Safety of vitamin D_3 in adults with multiple sclerosis[1–3]

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ABSTRACT

Background: Vitamin D_3 may have therapeutic potential in several diseases, including multiple sclerosis. High doses of vitamin D_3 may be required for therapeutic efficacy, and yet tolerability—in the present context, defined as the serum concentration of 25-hydroxyvitamin D [25(OH)D] that does not cause hypercalcemia—remains poorly characterized.

Objective: The objective of the study was to characterize the calcemic response to specific serum 25(OH)D concentrations.

Design: In a 28-wk protocol, 12 patients in an active phase of multiple sclerosis were given 1200 mg elemental Ca/d along with progressively increasing doses of vitamin D_3: from 700 to 7000 μg/wk (from 28 000 to 280 000 IU/wk).

Results: Mean ($\pm$ SD) serum concentrations of 25(OH)D initially were 78 $\pm$ 35 nmol/L and rose to 386 $\pm$ 157 nmol/L ($P < 0.001$). Serum calcium concentrations and the urinary ratio of calcium to creatinine neither increased in mean values nor exceeded reference values for any participant (2.1–2.6 mmol/L and $<$1.0, respectively). Liver enzymes, serum creatinine, electrolytes, serum protein, and parathyroid hormone did not change according to Bonferroni repeated-measures statistics, although parathyroid hormone did decline significantly according to the paired *t* test. Disease progression and activity were not affected, but the number of gadolinium-enhancing lesions per patient (assessed with a nuclear magnetic brain scan) decreased from the initial mean of 1.75 to the end-of-study mean of 0.83 ($P = 0.03$).

Conclusions: Patients' serum 25(OH)D concentrations reached twice the top of the physiologic range without eliciting hypercalcemia or hypercalciuria. The data support the feasibility of pharmacologic doses of vitamin D_3 for clinical research, and they provide objective evidence that vitamin D intake beyond the current upper limit is safe by a large margin. *Am J Clin Nutr* 2007;86:645–51.

KEY WORDS Vitamin D, safety, 25-hydroxyvitamin D, 25(OH)D, multiple sclerosis

INTRODUCTION

The safety of vitamin D remains contentious, especially in the United Kingdom, where the guidance level (the publicly stated safe limit) is exceptionally conservative at 25 μg/d (1000 IU/d) (1, 2). In Canada and the United States, the upper limit of intake (UL) for vitamin D is 50 μg/d (2000 IU/d) (3). These values were obtained by determining an intake that functioned as the no-observable-adverse-effects-level (NOAEL) and then adjusting this level downward by dividing the NOAEL by an uncertainty factor (UF) (4). Evidence from studies conducted since the establishment of the UL value suggests that it is much too low. Intakes of 100 μg/d (4000 IU/d) (5) and 250 μg/d (10 000 IU/d) (6) have been shown to be safe. In fact, fracture prevention studies suggest that the desirable serum 25-hydroxyvitamin D [25(OH)D] concentration exceeds 75 nmol/L (7–9). To attain and sustain these concentrations throughout the year, many adults require vitamin D intakes of $>$20–25 μg/d (800–1000 IU/d) (10, 11).

There is much interest in the role of vitamin D_3 in many aspects of health and disease. The rationale for vitamin D_3 treatment in multiple sclerosis (MS) is that metabolites of vitamin D_3 function as paracrine immune modulators (12), decreasing the proliferation of proinflammatory T lymphocytes and decreasing the production of cytokines, both of which contribute to the pathogenesis of MS (13–15). In experimental allergic encephalomyelitis (EAE), the mouse model of MS, treatment with 1,25-dihydroxyvitamin D_3 [1,25$(OH)_2D_3$] (the active form of vitamin D) prevented EAE in asymptomatic mice and lessened the severity of disease in mice with active EAE (16–18). In patients with congestive heart failure, vitamin D_3 treatment (50 μg/d or 2000 IU/d) affected cytokine profiles (19) in a way that would be desirable for patients with MS. The seasonal fluctuation in the number of gadolinium-enhancing lesions determined by magnetic resonance imaging (MRI) tend to be fewest at the times when serum 25(OH)D concentrations are highest (20, 21). Taken together, the data suggest that vitamin D_3 may play a role in the regulation of clinical disease activity.

