Osteoporos Int (2014) 25:2347–2357
DOI 10.1007/s00198-014-2749-7

REVIEW

Skeletal and nonskeletal effects of vitamin D: is vitamin D a tonic for bone and other tissues?

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Received: 9 March 2014 / Accepted: 12 May 2014 / Published online: 21 May 2014

Abstract The vitamin D endocrine system is critical for the maintenance of circulating calcium concentrations, but recently, there has been advocacy for the widespread use of vitamin D supplements to improve skeletal and nonskeletal health. Recent studies of tissue-selective vitamin D receptor knockout mice indicate that the principal action of vitamin D responsible for the maintenance of calcium homoeostasis is the regulation of intestinal calcium absorption. High levels of vitamin D can increase bone resorption and impair mineralization, consistent with its role in maintaining circulating calcium concentrations. These findings suggest that circumspection is appropriate in its clinical use. There is now substantial clinical trial data with vitamin D supplements, which fails to establish their efficacy on bone density or the prevention of falls or fractures. However, some trials in frail and/or vitamin D-deficient populations have produced positive outcomes. Where there are positive effects of vitamin D supplementation on skeletal outcomes, these are mainly seen in cohorts with baseline circulating 25-hydroxyvitamin D (25(OH)D) levels in the range 25–40 nmol/L or lower. A great diversity of nonskeletal conditions have been associated with low 25(OH)D, but there is little evidence for efficacy of vitamin D supplementation for such end-points. At present, supplements should be advised for populations with risk factors (e.g., lifestyle, skin color, and frailty) for having serum 25(OH)D levels in the 25- to 40-nmol/L range or below. A dose of ≤800 IU/day is adequate. This approach will maintain 25(OH)D levels well above the threshold for osteomalacia and makes allowance for the poor accuracy and precision of some 25(OH)D assays.

Keywords Calcium · Falls · Fracture · Nutrition · Osteomalacia · Osteoporosis · Vitamin D

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Introduction

The vitamin D endocrine system plays a primary role in the maintenance of extracellular fluid calcium concentrations. This function was deduced originally from the observation that patients with severe vitamin D deficiency become hypocalcemic, with other consequences, such as rickets/osteomalacia, following from that. Animal models of vitamin D deficiency and the development of vitamin D receptor (VDR) knockout mouse models have confirmed this belief. However, in the last decade, there has been growing advocacy for achieving higher circulating levels of 25-hydroxyvitamin D (25(OH)D) than are necessary for maintenance of normocalcemia, in the hope that this has additional benefits for bone health. Observations of associations between circulating 25(OH)D levels and a number of other conditions have extended this advocacy to a very broad range of nonskeletal conditions. Thus, vitamin D has been advanced in some quarters as a safe and effective "tonic" for bone and nonskeletal tissues, and this has led to advocacy for widespread vitamin D supplementation, often in doses much higher than those (400–800 IU/day) conventionally used. The major changes in clinical practice which this advocacy is leading to, make it timely to review recent laboratory studies, which address the mechanisms of action of vitamin D on skeletal and nonskeletal tissues and trial data on clinical end-points. Thus, a determination of both the safety and effectiveness of current supplementation practices in adults can be made.

Vitamin D and bone

Mechanism of vitamin D actions on bone

While cells of the osteoblast lineage, including osteocytes, express VDR, these receptors are also widespread outside of the skeleton. Just how widespread remains a matter of controversy [1, 2], though there is evidence of gene regulation in a variety of tissues by vitamin D [3, 4]. Studies involving tissue-specific knockout of VDR indicate that VDR in bone is not critical to the maintenance of bone health. Thus, the systemic VDR knockout mouse has osteomalacia and reduced bone mass, but this can be completely corrected by the provision of large enough doses of calcium and phosphate [5]. However, if VDR is only selectively knocked out in the enterocytes, the skeletal abnormalities seen in the systemic knockout model are reproduced [6]. Complementing this is the demonstration that the skeletal abnormalities of the VDR global knockout mouse can be corrected by selective replacement of VDR in enterocytes alone [7, 8]. Thus, VDR expression in enterocytes is both necessary and adequate for normal skeletal mineralization.

These findings pose the question as to the function of the VDR in bone. It appears that selective knockout in bone results in increases in bone mass [6, 9, 10] mediated by the effects of VDR in osteoblastic cells to regulate receptor activator of nuclear factor kappa-B ligand (RANKL) and osteoprotegerin, to promote osteoclastogenesis [4, 10]. Tanaka et al. performed a similar experiment by transplanting the femora from either wild-type or VDR knockout mice into normal mice. The VDR knockout bone in a wild-type environment had a 40 % higher bone mineral density (BMD) than the wild-type bone in the same environment [9], again suggesting that the VDR in bone mediates resorption rather than formation. Single large doses of vitamin D increase bone resorption markers acutely in clinical studies [11–13], and vitamin D intoxication is associated with sustained increases in bone resorption [14], confirming that these findings are reflected in human studies.

