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Vitamin D3 Supplementation in Relapsing-Remitting Multiple Sclerosis: Considering the Safety Issues

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Abstract

Background: A number of studies have claimed hypovitaminosis D to be a potential risk factor in multiple sclerosis (MS). Furthermore, the beneficial effects of vitamin D3 supplementation in MS patients and in a variety of other autoimmune diseases have been widely reported.

Objective: We sought to determine the safety of vitamin D3 intake at 50,000 IU per week for 6 months in patients with Relapsing-Remitting MS (RR MS).

Methods: A group of patients with definite RR MS were prescribed with vitamin D3 at 50,000 IU per week for 6 consecutive months. Serum 25(OH)D3 levels and markers of safety and intoxication, including serum calcium, serum phosphate, alkaline phosphates, creatinin, intact parathyroid hormone (iPTH), and urine 24 hours calcium were measured at baseline and 6 months post-administration in all patients.

Results: After 6 months of vitamin D3 administration, the mean (±SD) serum concentration of 25(OH)D3 was increased, in all patients, from 17.52 ± 15 nmol/L at baseline level to 109.44 ± 34.9 nmol/L. The serum concentration levels of calcium, alkaline phosphates, creatinine, iPTH and the urinary calcium concentration at 24 hours remained at normal range of reference values for each participant (9.2 ± 4.2 mg/dl, 53 ± 7.5, 53 ± 7.5, 0.7 ± 0.3 mg/dl, 32.6 ± 11.6 and 119 ± 64 mg/24h, respectively). More importantly, there were no symptoms of vitamin D3 toxicity in patients.

Conclusions: Our data confirmed the safety and tolerability of a pharmacological dose of vitamin D3 and further emphasized that vitamin D3 intake beyond the physiological dosage of 400 IU per day is safe in definite RR MS patients.

Keywords: Multiple sclerosis; Relapsing remitting; Vitamin D3; Safety; Toxicity

Introduction

Multiple Sclerosis (MS), an inflammatory demyelinating disease of the central nervous system, affects young adults with females being affected twice as often as males [1]. Studies have suggested that vitamin D3 could play a role in the incidence and/or severity of MS, perhaps by affecting immunological function(s) [2]. A relationship between the geographic distribution of MS, exposure to sunlight, and vitamin D metabolism has been widely studied [3]. However, interestingly, despite adequate sun exposure in Iran, vitamin D deficiency is observed at a high frequency in the population, mainly amongst Iranian women, which may be due to the traditional clothing that prevents them from receiving adequate exposure to sunlight [4-6]. Clinical data from various studies have demonstrated reduced frequency of relapses in MS patients who received vitamin D and adequate sun exposure [7-10]. Furthermore, Cantorna et al. [11] have highlighted the importance of dietary calcium and 1, 25 dihydroxycholecalciferol in suppression of EAE in mice. They showed that while post-induction treatment with vitamin D3 and calcium ameliorated disease severity, the same treatment administered pre-induction of EAE suppressed disease development. Given the already known benefits of vitamin D3 in MS, clinically and experimentally, the question still withstands as to what the safe, yet therapeutically effective, dosage of vitamin D3 for patients with RR MS would be. In this study we aimed to establish the tolerability and safety of a high dose vitamin D3 regime in patients with RR MS over 24 weeks.

Material and Methods

Patient enrollment was limited to Multiple Sclerosis Clinic patients at the Department of Neurology, Multiple Sclerosis Research Unit, Shahed University, Tehran, Iran. Patients considered eligible by clinic physician were asked if they were interested in participating in the study. If patients were interested, author Dr. Nabavi would speak with the patients at their request. Thus, a group of 40 patients with definite RR MS were randomly selected (31 females and 9 males) at the age range of 18-55 years. All patients demonstrated a mean EDSS score of 1.5 and mean disease duration of 18 months, based on the 2005 McDonald criteria. Patients with a history of renal stones or renal dysfunction as well as patients with co-morbid granulomatosis diseases (including sarcoidosis, tuberculosis and lymphoma) were excluded from the study. Prior to vitamin D3 administration, serum levels of all participating patients were examined for baseline vitamin D3 measurements.

