37	75 ± 3	F, M	BTM: CTX in 600,000 IU and 300,000 IU groups, BAP unchanged in these groups but increased in 100,000 IU group	Yes	0/37
Von Restorff et al. [35]	33	81 ± 6	F, M	Serum 25(OH)D	Yes	$N = 2/33$ at 3 months
Pekkarinen et al. [71]	40	74 (range 69–79)	F	Serum 25(OH)D and bone formation marker (P1NP), P1NP decreased in both groups at 12 months	Yes	$n = 0/40$

Table 1 continued

Reference	Participant characteristics			Outcomes		
	Number of participants	Age (years)	Gender	Primary outcome	Hypercalcemia reported (yes/no)	Proportion of hypercalcemia
Trivedi et al. [46]	$n = 124$ with biochemistry in vitamin D group	75 ± 5	F, M	Fracture rate and total mortality 22 % reduction in fractures in vitamin D group vs. placebo	No	N/A
Giusti et al. [8]	60	73 ± 5	F	Serum 25(OH)D and PTH	Yes	0/60 Mean corrected serum calcium significantly increased at 6 months
Jorde et al. [72]	441	21–70 range (median N/A)	F, M	Beck Depression Inventory score	Yes	5/441 ($n = 1$ placebo, $n = 3$ group 1 and $n = 1$ group 2)
Grimnes et al. [34]	297	50–80	F	BMD and bone turnover markers, no difference between groups in change in BMD	Yes	Modest hypercalcemia 9/149 in high-dose group, 4/148 in standard-dose group
Vieth et al. [73]	64	54 ± 11y	F, M	Serum 25(OH)D and PTH and measures of well-being (seasonal health questionnaire by Thomson and Cowan)	Yes	0/64
Heaney et al. [37]	67	39 ± 11	M	Serum 25(OH)D	No	N/A
Law et al. [74]	18/3,717	85 (SD N/A)	F, M	Falls and fractures: no difference between vitamin D and control groups	Yes	0/118
Aloia et al.[75]	35 (on vitamin D)	55 (20–80)	F, M	Parathyroid hormone and BTM, BTM increased in vitamin D alone group	Yes	0/35

Vitamin D doses expressed in international units (IU). *D_2* vitamin D_2 (ergocalciferol), *D_3* vitamin D_3 (cholecalciferol), *IM* intramuscular injection, *25(OH)D* serum 25-hydroxyvitamin D levels (nmol/L), *1,25(OH)D* serum 1,25-dihydroxyvitamin D (levels quoted as mean and standard deviation unless stated otherwise), *IQR* interquartile range, *N/A* not available, *RIA* radioimmunoassay, *HPLC* high-pressure liquid chromatography, *BTM* bone turnover markers, *CTX* C-terminal telopeptides (bone resorption marker), *BAP* bone-specific alkaline phosphatase, *P1NP* amino-terminal propeptide of type 1 procollagen (bone formation markers), *F* female, *M* male

Table 2 Observational studies with evidence of harm at higher end of vitamin D status