Recent work has demonstrated that, in addition to the stimulation of bone resorption, a further direct action of vitamin D on bone is to inhibit mineralization through increasing local levels of the mineralization inhibitor, pyrophosphate [6]. These experiments reinforce the concept of the vitamin D endocrine system as primarily for the maintenance of circulating calcium levels (which are critical to the function of excitable tissues such as the heart, nervous system, and muscle) and that this priority will be met at the expense of bone mass and mineralization, if necessary. Thus, in situations of very low dietary calcium intake, bone becomes a reservoir from which calcium can be drawn to maintain normocalcemia. In normal physiology, this is the only circumstance in which very high levels of vitamin D metabolites will be produced. However, with the use of increasing doses of vitamin D supplements, consideration needs to be given to the possibility that these adverse effects on bone mineralization and mass might result. Indeed, some studies of high-dose calciferol and/or 1-hydroxylated vitamin D metabolites do show increased bone loss [15] and fractures [16, 17]. High levels of 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) also act via the osteocytic VDR to increase circulating levels of FGF23, which limits the extent of secondary hyperparathyroidism and the production of $1,25(OH)_2D$ and has a phosphaturic effect on the kidney. The resulting reduction in phosphate levels may also inhibit mineralization.

These findings suggest that the relationship between circulating 25(OH)D and bone resorption is biphasic. At low 25(OH)D levels, secondary hyperparathyroidism occurs and maintains serum calcium levels by increasing production of RANKL and rates of bone resorption. High levels of 25(OH)D which result in high free $1,25(OH)_2D$ levels (either through increased production of $1,25(OH)_2D$ or through displacement of it from its binding protein) can also result in increased RANKL and bone resorption, directly stimulated by activation of the VDR. The VDR-mediated inhibition of bone mineralization will exacerbate these adverse skeletal effects. This suggests that the clinical challenge is not to maximize vitamin D loading of patients but to identify the levels of vitamin D metabolites which are associated with a nadir in bone resorption. This biphasic relationship is illustrated in Fig. 1.

Clinical consequences of declining vitamin D levels

As vitamin D levels decline, some individuals develop secondary hyperparathyroidism, but a considerable proportion do not [18]. The reasons for this variable response are not entirely clear, though a number of factors other than vitamin D status are known to influence parathyroid hormone levels, such as fat mass, season, physical exercise, renal function, and dietary calcium intake [19–21]. Secondary hyperparathyroidism appears to drive accelerated bone loss, and Arabi has reported

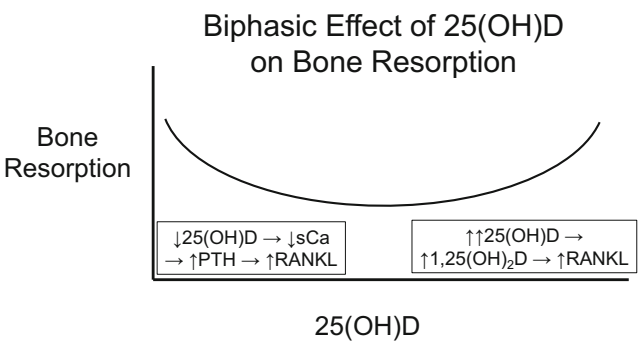

Fig. 1 Schematic representation of the consequences of very low and very high levels of vitamin D on bone resorption. See text for further details

that accelerated bone loss in older adults is not seen in vitamin D-deficient subjects with normal parathyroid hormone levels but only in those with secondary hyperparathyroidism [22]. Using cross-sectional data from older adults, Need has demonstrated that 25(OH)D levels of <15 nmol/L are associated with reductions in both $1,25(OH)_2D$ and intestinal calcium absorption and with increases in serum alkaline phosphatase activity [23]. In a similar cross-sectional database, Lips has shown an inverse relationship between 25(OH)D and parathyroid hormone over a wide range but with a steeper increase in parathyroid hormone (PTH) levels once 25(OH)D is <50 nmol/L [24]. However, bone turnover markers only increased when 25(OH)D was less than about 30 nmol/L—elevations of PTH without increased turnover markers are unlikely to be deleterious. While these two studies differ in the threshold at which adverse biochemical consequences of vitamin D deficiency are seen, they do agree in suggesting that it is in the range of 15–30 nmol/L. The well-recognized inaccuracies of 25(OH)D assays could easily account for a discrepancy of this magnitude.

Effects of vitamin D supplementation

Biochemistry

Many studies have addressed the effect of vitamin D supplements on circulating levels of 25(OH)D. The recent comprehensive study of Gallagher in postmenopausal women with mean baseline 25(OH)D levels of 40 nmol/L (all <50 nmol/L), showed a clear dose–response which was nonlinear [25]. Thus, 800 IU/day is clearly superior to 400 IU/day, but the effect plateaus as the doses progressively increase to 4800 IU/day. This plateauing of effect suggests homeostatic regulation of 25(OH)D levels, probably as a mechanism for preventing vitamin D intoxication. This study showed minimal increments in intestinal calcium absorption associated with vitamin D supplementation [26], and this finding has been confirmed in a further study of young women with mean baseline 25(OH)D levels of 34 nmol/L, in whom supplementation produced no significant effects on intestinal calcium absorption over 12 months [27]. These studies should not be interpreted to indicate that vitamin D does not influence intestinal calcium absorption but rather that the effect is already maximal at circulating 25(OH)D levels of 34–40 nmol/L, consistent with the data from Need, cited above, and other studies recently surveyed by Bouillon [28].

