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The role of vitamin D in the prevention of osteoporosis

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Abstract

The need for vitamin D to prevent rickets was the drive for selection of lighter skin color in temperate climates. Anthropologists also know that as human populations developed more sedentary lifestyles, this coincided with a decline in bone quantity, quality, and fracture resistance. Since osteoporosis occurs after the reproductive years, there is no way that natural selection could have adapted our biology to prevent it. However, osteoporosis can be largely prevented by optimizing physical activity, and the vitamin D-related factors of environment, and nutrition. The role of vitamin D_3 in osteoporosis is conclusively established from a very simple meta-analysis of the four randomized, placebo-controlled clinical trials into the effect of 20 μg (800 IU) per day. These have all demonstrated that this dose prevents approximately 30% of hip or non-vertebral fractures compared to placebo, in adults older than 65 years. Intakes less than this have never been found effective. The lowest average serum 25-hydroxyvitamin D concentration in any study demonstrating fracture reduction was 74 nmol/L. Thus, 25-hydroxyvitamin D levels in older adults should exceed this amount. The role of vitamin D supplementation is to provide humans with the nutrient in an amount closer to our species' biological norm. This amount of vitamin D results in the optimal function of many aspects of health, including balance and muscle strength that lessen the risk of fracture beyond what is possible via the quality and quantity of bone itself.

Key words: *Cholecalciferol, fractures, nutrition, 25-hydroxyvitamin D*

Introduction

The term, osteoporosis, refers to a histological assessment of bone by a pathologist, and it is defined by diminished quantity of bone mineral per unit volume of whole bone. What bone there is, is of normal quality. The World Health Organization defines osteoporosis based on a bone mineral density measurement 2.5 standard deviations below the mean of young women or men. From the perspective of the patient, osteoporosis is simply a risk factor for the only clinical event the patient should care about – whether she or he will fracture bones.

Osteoporosis is at least partly a consequence of insufficient supplies of the nutrient, vitamin D (1,2). Vitamin D nutrition is extremely important for anyone interested in osteoporosis, because this is by far the easiest and cheapest thing that we can do something about. Calcium nutrition is also important of course, but the evidence that calcium alone prevents fractures is minimal. In contrast, the evidence for the fracture-preventing effects of vitamin D – even when given by itself – is so striking that everyone should know about it.

Parfitt has classified the hyperparathyroidism that is secondary to low calcidiol (25(OH)D) levels according to clinical, biochemical and bone histomorphometric indices. He proposes that the more severe form of vitamin D deficiency that causes rickets and osteomalacia is associated with 25(OH)D concentrations $<$ 25 nmol/L (10 ng/mL). In patients with a less severe form of vitamin D insufficiency, he reported that the average 25(OH)D concentrations were 75 nmol/L (30 ng/mL) (2). This value for the 25(OH)D concentration is identical to what a consensus panel later concluded should be the minimum desirable value for the prevention and treatment of osteoporosis, is based upon suppression of parathyroid hormone (PTH) and the 25(OH)D levels observed in fracture-prevention studies (3). Fragility fractures are the clinical event of osteoporosis, and for this, bone density predicts approximately half the risk.

Human evolution could not have adapted our species to prevent of vitamin D-related osteoporosis

There is nothing more vague in nutrition than the dose of vitamin D we should consider physiological or natural for the human species, compared to what

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we should consider pharmacological. One problem is that none of us live the lifestyle that we should regard as 'natural' for the human species. Current 'normal-range' values for 25(OH)D are certainly less than normal in the broader context of human biology. This concept is not new. During the early history of vitamin D, Leslie J. Harris wrote the following: "How far is it 'natural' to live in this sunless climate of ours? In more natural sunnier climates such [vitamin D] treatment would not be necessary. And how much of our life – our habits of clothing, shelter artificial heating, and in fact the whole complex fabric of our artificial civilization with its incessant interference with primitive behavior – is natural?"(4).

It is well known to anthropologists, that as human populations developed technologies that made possible our more sedentary lifestyles, this coincided with a decline in bone quantity, quality, and fracture resistance (5,6). These features of osteoporosis remain even with adjustments for age at death of those studied. These findings have implications for modern populations with their more rapid rates of bone loss and increased risk of fracture. Even today, the age-adjusted incidence of osteoporosis and its characteristic fractures tend to increase along with the gross-domestic product of populations. Based on what we know of human biology, osteoporosis can be largely prevented by optimizing physical activity, environment, and nutrition.