Reference	Study design	Population characteristics	Outcome	Methodology for 25(OH)D	Comments
Ensrud et al. [53]	Observational: frailty categorized as robust, intermediate, or frail	$N = 6{,}307$ women aged >69 years, Caucasian, USA (SOF)	Odds of frailty in those 25(OH)D >75 nmol/L compared to referent of 50–74 nmol/L group, odds ratio 1.32 (1.06–1.63)	LC–MS/MS method for D_3	As supplements during study period 1992–1998 were all vitamin D_2 not D_3, the influence of supplements was not included in vitamin D status
Chen et al. [76]	Case–cohort study nested within the General Population Trial of Linxian, China	Measured pretrial serum 25(OH)D levels in 979 cases and 1,105 cohort participants, cases were diagnosed with cancer during 5.25 years of follow-up	Esophageal and gastric cancers, in men there was an increased risk of developing esophageal cancer for those in the highest (4th) quartile of 25(OH)D level at baseline: HR 1.77 (1.16–2.70), $p = 0.0033$	Enzyme immunoassay (IDS)	Prospectively examines the relationship between pretrial 25(OH)D status and risk of developing esophageal or gastric cancer, no association found in women
Michaelsson et al. [54]	Uppsala Longitudinal Study of adult men	$n = 1{,}194$ Swedish men, 12.7 years follow-up, 49 % died	Both low (<46 nmol/L) and high (>98 nmol/L) serum 25(OH)D associated with increased total mortality and cancer risk, for higher 25(OH)D risk HR (95 % CI): total mortality 1.67 (1.12–2.49) cancer mortality 2.64 (1.46–4.78)	HPLC mass spectrometry	
Ahn et al. [77]	Prospective case–control study nested within the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial	$n = 749$ cases and $n = 781$ controls, blood used for serum 25(OH)D level was drawn at least 8 years prior to diagnosis of cancer	"Higher serum 25(OH)D status was not associated with lower risk of prostate cancer; indeed higher 25(OH)D levels may be associated with an increased risk of aggressive cancer"	RIA	
Tuohimaa et al. [78]	Longitudinal nested case–control study, data from men who donated blood samples stored in biobanks in Finland, Norway, and Sweden	$n = 622$ cases and 1,451 matched controls	Both low (≤19 nmol/L) and high ≥80 nmol/L serum 25(OH)D associated with higher prostate cancer risk	RIA (Incstar)	The authors suggest that a high vitamin D level might lead to vitamin D resistance through increased inactivation via enhanced expression of 24-hydroxylase
Stolzenberg-Solomon et al. [79]	Pancreatic cancer risk	200 cases and 400 matched controls, nested case–control using prediagnostic 25(OH)D male smokers aged 50–69 years	Higher vitamin D status associated with 3-fold increased risk for pancreatic cancer, odds ratio (95 % CI) 2.9 (1.6–5.5), >65 vs. <32 nmol/L groups	RIA (DiaSorin)	Smoking duration and smoking intensity did not differ between cases and controls
Stolzenberg-Solomon et al. [80]	Pancreatic cancer risk within the Prostate, Lung, Colorectal and Ovarian Screening Trial	$n = 184$ cases and 2 to 1 matched control to case, nested case–control study using prediagnostic serum 25(OH)D, men and women aged 55–74 years	25(OH)D levels were not associated with risk of pancreatic cancer overall, report positive associations in those with low solar UBV exposure	RIA	Did not confirm the strong positive findings observed in the earlier study in male Finnish smokers
McGrath et al. [55]	Used Danish national registers and neonatal biobank	$n = 424$ individuals with schizophrenia, 424 matched without schizophrenia	Both low and high levels of neonatal vitamin D status associated with increased risk of developing schizophrenia	LS-MS	*U*-shaped curve was not explained by a wide variety of variables

Vitamin D doses expressed in international units (IU). *D_2* vitamin D_2 (ergocalciferol), *D_3* vitamin D_3 (cholecalciferol), *IM* intramuscular injection, *25(OH)D* serum 25-hydroxyvitamin D (nmol/L), *1,25(OH)D* serum 1,25-dihydroxyvitamin D (levels quoted as mean and standard deviation unless stated otherwise), *IQR* inter-quartile range, *N/A* not available, *RIA* radioimmunoassay, *HPLC* high-pressure liquid chromatography, *LC–MS/MS* liquid chromatography coupled with tandem mass spectrometry, *HR* hazard ratio (95 % confidence interval), *RR* relative risk (95 % confidence interval), *BTM* bone turnover markers, *CTX* C-terminal-telopeptide (bone resorption marker), *BAP* bone-specific alkaline phosphatase, *P1NP* amino-terminal propeptide of type 1 procollagen (bone formation markers), *F* females, *M* males

that intermittent high-dose regimens would be a safe and effective alternative in patients with poor compliance [36]. As reported in individual trials [8, 9, 37], there appears to be significant variation in the level of serum 25(OH)D reached when individuals are given the same dose and form of the vitamin.