The therapeutic use of pharmacologic doses of vitamin D_3 for MS or for any other disease requires tolerability studies, but they remain lacking (2, 22–24). To this end, we conducted a phase I trial to characterize the tolerability of the serum 25(OH)D concentrations achieved through administration of pharmacologic doses of vitamin D_3 to patients with MS.

The primary purpose of this study was to show the tolerability of high serum concentrations of 25(OH)D for future efficacy studies of vitamin D treatment in MS. The known toxicity of vitamin D relates solely to calcium metabolism. As a group,

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patients with MS do not have a primary abnormality in bone and mineral homeostasis.

SUBJECTS AND METHODS

Subjects

Between December 2003 and January 2005, we enrolled 12 patients with clinically definite relapsing remitting (RR) MS or secondary progressive (SP) MS as determined by the criteria of McDonald et al (25). All subjects were patients at the MS Clinic at St Michael's Hospital (Toronto, Canada). Inclusion criteria included Expanded Disability Status Scale (EDSS) scores of 0 to 7 and ≥1 gadolinium-enhancing lesion found by MRI of the brain. Subjects were allowed to continue using 1 of the 4 MS disease-modifying drugs (Avonex; Biogen Idec, Cambridge, MA; Rebif; Serono, Rockland, MA; Betaseron; Berlex, Montville, NJ; or Copaxone; Teva, North Wales, PA) if already receiving this therapy. Exclusion criteria included a history of renal stones or dysfunction, cardiac disease, and comorbid granulomatous disease (including sarcoidosis, tuberculosis, silicosis, chronic or active fungal infections, or lymphoma).

Written informed consent was obtained from each subject. The St Michael's Hospital Research Ethics Board approved this study.

Outcome measures

Once screened for the presence on MRI of a gadolinium-enhancing lesion, patients with positive scans underwent baseline neurologic examination with EDSS scoring (a measure of disability in MS in which 8 functional systems are scored) and ambulation index [(AI) a 25-foot timed walk and measure of disability in MS] scoring. We screened 24 subjects to identify 12 patients with active disease. These tests, including MRI, were repeated at trial completion.

Serum biochemical analysis was conducted at screening and at each study visit for the following: calcium, 25(OH)D, parathyroid hormone (PTH), and renal function (creatinine). As an adjunct to safety testing, we periodically measured electrolytes and liver function enzymes [ie, amylase, alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP)]. For every urine test, one random urine sample was obtained the evening before, and another was obtained the morning of each study visit. Ratios of calcium to creatinine (Ca:Cr) were calculated on the basis of molar concentrations of calcium and creatinine. The average of each pair of ratios is presented in the Results section.

We measured PTH by using the Immulite 2000 analyzer (DPC, Los Angeles, CA). A radioimmunoassay kit (DiaSorin, Stillwater, MN) was used to measure serum 25(OH)D concentrations. Other serum and urine biochemical analysis were measured on the Synchron LX-20 analyzer (Beckman, Fullerton, CA) in the clinical laboratory at St Michael's Hospital.

Toxicity of vitamin D_3 manifests as hypercalcemia or hypercalcuria and can be detected by monitoring urine and serum calcium concentrations. For the present study, toxicity of vitamin D_3 was defined as the presence of hypercalcemia; ie, serum total calcium >2.75 mmol/L on one occasion, and a molar Ca:Cr urinary concentration >1.0 on more than one occasion. Nuclear MRI scans of the brain were quantified by using tools embedded in MAGICWEB MRI software (Siemens Medical Solutions, Malvern, PA).