During the evolution of our species, requirements for vitamin D were satisfied by the life of the naked ape in the environment for which its genome was optimized, through natural selection. One hundred millennia ago, the horn of Africa was the original, natural environment for the modern *homo sapiens*. Our genome and our biology are not thought to have changed since that time. However, we have migrated away from tropical climes, and most of us avoid exposing skin to the vitamin D-forming rays of sunshine. We cover ourselves with clothing, and we stay indoors. Many of us live in regions like northern Europe, where for most of the year, sunshine does not contain the ultraviolet light B light (UVB, 285–300 nm) necessary to produce vitamin D in unprotected skin (7). If we can separate ourselves from modern life for a moment, and look at human biology from the perspective of a dispassionate observer, then we could easily come to see osteoporosis as a harmful side-effect of modern human culture. The most likely harmful consequences of sun-deprived modern life are those diseases and conditions whose severity or incidence correlate with the supply of sunshine – either across the seasons, or across latitudes.

Key messages

- Vitamin D_3 at the dose of 20 μg (800 IU) daily has been consistently found to prevent fractures in adults older than 65 yrs.
- Patients' serum 25-hydroxyvitamin D concentration should exceed 74 nmol/L to prevent fracture.

Diseases whose incidence and mortality varies with UVB include hypertension, breast, colon, and prostate cancers (8–10), as well as diabetes and multiple sclerosis (11,12).

Rickets was the driving force for the process that has produced the latitudinal gradation of skin color of human populations (13,14). Our need for vitamin D is the cause of a variation in skin color – the most striking phenotypic difference across human populations. While we recognize excessive curvature of long bones as a sign of rickets and vitamin D deficiency, a misshapen pelvis is also a common result. Even if a woman did not have rickets during childhood, marginal vitamin D insufficiency caused bouts of osteomalacia that resulted in a progressive reshaping of the pelvis – to the point where natural childbirth was no longer possible (15–17). It is rare to find evidence of rickets in ancient populations because family lines susceptible to it died off very quickly.

Although black skin is natural and optimal for equatorial latitudes because it protects the skin, its main advantage for reproduction of our species is that it prevents the UV-induced breakdown of micronutrients like folic acid as they circulate through capillaries near the surface of the skin (7,14). However, at latitudes farther away from the equator, the process of natural selection favors whiter skin, because this permits dermal generation of sufficient vitamin D when the amount of UVB in sunlight is diminished. In this case 'sufficient' vitamin D refers only to an amount of vitamin D that is enough to permit and maintain a normally shaped female pelvis. Osteoporosis generally occurs late in life and could not have played a role in the ability of women to give birth; therefore, natural selection could have compensated completely to prevent osteoporosis. Our genetics and our biology are optimized for the conditions of the first humans who surely walked this world without clothing in sunny, equatorial latitudes. In the remainder of this paper, we address the question of how much vitamin D may be optimal for the prevention of osteoporosis.

Vitamin D and osteoporosis

Summary of randomized-controlled clinical trials of fracture-prevention using vitamin D, with or without calcium

The following relates to studies summarized in Table I. Not one of the studies at doses of vitamin D_3 less than 20 μg/day was effective in reducing fracture risk (18,19). However, all four the studies using approximately 20 μg/day of vitamin D_3 showed a reduction in fracture risk (18,20–24). This dose includes the known background intake; from the work by Dawson-Hughes on background intake, this was 5 μg/day (21). The vitamin D_3 dose of 20 μg/day is the lowest dose that has shown fracture reduction in randomized clinical trials. This is the only nutrient with a demonstrable effect on fractures. There is no need for a complex meta-analysis to be convinced that the findings are conclusive. Four out of four randomized, placebo-controlled clinical trials demonstrated that 20 μg/day of vitamin D_3 lowers fracture risk in adults over age 65 by about 30%. Even with a crude coin flip, the probability of obtaining the same result by luck is $P=0.0325$.