Table 3 Clinical trials of vitamin D with intermittent dose intervals between 1 week and 1 year

Reference	Sample size	Study subjects	Treatment dose and duration	Primary outcome	Type of control (double-blind unless stated otherwise)	Baseline 25(OH)D status (nmol/L)	Reported adverse effect attributable to treatment	Outcomes	Comments
Heikinheimo [50]	$n = 799$	Age >75 years, 79 % female	Single annual dose IM 150,000 IU or 300,000 IU 3 years	Fracture	Unblinded control with no placebo	Outpatient group: 49 ± 14 municipal home group: 45 ± 16	None reported	Fracture rate 16 % vs. 22 %, $p = 0.034$; vitamin D and control groups, respectively	Some design and protocol flaws to this study
Smith et al. [28]	$n = 9{,}440$	Age 79 years median, IQR 77–83, 54 % female	Single annual IM dose D_2 300,000 IU 3 years	Risk of first fracture (nonvertebral fractures)	Placebo	57 ± 24	Females only: HR (95 % CI) hip or femur 1.80 (1.12–2.90), any nonvertebral 1.21 (1.0–1.47)	Fractures—all nonvertebral; men and women HR = 1.09 (0.93–1.28), $p = 0.29$ for any first fracture	
Sanders et al. [27]	$n = 2{,}256$	Women, median age 76 years (IQR 73—80), community-dwelling	Single annual oral dose 500,000 IU, intervention 3–5 years	Fractures and falls	Placebo	49 (IQR 40–63), subgroup $n = 137$	Falls RR = 1.15 (1.02–1.30), $p = 0.03$; fractures RR = 1.26 (1.00–1.59), $p = 0.047$	Falls and fractures, results per previous column	Temporal pattern of increased risk in first 3 months postdose, no differences between groups in indices of mental well-being (Sanders et al. [49])
Rossini et al. [48]	$n = 37$	Adults aged 75 ± 3 years	Single oral dose D_3 randomized to 600,000, 300,000, or 100,000 IU; follow-up 90 days	BTM and vitamin D status	Unblinded, no placebo, controls $n = 24$	Baseline 25D level: 60 ± 17 nmol/L	Dose-dependent acute increases in CTX	Mean serum PTH level decreased in all 3 groups, remained < baseline in 600,000 group, returned to baseline by 60 days in 300,000 group and within a few days in 100,000 group; no changes were observed in BAP in 600,000 and 300,000 groups but rose by 15–23 % in 100,000 group	Results may explain fracture reduction benefit in RCT using 100,000 IU/4 months (Trivedi et al. [46]) and unexpected increase in RCT using 500,000 IU (Sanders et al. [27])
Jorde et al. [72]	$n = 441$	282 women, overweight and obese; BMI 28–47, aged 21–70 years	3 groups: weekly dose D^3 group 1: 40,000 IU, group 2: 20,000 IU, group 3: placebo; all given calcium 500 mg/day intervention 1 year	Symptoms of depression in overweight/obese adults	Placebo	53 (range 11–112)	N/A	Symptoms of depression, using BDI score, significant reduction (improvement) in high-dose group, although serum 25(OH)D levels did not correlate with BDI scores; high-dose group had improved scores at 1 year	Overweight subjects with serum 25D levels <40 nmol/L had higher (more depressive) scores compared to subjects with 25D levels >40 nmol/L