TABLE 1
Vitamin D_3 dose-escalation schedule

		Supplementation		
		Vitamin D_3		
Study visit[1]	Stage of the study	μg/wk	IU/wk	Calcium (mg/d)
1	1–2 wk	0	0	1200
2	3–4 wk	700	28 000	1200
3	5–10 wk	1400	56 000	1200
4	11–16 wk	2800	112 000	1200
5	17–22 wk	5600	224 000	1200
6	23–28 wk	7000	280 000	1200
7[2]	≈3 mo later	—	—	—

[1] Each study visit occurred on the first day of the week.
[2] Vitamin D_3 and calcium supplementation were discontinued after 28 wk.

Interventions

Vitamin D_3 supplementation, begun at 700 μg/wk (28 000 IU/wk) and escalating to 7000 μg/wk (280 000 IU/wk), was given according to the schedule shown in **Table 1**. Vitamin D_3 doses were given as a once-weekly oral dose in ethanol solution added to a drink (26, 27). Participants were given a supply of 1200 mg powdered Ca/d to be taken orally throughout the study.

Vitamin D_3 supplementation was started after 2 wk of supplementation with calcium alone. The first dose, 700 μg/wk, was given for only 2 wk to rule out hypersensitivity to vitamin D_3; all subsequent doses were given for 6 wk before the dose was increased.

Materials

US Pharmacopoeia (USP)–grade vitamin D_3 (cholecalciferol) was purchased in crystalline form from Sigma (St Louis) and dissolved in USP-grade ethanol. Ultraviolet absorption spectra obtained on a diode array spectrophotometer (Hewlett-Packard, Palo Alto, CA) were used for the measurement of the molar concentration of vitamin D_3 (which was made by using an extinction coefficient of 18 300 $AU \cdot mol^{-1} \cdot L^{-1}$) as described previously (28). Quality-control testing of each vitamin D_3 batch was performed before administration and again on study completion. Vitamin D_3 doses were prepared as one concentration of 700 μg/mL (28 000 IU/mL) to be taken once a week. At higher doses, participants took multiple-milliliter doses of 700 μg vitamin D_3/mL (eg, participants took 4-mL doses of 700 μg vitamin D_3/mL 1 time/wk). The ultraviolet absorptivity at 265 nm was 31.7 AU/cm path length. Tricalcium phosphate powder (Rhodia, Cranbury, NJ) was provided for subjects to mix with food or a beverage; this yielded 1200 mg elemental Ca/d.

Statistical analysis

We used SPSS software (version 12.0; SPSS Inc, Chicago, IL) for statistical analysis and graphic presentation of results. Descriptive statistics, paired *t* testing, and Wilcoxon's sign-ranked comparisons were used to analyze the results. For repeated measurements [eg, serum 25(OH)D at baseline compared with that at visits 1–7], paired *t* testing was used in conjunction with Holm's

TABLE 2
Demographic characteristics of subjects at study enrollment[1]

	Male ($n = 5$)	Female ($n = 7$)	Overall ($n = 12$)
Mean age (y)	38.0 ± 6.0[2]	39.3 ± 10.2	38.8 ± 8.4
Mean EDSS	4.3 ± 2.7	3.7 ± 2.2	4.0 ± 2.3
RRMS (*n*)	4	3	7
SPMS (*n*)	1	4	5
DMD (*n*)	2	3	5

[1] EDSS, expanded disability status scale; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; DMD, disease-modifying drug.
[2] $\bar{x}$ ± SD (all such values).

adjusted Bonferroni for significance testing. Mean ± SD values are given.