Whether or not additional calcium is needed in concert with vitamin D is difficult to tell, because for most of the studies that showed fracture prevention, the focus of interest was calcium, with vitamin D simply added on. This was the case for the French DECALIOS studies that were designed to support use of a calcium supplement product (20,22), but to their credit, the authors were able to provide an amount of vitamin D that their earlier work had shown would suppress PTH (25). Fortunately also, Chapuy et al. changed from their earlier use of vitamin D_2, to the use of vitamin D_3. Fortunate because there is still no study that has used vitamin D_2, where treatment was effective in lowering risk of fracture. For example, one study using what should be a comparatively large dose of 10000 IU/week of vitamin D_2 revealed a remarkable ineffectiveness of that compound (26).

Two randomized, controlled studies show that vitamin D_3 given by itself in doses of either 100,000 IU (2500 μg) every 4 months (23), or 750 μg annually (27) reduces the occurrence of fractures. The report by Trivedi et al. should be particularly inspiring for anyone interested in the primary prevention of osteoporosis (prevention before any sign of the disease). Those authors solicited a cohort that was primarily healthy men, and they were not selected for osteoporosis. Over the 5 years of follow-up, there was a 30% reduction in the incidence of hip fractures in those who received vitamin D, compared to those who received placebo.

Table I. Randomized, placebo-controlled clinical trials of vitamin D_3 to treat fractures in the elderly.

First author and year of study	Mean age	*n* men	*n* women	Dose of vitamin D μg/day (IU/d)	Calcium mg/day	Control group initial 25(OH)D nmol/L	Duration years	Final 25(OH)D nmol/L	RR[e] of non-vertebral fractures or total fractures (treatment *versus* control, (95% CI))	RR[e] of hip fractures (treatment *versus* control, (95% CI))
Chapuy 1992 (20)	84	nil	3270	20 μg (800 IU)	1200	28	1.5	105 **c**	0.75 (0.61-0.91)	0.57 (0.37-0.90)
Chapuy 2002 (22)	85	nil	583	20 μg (800 IU)	1200	22.5	2	82.5 **c**	0.99	0.59 (0.33-1.04)
Dawson-Hughes 1997 (21)	70.5	176	213	17.5 μg (700) **a**	500	82.5	3	112 **c**	0.46 (0.22-.91)	Too few
Trivedi 2003 (23)	76	2037	649	20 μg (820 IU)	nil	53	5	74	0.78 (0.61-.99)	0.67 (0.48-0.93)
Lips 1996 (71)	80	662	1916	10 μg (400 IU)	Nil **b**	23	3.5	60	1.04 (0.77-1.41)	1.204589466
Meyer 2002 (72)	85	286	858	10 μg (400 IU)	nil	46	2	64	0.92 (0.66-1.27)	1.09 (0.73-1.63)

a. background vitamin D intake was 5 μg (200 IU)/day in addition to this. **b**. subjects were asked to consume dairy products to yield 800–1000 mg total calcium/day; compliance for calcium not assured. **c**. measured with 25(OH)D assays that read higher than the current convention [73]. **d**. none of the studies in this table used vitamin D_2; no studies using vitamin D_2 [26] have shown fracture prevention or bone preservation. [e] Relative risk (RR) is the ratio of the number of fractures per group size in the treated *versus* the control groups; confidence interval (CI) indicates the central 95% limits of certainty for the relative risk value.

Bone density declines more quickly during winter than during summer. Vitamin D_3 supplements (about 20 μg (800 IU) per day) combined with calcium eliminate the faster fall in bone density during winter (28,29). Furthermore, three studies showed that the combination of calcium and 20 μg vitamin D_3 together lower fracture risk in adults older than age 65 (20–22).

Less occurrence of fractures is evident even within the first year of these studies (though not statistically significant in the studies individually) when bone density has not increased by enough to account for the fewer fractures (21). The explanation for this may be that vitamin D_3 improves muscle strength and balance. This reduces the occurrence of the falls that produce the fractures. Interventional studies with 20 μg/day of vitamin D_3 show that in the elderly balance is improved, and falls reduced (30–32). Cross-sectional work shows similar benefits of vitamin D_3 nutrition in elderly attending a falls-clinic. In those with serum 25(OH)D levels <28 nmol/L there were impairments in balance, reflexes, and there were more falls than those with 25(OH)D over 44 nmol/L (>17.5 μg/L) (33).