Vitamin D supplementation does reverse the secondary hyperparathyroidism associated with its deficiency, and this is a threshold phenomenon. Thus, Bacon et al. have shown that at 25(OH)D levels of <50 nmol/L, there is suppression of PTH with vitamin D supplementation and that this is more marked at progressively lower levels of 25(OH)D [29]. This is very similar to the data of Malabanan published previously [30]. However, at 25(OH)D levels of >50 nmol/L, there is no effect in either study.

Bone mineral density

Perhaps more clinically important than these biochemical changes, is the effect of vitamin D supplementation on bone density. Numerous trials have addressed this question, and some have tended to cite one or two older studies which appeared to demonstrate a beneficial effect. However, there have been numerous publications in this area in recent years, which motivated us to systematically review all of the trials carried out in adults [31]. At the time of the performance of that analysis, there were 23 randomized, controlled trials in adults, which together comprised over 4,000 subjects. Table 1 shows the clinical characteristics of the subjects in those studies, together with a further three studies published since the time of that analysis. The table also indicates whether there were significant effects of the intervention on bone density. As can be seen, a minority of studies found statistically significant effects at a single site, or in the case of the Islam study, at two proximal femoral sites. In those studies finding positive effects at the femur, there was no benefit at the spine and vice versa. Two studies found significant detrimental effects on total body BMD.

Meta-analysis of the 23 studies demonstrated a weighted mean difference in lumbar spine BMD of 0.0 % over a mean trial duration of 2 years. In the femoral neck, however, there was a significant benefit (0.8 % (95 % confidence interval (95 % CI), 0.2, 1.4), $P=0.005$), but this was not reproduced at the total hip (weighted mean difference, 0.2 % (95 % CI, −0.1, 0.4)). In the forearm and total body, there were downward trends in the bone density effects. In subgroup analyses, no effect of vitamin D was observed with doses of ≥800 IU/day, whereas lower doses led to significant benefits at both the lumbar spine (0.4 % (95 % CI, 0.0, 0.8)) and the femoral neck (1.4 % (95 % CI, 0.4, 2.4)). There was a nonsignificant trend suggesting that baseline 25(OH)D levels influenced outcome—in trials where baseline 25(OH)D was <50 nmol/L, there was a significant effect at the femoral neck (1 % (95 % CI, 0.2, 1.9)), whereas when 25(OH)D was ≥50 nmol/L, there was no benefit (0.5 % (95 % CI, −0.2, 1.3)). Study duration or co-administration of calcium did not contribute significantly. Examination of the individual trials in Table 1 is consistent with these findings. Apart from the two Dawson-Hughes studies, in which the 25(OH)D assays may have been inaccurate [32] and which were carried out in sequence in the same cohort of women who had dietary calcium intakes of <400 mg/day, significant benefit was only seen in trials where the mean baseline 25(OH)D ranges from 25 to 40 nmol/L and, even in these, the effects were small. Thus, these data suggest that supplementation of individuals with 25(OH)D above this range does not benefit BMD and may even be detrimental.

Table 1 Randomized controlled trials of vitamin D on bone mineral density in adults

Study	*t* (m)	Number[a]	Mean age (range)	Baseline 25OHD (nmol/L)	Spine	Total hip	Femoral neck	Forearm	Total body
Christiansen[d]	24	149	50 (45–54)	–				NS	
Dawson-Hughes[d]	12	276	62	71	+				NS
Dawson-Hughes[d]	24	261	64	66	NS		+		NS
Ooms[d]	24	348	80 (>70)	26		NS	+	NS	
Tuppurainen[d]	48	45	55 (50–59)	–	NS		NS		
Komulainen (HRT)[d]	60	231	53	27	NS		NS		
Komulainen (no HRT)	60	227	53	28	NS		NS		
Hunter[d]	24	158	59 (47–70)	71	NS	NS	NS	NS	NS
Patel[d]	12	70	47 (24–70)	72	NS	NS	NS		–
Venkatachalam[d]	24	50	54	–	NS	NS			
Cooper[d]	24	187	56	82	NS	NS	NS	NS	
Harwood[d]	12	75	80 (67–92)	29	NS	+	NS		
Aloia[d]	36	208	61 (50–75)	46	NS	NS		NS	NS
Zhu (a)[d]	60	79	75 (70–80)	68		NS			
Zhu (b)[d]	12	302	77	44		NS			NS
Andersen[d]	12	173	37	16	NS				–
Viljakainen[d]	6	54	29 (21–49)	64				NS	
Islam[d]	12	100	22	36	NS	+	+		
Jorde[d]	12	421	47 (21–70)	58	NS	NS			
Verschueren[d]	6	113	80 (70–)	53		NS			
Grimnes[d]	12	297	63 (50–80)	71	NS	NS	NS		NS
Rastelli[d]	6	60	62	57	NS	NS	NS		
Steffensen[d]	22	71	40 (18–50)	56	NS	NS		NS	
Nieves[d]	24	127	62	100	NS	NS			
Iuliano-Burns [68][e]	12	110	41 (24–65)	60	NS	NS	NS		
Wamberg [69][e]	6	52	40 (18–50)	35	NS	NS	NS	+/NS[b]	NS
Macdonald [70][e]	12	305	(60–70)	34	NS	+/NS[c]			

t is trial duration in months, *NS* no significant effect at that skeletal site in that study, "+" positive effect of vitamin D, "–" negative effect

