REVIEW

Correcting poor vitamin D status: Do older adults need higher repletion doses of vitamin D_3 than younger adults?

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We conducted an examination of recent studies to determine whether older adults (≥65 years) need higher levels of supplementary vitamin D than young adults when attempting to replete vitamin D status in deficient subjects, *i.e.* those with levels of 25-hydroxyvitamin D less than 75 nmol/L. As data on repletion with vitamin D_2 have recently been published, we restricted our discussion to the use of vitamin D_3 from dietary supplements, prescriptions for large oral doses, and bolus dosing or injections. Most published dosing regimens failed to achieve 75 nmol/L in most all subjects, whether young adults (<65 years) or older adults (≥65 years). Whether as daily or bolus oral supplementation, elderly subjects appeared to need more vitamin D3 compared with younger adults, however, baseline levels, endpoints, study duration, compliance, and other factors were different among studies. To ensure most subjects are replete in vitamin D, a daily dose of more than 50 μg (2000 IU) in younger and 125 μg (5000 IU) is required. Other strategies including bolus and loading doses are described. No study reported adverse effects of using oral intakes about the current upper level of 50 μg (2000 IU).

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1 Introduction

It has been shown convincingly that Vitamin D has many functions beyond its role in calcium and bone health. With this new knowledge has come the recognition that Vitamin D insufficiency and deficiency is at epidemic proportions worldwide. In temperate countries more than half of the population is at risk and worldwide, even in tropical countries, vitamin D deficiency is a very serious concern due to changes in living and working conditions [1, 2]. A difficult task is determining a level of dietary intake which will be effective at quick repletion to what scientists believe to be the appropriate level of vitamin D activity in the body. Vitamin D, a fat-soluble vitamin, is provided through the diet and through skin synthesis with exposure to sunlight (specifically ultraviolet B radiation). Vitamin D intake from foods is limited, with few natural sources (*e.g.* fatty fish) and fortified foods (depending on the country). Vitamin D produced from precursor molecules in the skin after exposure to sunlight is also limited as given the angle of the sun in winter, its rays do not have sufficient energy to penetrate the skin; nor can UVB travel through clothing, glass, sunscreen, or skin with a high melanin content [3]. Thus, supplemental sources of vitamin D are more commonly used for repletion, yet the dose and time needed for repletion to occur are critical factors for successfully alleviating deficiency.

Determining need for vitamin D is difficult as factors such as sunlight exposure with appropriate UVB, age-related

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Abbreviations: DRI, Dietary Reference Intake; **1,25(OH)$_2$D,** 1,25-dihydroxyvitamin D; **25(OH)D,** 25-hydroxyvitamin D

changes in cutaneous vitamin D formation through the skin, and availability of foods containing vitamin D all contribute to our inability to provide a single amount as a recommendation for intake. Since 1991, it has been recognized that the elderly are at high risk for vitamin D deficiency, particularly institutionalized elderly [4] and this concern continues today [5]. Recommendations for vitamin D in the current 1997 Dietary Reference Intakes (DRIs) reflect an age effect by having a higher recommendation for persons 50–70 years, for which the current recommendations are 400 and 600 IU for those over 70 years, compared with younger adults whose current DRI is 200 IU [6]. It is recognized that as we age, there is a lessened ability to make vitamin D3 in skin due to lack of the precursor 7-dehydrocholesterol [7]. In making recommendations for repletion for young *versus* older adults, it is not known if there is a higher intake required for the latter group. One study has demonstrated that young and old adults replete similarly [8]; however, a systematic examination of whether older adults need higher levels of supplementary vitamin D than young adults when attempting to improve vitamin D status is lacking.

The purpose of this article is to determine the repletion levels needed for vitamin D supplements in young and old adults. We define repletion as achieving a level of serum 25-hydroxyvitamin D above 75 nmol/L, a level most consistently associated with normal suppression of parathyroid hormone, and improvement in clinical outcomes such as fracture risk. A secondary purpose was to locate most, if not all, repletion studies in young and old adults, and to compare findings. To this end, we examined the efficacy of varying doses of vitamin D in clinical trials which monitored vitamin D status in both young and old adults. As data on repletion with vitamin D_2 have recently been published [9], we will restrict our discussion to the use of vitamin D_3 from dietary supplements, prescriptions for large oral doses, and bolus dosing or injections.