Table 3 continued

Reference	Sample size	Study subjects	Treatment dose and duration	Primary outcome	Type of control (double-blind unless stated otherwise)	Baseline 25(OH)D status (nmol/L)	Reported adverse effect attributable to treatment	Outcomes	Comments
Lyons et al. [56]	$n = 3,440$ (2,624 women)	Adults in residential care, aged 84 ± 8 years	4-monthly dose D_2 oral 100,000 IU, intervention 3 years	Risk of first fracture	Placebo	Unknown	N/A	Risk of first fracture HR = 0.95 (0.79–1.15)	End of study 25(OH)D only (DiaSorin RIA) 80 vs. 54 nmol/L ($n = 102$, vitamin D vs. controls, respectively); 55 % died during the intervention with no difference between groups
Trivedi et al. [46]	$n = 2,686$ (76 % men)	Community-dwelling adults, aged 75 ± 5 years	4-monthly dose D_3 100,000 IU, intervention 5 years	Risk of first fracture	Placebo	N/A	N/A	RR (95 % CI) any first fracture 0.78 (0.61–0.99, $P = 0.04$), first hip, wrist or forearm or vertebralfracture: 0.67 (0.48, 0.93; $P = 0.02$)	No significant effects of vitamin D on total mortality or incidence of cancer or cardiovascular disease
Law et al. [74]	$N = 3,717$ (76 % women)	Residential aged care, average age 85 years (SD N/A)	Vitamin D_2 100,000 IU 3- monthly dose, follow-up 10 months (IQR 7–14)	Non-vertebral fractures	Cluster randomized, no placebo given	47 (35–102, 90th percentile) in $n = 18$ (1 % of vitamin D group)	No significant difference between groups but fracture rate was "directionally higher in treated group"	RR (95 % CI) all nonvertebral fractures: 1.48 (0.99– 2.20), Hip fractures: 1.36 (0.80–2.34), falls: 1.09 (0.95, 1.25)	

Table 4 Clinical trials of vitamin D with daily dose regimens and evidence of possible adversity

Reference	Sample size	Study subjects	Treatment dose and duration	Primary outcome (ascertainment)	Type of control (double-blind unless stated otherwise)	Baseline 25(OH)D status nmol/L	Reported adverse effect attributable to treatment	Comments
Flicker et al. [81]	$n = 117$	$n = 117$ participants with mild cognitive impairment	1,000 IU D_3 intervention 18 months	Cognitive function (CAMCOG)	Placebo	49 ± 12 nmol	Vitamin D group more likely to deteriorate than placebo group; overall change in CAMCOG score was –0.70 (–1.43 to 0.02)	Serum 25D: 6-month 78 ± 22 nmol/L, 12-month 84 ± 21 nmol/L.
Stein et al. [82]	$n = 32$	Aged >60 years, with mild–moderate Alzheimer disease, titrated high dose for 8 weeks then immediately randomized to nasal insulin for 48 h	All participants had 8-week "run-in" period of daily low-dose vitamin D_2 (1,000 IU), then were group-randomized to high-dose vitamin D_2 or placebo; high dose consisted of 2 weeks of 36,000 lU/day, followed by 0–36,000 lU/day titrated to aim for serum 25D level maintained in the range 130–175 nmol/L; titrations were done at 2, 4, and 6 weeks; intervention 16 weeks	Cognitive function and dementia-induced disability (Alzheimer disease assessment scale-cognitive subscale (ADAS-cog); disability assessment in dementia (after high-dose vitamin D)	Placebo	49 (median) IQR N/A 60 (56–70) at commencement of high-dose regimen	The authors conclude "the RCT found no benefit from adding high-dose vitamin D to ongoing low-dose vitamin D supplementation. In the RCT, serum 25D concentrations were generally supra-physiologic and may have had no additional effect."	Median 25(OH)D 60 nmol/L at 8 weeks on 1,000 IU/day group and 187 nmol/L after a further 8-week high-dose vitamin D
Grimnes et al. [34]	$n = 297$	Women aged 50–80 years, T score BMD < –2.0 at either site	Daily dose 6,500 or 800 IU D_3, both groups given 1,000 mg calcium/day, intervention 1 year	BMD at hip and spine	Low (800 IU) vs. high (6,500 71 ± 23 IU), no placebo	71 ± 23	Authors suggest that standard dose (800 IU/day) was more efficient as bone formation marker P1NP had more pronounced reduction in this group	BMD, no significant differences between groups; bone turnover reduced in both groups
Bischoff-Ferrari et al. [83]	$n = 173$ (79 % women)	Adults with acute hip fracture aged 65+ years	Either 2,000 or 800 IU D_3, factorial design: extended vs. standard physiotherapy and vitamin D 2,000 vs. 800 IU/day, intervention 12 months	Rate of falls	High (2,000 IU) vs. standard fewer hospital re- care lower dose (800 IU)	32 ± 20	Falls rate shows trend to be higher in 2,000 vs. 800 IU daily dose rate of falls per observed patient-year 1.63 vs. 1.25. adjusted relative rate difference 28 % (–4 to 68)	Higher dose group had fewer hospital readmission during 12-month follow up: Adjusted RR (95 %C.I) −39 (−62, −1)