In adults younger than 70 years, the risk of osteoporotic fracture is difficult to assess because non-traumatic fractures are so rare that an uneconomically feasible number of subjects are required to achieve the statistical power needed with a randomized interventional study. Nonetheless, there is evidence that vitamin D_3 intake prevents fractures in women who are younger than 65 years. The Nurses Health Study is a cross-sectional study looking at more than *one million* person-years of follow-up. Feskanich et al. reported that in postmenopausal women younger than 65 yrs, there was a 37% lower risk of osteoporotic fracture in women who reported consumption of vitamin D in amounts of at least 12.5 μg/day (>500 IU/day), compared to women consuming less than 3.5 μg/day vitamin D (<150 IU/day) (34). Interestingly, reported intake of calcium did not relate to fracture incidence. This might have been expected in a cross-sectional study, because women with a family history of osteoporosis would have been more likely to take additional calcium.

Other reports focusing on bone density preservation in the early postmenopausal period have failed to show any benefit of supplementing with vitamin D. Hunter et al. randomized twins to take 20 μg/day of vitamin D_3 or placebo (35). Cooper et al. randomized women to vitamin D_2, 250 μg/week, or placebo (26). In both these studies, mean 25(OH)D concentrations were already relatively high at baseline and in the control groups (25(OH)D=70 to 83 nmol/L). The vitamin D increased 25(OH)D by 35% compared to the placebo (35) or by 12% (26). Because those doses produced only a moderate change in 25(OH)D, it is not surprising that the findings were negative. The study by Hunter suggests that when 25(OH)D concentrations approach 70–80 nmol/L, the benefit of vitamin D for osteoporosis prevention may be reaching an asymptote. However, the appearance of an asymptote may simply reflect a lack of statistical power, because very few adults have 25(OH)D levels higher than 100 nmol/L.

Data derived from large cross-sectional cohorts can produce very impressive statistical power to support a concept. Data from The National Health and Nutrition Examination Survey (NHANES) from the U S A show that bone density correlates positively with 25(OH)D concentrations as these rise toward and beyond 100 nmol/L for white women (36).

Concentrations of 25(OH)D have only modest effects on bone turnover markers. Devine et al. failed to detect changes in bone markers when 10 μg/day of vitamin D_3 was given to elderly women (37). A larger, cross-sectional study showed that higher 25(OH)D concentrations correlated with lower urinary excretions of hydroxyproline, pyridinoline, deoxy-pyridinoline, and lower plasma alkaline phosphatase and PTH concentrations (38). In a cross-section of younger, healthy adults, bone markers are higher in the winter season (39). Likewise, the elderly show wintertime increases in bone turnover markers (40). Winter is also the season of greater loss of bone mineral density (40), and vitamin D supplementation can overcome this (41). In a randomized controlled trial, vitamin D supplementation of elderly women insufficient in vitamin D resulted in lower bone turnover markers than with calcium supplementation alone (31). The data available on bone markers indicate that 25(OH)D concentrations greater than 60 to 80 nmol/L may be approaching an asymptote in terms of bone *per se*, because there is no evidence of further suppression of bone turnover if initial 25(OH)D concentrations already exceed 60 nmol/L.

Several reports show that active absorption of calcium through the gut correlates with 25(OH)D concentrations (31,37,42,43). This relationship does not appear to reach a plateau, so that an 'optimal' 25(OH)D concentration cannot be determined based on calcium absorption. What it does suggest, is that the dietary requirement for calcium may be lower with higher 25(OH)D concentrations.

