Optimal Vitamin D Dosage in Multiple Sclerosis Patients with Vitamin D Deficiency

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Abstract

Our pilot study compared the efficacy of two different doses of vitamin D3 in raising serum vitamin D levels to a level greater than 50 ng/ml. Patients were randomized into two groups with one group taking vitamin D3 5,000 IU/daily and the other taking vitamin D3 50,000 IU/weekly. Twenty-three patients successfully completed our study; 12 in the 5,000 IU/daily group and 11 in the 50,000 IU/weekly group. We administered post-study surveys to assess patient compliance, UV exposure, and barriers to treatment.

Our results showed no significant difference in efficacy between the two groups and suboptimal efficacy overall with only 58% of the 5,000 IU/daily patients and 54% of the 50,000 IU/weekly patients achieving goal vitamin D levels of > 50ng/ml. The major weaknesses of our study were a small sample size and a large difference in average follow up interval between the two groups. Further studies are warranted to explore the obstacles to successful vitamin D repletion.

Introduction

Epidemiologic studies have shown that increased levels of vitamin D obtained from sun exposure, diet or supplementation are associated with a lower risk of MS onset and disease progression[1-3]. Hence, there is great interest in knowing the ideal serum vitamin level which can be used for immune modulation.

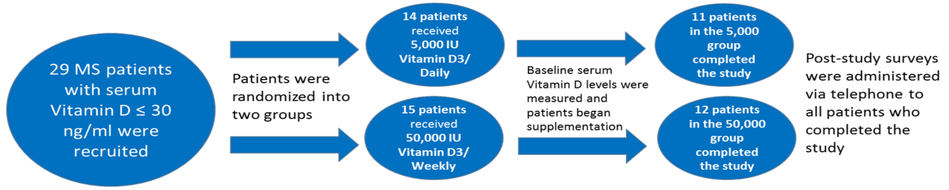
A prospective cohort study concluded that vitamin D has a therapeutic, dose dependent effect with each 4 ng/ml increase in serum vitamin D resulting in a 12% reduction in risk of relapse in patients with relapsing-remitting multiple sclerosis (RRMS) [4]. It is hypothesized that vitamin D exerts this therapeutic effect by modulating several types of immune cells that express vitamin D receptors and decreasing inflammation [5].

Based on these findings, many clinicians have begun supplementing MS patients with vitamin D. Currently there are no guidelines indicating the optimal dose for vitamin D supplementation in MS. There is also ambiguity in the literature about what level serum vitamin D levels clinicians should target.

In order to gain more information about what constitutes an effective vitamin D supplementation protocol in MS patients with vitamin D deficiency we conducted a randomized prospective study to compare the efficacy of two dosage regimens: 5,000 IU vitamin D3 daily vs 50,000 IU vitamin D3/weekly.

Methods

At our MS Center, we recruited 29 patients with MS and vitamin D deficiency defined as serum vitamin D levels ≤ 30 ng/ml. This threshold is based upon data which shows that a level less than 30mg.ml is associated with an increased risk for conversion to clinically definite MS and worsened disease progression [6].
Patients recruited included those with RRMS and SPMS. Patients were randomized to receive vitamin D3 5,000 IU daily or vitamin D3 50,000 IU weekly. We chose vitamin D3 over vitamin D2 based on data indicating that vitamin D3 may be 2-3x more effective than vitamin D2 at increasing plasma levels of vitamin D [7]. We measured serum total vitamin D at the beginning of the study and at the patient's next follow up visit. Post-study surveys were administered to all patients who completed the study to assess medication compliance, UV exposure, and barriers to treatment.



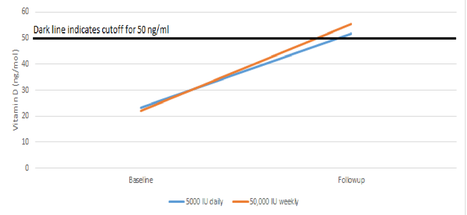
Results

There were no significant differences in the baseline characteristics of either groups indicating successful pre-study randomization. We used the t-test and chi-squared test for statistical analysis and found no significant difference between the two supplementation groups in regards to follow up serum vitamin D level, rate of change in the level of vitamin D, or percentage of patients who achieved a serum vitamin D level > 50 ng/ml.

Table 1: Baseline Characteristics and final results	5,000 IU Vitamin D3/ Daily	50,000 IU Vitamin D3/ Weekly	
No. of patients	12	11	
Average age (years)	51.08	49.64	
Males/Females	4 M, 8 F	5 M, 6 F	T-test, p value
Average baseline serum Vitamin D, ng/ml (SD)	23.35 (5.58)	22.12 (6.26)	0.62
Average follow up serum Vitamin D, ng/ml (SD)	51.85 (13.02)	55.52 (26.39)	0.68
Average Change in Vitamin D, ng/ml (SD)	28.5 (12.51)	30.62 (29.22)	0.61
Days between blood test (SD)	125.83 (69.80)	179 (81.11)	0.11
Number of patients to achieve serum Vitamin D > 50 ng/ml (percentage)	7 (58.33%)	6 (54.54%)	0.85*

*Calculated based on chi square test

Figure 1. Average Change in Vitamin D Level (ng/ml)



*We defined serum Vitamin D levels between 50-75 ng/ml as optimal for patients with Multiple Sclerosis