2 Vitamin D status

To achieve the benefits of vitamin D, one requires sufficient skin synthesis and/or intake to maintain adequate plasma levels of the transport form of vitamin D which is 25-hydroxyvitamin D (25(OH)D). This metabolite subsequently undergoes hydroxylation to form the active metabolite, 1,25-dihydroxyvitamin D [1,25$(OH)_2$D]. The term ''vitamin D'' represents both the molecular precursors of 25(OH)D and all the compounds having or potentially having the activity that we associate with the active metabolite of vitamin D. To avoid confusion, in this article, the term ''vitamin D'' will be used only in reference to the precursor molecule, whereas ''vitamin D activity'' refers to the ultimate actions of the 1,25$(OH)_2$D molecule. The dietary precursor molecule can be further designated as cholecalciferol (commonly called vitamin D_3) which is the form made in the skin of mammals or ergocalciferol (commonly called vitamin D_2) which is made after irradiation of yeast or fungi-derived molecules. Unless a specific difference is noted between vitamins D_2 and D_3, then ''D'' with no subscript is used. As indicated above, the studies examined in this article used vitamin D_3. Differences in metabolism between vitamins D_2 and D_3 exist [10], nevertheless, there is an indication that vitamin D_2 given frequently (*i.e.* daily) but not necessarily in bolus amounts, is as effective as daily vitamin D_3 [11].

To relate vitamin D intake to status, *i.e.* serum levels of 25(OH)D, it is important to understand how terminology is defined. There is consensus that *deficiency* represents levels not sufficient to provide protection against osteomalacia, osteoporosis, and falls; *optimal* represents levels that are adequate enough to substantially decrease risk of chronic diseases associated with vitamin D; *sufficiency* includes those values above deficiency but less than optimal. In relating these to the measures of 25(OH)D, current thinking considers d*eficiency* of vitamin D activity is the level of 25(OH)D $<$75 nmol/L (30 ng/mL); *sufficiency* is defined as between 75 and 100 nmol/L (8–30 ng/mL); *optimal* vitamin D status is believed to be achieved when the levels are above 100 nmol/L (40 ng/mL) [12]. The greatest hurdle in determining maintenance and repletion needs to achieve optimal vitamin D status lies in the significant differences in measurement of serum 25(OH)D that occurs with the various assays currently in use.

2.1 Factors affecting 25-hydroxyvitamin D levels

There are several methods used for measurement of 25(OH)D, and this situation has created some confusion regarding comparability between studies [13, 14] . Discussion of assay differences is beyond the scope of this article, but assay type has been documented for each study included in Table 1. In addition, assay variability and between-laboratory imprecision together may be responsible for a 20% deviation between a laboratory result and the true measure [15]. A further cause of variability is within-individual (biological) variation, which may be as high as 19%, although much of this measure may be reflecting seasonal changes in sun exposure [15]. Finally, there are aspects of the production of 25(OH)D that affect its accumulation in serum. If the substrate, *i.e.* vitamin D_3 or vitamin D_2, is low, then this limits the rate of synthesis of 25(OH)D [16]. At lower intakes or sun exposures, the amount of vitamin D_3 or vitamin D_2 limits synthesis of 25(OH)D [16]. Over time, an increase in 25(OH)D produces an increase in the rate of catabolism, by inducing 1,25(OH)2D-24-hydroxylase (CYP24, also called 25(OH)D-24-hydroxylase). Thus, as the precursor molecule is made more available, there is an accelerated catabolism of vitamin D metabolites [17] such that levels of all the metabolites plateau.

Differences in dietary intake should be reflected as differences in levels of 25(OH)D; however, this is difficult to

Table 1. Repletion of vitamin D in subjects with poor vitamin D status (<75 nmol/L) by daily or bolus dosing using oral vitamin D_3 with subjects grouped by age and by order of magnitude of dose