Dosage considerations

The history of vitamin D intake recommendations highlights how hard it is to establish an appropriate

dose before the nature of a compound is understood very well. In northern Europe since the 18th century, a teaspoonful of cod liver oil has been a folk remedy whose purpose it was to help infants thrive. This spoonful contained variable amounts of vitamin D, but typically less than 400 IU of vitamin D_3. The 375 IU (9 μg) of vitamin D_3 contained in that teaspoon (44) was confirmed only recently as being appropriate for infants (45–47). Compared to the adult, vitamin D nutrition in the infant and child has been well characterized. Until it became clear in the past two decades, that vitamin D might actually affect the health of adults, there was no thought directed at how much vitamin D adults might need. The dose of 20 μg/day of vitamin D_3 (cholecalciferol) now recommended for prevention or treatment of osteoporosis (48) was originally selected because it was easy to double the 10 μg/day dose present in formulations of vitamin D_2 (ergocalciferol). In the 1980s, Chapuy and Meunier found that 20 μg/day of ergocalciferol produced a statistical suppression of PTH in the elderly, but half that dose had no significant effect (25). When they carried out their fracture-prevention studies later, the group changed the form of vitamin D used in their studies. This was because of a report by Tjellesen, suggesting that vitamin D_3 was more effective than vitamin D_2(49). The change was fortuitous, because subsequent studies using vitamin D_2(26) have not matched the efficacy reported with vitamin D_3.

The fact that 20 μg/d of vitamin D_3 prevents fractures is not proof that this is the optimal dose for osteoporosis. This is only the lowest dose that consistently shows a statistically significant response. Because vitamin D is regarded as only a nutrient and freely available, there has never been a commercial incentive to optimize the dose. It could be argued that the commercial incentive is actually to underdose with vitamin D in clinical trials, to make proprietary products look better. There are no studies of osteoporosis prevention at a vitamin D dose beyond the 20 μg/day. Knowledge of the dose-response curve for vitamin D and osteoporosis is very limited (Figure 1).

The responsiveness to vitamin D administration, based on the nmol/L increase in 25(OH)D per μg of vitamin D consumed per day, increases with: 1) lower vitamin D dosage; 2) lower initial 25(OH)D concentration; 3) longer duration of supplementation; and 4) lower body mass. The conventional way to improve vitamin D nutritional status has been to give vitamin D_3 or vitamin D_2 (ergocalciferol). Until recently, availability of 25(OH)D was another option (50), but the product has been discontinued by Organon (NJ, USA). The company's discontinuation of 25(OH)D may have made sense, because

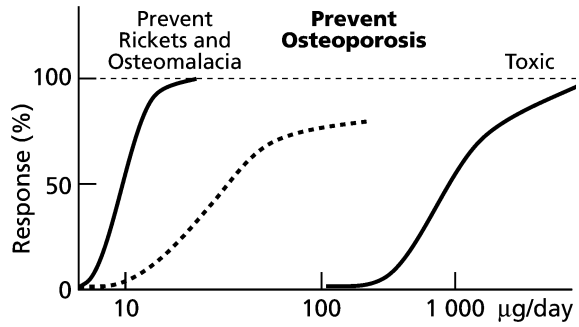

Figure 1. Relative dose-response effects of vitamin D intake on prevention of bone disease and possible toxicity. Since it is unlikely that any dose of vitamin D can entirely prevent or cure osteoporosis, the osteoporosis dose-response curve does not reach 100%. However, doses essential for preventing osteoporosis are higher than those needed to prevent rickets and osteomalacia, and they are far lower than anything that might be implicated as harmful. To convert from the more contemporary units in this figure, to the traditional IU for vitamin D, multiply by 40 (i.e. 10 μg=10 mcg=400 IU).

the objective of increasing plasma 25(OH)D concentrations can be almost as easily achieved by providing enough vitamin D_3.

Hormonal 1,25(OH)2D is not an alternative to nutritional vitamin D

For most of the 20th century, there was no debate, that vitamin D was a nutrient. It was known as 'the sunshine vitamin'. Confusion arose when it was realized that the active form of the vitamin D molecule was $1,25(OH)_2D$ (calcitriol), which is a hormone in the true sense of the word. Official nutrition reports in both North America (51) and Europe (52) now describe nutritional vitamin D as perhaps more suitably referred to as a 'hormone' than a nutrient. However, vitamin D is no more a hormone than is cholesterol, because vitamin D is only the raw material needed for synthesis of calcitriol. The purpose of supplementing with vitamin D is to optimize the natural functions of the endocrine/paracrine systems that require it.