Vitamin D3 was administered orally at 50,000 IU, once per week.

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Serum and urine biochemical analysis were conducted prior to treatment and 6 months post-treatment in all patients. Serum calcium and creatinine concentrations were also monitored every two months. Circulating intact parathyroid hormone (iPTH) concentrations were measured using an immunoradiometric assay (Immune diagnostic system Ltd, Bolden, UK), and values between 15 to 65 pg/ml were noted as the reference range. Alkaline phosphatase was measured by enzymatic colorimetry using a Pars Azmoon kit (Pars Azmoon, Iran). Serum calcium and phosphorous were measured via colorimetery using the Kavoshyar enzyme kit (Kavoshyar, Iran) or Sheem enzyme kit (Sheem enzyme, Iran), respectively. Serum 25(OH)D3 concentrations were measured by ELISA method using the 25(OH) vitamin D3 kit (Immune diagnostic system Ltd, Bolden, UK), and concentrations less than 72 nmol/L were considered vitamin D deficient. The inter-assay co-efficient of variations for 25(OH) D3 was reported as 3.6. Furthermore, vitamin D3 toxicity was defined by the presence of hypercalcemia (total calcium concentration in serum >10.5 mg/dl), and hypercalciuria (urine calcium concentration > 320 mg/24 hrs).

All quantitative data were presented as mean ± the standard deviation (SD). SPSS software (version 16.0) was used to examine the significance of all analysis.

Results

In order to verify whether vitamin D3 administered at high dose (50,000 IU) in RR MS patients can achieve satisfactory serum levels without causing any toxicity in patients, we conducted a study in which 31 females and 9 males with RR MS participated. Our treatment regime included the oral administration of vitamin D3 once per week for 24 consecutive weeks. The mean age of all subjects was 32 years with mean EDSS of 1.5 and mean disease duration of 18 months (Table 1). The baseline and post-24 week's biochemical measurements are demonstrated in (Table 2). Our results showed that, in response to treatment, the serum levels of 25(OH)D3 significantly increased from the mean baseline value of 17.52 ± 15 nmol/L to 109.44 ± 34.9 nmol/L at 24 weeks. The latter indicated successful intake of our treatment by all the patients (Table 1). Findings from our other biochemical measurement showed that, encouragingly, none of the patients developed hypercalcemia after the course of vitamin D3 intake; the serum concentration levels of calcium, alkaline phosphates and creatinine, as well as the urinary calcium concentration at 24 hours remained at normal range of reference values (9.2 ± 4.2 mg/dl, 53 ± 7.5 IU/L, 0.7 ± 0.3 mg/dl, 32.6 ± 11.6 pmol/L and 119 ± 64 mg/24 h respectively; Table 1). Even though there was a significant difference in serum levels of iPTH between the basal and post-6 months vitamin D3 administration (62 ± 20 pg/ml versus 32.6 ± 11.6 pg/ml, respectively), both measured values remained within the reference laboratory ranges of 15 - 65 pg/ml. Furthermore, no clinical adversity was reported within the course of vitamin D3 intake in any of the patients.

Age (mean ± SD)	32 ± 10
Number of Patients: Female (F), Male (M)	31 (F), 9(M)
EDSS Score Points	1.5
Duration of RR MS (months)	18

Table 1: The clinical characteristics of RR MS patients included in this study.

Biochemical markers	Mean concentrations pre-vitamin D3 administration	Mean concentrations 6 months post-vitamin D3 administration
Serum calcium (mg/dl)	9.4 ± 3.2	9.2 ± 4.2
Serum phosphate (mg/dl)	3.4 ± 0.4	3.7 ± 0.6
Serum alkaline phosphatase (IU/L)	74 ± 12.5	53 ± 7.5
Serum creatinine (mg/dl)	0.7 ± 0.3	0.7 ± 0.5
Intact parathyroid hormone (pmol/L)	62 ± 20*	32.6 ± 11.6*
Serum 25(OH)D3 (nmol/L)	17.52 ± 15**	109.44 ± 34.9**
24 hours urinary calcium (mg/24 hrs)	97.4 ± 73	119 ± 64

Table 2: The effects of vitamin D3 administration at 50,000 IU on the biochemical measures in 40 RR MS patients (31 females and 9 males), pre- and post-six months vitamin D3 administration. Data presented as mean ±SD; * $P<0.05$, ** $P<0.01$.