Reference [ref no.] study site	Age (*n*)	Dosing schedule duration	Baseline 25(OH)D	Repletion effect (study goal in nmol/L)	Efficacy of dose for repletion
Middle age and older adults					
Harris, 2002 [8] Boston, MA, USA	29±5 years (*n* = 25)	Daily D_3 of 20 μg/d for 8 wk	Mean 60 nmol/L[a) b)]	Achieved mean of 83 nmol/L; young and old subjects had similar effect	Daily 20 μg for 8 wk effective for only some; all subjects >50 nmol/L
Aloia, 2008 [22] Mineola, NY, USA	18–65 years (*n* = 65)	Daily D_3 of 50 μg/d for higher and 100 μg/d for lower baseline groups for 9–18 wk	Lowest group was 41±14; highest was 60±12 nmol/L (all below 75 nmol/L)[b) c)]	Subjects met or exceeded 75 nmol/L; no difference in response of Caucasian or African-American subjects	Daily 50 μg effective to achieve ≥75 nmol/L in 70% by 9 wk, in 90% by 18 wk if deficiency moderate (>50 nmol/L) at baseline. Daily 100 μg effective to achieve ≥75 nmol/L in 70% by 9 wk, in 90% by 18 wk if deficient (<50 nmol/L) at baseline
Vieth, 2001 [23] Toronto CA, USA	41±9 years (*n* = 61)	Daily D_3 of 100 μg/d for 2–5 months	Mean of 40 nmol/L[b) c)]	By 3 months, 88% of subjects achieved 75 nmol/L	Daily 100 μg for 12 wk effective for 88%; 25(OH)D plateau at 3 months
Von Hurst, 2009 [24] North Island NZ♯)	42±10 years (*n* = 42)	Daily D_3 of 100 μg/d for 24 wk	Mean 21 nmol/L 25th, 75th percentile: 11, 40[b) c)]	Achieved mean of 80 nmol/L by 3 months; Asian women with insulin resistance	Daily 100 μg for 12 wk effective for 50%
Leventis, 2009 [25] London UK♯	Mean 43 years≥ 23 years(19)	Single dose of 7500 μg/d D_3 followed for 6–24 wk	Mean 27 (range 5–40) nmol/L[d) e)]	Achieved mean (range) of 135 (65–214) nmol/L by 6 wk that declined to 43 (23–78) nmol/L by 24 wk	Bolus 7500 μg effective in raising 25(OH)D for 80–90% at 6 wk and ~50% at 12 wk, but no one at 24 wk
Elderly					
Chel, 2007 [26] The Netherlands♯	84±6.2 years All >70 years (*n* = 55)	Daily D_3 15 μg/d for 2 months, continued for 4 months, as daily, weekly or monthly dose	Mean of 24 ± nmol/L (100% below 75 nmol/L)[c) f)]	At 2 months, group mean 60 nmol/L (13% above 75 nmol/L); at 4 months, 70 nmol/L (37% above 75 nmol/L)	Daily 15 μg for 8 wk not effective, and for 16 wk effective in about 33% in severely deficient subjects; Daily more effective than weekly or monthly, likely due to nursing staff preference for daily
Harris, 2002 [8] Boston, MA, USA	73±5 years (*n* = 26)	Daily D_3 of 20 μg/d for 8 wk	Mean 62 nmol/L[a) b)]	Achieved mean of 84 nmol/L, similar to younger subjects	Daily 20 μg for 8 wk effective for some; all subjects >50 nmol/L

Table 1. Continued

Reference [ref no.] study site	Age (*n*)	Dosing schedule duration	Baseline 25(OH)D	Repletion effect (study goal in nmol/L)	Efficacy of dose for repletion
Ish-Shalom, 2008 [27] Haifa, Israel♯	81±8 years (*n* = 17 in daily group)	37.5 μg/d D_3 for 8 wk as daily, weekly or monthly dose	Mean ~40 nmol/L[c) f)]	Over 50% in daily group achieved 75 nmol/L	Daily 37.5 μg for 8 wk effective for some >50% if deficiency moderate (weekly and month similar in efficacy)
Mocanu, 2009[28] Iasi, Romania♯	71±7 years≥58 years (*n* = 45)	Daily 125 μg/d D_3 for 1 year; vitamin D added to bread dough before baking so loses may have occurred	Mean 29 nmol/L[c) f)]	Achieved mean of approx. 120 nmol/L	By 3 months 125 μg/d *per* day, 75%, and at 1 year, 92% met or exceeded 75 nmol/L
Bacon, 2008 [29] Auckland NZ♯	81±6 years (*n* = 22)	Monthly dose of 1250 μg/d D_3 followed for 9 months	50±25 nmol/L[c) f)]	Achieved mean of ~80 nmol/L by 3 months and maintained this	Monthly 1250 μg (~40 μg/d) effective in raising mean 25(OH)D to above 75 nmol/L for at least half of the subjects
Khaw, 1994 [30] Cambridge UK♯	63–75 years (*n* = 95)	Single dose of 2500 μg/d D_3 followed for 6 wk	Means of groups ranged 30–39 nmol/L[b) g)]	Treatment group gained 20 nmol/L	Bolus 2500 μg not effective in raising 25(OH)D to 75 nmol/L for most subjects when measured at 6 wk
Romagnoli, 2008 [31] Rome, Italy♯	79±8 years (*n* = 8)	Single dose of 7500 μg/d D_3 followed for 0.5–30 wk	33±25 nmol/L[b) c) f)]	Achieved mean of ~180 nmol/L by 4 wk then declined to 130 nmol/L by 8 wk	Bolus 7500 μg effective in raising mean 25(OH)D above 100 nmol/L for 8 wk
Bacon, 2008 [29] Auckland NZ♯	83±6 years (*n* = 19)	Single dose of 12 500 μg/d D_3 followed for 9 months	58±25 nmol/L[c) f)]	Achieved mean of ~120 nmol/L by 1 months then declined to 80 nmol/L by 3 months and 70 by 9 months	Bolus 12 500 μg effective in raising mean 25(OH)D above 75 nmol/L for ~5 months for at least half of the subjects