[a] Number of participants randomized. BMD results are shown in the right-hand columns

[b] Significant effect at ultra-distal forearm but not in total forearm

[c] Benefit in 1000 IU/day group, not in 400 IU/day group

[d] Studies that were included in our recent systematic review [31]

[e] Studies that have been published more recently

A skeptic could be tempted to interpret the meta-analysis of vitamin D effects on BMD to indicate that vitamin D status has little effect on bone health. We need to remind ourselves that with severe vitamin D deficiency, osteomalacia occurs, and this leads to a profound demineralization of the bone. El-Desouki published a description of 96 women with a clinical diagnosis of osteomalacia, all of whom had serum 25(OH)D levels of <25 nmol/L [33]. Over a 12-month period after vitamin D replacement, lumbar spine density increased by 51 % and femoral neck BMD by 16 %. This clearly demonstrates the marked adverse effects of severe vitamin D deficiency on the skeleton and its reversibility with supplements, but it demonstrates that the threshold for these effects is somewhere <25 nmol/L. It is likely that within randomized, controlled trials of severely vitamin D-deficient populations, some individuals do in fact have osteomalacia and demonstrate the substantial effects seen in the El-Desouki case series.

Fractures

To the casual observer of the vitamin D literature, the data on anti-fracture efficacy is perhaps the most confusing. For instance, the Cochrane analysis concludes that "vitamin D alone is unlikely to prevent fracture" [34] very similar to the conclusions from the DIPART analysis "vitamin D given alone … is not effective in preventing fractures" [35]. By contrast, Bischoff-Ferrari concludes that "high-dose vitamin D supplementation (≥800 IU daily) was somewhat favorable in the

prevention of hip fracture and any nonvertebral fracture in persons 65 years of age or older" [36]. These apparent discrepancies relate to two issues. The first is whether studies in which calcium plus vitamin D is the intervention are pooled with those in which the intervention is vitamin D alone, and the second is the use of what are, in effect, compliers analyses by Bischoff-Ferrari.

The Cochrane and DIPART analyses make these distinctions explicit. Thus, in the Cochrane analysis, the relative risk (RR) of hip fracture with vitamin D alone is 1.15 (95 % CI, 0.99, 1.33), whereas with vitamin D plus calcium, the RR is 0.84 (95 % CI, 0.73, 0.96). For any fracture, DIPART found the RR for vitamin D alone to be 1.01 (95 % CI, 0.92, 1.12) and for trials of calcium plus vitamin D, 0.92 (95 % CI, 0.86, 0.99). As calcium supplements have an unequivocal (though modest) antiresorptive effect, decreasing turnover by about 20 % and reducing postmenopausal bone loss by approximately one third [37], treating vitamin D alone and vitamin D plus calcium as equivalent interventions is inappropriate. Indeed, analyses focused on the anti-fracture efficacy of calcium have demonstrated that calcium alone is comparable in efficacy to calcium plus vitamin D [38], implying that the addition of vitamin D is without effect.

By contrast, the Bischoff-Ferrari analysis does not distinguish between these two interventions and also carried out post hoc analyses of each trial aimed at determining the actual intake of vitamin D in the active group. This was based on the individual's adherence to trial medication, the supplement dose used in the trial, and supplement use outside of the study protocol. It appears that these adjustments were made for the vitamin D-supplemented groups but not the control group. Thus, the trial subjects identified as having vitamin D intakes of >800 IU/day, in whom benefit was found, are a group of compliers from the vitamin D groups who are then compared with unselected subjects from the placebo groups. Compliers and noncompliers are not comparable in a number of ways, illustrated by the trend in the FIT study towards lower hip fracture risk among placebo group compliers compared with noncompliers from the same group [39]. Among the studies in which vitamin D intakes of >800 IU/day were achieved, only one used vitamin D alone (as opposed to vitamin D plus calcium) and it found a RR of fracture nonsignificantly greater than 1, quite consistent with the absence of effect reported by the other two major meta-analyses. A detailed critique of the Bischoff-Ferrari analysis has been published [40].

When considering these fracture efficacy studies, it is important to recognize the substantial influence of the Chapuy study [41, 42] and to note the ways in which it differs from most of the other studies in this area. This study, like the subsequent study from the same authors [43], was in frail elderly women living in institutions. In the first of these studies, calcium intakes were only 500 mg/day and mean 25(OH)D was 25 nmol/L in placebo subjects 12 months into the study (13.7 nmol/L following correction for assay problems) [32]. The calcium plus vitamin D intervention produced a between-groups difference in total hip bone density of 7.3 %, an effect which has not been produced by calcium or vitamin D in any subsequent study nor, for that matter, by any other anti-osteoporotic medication. This large increase in bone density is really only explicable as a response to the treatment of osteomalacia in at least a subset of the trial patients. In contrast, when the effects of vitamin D plus calcium are studied in community-dwelling individuals who are likely to have less-severe nutritional and sunlight deprivation, the RR of hip fracture is 1.12 (95 % CI, 0.88, 1.44), in contrast to the meta-analyzed value from the two Chapuy studies of 0.75 (0.62, 0.92) [44] (Fig. 2). In summary, analyses which suggest that vitamin D, with or without calcium, prevent fractures are substantially influenced by the two Chapuy studies, yet these studies were carried out in frail elderly women in institutions and are not generalizable to community-dwelling populations.