Age expressed as mean ± SD or median and interquartile range (IQR). Oral dose expressed in international units (IU). D_2 vitamin D_2 (ergocalciferol), D_3 vitamin D_3 (cholecalciferol), *IM* intramuscular injection, *25(OH)D* serum 25-hydroxyvitamin D (nmol/L), *1,25(OH)D* serum 1,25-dihydroxyvitamin D (levels quoted as mean and standard deviation unless stated otherwise), *BDI* Beck Depression Inventory, *CAMCOG* Cambridge Cognitive, *BTM* bone turnover markers, *CTX* C-terminal telopeptides (bone resorption marker), *BAP* bone-specific alkaline phosphatase (bone formation marker), *F* female, *M* male, *RR* relative risk (95 % confidence interval), *N/A* not available/applicable

There is a caveat that earlier studies were reliant on 25(OH)D assays that have shown considerable intra- and intersample variation in the assessment of serum 25(OH)D concentrations and were unreliable in measuring serum D_2 levels [38]. Although the performance of radioimmunoassay and enzyme-linked assays is acceptable, the bias and imprecision of many automated methods may be problematic at the lower, clinically and analytically important range (<50 nmol/L) of the assay [2].

Evidence from Observational Studies

A majority of observational studies have reported that vitamin D is associated with a beneficial effect on risk of colon, breast, prostate, and ovarian cancers [39]. Since vitamin D synthesis and serum 25(OH)D levels are inversely correlated with latitude and positively correlated with sunlight, some studies have "mapped" disease incidence rates with latitude to investigate a possible protective effect of vitamin D status and risk of disease. Encouragingly, there is a consistency of findings between geographic studies and "serum" studies where samples of the population have had biochemistry assessments, ideally with the blood collection point several years prior to any diagnosis of cancer or other disease of interest [39]. Vitamin D and its metabolites are thought to reduce the incidence of many types of cancer by inhibiting tumor angiogenesis and hyperproliferation as well as stimulating cellular apoptosis [40]. Since vitamin D regulates a gamut of physiological processes, including immune modulation, resistance to oxidative stress, and modulation of other hormones, it is not surprising that low vitamin D has been associated with increased risk of several cancers and chronic diseases [41] as well as cancer mortality [42]. Nevertheless, there are now several observational studies reporting a *U*- or *J*-shaped association between disease and serum 25(OH)D and latitude and/or ultraviolet B radiation levels, where those in the highest percentiles have an inverse risk compared with those in the lowest (Table 2) [43]. While cross-sectional data have many limitations, the findings are hypothesis-generating [44] and can be used to develop protocols for RCTs. The findings from prospective case–control cohort studies where blood collection occurred many years prior to diagnosis add another dimension to the evidence. The results from these studies generally support vitamin D supplementation in those with "low" vitamin D status. However, the findings argue for caution before increasing 25(OH)D levels and associated dosing regimens beyond evidence clearly supported by RCTs and meta-analyses [45].