To convert microgram vitamin D to IU, multiply by 40; To convert nmol/L 25(OH)D to ng/mL, divide by 2.5. ♯Country does not routinely fortify foods with vitamin D.
25-Hydroxyvitamin D Assay procedure:
a) HPLC.
b) RIA - Diasorin,
c) RIA - Nichols Advantage,
d) Competitive binding assay.
Season Study conducted if less than 6 months in duration:
e) Winter months,
f) Indoor residents,
g) Spring.

confirm unless data are analyzed in the absence of sun exposure. In a small study of approximately 100 university students living near Toronto Canada who were measured for 25(OH)D near the end of winter, we found a significant correlation between dietary intake of vitamin D and levels of 25(OH)D [18]. In contrast, dietary intake of over 16 000 Americans in NHANES III revealed that diet influence on vitamin D status is probably minimal and it follows that most of our vitamin D is derived from sunlight exposure [19]. In this article, we primarily focus on those subjects who were tested in the absence of sun exposure, and indicate the season and conditions of the study with respect to potential for sun exposure having affected results.

2.2 Vitamin D recommendations for younger *versus* older adults

Since publication of the 1997 recommendations for vitamin D [6] as part of the DRI process, much has been learned in the past decade regarding vitamin D's metabolism. As indicated above, recommendations for vitamin D in the 1997 DRIs reflect an age effect by having a 100% higher recommendation for persons 50–70 years, and a 200% higher recommendation for persons over 70 years, compared with younger adults [6]. It is also well recognized that as we age, there is a lessened ability to make vitamin D3 in skin due to lack of the precursor 7-dehydrocholesterol [7]. A new panel has been convened to make new recommendations for vitamin D, but in the meantime, other professional groups have made recommendations on interim vitamin D intakes and these have focused on a greater need for vitamin D with age. For example, in 2005, the elderly were considered among those with ''special needs'' for vitamin D in the Dietary Guidelines for American [20] (http://www.healthierus.gov/dietaryguidelines); high risk groups were defined as being unable under usual circumstances to make cholecalciferol in skin and thus were advised to consume an additional 25 μg (1000 IU). It is now known that this amount of vitamin D will not raise 25(OH)D to levels that are above deficiency (>75 nmol/L) in most people, whether young or old [12, 21, 22].

2.3 Repletion of vitamin D in young and older adults

Data from repletion studies for adults 65 years and younger with vitamin D_3 are summarized in Table 1 [8, 22–25]. Studies were chosen where baseline levels of 25(OH)D were well below 75 nmol/L (*i.e.* deficient). Although an optimum 25(OH)D is considered to be 100 nmol/L (40 ng/mL), most studies were conducted to achieve a sufficient level of 75 nmol/L (30 ng/mL). In younger adults, a daily dose of 20 μg (800 IU) for 8 wk resulted in a group mean exceeding 75 nmol/L, however, this would indicate that almost half of the subjects were below this cut-off [8]. If subjects started the dosing with levels above 55 nmol/L, then a dose of 95 μg (3800 IU) for 9 wk effectively raised all subjects above 75 nmol/L when there was a complete absence of sun exposure [22]. However, in the same study, if subjects started the dosing with levels below 55 nmol/L, then a dose of 125 μg (5000 IU) was necessary to raise subjects above 75 nmol/L. Similar findings were seen when subjects received a dose of 100 μg (4000 IU) for 12 wk, where almost 90% achieved 75 nmol/L in one study [23], but a similar dose achieved only a repletion of 50% of the group [24]. However, in the latter study, compliance was likely poor.

Data from repletion studies for older adults with vitamin D_3 are also summarized in Table 1 [8, 26–31]. Again, most studies targeted a level for 25(OH)D of 75 nmol/L (30 ng/ml). In older adults, a daily dose of 20 μg (800 IU) for 8 wk resulted in a group mean exceeding 75 nmol/L, the same results as in younger adults [8], however a higher dose of 37.5 μg (1500 IU) for 8 wk was required to achieve most group members having values over 75 nmol/L [27]. For the majority of elderly nursing home residents living in a temperate climate, to achieve 25(OH)D levels over 75 nmol/L, a dose of 125 μg (5000 IU) for more than 12 wk (measured at 52 wk) was needed [28]. This is in contrast to a study in younger adults [23] by the same group where 100 μg (4000 IU) was effective for most to achieve 25(OH)D levels over 75 nmol/L by 12 wk. However, baseline levels in the older adults were lower, so that fact that 125 μg (5000 IU) was similarly effective for the older subjects as 100 μg (4000 IU) may reflect this difference. Thus it appears that higher intakes of vitamin D_3 are required to replete older adults compared with younger adults in the absence of sunshine because of the formers' lower baseline status.