Optimal 25(OH)D for bone health

The studies discussed above allow us to update the estimate of the optimal 25(OH)D levels for bone health. Focusing on intervention rather than cross-sectional studies, we see that only when 25(OH)D is <50 nmol/L does vitamin D supplementation result in suppression of PTH. The absence of effect of vitamin D supplementation on intestinal calcium absorption in the two recent Gallagher studies suggests that this parameter is already optimal at levels of 34–40 nmol/L. In the trials assessing bone density, vitamin D supplementation is beneficial only when baseline 25(OH)D is in the 25- to 40-nmol/L range, and substantial effects are only seen in patients likely to be osteomalacic (i.e., 25(OH)D, <<25 nmol/L). An individual patient analysis that relates BMD change to baseline 25(OH)D is needed to better determine optimal 25(OH)D levels for this endpoint. There is no clear evidence of fracture prevention with vitamin D alone, though the positive effects of vitamin D plus calcium found by Chapuy were in patients with mean 25(OH)D levels of about 14 nmol/L. Taken together, these data suggest that levels above 25–40 nmol/L are satisfactory for bone health. This estimate is conservative, as hard evidence of skeletal pathology is only available at lower levels. Such conservatism is appropriate because of the inaccuracies of the 25(OH)D assays and the importance of preventing osteomalacia. A level of 40 nmol/L was identified by the recent Institute of Medicine report as a threshold for bone health, based substantially on data from histological studies [45].

The advocacy for much higher 25(OH)D levels has come from the analyses of achieved 25(OH)D levels in trials, reported by Bischoff-Ferrari [46]. This has the same issues as that group's more recent meta-analysis discussed above, in that it fails to distinguish between studies of

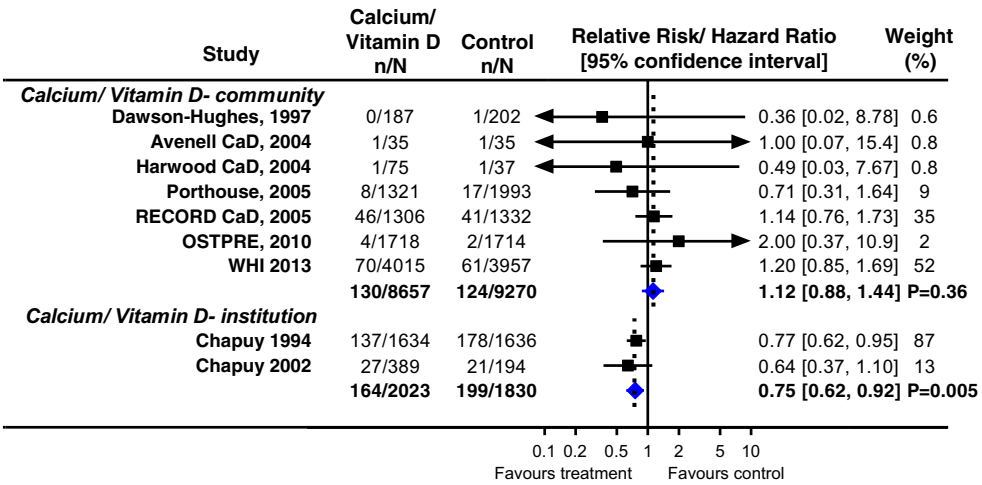

Fig. 2 Meta-analysis of the effects of vitamin D with calcium on hip fracture risk in randomized controlled trials. Studies have been divided according to the residential status of their participants. The classification of the Harwood study is debatable, as subjects were in hospital following fractures at trial entry, though most had been community dwelling previously. The WHI data are for those women not randomized to estrogen, since a significant interaction was found between estrogen and randomization to calcium plus vitamin D [67]. More details have been published previously [44] (Copyright MJ Bolland 2013, used with permission)

vitamin D alone and those in which calcium and vitamin D were co-administered, again particularly the Chapuy study. When the four studies from that analysis in which the comparator groups differed only in vitamin D intake are considered, the achieved 25(OH)D levels fall into a narrow range (62–74 nmol/L) and do not explain the differences in anti-fracture efficacy between the studies.

Nonskeletal effects of vitamin D

Falls

Severe vitamin D deficiency is associated with myopathy, presenting with pain, weakness, and changes on electromyography and biopsy [47], though a recent study of athletes with 25(OH)D levels of <25 nmol/L did not find evidence of weakness [48] nor did does raising 25(OH)D from 27 to >50 nmol/L change muscle strength [49]. These findings have led to the hypothesis that vitamin D deficiency in frail elderly people may increase their propensity to fall. Thus, there have been a large number of trials of vitamin D supplementation for falls prevention. Like the fracture data in this area, trial results have been subjected to repeated meta-analyses, sometimes with contradictory outcomes. As for fractures, variable patterns of co-administration of calcium supplements have complicated trial interpretation. The recent meta-analysis commissioned by the Endocrine Society found that the odds ratio for falling in those randomized to vitamin D supplements with or without calcium was 0.86 (95 % CI, 0.77, 0.96) but with vitamin D alone, there was no significant effect (odds ratio, 0.97 (95 % CI, 0.84, 1.11)) [50]. A statistically significant interaction was found between falls risk and calcium co-administration status: trials which compared calcium plus D to calcium alone appeared to show a greater effect than those comparing calcium plus D with control. This could be a chance finding; otherwise, it implies an adverse effect of calcium administration in the control group. Studies carried out in populations considered on clinical grounds to be at risk of vitamin D deficiency, showed a substantial reduction in falls risk (odds ratio, 0.53 (95 % CI, 0.39, 0.72)), though re-analysis of these data indicate that categorizing trials by actual baseline 25(OH)D levels does not confirm this finding (Fig. 3a). The Endocrine Society analysis includes falls from the first Chapuy study [41], though these were not reported by Chapuy—they appear to have been inferred from the fracture data.