RESULTS

The demographic characteristics of the patients in this study at baseline are shown in **Table 2**. Baseline and end-of-study mean serum 25(OH)D, calcium, PTH, and creatinine concentrations and urinary Ca:Cr are shown in **Table 3**. Paired *t* testing at every follow-up time point indicated no significant change in serum calcium concentrations from pretreatment values during the 28-wk protocol of escalating doses of vitamin D_3. None of the patients developed hypercalcemia. Serum calcium concentrations remained within the reference range (2.1–2.6 mmol/L). Likewise there was no significant change in urinary Ca:Cr. The urinary Ca:Cr did not exceed 1.0 for any participant over the course of the dose-escalation schedule (**Figure 1**). In one subject, the urinary Ca:Cr reached 1.0 on 2 separate occasions, at baseline and again at the final visit. In both instances, the patient was brought back a week later to repeat the urinary Ca:Cr measurement; both times, the high ratio had resolved. Serum 25(OH)D concentrations were significantly increased from the mean baseline values of 78.2 ± 35.3 nmol/L to 385.5 ± 157.0 nmol/L at trial completion ($P < 0.001$) (**Figure 2**). PTH concentrations at trial completion were lower than those at baseline (**Figure 3**), but the difference was not statistically significant according to the statistical method appropriate for post hoc comparisons among repeated measures. As should be expected, baseline and final PTH values were significantly different according to the paired *t* test ($P = 0.02$). Serum creatinine concentrations, a reflection of kidney function, remained stable and within the reference ranges throughout the trial in all participants.

Serum protein, electrolytes, urea, and liver function enzymes were also measured (*See* Table S1 under "Supplemental data" in the current online issue at www.ajcn.org). All remained within clinical reference ranges, and there were no significant differences by paired *t* test between baseline values and values after the last dose of vitamin D_3 (7000 μg/wk or 280 000 IU/wk).

No adverse clinical effects were seen in any patient throughout the 28-wk trial. MRI studies of the brain with and without gadolinium contrast were obtained for each participant at the beginning and end of the study to ensure that the pharmacologic doses of vitamin D_3 together with calcium did not result in measurable changes consistent with a worsening of disease activity in the form of new or enlarged gadolinium-enhancing lesions (*See* Table S2 under "Supplementary data" in the current online issue at www.ajcn.org). At baseline, each MRI scan showed ≥1 gadolinium-enhancing lesion as an inclusion criterion (median: 1; range: 1–6). The median number of gadolinium-enhancing MRI lesions, new and enlarged, remained unchanged after 28 wk of therapy (median: 1; range: 0–2). In 4 patients with gandolinium-enhancing lesions at baseline, these had resolved entirely by study completion. The remaining 8 patients had gadolinium-enhancing lesions on MRI, but the number of lesions per patient had declined. The mean number of gadolinium-enhancing lesions in the 12 study subjects was significantly lower at trial completion (0.83 ± 0.72) than at baseline (1.75 ± 1.42) ($P = 0.03$, Wilcoxon's signed-ranks test).

Relapse activity was monitored for the 12 mo before enrollment, during the 28-wk trial period, and for up to 4 mo after study completion (*See* Table S2 under "Supplemental data" in the current online issue at www.ajcn.org). Eight patients experienced a total of 11 relapses in the year before the beginning of the trial. Five participants experienced a total of 9 relapses during the 28-wk study period; 4 of those 9 relapses occurred in 1 patient. Relapses were treated as deemed appropriate by the neurologist. In one case, pulse steroid therapy was used. Seven participants did not experience any relapse events during the study period or follow-up (total, 10 mo). There was no statistically significant difference between annualized relapse rates at baseline and completion of the study.

Disease progression was monitored through measurements of the EDSS and AI at baseline and study completion (*See* Table S2 under "Supplemental data" in the current online issue at www.

TABLE 3
Effect of the full protocol of vitamin D_3 supplementation on biochemical measures: comparison of baseline values and values after a 28-wk vitamin D_3 treatment (100–1000 μg/d)[1]

	Subjects	Serum 25(OH)D	Serum calcium	Urinary calcium: creatinine	PTH	Creatinine
	n	*nmol/L*	*mmol/L*		*pmol/L*	*μmol/L*
Baseline	12	78.2 ± 35.3[a,2]	2.36 ± 0.09[a]	0.42 ± 0.31[a]	2.75 ± 1.54[a]	69.08 ± 22.75[a]
Trial completion	12	385.5 ± 157.0[b]	2.23 ± 0.43[a]	0.47 ± 0.28[a]	1.81 ± 1.15[a]	70.42 ± 15.23[a]
Reference values[3]		<250	2.1–2.6	<1.0	1.3–5.4	50–110

[1] 25(OH)D, 25-hydroxyvitamin D; PTH, parathyroid hormone. Values in a column with different superscript letters are significantly different, $P < 0.001$ (paired *t* test with Holm's adjusted Bonferroni correction).
[2] $\bar{x}$ ± SD (all such values).
[3] The normal distribution as obtained in the clinical laboratory at St Michael's Hospital (Toronto, Canada).