In Table 1, data from several studies on bolus loading for raising 25(OH) D are provided. Only one study was found for young adults. They were given 7500 μg (300 000 IU) of vitamin D_3 for 6 wk and were mostly replete (*i.e.* mean of group at 135 nmol/L, with 10–20% of group members below 75 nmol/L) [25]. There were several studies of bolus doses in older adults. A lower dose of 2500 μg (100 000 IU) had little effect on 25(OH)D levels in elderly subjects [30]. When older subjects were given 7500 μg (300 000 IU) for 8 wk, only 50% of the group achieved sufficiency [31]. A large bolus dose of 12 500 μg (500 000 IU) raised mean 25(OH)D levels to slightly above 75 nmol/L for about 5 months, as did monthly dosing with 12 500 μg (30 000 IU) [29]. Although the number of studies is small, the results are consistent suggesting that a large bolus dose of vitamin D is less effective in older adults than in younger adults. In a study where the age range included both young and older adults [32], two bolus doses of 2500 μg (100 000 IU) every 2 wk resulted in a rise in 25(OH)D from 40 to 90 nmol/L by 1 month. These data indicate that in 1 month, the equivalent of a daily dose of more than 100 μg is required for repletion.

2.4 Evidence that the elderly may need more vitamin D during repletion

The data summarized in Table 1 were examined to determine whether older adults (>age 65 years) needed more supplemental vitamin D for repletion. It must be noted that in several of the studies, baseline levels of 25(OH)D were lower on the older subjects. However, in addition to this observation, that older adults are more at risk of vitamin D deficiency, there may be other reasons why elderly adults may need more dietary (supplemental) vitamin D_3 for repletion than younger adults. These include poorer absorption with advancing age, possibly due to less stomach and intestinal enzymes and other factors. As pointed out recently, ''Vitamin D malabsorption aggravates the hypovitaminosis D that is so common in older persons'' [33]. Since vitamin D like other fat soluble vitamins is absorbed via the chylomicron pathway in the small intestine, the presence of lipid in the intestinal tract will facilitate absorption. Nevertheless, very low fat foods such as orange juice have been shown to be effective vehicles for promoting vitamin D absorption [34]. Once dietary vitamin D is absorbed, it binds with vitamin D binding protein responsible for transporting the parent compound in the blood. Since transport is dependent on the synthesis of vitamin D binding protein, this process may be limited in the elderly due to the lower rate of hepatic protein synthesis with increasing age [35]. Once in the blood, vitamin D is rapidly converted to 25(OH)D or taken up by adipose and muscle. Older adults have less muscle than younger adults and so may be limited in storage, as muscle is a significant storage site for vitamin D [35]. Vitamin D stored in adipose may not be readily available for conversion to 25(OH)D at a later time.

2.5 A model for vitamin D3 repletion of older adults

Recently, a combined study gave a large loading dose of vitamin D_3 of 12 500 μg (500 000 IU) and then provided monthly doses of 1250 μg (50 000 IU) [29]. As shown in Fig. 1, this protocol resulted in a quick repletion of 25(OH)D after only 4 wk in subjects who had initial levels below 40 nmol/L, and the continual monthly doses kept mean 25(OH)D levels close to 90 nmol/L. The monthly maintenance dose of 1250 μg (50 000 IU) is equivalent to 33 μg/day (1330 IU/d), an amount not much more than some public health recommendations. In contrast, in the same study, providing only the monthly doses of 1250 μg (50 000 IU) without first loading, took 9 months to reach the maintenance level of the loading+monthly dose group. Also as shown in Fig. 1, if subjects begin repletion at a higher level of 25(OH)D, by 9 months all groups were at similar levels of 25(OH)D [29]. We cannot rule out some sun exposure as subjects in this study, with an average age of 82 years, lived in the north island of New Zealand.