We have recently repeated the analysis with stricter inclusion criteria and utilizing all available data from factorial and multi-arm studies and found no effect of vitamin D with or without calcium on falls in 20 randomized controlled trials involving 29,535 participants [51]. However, there was heterogeneity in this analysis, and Fig. 3b again suggests different outcomes among trials in the three treatment subgroups: there was no effect of vitamin D alone on falls nor of vitamin D plus calcium compared with controls, but there was a 16 % reduction in falls in those trials comparing vitamin D plus calcium with calcium. Other subgroup analyses showed no influence on outcome of baseline 25(OH)D, achieved 25(OH)D, study duration, residential status, or whether falls were primary or secondary endpoints.

The Cochrane analysis of trials in community-dwelling individuals found no benefit (risk ratio, 1.0 (95 % CI, 0.93, 1.07)) unless trial subjects were preselected for vitamin D deficiency, where the risk ratio was 0.70 (95 % CI, 0.56, 0.87) [52]. However, the criteria for vitamin D deficiency in

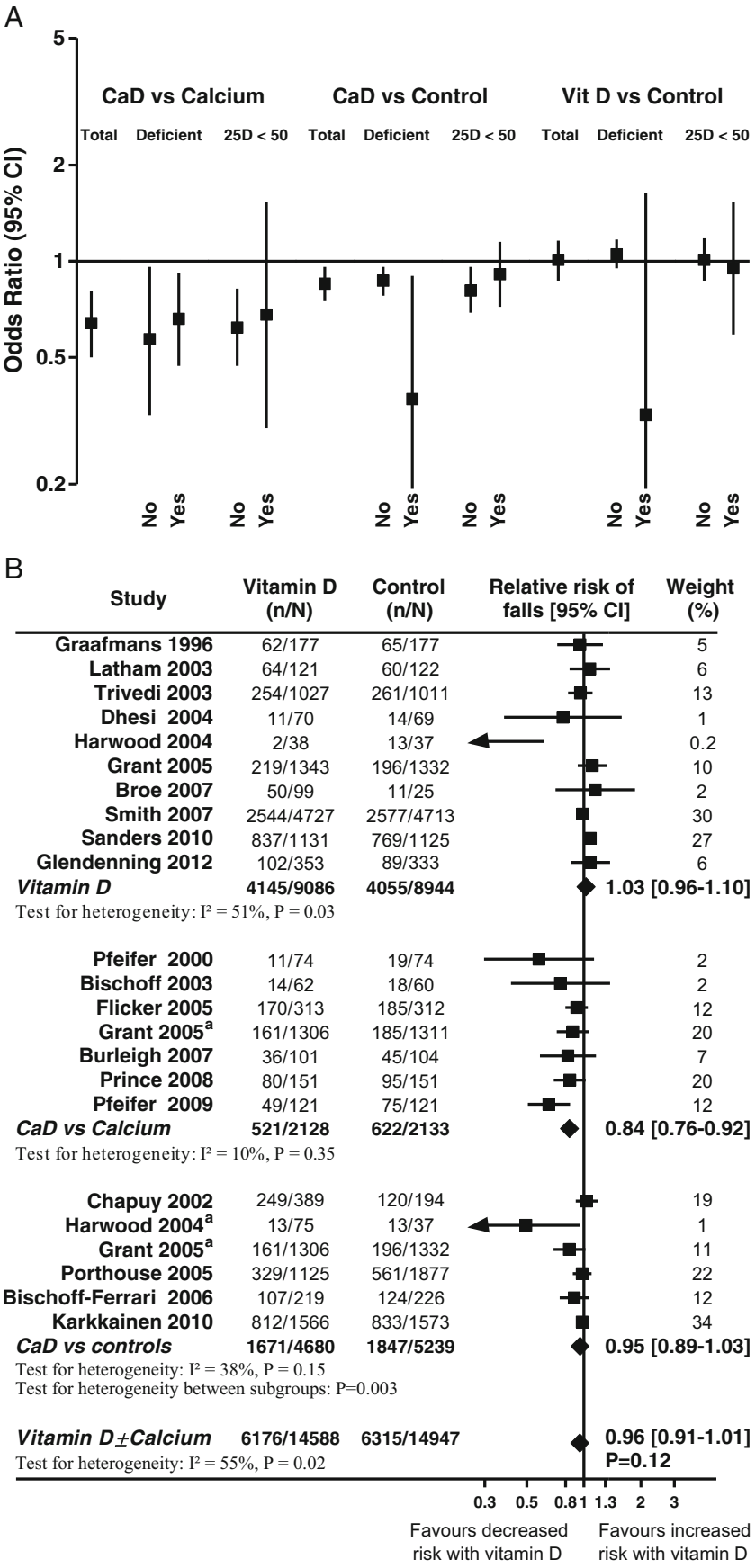

Fig. 3 Meta-analyses of the effects of vitamin D supplementation on falls. **a** Re-analysis of the data presented by Murad [50]. Data are grouped by intervention and by vitamin D status. Murad et al. categorized the subjects in each study as being vitamin D deficient or not ("yes" and "no" herein, respectively), based on their clinical characteristics (*deficient*). We have further categorized studies according to whether the actual mean 25(OH)D level was <50 nmol/L at baseline or not ("yes" and "no" herein, respectively). For the studies comparing calcium plus vitamin D with calcium, these distinctions make little difference to the outcome. However, for the other two study designs, the two definitions of vitamin D deficiency produce quite different outcomes (copyright MJ Bolland 2013, used with permission). **b** Random effects meta-analyses of vitamin D, vitamin D with calcium versus calcium, vitamin D with calcium versus controls, and vitamin D with or without calcium on falls. Details of the trials are provided elsewhere [55]. *Superscripted* "a" indicates multi-arm or factorial studies permitting a separate comparison of vitamin D with calcium versus controls or calcium (copyright MJ Bolland 2013, used with permission)

the latter group of studies were variable and not particularly strict (i.e., 25(OH)D of <30, <50, and <78 nmol/L, in the respective studies). In care facilities, on the other hand, Cochrane found that vitamin D supplementation reduced the rate of falls (rate ratio, 0.63 (95 % CI, 0.46, 0.86); 5 trials, 4,603 participants) but not risk of falling (RR, 0.99 (95 % CI, 0.90, 1.08); 6 trials, 5,186 participants) [53]. Bischoff-Ferrari has also meta-analyzed these data but used very restrictive criteria for study inclusion, most qualifying studies being in institutionalized settings [54]. She concluded that vitamin D in doses of >700 IU/day reduced falls risk (RR, 0.81 (95 % CI, 0.71, 0.92); n=1,921 from 7 trials), whereas lower doses did not (RR, 1.10 (95 % CI, 0.89, 1.35); n=505 from 2 trials). Thus, the information is contradictory with indications that vitamin D supplements might reduce falls in frail individuals but clear evidence that this intervention is ineffective in nondeficient individuals in the community.