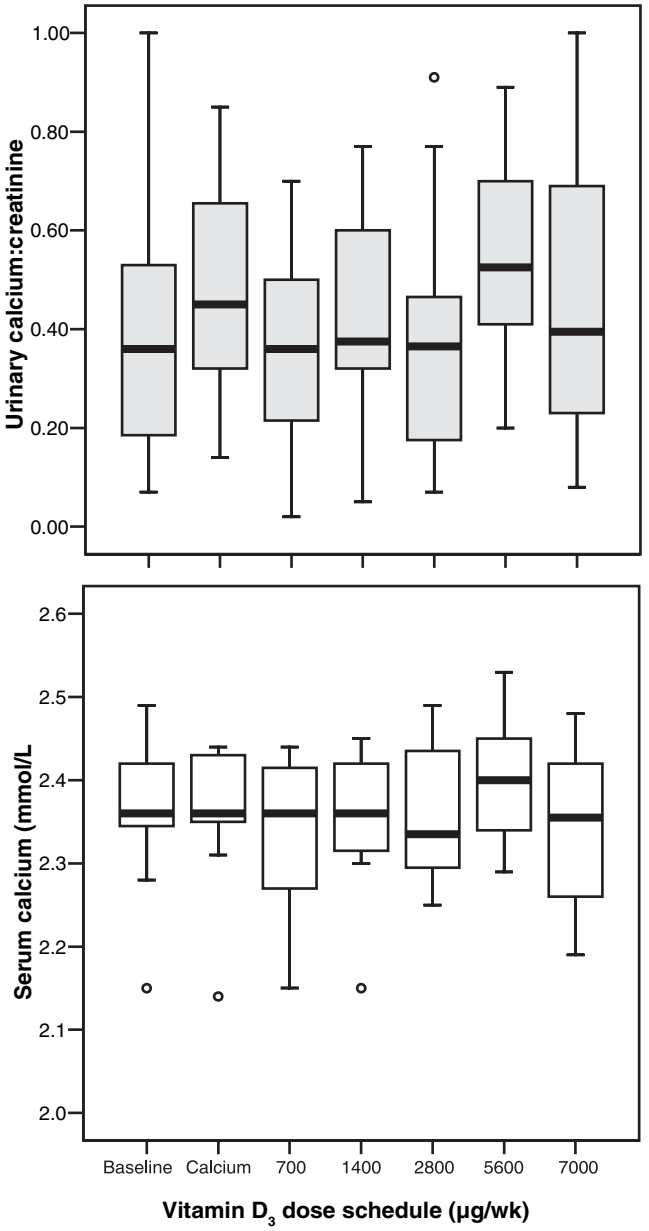

FIGURE 1. Serum and urinary calcium concentrations in response to supplementation with oral vitamin D_3. Boxes represent the range of the central 50% of the sample population, the whiskers show the highest and lowest values, and the bold line indicates the median value. ○, outliers. The calcium measurement represents the calcium concentrations after a 2-wk supplementation with calcium (1200 mg/d) alone. Vitamin D_3 supplementation was taken for 6 wk at each dose after the first dose; that dose, 700 μg/wk (28 000 IU/wk), was taken by study participants for 2 wk only. No statistically significant effects were detected between time points. There was no occurrence of hypercalcemia (serum calcium > 2.6 mmol/L) or hypercalciuria (ratio of urinary calcium to creatinine > 1.0).