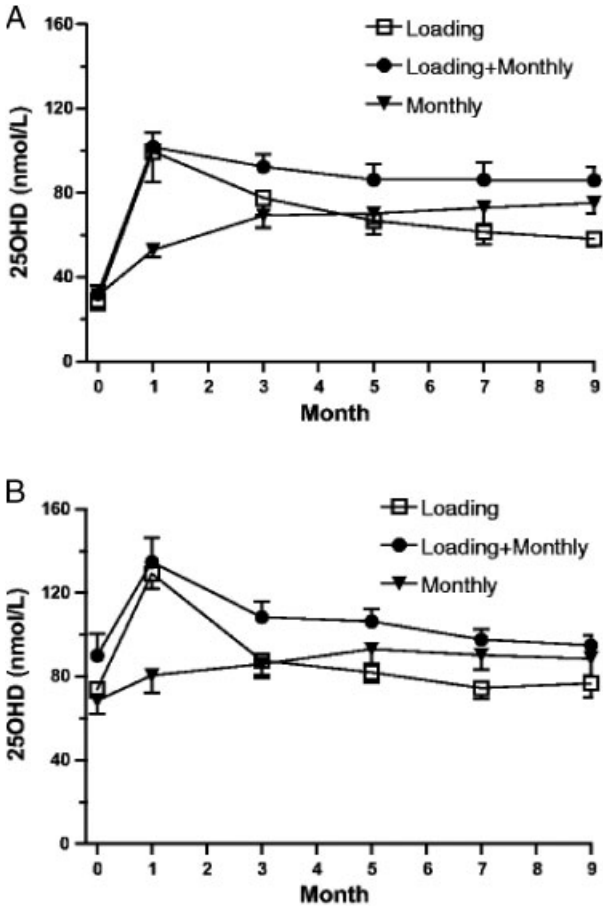

Figure 1. Effects of three regimens of oral vitamin D3 supplementation to elderly (>65 years) subjects. The loading dose was 12 500 μg (500 000 IU); the monthly dose was 1250 μg (50 000 IU). Reference [29] used with kind permission from Springer Science +Business Media.

2.6 Other modes of repletion

There are other ways to replete vitamin D-deficient young and older adults than daily oral or bolus loading of supplementary vitamin D. A review of vitamin D_2 protocols in an Atlanta GA hospital indicated that when ergocalciferol in 1250 μg (50 000 IU) daily doses was given three times weekly for 6 wk, 82% study subjects achieved circulating levels of 75 nmol/L [9]. This regimen was also found to be effective in nursing home residents in the northern USA [36]. As there are few head-to-head comparisons of these two forms of precursor or parent molecules, and given the differences in location, assays and other factors, it is not possible to conclude whether this regimen is as effective as those summarized in Table 1.

It is possible to give 25(OH)D_3, also called calcidiol, directly. Oral doses of calcidiol have been investigated in several recent studies in countries such as Spain and Switzerland where preparations are available. Larrosa *et al.* [37] gave vitamin D-deficient patients in long-term care 16 000

IU calcidiol weekly once for 4 wk, at which time 92.5% of the patients achieved 25(OH)D levels over 100 nmol/L.

2.7 Safety considerations of loading doses

The daily tolerable upper-intake level for vitamin D of 50 μg (2000 IU) was established in 1997 to discourage potentially dangerous self-medication [6]. The upper-intake level represents a safe intake (*i.e.* zero risk of adverse effects in an otherwise health person), however, when a patient is undergoing therapeutic treatment under a health professional's care, this amount can be exceeded. What might be expected with high doses of vitamin D (precursor or calcidiol) is hypercalemia and/or hypercalciuria. Excessive production of 25(OH)D can lead to toxicity, but only at levels of circulating 25(OH)D well above 220 nmol/L in adults [38]. In every study reported in Table 1, as well as in other cited articles, there were no reports of hypercalciuria or hypercalcemia.

3 Concluding remarks

We have described studies that were conducted to determine efficacious protocols for repletion of vitamin D-deficient subjects. There were many differences among studies, including baseline levels, endpoints, study duration, and compliance. The doses and total time for repleting older adults with vitamin D3 appeared to be greater than for younger adults, in part due to the lower starting baseline vitamin D status. To ensure almost all subjects are replete in vitamin D, a daily dose of more than 50 μg (2000 IU) in younger and 125 μg (5000 IU) is required. Several regimens, such as loading with a high dose (12 500 μg) of vitamin D_3 and then giving 1250 μg monthly, provide enough vitamin D3 so that most patients would achieve and maintain 25(OH)D levels at or above 75 nmol/L. A promising loading regimen is to provide calcidiol (25(OH)D) itself. All the studies reviewed reported that subjects were free of adverse effects, indicating that the vitamin D_3 protocols were safe during the observed dosing periods.

The findings and conclusions presented in this article are those of the authors and do not necessarily represent the views or opinions of the US Food and Drug Administration. Mention of trade names, product labels or food manufacturers does not constitute endorsement or recommendation for use by the US Food and Drug Administration.

The authors have declared no conflict of interest.

4 References

[1] Mithal, A., Wahl, D. A., Bonjour, J. P., Burckhardt. P. *et al.*, Morales-Torres, J. on behalf of the IOF Committee of Scientific Advisors (CSA) Nutrition Working Group. Global vitamin D status and determinants of hypovitaminosis D. *Osteoporos. Int.* 2009, Aug 19 (Epub ahead of print).