One explanation for the variability of the responses of falls to vitamin D could be that vitamin D deficiency does not directly result in myopathy. Severe vitamin D deficiency is usually associated with hypophosphatemia, as a result of excess of both PTH and FGF23, and hypophosphatemia can cause muscle weakness and pain quite independently of vitamin D deficiency [55]. The recent work suggesting that skeletal muscle does not have significant expression of VDR [2] has been followed by rat studies which demonstrate that the myopathy of vitamin D deficiency is mediated by the accompanying hypophosphatemia and that the muscle abnormality can be completely corrected by phosphate repletion without vitamin D supplementation [56]. This would be consistent with the data in Fig. 3a, which indicate that it is clinical risk factors for physical frailty and poor nutrition (which themselves could contribute to hypophosphatemia), which are associated with responsiveness to vitamin D supplementation, rather than low levels of 25(OH)D per se. This mechanism could also explain the surprising finding that calcium plus vitamin D is better than calcium alone but not better than control. Possibly, giving calcium alone to a clinically frail control group exacerbates their phosphate depletion and, thus, their propensity to fall. If this hypothesis is correct, it suggests that attention to undernutrition in general is more important than simple supplementation with vitamin D. This is a hypothesis which is amenable to testing in clinical trials. A further possibility is that renal impairment, with its associated decline in $1,25(OH)_2D$, influences falls [57]. Decreasing creatinine clearance is associated with an increase in number of falls in untreated women but not in women receiving calcitriol [58].

There is a widespread belief that vitamin D deficiency presents as musculoskeletal pain, which is reversible with supplementation. Arvold recently assessed this in a randomized, controlled trial of primary care patients with 25(OH)D levels between 25 and 63 nmol/L; the mean value being 45 nmol/L. Scores for fatigue, musculoskeletal pain, and depressed mood did not change significantly over an 8-week period, even though the vitamin D supplementation raised 25(OH)D levels to a mean level of 113 nmol/L [59].

Other disease associations

In recent years, there has been an avalanche of publications describing associations of serum 25(OH)D with a wide variety of pathologies. In order to determine the size of this literature and the range of conditions with which vitamin D status is associated, we searched Web of Science from mid-November 2012 to mid-January 2013. In this 2-month period, 92 publications reporting associations between 25(OH)D and specific medical conditions were found. Twenty of these reported the incidence of vitamin D deficiency (in relation to a predefined normal range) within a particular condition, whereas the balance of original studies compared patients with controls or related disease severity to 25(OH)D levels within a cohort. Fifteen of these 92 publications were reviews of disease associations of 25(OH)D. The described associations represented 53 distinct diseases and are listed in Table 2. Most