RCTs Demonstrating Harm

The evidence of harm relating to high-dose vitamin D centers on the findings of two RCTs that used annual high-dose vitamin D (Table 3), although results from RCTs using lower, more frequent dosing regimens have not been consistently clear. The different forms of the vitamin used in the studies and the different delivery modes demonstrate that the adverse outcomes are not restricted to one form of the vitamin. Neither study included calcium supplementation as part of the protocol. In the British "Wessex" study, 9,440 community-dwelling participants (4,354 men and 5,086 women) aged 75–100 years were randomly allocated to receive an annual injection of 300,000 IU vitamin D_2 or matching placebo every autumn over 3 years [28]. In the entire cohort the risk of any first fracture was not different in the two treatment groups. However, the vitamin D group showed an increased risk of hip/femur fracture (hazard ratio [HR] = 1.49, 95 % confidence interval [CI] 1.02–2.18) and hip/femur/wrist fracture (HR = 1.40, 95 % CI 1.07–1.82). Analysis of the female subjects showed that vitamin D treatment was associated with a borderline increased risk of any nonvertebral fracture (HR = 1.21, 95 % CI 1.00–1.47) and increased risk of hip/femur (HR = 1.80, 95 % CI 1.12–2.90) and hip/femur/wrist fracture (HR = 1.59, 95 % CI 1.17–2.16). However, vitamin D treatment was not associated with increased risk of any fracture in males. No effect on falls was observed, although this was not a primary outcome and falls were ascertained by 6-monthly recall. The other study, of 2,256 community-dwelling Australian women aged 70–92 years randomly allocated to receive an annual oral dose of 500,000 IU vitamin D_3, demonstrated a 15 % (95 % CI 1.02–1.30) increased rate of falls and a 26 % (95 % CI 1.00–1.59) increased rate of fractures [27]. A temporal pattern was observed, with the greatest increase occurring in the first 3 months after dosing (falls: p for homogeneity = 0.02). A temporal pattern of risk was not demonstrated in the Wessex study, although the 6-monthly ascertainment of fractures did not optimize this post hoc analysis (unpublished).

Serial biochemistry was performed only in a very small proportion of participants in both these RCTs (0.04 % and 6.1 % participants; Smith et al. [28] and Sanders et al. [27], respectively). Neither study recruited participants based on low 25(OH)D levels at screening. We are unable to infer that the adverse effects are confined to participants whose 25(OH)D levels were either deficient/insufficient or replete at baseline. It is well documented that the incremental increase in serum 25(OH)D is likely to be lower in those already replete prior to supplementation [24], and there is substantial variation in dose–response curves between

individuals [8, 9]. There is therefore no evidence base to justify large annual loading doses of vitamin D to specific groups based on their baseline 25(OH)D level. Based on the reduction in fractures using 4-monthly dosing regimens in the Trivedi et al. [46] RCT and the biochemical results by Bacon et al. [24] and Ilahi et al. [47], it seems prudent to restrict intermittent higher doses to intervals not greater than 2–4 months. However, the reasoning is speculative, and RCT evidence with physical outcomes using a variety of dosing regimens is urgently needed. The fall characteristics from the Australian study do not suggest that the increased falls were attributable to one subgroup of participants experiencing the most falls. The proportion of participants falling multiple times did not vary between the vitamin D and placebo groups (unpublished data), and Kaplan–Meier plots of time to first fall show significant differences between the groups ($p = 0.003$). In another recent publication, a small group ($n = 12$) of older (mean age 73 years) subjects was treated with a single oral dose of 600,000 IU vitamin D_3 [48]. Serum 25(OH)D increased from 54 ± 14 nmol/L at baseline to 168 ± 43 nmol/L at day 3 when the bone turnover markers C-terminal telopeptide (CTX) and N-terminal telopeptide (NTX) peaked at over 50 % above baseline. PTH decreased and 1,25-dihydroxyvitamin D (1,25[OH]D) increased by 25–50 % [48]. Rossini and colleagues [48] suggest that this transient increase in bone turnover markers may explain the negative clinical results obtained in studies using intermittent high-dose vitamin D. Sanders and colleagues [49] have also reported increased bone turnover among a sample of participants who underwent biochemistry assessments and had a very high incremental rise in serum 25(OH)D levels. While increased bone turnover may contribute to the demonstrated increase in fracture risk, this does not explain the clear evidence of increased falls in the Australian study (Table 3).