[2] Babu, U. S., Calvo M. S., Modern India and the vitamin D dilemma: evidence supporting the need for National fortification and supplementation programs. *Mol. Nutr. Food Res.* This issue.

[3] Webb, A. R., Engelsen, O., Calculated ultraviolet exposure levels for a healthy vitamin D status. *Photochem. Photobiol.* 2006, *82*, 1697–1703.

[4] Gloth 3rd, F. M., Tobin, J. D., Sherman, S. S., Hollis, B. W., Is the recommended daily allowance for vitamin D too low for the homebound elderly? *J. Am. Geriatr. Soc.* 1991, *39*, 137–141.

[5] Dixon, T., Mitchell, P., Beringer, T., Gallacher, S. *et al.*, An overview of the prevalence of 25-hydroxy-vitamin D inadequacy amongst elderly patients with or without fragility fracture in the United Kingdom. *Curr. Med. Res. Opin.* 2006, *22*, 405–415.

[6] Institute of Medicine. *Dietary Reference Intakes for Calcium Phosphorus, Magnesium, Vitamin D and Fluoride*, National Academy Press, Washington DC 1997.

[7] Holick, M. F., Matsuoka, L. Y., Wortsman, J., Age, vitamin D, and solar ultraviolet. *Lancet* 1989, *2*, 1104–1105.

[8] Harris, S. S., Dawson-Hughes,B., Plasma vitamin D and 25OHD responses of young and old men to supplementation with vitamin D3. *J. Am. Coll. Nutr.* 2002, *21*, 357–362.

[9] Pepper, K. J., Judd, S. E., Nanes, M. S., Tangpricha, V., Evaluation of vitamin D repletion regimens to correct vitamin D status in adults. *Endocr. Pract.* 2009, *15*, 95–103.

[10] Houghton, L. A., Vieth, R., The case against ergocalciferol (vitamin D_2) as a vitamin supplement. *Am. J. Clin. Nutr.* 2006, *84*, 694–697.

[11] Holick, M. F., Biancuzzo, R. M., Chen, T. C., Klein, E. K. *et al.*, Vitamin D2 is as effective as vitamin D3 in maintaining circulating concentrations of 25-hydroxyvitamin D. *J. Clin. Endocrinol. Metab.* 2008, *93*, 677–681.

[12] Vieth, R., Bischoff-Ferrari, H., Boucher, B. J., Dawson-Hughes, B. *et al.*, The urgent need to recommend an intake of vitamin D that is effective. *Am. J. Clin. Nutr.* 2007, *85*, 649–650.

[13] Roth, H. J., Schmidt-Gayk, H., Weber, H., Niederau, C., Accuracy and clinical implications of seven 25-hydroxyvitamin D methods compared with liquid chromatography–tandem mass spectrometry as a reference. *Ann. Clin. Biochem.* 2008, *45*, 153–159.

[14] Hollis, B. W., Assessment of vitamin D status and definition of a normal circulating range of 25-hydroxyvitamin D. *Curr. Opin. Endocrinol. Diabetes Obes.* 2008, *15*, 489–494.

[15] Binkley, N., Krueger, D., Evaluation and correction of low vitamin D status. *Curr. Osteoporos. Rep.* 2008, *6*, 95–99.

[16] Hollis, B. W., Wagner, C. L., Drezner, M. K., Binkley, N. C., Circulating vitamin D3 and 25-hydroxyvitamin D in humans: an important tool to define adequate nutritional vitamin D status. *J. Steroid. Biochem. Mol. Biol.* 2007, *103*, 631–634.

[17] Vieth, R., How to optimize vitamin D supplementation to prevent cancer, based on cellular adaptation and hydroxylase enzymology. *Anticancer Res.* 2009, *29*, 3675–3684.

[18] Gozdzik, A., Barta, J. L., Wu, C., Wagner, D. *et al.*, Low wintertime vitamin D levels in a sample of healthy young adults of diverse ancestry living in the Toronto area: associations with vitamin D intake and skin pigmentation. *Biomed. Chromatogr. Publ. Health* 2008, *8*, 336–342.

[19] Freedman, D. M., Looker, A. C., Chang, S. C., Graubard, B. I., Prospective study of serum vitamin D and cancer mortality in the United States. *J. Natl. Cancer Inst.* 2007, *99*, 1594–1602.

[20] United States Department of Health and Human Services and US Department of Agriculture. Dietary Guidelines for Americans, 6th edn, US Government Printing Office, Washington. 2005.