There are many studies looking into the use of the hormone, calcitriol, and analogs of it in the prevention and treatment of osteoporosis. By far the best review of this is by Papadimitropoulos et al. who found no evidence that calcitriol and its analogs offer any benefit over the use of plain, simple, safe and cheap vitamin D_3(53). Based on some reviews that focus on studies involving high doses of calcitriol compared to studies using pediatric doses of vitamin D_3, some have suggested that calcitriol or its analogs might be better under some conditions (54,55). If osteoporosis occurs because the vitamin D system is somehow deficient or defective, it makes little sense to resort to the use of the

relatively potent and more likely toxic hormone, calcitriol, to prevent osteoporosis. The fact never mentioned by those who advocate use of calcitriol for osteoporosis, is that rickets and osteomalacia usually exist despite normal – and often elevated – serum concentrations of calcitriol (56–59). Increases in vitamin D supply will not increase calcitriol levels unless the depletion of 25(OH)D is virtually absolute (60–63). As kidney function deteriorates, its endocrine capability also declines. A low serum calcitriol level is more often a measure of impaired renal function than poor nutrition (63,64). The effect that aging has on calcitriol levels and on PTH can be overcome by raising the 25(OH)D concentration (15,65). If osteoporosis is to be prevented, there is no role for calcitriol or its analogs which, at best, might be considered as an unproven alternative to vitamin D nutrition in the treatment of active osteoporosis. These agents must be used under the care of the physician and do not have a role in prevention of osteoporosis.

Conclusions and commentary

In 1997, when the Food and Nutrition Board last reviewed this nutrient, there was no evidence that intakes of vitamin D below 20 μg (800 IU)/day would have any measurable health effect in adults. All data available at the time showed that to lower risk of fracture, adults needed to consume 20 μg/day (20,21,66). Based on the study of Chapuy et al. alone, a British report had determined only from the costs of treating fractures, that there was justification to supplement all women in British nursing homes with vitamin D_3(67). Little has resulted from any of this. The final recommendations of the Food and Nutrition Board established values for vitamin D intakes that were 15 μg (600 IU)/day for those over age 70 years, and recommendations for younger adults were even lower (51). The Food and Nutrition Board openly admitted that there was no evidence that these intakes would do anything (68). Since that 1997 report, all of the new evidence that vitamin D has an effect on bone density, fractures, or muscle function confirms that adults require at least 20 μg/day of vitamin D in the vitamin D_3 form, not the vitamin D_2 form (22,23,31,69). Recently, new products have become available that combine daily, two-pill doses of calcium and vitamin D_3 in the amounts of 1000–1200 mg calcium and 800 IU vitamin D_3 that have consistently shown fracture prevention.

In relation to the question of what the optimal 25(OH)D concentration may be for prevention of osteoporosis, current evidence points to a serum level of 70–80 nmol/L as the minimum concentration to aim for. However, the dose-response curve for this nutrient has been explored only part of the way. The physiological range extends to 25(OH)D concentrations higher than 200 nmol/L for humans. The pharmacological range for 25(OH)D concentrations beyond that has not been touched on in any context pertinent to osteoporosis. It cannot be assumed that anything higher than a 'normal' concentration of 25(OH)D is harmful. Further health benefits cannot be ruled out for 25(OH)D concentrations in the pharmacological range. This field deserves more clinical research, because the cost of vitamin D is trivial compared to its potential benefits.

The evidence from randomized controlled clinical trials summarized in Table I is so convincing that it changes the ethical background for future research in the field of osteoporosis. We cannot continue to offer the control group only 10 μg (400 IU)/day – this amounts to a homeopathic dose of vitamin D. Ethical considerations demand that we treat patients in any control group according to the best knowledge to date (70). However, to evaluate doses of vitamin D_3 beyond 20 μg (800 IU)/day will probably require studies in which a daily dose of 20 μg is given to the control group, against which any higher dose must be shown to be superior. This kind research will be far more demanding than what has been done in the past because the greatest step in efficacy has almost certainly been achieved with 800 IU/day. Studies addressing the issue of an optimal dose of vitamin D_3 will require greater numbers of participants than the studies published to date. Although doses of vitamin D_3 higher than 20 μg/day probably will offer additional benefits for osteoporosis, further research is faced with the need to deal with incrementally diminishing returns.

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