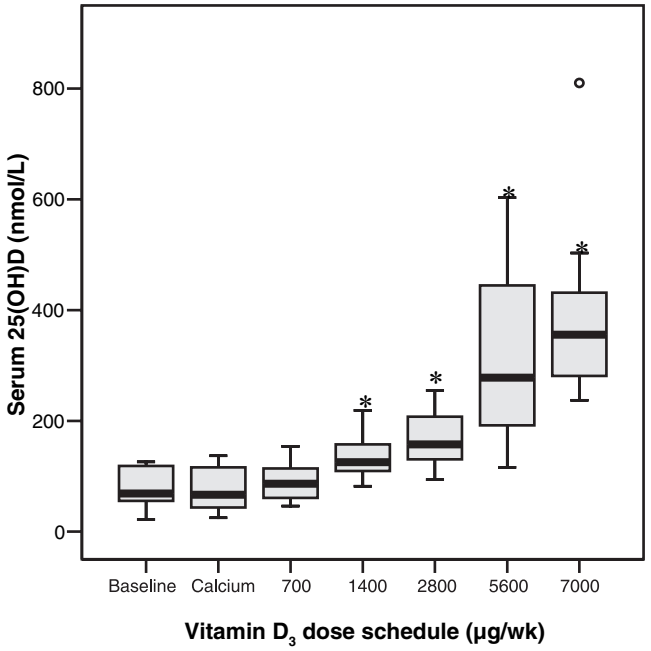

FIGURE 2. Serum concentrations of 25-hydroxyvitamin D [25(OH)D] corresponding to oral supplementation with vitamin D_3. Boxes represent the range of the central 50% of the sample population, the whiskers show the highest and lowest values, and the line indicates the median value. ○, outliers. The calcium measurement represents the corresponding 25(OH)D concentration after a 2-wk supplementation with calcium (1200 mg/d) alone. Vitamin D_3 supplementation was taken for 6 wk at each dose after the first dose; that dose, 700 μg/wk (28 000 IU/wk), was taken by study participants for 2 wk only. Concentrations of 25(OH)D at each study visit during treatment were compared with those of the baseline sample by using paired *t* testing with Holm's adjusted Bonferonni correction. *Significantly different from baseline, $P < 0.001$.

ajcn.org). EDSS remained unchanged for 4 patients. There were no significant changes in either EDSS or AI.

DISCUSSION

The present protocol was designed to test the tolerability of the specific 25(OH)D concentrations attained—and not the long-term effects of the vitamin D_3 doses used. Even though vitamin D per se is cleared from the circulation within 2 or 3 d, its effect on serum 25(OH)D concentration exhibits a half-life that is on the order of 2 mo, which makes the complete attainment of a plateau in the 25(OH)D concentration impractical for a study of this nature (29, 30).

Concerns about the safety of vitamin D and calcium have been raised recently, because the Women's Health Initiative study showed a 17% greater hazard ratio for kidney stones in women randomly assigned to receive calcium and vitamin D than in those receiving placebo (31). The dose of vitamin D used for that trial was 10 μg/d (400 IU/d), which was too small to produce a convincing change in serum 25(OH)D. Furthermore, the mean background intake of calcium in that study was 1100 mg/d, onto which the intervention added 1200 mg Ca/d. In the Women's Health Initiative study, the increase in risk of kidney stones was attributable to calcium intakes near the UL of 2500 mg/d, and not to the vitamin D. In fact, across more modest calcium intakes, calcium and vitamin D are associated with a lower risk of kidney stone formation (32).