[21] Holick, M. F., Vitamin D deficiency. *N. Engl. J. Med.* 2007, *357*, 266–281.

[22] Aloia, J. F., Patel, M., DiMaano, R., Li-Ng, M. *et al.*, Vitamin D intake to attain a desired serum 25-hydroxyvitamin D Concentration. *Am. J. Clin. Nutr.* 2008, *87*, 1952–1958.

[23] Vieth, R., Chan, P. C.-R., MacFarlane, G. D., Efficacy and safety of vitamin D_3 intake exceeding the lowest observed adverse effect level. *Am. J. Clin. Nutr.* 2001, *73*, 288–294.

[24] Von Hurst, P. R., Stonehouse, W., Coad, J., Vitamin D supplementation reduces insulin resistance in South Asian women living in New Zealand who are insulin resistant and vitamin D deficient – a randomized, placebo-controlled trial. *Br. J Nutr.* 2010, *103*, 549–555.

[25] Leventis, P., Kiely, P. D. W., The tolerability and biochemical effects of high-dose bolus vitamin D2 and D3 supplementation in patients with vitamin D insufficiency. *Scand. J. Rheumatol.* 2009, *38*, 149–153.

[26] Chel, V., Wijnhoven, A. H. A., Smit, J. H., Ooms, M., Lips, P., Efficacy of different doses and time intervals of oral vitamin D supplementation with or without calcium in elderly nursing home residents *Osteoporos. Int.* 2007, *19*, 663–671.

[27] Ish-Shalom, S., Segal, E., Salganik, T., Raz, B. *et al.*, Comparison of daily, weekly, and monthly vitamin D3 in ethanol dosing protocols for two months in elderly hip fracture patients. *J. Clin. Endocrinol. Metab.* 2008, *93*, 3430–3455.

[28] Mocanu, V., Stitt, P. A., Costan, A. R., Voroniuc, O. *et al.*, Long-term effects of giving nursing home residents bread fortified with 125 μg (5000 IU) vitamin D_3 per daily serving. *Am. J. Clin. Nutr.* 2009, *89*, 1132–1137.

[29] Bacon, C. J., Gamble, G. D., Horne, A. M., Scott, M. A., Reid, I. R., High-dose oral vitamin D3 supplementation in the elderly. *Osteoporos. Int.* 2009, *20*, 1407–1415.

[30] Khaw, K. T., Scragg, R., Murphy, S., Single-dose cholecalciferol suppresses the winter increase in parathyroid hormone concentrations in healthy older men and women: a randomized trial. *Am. J. Clin. Nutr.* 1994, *59*, 1040–1044.

[31] Romagnoli, E., Mascia, M. L., Cipriani, C., Fassino, V. *et al.*, Short and long term variation in serum calciotrophic hormones after a single very large dose of ergocalciferol (vitamin D2) or cholecalciferol (vitamin D3) in the elderly. *J. Clin. Endo. Metab.* 2008, *93*, 3015–3020.

[32] Tai, K., Need, A. G., Horowitz, M., Chapman, I. M., Glucose tolerance and vitamin D: effects of treating vitamin D deficiency. *Nutrition* 2008, *24*, 950–956.

[33] Bhutto, A., Morley, J. E., The clinical significance of gastrointestinal changes with aging. *Curr. Opin. Clin. Nutr. Metab. Care* 2008, *11*, 651–660.

[34] Tangpricha, V., Koutkia, P., Rieke, S. M., Chen, T. C. *et al.*, Fortification of orange juice with vitamin D: a novel approach for enhancing vitamin D nutritional health. *Am. J. Clin. Nutr.* 2003, *77*, 1478–1483.

[35] Kimball, S., Fuleihan, G. E.-H., Vieth, R., Vitamin D: a growing perspective. *Crit. Rev. Clin. Lab. Sci.* 2008, *45*, 339–414.

[36] Przybelski, R., Agrawal, S., Krueger, D., Engelke, J. A. *et al.*, Rapid correction of low vitamin D status in nursing home residents. *Osteoporos. Int.* 2008, *19*, 1621–1628.

[37] Larrosa, M., Casado, E., Gómez, A., Moreno, M. *et al.*, Colecalciferol o calcidiol: qué metabolito utilizar en el deficit de vitamina D. REEMO 2006, 16, 48–52 as described in Larrosa M Casado E Vázquez I. Navarro N., Gratacòs., J. Comment on Przybelski et al., rapid correction of low vitamin D status in nursing home residents. *Osteoporos. Int.* 2009, 19, 1621–1628.

[38] Hathcock, J. N., Shao, A., Vieth, R., Heaney, R. P., Risk assessment for vitamin D. *Am. J. Clin. Nutr.* 2007, *85*, 6–18.