Speculative Mechanisms

The mechanism by which high-dose vitamin D might increase falls and fracture is uncertain. The opposing outcomes of two studies [28, 46] that used the same total annual dose (300,000 IU intramuscularly) suggest that the dosing regimen (i.e., 4-monthly vs. annually) rather than the total dose might determine the outcome. While a dosing interval of 12 months is equivalent to four biological half-lives of vitamin D, at the time these two studies were conducted there was biochemical evidence of safety and preliminary evidence that these intermittent bolus doses may be efficacious at decreasing fracture risk in older women [36, 46, 50]. In addition, the Australian study team was specifically addressing the drop in vitamin D and increased fractures that occurs during winter [51]. The line of reasoning regarding the dosing interval is supported by the temporal risk pattern observed in the study of Sanders et al. [27] and the fact that harm has not been reported in the numerous studies that have used more frequent dosing [52]. However, the lower-level evidence of a *U*-shaped dose–response curve reported in some observational studies [53–55] is not consistent with a temporal pattern since it is unlikely that those in the highest quintile of vitamin D status in the community use high intermittent doses of supplemental vitamin D. However, it is possible that seasonal fluctuations in 25(OH)D levels may contribute to this apparent phenomenon. Vieth [26] contends that a *U*- or *J*-shaped curve of risk is observed only in populations residing farther away from the equator and who, therefore, have greater seasonal fluctuations. It is argued that the annual downward phase in seasonal cycles almost definitely creates a non-steady-state situation for the paracrine production of 1,25(OH)D responsible for the noncalcemic effects of vitamin D. It is also possible the adverse mechanism may be associated with gender since Smith and colleagues [28] did not demonstrate an increased fracture risk among men and the majority of participants in the Trivedi et al. [46] study demonstrating a reduced fracture risk using 100,000 IU every 4 months were men (76 %). A Welsh RCT using the same dosing regimen as Trivedi et al. [46] but with 76 % women reported no difference in fracture outcome [56] (Tables 1, 3). In addition, the Australian RCT recruited only women [27]. There is also weak evidence from RCTs using more frequent dosing regimens that the mechanism is not a single aspect but may be more complex (Table 4).

It has been hypothesized that the increased numbers of falls and fractures may have, ironically, resulted from the benefits of vitamin D in that the older women randomized to vitamin D felt better and consequentially engaged in more "at-risk" falls behavior [52]. However, the Australian authors subsequently published mental well-being outcomes of this study. No significant differences were detected in any of the measured outcomes of mental health [57], making this explanation less likely. No differences between the groups relating to the circumstances or activity of the fall events has been identified (unpublished).

In their editorial, Dawson-Hughes and Harris [52] also hypothesized that the 500,000 IU dose may have triggered a "short-term protective" reaction in which CYP24 (25-hydroxyvitamin D-24-hydroxylase), the enzyme that catabolizes 1,25(OH)D, was upregulated, resulting in decreased blood and tissue levels of 1,25(OH)D. Although this hypothesis is consistent with results from an animal study [58], both the Wessex [28] and Rossini et al. [48] studies demonstrated increases (25–50 %) in serum 1,25(OH)D in those who had serial biochemistry