Table 2 Conditions associated with vitamin D deficiency

Cardiovascular
Venous thromboembolism, heart disease, myocardial infarction, aortic dilatation, and orthostatic hypotension
Respiratory
Bronchiectasis, asthma, bronchiolitis, acute respiratory infection, lung injury, lung function, and lung disease
Metabolic
Metabolic syndrome, diabetes, diabetic nephropathy, infertility (male), chronic kidney disease, and renal transplant
Infection
Infections and leprosy
Cancer
Breast, past cancer of childhood, ovarian, and lung
Musculoskeletal
Muscle strength, osteoarthritis, rheumatoid arthritis, juvenile arthritis, and hip fracture
Mortality
Neurological
Multiple sclerosis, cognition, myasthenia gravis, meningomyelocele, headache, stroke, depression, forensic psychiatric illness, spinal cord injury, Alzheimer's disease, and falls
Gastrointestinal
Inflammatory bowel disease, chronic hepatitis, cirrhosis, and pancreatitis
Other
Pregnancy, preterm birth, critical illness, urinary incontinence, familial Mediterranean fever, obstructive sleep apnea, psoriasis, burns, eczema, perioperative risk score, and weight gain

These conditions were reported to be associated with serum 25(OH)D levels in a search of papers published over a 2-month period in the late 2012, as described in the text

authors inferred a causal relationship between lower 25(OH)D levels and the associated disease, and many therefore advocated vitamin D supplementation based on these observational study results. The fact that most major organ systems and a wide variety of pathological processes (infection, inflammation, neoplasia, psychiatric illness, metabolic disease, developmental abnormalities, and trauma) are implicated makes an etiologic role for vitamin D in each of them both implausible and without precedent. Journal editors should consider whether the amount of space devoted to these studies is justifiable.

This implausibility is strengthened by the generally negative results of large vitamin D intervention studies reporting vascular events, fractures, and cancers [60, 61], and the negative findings of recent meta-analyses of the effects of vitamin D supplementation on cardiovascular disease [62], cancer [63], and fractures [35]. We have recently explored this evidence in more detail by assessing the effects of vitamin D supplementation (with or without calcium) on myocardial infarction, stroke, cancer, and mortality in trial sequential analyses [64]. We used a 5 % risk reduction threshold for mortality and 15 % for other endpoints. The effect estimates for myocardial infarction/ischaemic heart disease (9 trials, n=48,647), stroke/cerebrovascular disease (8 trials, n=46,431), and cancer (7 trials, n=48,167), lay within the futility boundary, providing evidence that vitamin D supplementation does not alter the RR of any of these endpoints by ≥15 % and that further trials are unlikely to influence that conclusion. Vitamin D with or without calcium was associated with a RR of death of 0.96 (95 % CI, 0.93, 1.00; 38 trials, n=81,173), but the effect estimate lay between the superiority and futility boundaries indicating that uncertainty remains with respect to its effects on mortality. Autier has recently documented this inconsistency between the observational and trial data in this area [65].

These findings suggest that vitamin D deficiency is more likely to be the result of diverse disease processes, rather than their cause. Individuals who are unwell are less likely to exercise outdoors and thus be exposed to sunlight. In addition, obesity is associated with low 25(OH)D levels (probably as a result of sequestration of this fat soluble vitamin into adipose tissue), and many of the pathologies associated with low levels of vitamin D are more frequent in the obese. Some traumatic and/or inflammatory conditions are associated with abrupt and substantial reductions in levels of 25(OH)D [66], and proteinuric kidney disease is associated with urinary loss of vitamin D-binding protein. Thus, most disease associations of vitamin D are likely to be epiphenomena rather than etiologic.

Conclusions

While our knowledge of vitamin D biology continues to move forward, understanding of the clinical role of vitamin D has changed little in the last 20 years. The certainties then and now are that severely reduced levels of 25(OH)D produce osteomalacia, which is readily responsive to supplementation with small doses of vitamin D. In the last 20 years, the very clear *association* of circulating 25(OH)D with a number of skeletal and nonskeletal endpoints has resulted in the widespread assumption that these relationships are causal. However, a very substantial body of clinical trials has failed to establish clear evidence of benefit from vitamin D supplementation. It is possible that supplementation improves bone density, reduces fractures, and reduces falls, but all of these effects are probably only present when baseline levels of 25(OH)D are in the 25- to 40-nmol/L range or lower. If further trials of these endpoints are to be undertaken, then they should concentrate on populations where are such levels are prevalent.

With respect to nonskeletal endpoints, recent analyses [64] indicate the futility of further trials similar to those already undertaken. This suggests that if vitamin D supplementation is going to influence any nonskeletal endpoints, it will also be in populations with lower levels of 25(OH)D than have been trialed to date. There is little indication that the current enthusiasm for high-dose vitamin D supplementation will be successful, as doses greater than 1,000 IU/day are on the flatter part of the 25(OH)D dose–response curve, and there is already evidence of adverse effects from pushing serum 25(OH)D to levels of >100 nmol/L [16].

To revisit the question posed in the title of this review, is vitamin D a tonic for bone and soft tissue? Probably not, but levels of <25–40 nmol/L do have significant adverse consequences, so should be prevented. However, as with any potent bioactive compound, more is not necessarily better, and use of vitamin D should be based on trial data, not on inferences drawn from studies of associations.

Acknowledgments This study is supported by the Health Research Council of New Zealand.

Conflicts of interest None.

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