Discussion

The aim of this study was to determine whether vitamin D3 intake beyond the physiological dose of 400 IU per day would be safe in RR MS patients over a course of 6 months. In a group of 40 RR MS patients, consisting of 31 females and 9 males, vitamin D3 was orally administered at 50,000 IU, once per week, for 24 consecutive weeks. Our results showed that such employed regime concluded safely and without any observed laboratory or clinical side effects in the RR MS patients. Furthermore, we did not detect any hypercalcemia, hypercalciuria, or compensation of calcium metabolism. Given the high prevalence of vitamin D3 deficiency (60% - 95% of population), our results reported here serve as encouraging preliminary evidence for the safe use of vitamin D3 at higher doses than that currently employed in practice, without any concerns about laboratory or clinical toxicity in patients. Although studying the effect(s) of such high dose vitamin D3 administration in the course and severity of RR MS was not the priority of this study, others have clearly demonstrated the beneficial effects of such regime in MS. Indeed, Mowry et al. [12] have reported a 34% reduction in the rate of subsequent relapses observed in patients that were orally administered with vitamin D3 supplement. Other groups have assessed the effects of 25 μg (1000 IU) vitamin D3 administration per day on the cytokine profile in patients with relapsing MS and found higher concentrations of anti-inflammatory tumor growth factor β1 (TGF-β1), but lower concentrations of inflammatory interlukin-2 (IL-2) [13]. Furthermore, in another study, 15 patients received 1000 IU vitamin D3 per day for 48 weeks and experienced 50% reduction in relapses [14].

Similar to our findings, a team of researchers have recently demonstrated that the use of high dose vitamin D3 (14,000 IU per day) during a 28 weeks protocol did not induce hypercalcemia or notable side effects, despite serum vitamin D levels of 400 nmol/l [15]. Moreover, escalation trials supplementing up to 40,000 IU per day for 28 weeks and up to 10,000 IU per day for 12 weeks did not report either significant elevation of serum creatinine levels or calcification in the kidney [16]. Kennel et al. [17] recently reported that supplementation with 800 to 1000 IU per day of vitamin D3 or 50,000 IU per month is safe for healthy subjects. Furthermore, the Endocrine Society's clinical guideline recommended vitamin D3 consumption levels of 1500-2000 IU per day, with a maximum limit of 10,000 IU per day, for patients at risk of vitamin D deficiency [18].

Here, the main focus of our study was to assess the safety and tolerability of vitamin D3 supplementation at 50,000 IU per week, supplemented for 24 consecutive weeks, in RR MS patients. Although other high doses of vitamin D3 have been tested in patients over different time periods, as described above, most studies have focused on hypercalcemia as the marker for vitamin D3 toxicity. Thus, by reporting the serum concentration levels of calcium, alkaline phosphates,

creatinine, and iPTH, as well as the urinary calcium concentration at 24 hours, we have used a diverse range of biochemical markers for vitamin D3 toxicity in patients to report that the oral administration of 50,000 IU vitamin D3 in RR MS patients on a weekly basis, for 24 consecutive weeks, is safe and without any signs of laboratory or clinical toxicity. In order to establish whether our employed vitamin D3 regimen at 50,000 IU per week can be tolerated in RR MS patients for longer than 6 months, in a separate study with RR MS patients, we have been monitoring the same measures of toxicity in patients taking 50,000 IU of vitamin D3 per week for one year. The study is currently ongoing.

In conclusion, our results demonstrated the safety of a high dose vitamin D3 regime during a period of 6 months without exposing patients with RR MS to any adverse biochemical or clinical events. Should further reports confirm vitamin D3 supplementation in RR MS patients as beneficial, it is encouraging to know that vitamin D3 doses can be increased, according to each patient's needs, without having to worry about issues concerning toxicity.

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