The circulating 25(OH)D concentrations that have convincingly manifested toxicity as hypercalcemia and increased urinary calcium exceed 700 nmol/L (33–35). For the patients in the present study who have MS and no underlying disorder of bone and mineral metabolism, serum 25(OH)D concentrations averaged 386 nmol/L, and there was no detrimental sign of calcium metabolism. Although it is well known that vitamin D increases

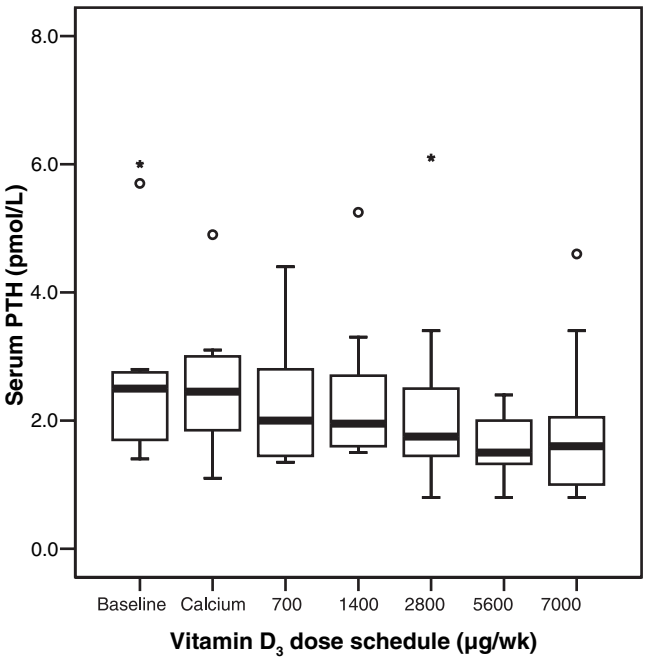

FIGURE 3. Parathyroid hormone (PTH) concentrations in response to oral dosing with vitamin D_3. Boxes represent the range of the central 50% of the sample population, the whiskers show the highest and lowest values, and the bold line indicates the median value. ○, outliers. The calcium measurement represents the corresponding PTH concentration after a 2-wk supplementation with calcium (1200 mg/d) alone. Vitamin D_3 supplementation was taken for 6 wk at each dose after the first dose; that dose, 700 μg/wk (28 000 IU/wk), was taken by study participants for 2 wk only.

the intestinal absorption of calcium, that effect is subject to physiologic regulation (36). Once the 25(OH)D concentration exceeds 80 nmol/L, higher concentrations have no further effect on intestinal calcium absorption (11). In adults, calcium balance is essentially neutral; therefore, urinary calcium excretion approximates the net calcium absorption from the gut. The steady values for urinary calcium shown in Figure 1 are consistent with the findings of Heaney et al (36) that calcium absorption attains a plateau once the circulating 25(OH)D concentrations exceed 80 nmol/L.

It has been postulated for some time that vitamin D_3 supplementation could benefit patients with MS and, potentially, a variety of autoimmune diseases (37). Goldberg et al (38) treated 10 MS patients with 125 μg (5000 IU) vitamin D_3/d in the form of cod liver oil. They found a significant decrease in the number of relapses. Others assessed the effects of 25 μg (1000 IU) vitamin D_3/d on the cytokine profiles in patients with MS and found higher concentrations of antiinflammatory tumor growth factor β1 with lower concentrations of inflammatory interleukin-2 (39). Use of 2.5 μg/d of the hormone calcitriol [1,25$(OH)_2$D] for 48 wk produced an outcome similar to that found by Goldberg et al—a 27% lower incidence of relapse rates during the study period (40). A key limitation in the design of all these studies is that the doses of vitamin D_3 were chosen arbitrarily. The rationale for the use of vitamin D_3 is to increase the concentration of 25(OH)D, which serves as the substrate for extrarenal, autocrine production of 1,25$(OH)_2$D without affecting the plasma 1,25$(OH)_2$D concentration. In fact, a previous clinical trial (27) and studies in rats (41), both by our group, found that vitamin D supplementation tended to lower the serum 1,25$(OH)_2$D concentration. We did not measure 1,25$(OH)_2$D in the present study because the focus was on parameters of clinical tolerability.