Table 2. Post-study survey results	How many times have you missed a dose of Vitamin D in the past month?				
	Never	1-4 times	More than 5 times	Stopped taking it/ Switched dose	Did not answer
5,000 IU D3/ Weekly	4	2	2	2	6
50,000 IU D3/ Monthly	3	2	0	3	5

Discussion

In clinical studies, vitamin D has demonstrated a dose dependent linear effect on raising serum vitamin D levels. One study showed that in patients with normal absorptive capacity, for every 100 units of Vitamin D given daily, serum 25(OH)D concentrations increase by approximately 0.7 to 1.0 ng/mL[8]. This would predict an average rise in serum Vitamin D of at least 35 ng/ml in our 5,000 IU daily group and a 50 ng/ml rise in our 50,000 IU weekly group. However, in our study the average increase was much less than predicted with an average rise of 28.5 ng/ml seen in the 5,000 IU group and a 30.62 ng/ml rise seen in the 50,000 IU weekly group. One possible reason for this difference is that vitamin D metabolism may be altered in patients with MS compared with the general population. This could also explain the increased risk of developing MS in the first place. On other hand, patients with MS may not be going outside as much depending on the degree of their disability. Therefore, higher doses of vitamin D supplementation may be needed to see the same pharmacologic effect noted in the general population.

Our study demonstrated no significant difference in serum vitamin D levels in MS patients with vitamin D deficiency taking vitamin D3 5,000 IU/day vs 50,000 IU/week. Additionally, both supplementation regimens demonstrated suboptimal efficacy given that by the end of the study, only 58% of the patients in the 5,000 group and 54% of the patients in the 50,000 reached our primary outcome of obtaining levels > 50 ng/ml. Given these findings, we recommend that the choice of supplementation be based on patient preference for a specific dosing interval, daily vs weekly, rather than perceived efficacy of one regimen over the other.

Our study had several limitations. Firstly, our sample size was small and it is possible that with a larger sample size we may have detected a significant difference in efficacy between the two regimens. Secondly, of this small sample size, 25% of the patients enrolled dropped out further decreasing power. Thirdly, the second measurement of vitamin D levels were checked at different times with an average difference of at least 50 days between the two groups. This confounds how we look at the rate of change in vitamin D levels. Nonetheless, we believe our study was a successful pilot study that demonstrated some of the challenges in the clinical setting regarding vitamin D supplementation in patients with MS.

In conclusion, how best to supplement vitamin D and which goal serum level to target remains elusive. However, it is becoming increasingly clear that targeting serum levels of at least 50 ng/ml may be important for immune modulation. Moreover, the potential therapeutic benefits of Vitamin D outweigh the potential side effects of over-supplementation consisting of hypercalcemia, hypercalcuria and thus renal calculi. These side effects serve as relatively benign early warning signs and have only been documented in patients with a serum Vitamin D > 88 ng/ml[8].

Conclusions

- Our pilot study showed no significant difference in serum vitamin D levels in MS patients with vitamin D deficiency taking 5,000 IU vitamin D3/daily vs 50,000 IU vitamin D3/weekly.
- We recommend that MS patients with vitamin D levels <30 ng/ml be supplemented with either 5,000 IU vitamin D3/daily or vitamin 50,000 IU vitamin D3/weekly based on patient preference in regards to daily vs weekly dosing.
- MS patients would likely benefit from higher doses of vitamin D given the excellent safety profile of vitamin D and the inverse relationship between serum vitamin D levels and MS development and disease progression.

References

1. Munger KL, Zhang SM, O'Reilly E, et al. Vitamin D intake and incidence of multiple sclerosis. *Neurology*. 2004;62(1):60-65.
2. Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. *JAMA*. 2006;296(23):2832-2838. doi: 296/23/2832 [pii].
3. van der Mei IA, Ponsonby AL, Dwyer T, et al. Vitamin D levels in people with multiple sclerosis and community controls in tasmania, australia. *J Neurol*. 2007;254(5):581-590. doi: 10.1007/s00415-006-0315-8 [doi].
4. Simpson S,Jr, Taylor B, Blizzard L, et al. Higher 25-hydroxyvitamin D is associated with lower relapse risk in multiple sclerosis. *Ann Neurol*. 2010;68(2):193-203.
5. Niino M. Vitamin D and its immunoregulatory role in multiple sclerosis. *Drugs Today (Barc)*. 2010;46(4):279-290. doi:
6. Dietary reference intakes for calcium and vitamin D - NCBI bookshelf. http://www.ncbi.nlm.nih.gov/books/NBK56070/. Accessed 4/13/2015, 2015.
7. Braithwaite MC, Kumar P, Tyagi C, Tomar LK, Choonara YE, Pillay V. Vitamin D therapy and related metabolomics: Is the calciferol dose and form the only requirements for successful clinical therapeutics? *Med Hypotheses*. 2013;81(4):656-663. doi: 10.1016/j.mehy.2013.07.022 [doi].
8. Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. *Am J Clin Nutr*. 1999;69(5):842-856.
9. Vieth R. Critique of the considerations for establishing the tolerable upper intake level for vitamin D: Critical need for revision upwards. *J Nutr*. 2006;136(4):1117-1122. doi: 136/4/1117 [pii].

Acknowledgments

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