assessments. From an evolutionary approach, Vieth [59] presents the argument that oral supplementation of vitamin D is needed to improve health outcomes by lessening the destabilizing effect of annual fluctuations in serum 25(OH)D. He argues that the paracrine regulation of 1,25(OH)D in many tissues is disrupted by unstable 25(OH)D levels and that this adversely affects bone mineral density, mental well-being, infection, and cancer risk. The profile of 25(OH)D levels from the two studies showing harm does not appear distinctly different from a range of high-dose biochemical studies (Table 1). Although there is no uniformity in the time points of 25(OH)D assessment, peak 25(OH)D levels from these studies tend to be around 120–140 nmol/L. Ilahi and colleagues [47] suggest that the dosing interval of intermittent dosing regimens be not greater than 70 days to ensure that 25(OH)D levels do not decline below a target of 70 nmol/L.

The increased risk of falls in the Australian study demonstrates that the adverse mechanism is not confined to the skeleton. Post hoc analysis of changes in muscle strength in a nested substudy of these older women who underwent annual physical functioning assessments suggests a decline in muscle strength in those whose 25(OH)D level showed the greatest fluctuation from baseline [60]. Since there are vitamin D receptors in muscle, a sudden increase in vitamin D receptor occupancy could have an adverse effect on muscle function [61]. Vitamin D receptors are also present in the central nervous system [62], so an adverse effect on balance or coordination is also possible. Another recent Australian RCT of 686 ambulant women aged at least 70 years reported neither a beneficial nor an adverse effect on falls or physical function using a 3-monthly dosing of 150,000 IU cholecalciferol compared to placebo [63]. The study intervention period was 9 months, and the baseline 25(OH)D level measured in a subgroup of 40 participants was 66 ± 23 nmol/L. A review by Stockton and colleagues [64] concluded that vitamin D supplementation does not have a significant effect on muscle strength in vitamin D–replete adults.

Concluding Summary

While epidemiological studies provide evidence that vitamin deficiencies are associated with an increased risk of chronic disorders and/or cancer, the consequent philosophy that higher doses of the vitamin are protective and confer a reduced risk of these diseases is flawed [65, 66]. Two recent editorials on high-dose vitamin D have drawn analogies from the "hard" lessons learned from RCTs on high-dose vitamins A, B, C, and E [65, 66]. Supraphysiological levels of the vitamin taken as supplements do not emulate the apparent benefits of diets high in food that contain those vitamins and other lifestyle factors [67]. The findings from two recent high-dose RCTs [27, 28] identify a potential harm associated with high-dose vitamin D and support the notion that vitamin D could be now added to this list. Thus, in addition to evidence from enzyme kinetics relating to vitamin D metabolism [44], there is now high-level RCT evidence that vitamin D supplementation has potential toxicities other than simply hypercalcemia/-uria. As our understanding of the pharmacokinetics of vitamin D metabolism becomes more sophisticated, clinical trials with novel dosing regimens should apply the principles of conventional pharmacology and vitamin D metabolism to the study design.

Interpretation of findings from many large RCTs has been limited by the lack of assessment of 25(OH)D status in the majority of participants. Future studies of supplementation should be adequately funded to allow comprehensive or universal measurement of serum 25(OH)D and related biochemical parameters [65, 68], with particular attention to large and rapid fluctuations in vitamin D status. Future studies should not base toxicity solely on the risk of hypercalcemia/-uria. There is an urgent need for dose-ranging studies with physical function outcomes [61, 64]. Emerging evidence from both observational studies and RCTs suggests that there should be a degree of caution about recommending high serum 25(OH)D concentrations for the entire population. Furthermore, a benefit of the higher doses commonly used in clinical practice on falls risk reduction needs to be demonstrated [69]. While it is recognized that intramuscular high-dose vitamin D preparations may be the only way of ensuring adequate vitamin D status in specific "at-risk" groups of patients, such as those suffering fat malabsorption, the safety of loading doses of vitamin D administered to the general population should be demonstrated before these regimens become recommended as routine clinical practice [65]. The current dilemma of defining vitamin D insufficiency and identifying safe and efficacious repletion regimens needs to be resolved.

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