As a Phase I trial, this study was not powered to detect changes in clinical outcomes in the patients. The evidence for tolerability to high intakes of vitamin D_3 is not relevant to MS patients only. Clinical testing of the subjects in the present study found no statistically significant increase in annualized relapse rate, disability score, or ambulatory index. We also established that high intakes of vitamin D_3 do not lead to an increase in gadolinium-enhancing lesions on MRI brain studies. In fact, the overall number of lesions per patient decreased significantly from baseline to the end of the trial. In the context of MS, the requirement of an active lesion at baseline for inclusion in this study could in part explain the reduction in the number of gadolinium-enhancing lesions on MRI and the lack of worsening of the relapse rate (not an inclusion criterion). Regression to the mean, because of the inclusion criteria, could account for the desirable clinical change during the study. EDSS scores would not naturally change over the course of a short-term study such as this; noise is the best explanation for all of the changes (either worsening or improvement) in EDSS that were seen.

Our rationale for studying higher doses of vitamin D_3 is to improve the paracrine production of 1,25$(OH)_2$D. The mechanisms by which 25(OH)D could affect brain and immune function have been shown in laboratory studies. 25-hydroxyvitamin D-1-α-hydroxylase has been found in the cerebrospinal fluid (42). The activity of extrarenal 1-α-hydroxylase follows first-order reaction kinetics in vivo, so that a greater supply of substrate should increase the production of 1,25$(OH)_2$D (43). Vitamin D receptor (VDR) has been found in the central nervous system (44, 45). 1,25$(OH)_2$D stimulates the production of neurotrophins (46) and suppresses neurotoxicity (47). Therefore, an adequate supply of substrate for paracrine production and the use of 1,25$(OH)_2$D in the central nervous system may improve immune regulation in an autoimmune disease such as MS.

The present findings should facilitate other investigations with higher doses of vitamin D_3. Furthermore, the present data justify a revision of the UL, or the guidance level for vitamin D (2). There is no evidence that adults with MS are different from healthy adults with respect to their tolerance of vitamin D; their disease is due to an inflammatory response. Serum 25(OH)D concentrations represent the combined contributions of cutaneous synthesis and oral ingestion of dietary sources of vitamin D. Within 15 min of full-body exposure at midday during the summer, white adults can produce vitamin D equivalent to an intake of 250 μg (10 000 IU) (30). A recent publication provided no evidence of toxicity resulting from such intakes (48), nor has a serum 25(OH)D concentration that is toxic been determined, although it is believed to be in excess of 250 nmol/L. It is therefore reasonable to expect that oral intakes of vitamin D_3 that produce serum concentrations of 25(OH)D such as those achieved with sun exposure will not cause hypercalcemia or hypercalciuria. That is what we have shown in this small population of patients whose 25(OH)D concentration at baseline already was relatively high. Our objective was not to determine the long-term safety of the vitamin D_3 doses per se but to assess the safety of the resulting serum 25(OH)D concentrations. Longer treatment with 7000 μg/wk (280 000 IU/wk) will produce higher concentrations of 25(OH)D than were observed here. If we apply the estimate of Heaney et al (6) that a 1-μg/d increase in intake

raises 25(OH)D by 0.7 nmol/L, then the average final increase in 25(OH)D observed here—ie, 308 nmol/L—represents a plateau 25(OH)D concentration equivalent to that resulting from the long-term intake of 440 μg (17 600 IU) vitamin D_3/d.

In summary, we have shown that serum concentrations of 25(OH)D in the range of 400 nmol/L can be attained without causing hypercalcemia or hypercalcuria, and they do not cause adverse clinical or paraclinical effects. These findings are encouraging for larger-scale clinical trials in MS and in other medical conditions that may respond to vitamin D. The widespread use of vitamin D supplements [25 μg (1000 IU)/d] has been advised as a simple way to improve many aspects of public health (7, 10). Because the guidance level for vitamin D in the United Kingdom remains at 25 μg/d (1000 IU/d), the British public may not be able to benefit from that advice. The present study provides an objective confirmation that the recent proposal by Hathcock et al is appropriate—ie, a UL of 250 μg/d (10 000 IU/d) for vitamin D intake can be justified (48).

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