Effect of Vitamin D on Multiple Sclerosis Relapse

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Introduction

Multiple Sclerosis (MS) is the most common immune-mediated inflammatory disease that attacks myelin and axons of the central nervous system (CNS).[1] MS can cause different cognitive and physical disabilities.[2] The cause of MS is currently unknown, yet it is thought that there are many genetic and environmental components which effect MS. Some of the environmental risk factors include Epstein-Barr virus inflections, cigarette smoking and low levels of vitamin D.[5,6] Where you live during childhood to adolescents is also a risk factor for MS, independent of whether or not you move to a different area later in life, known as the migration-effect.

Research has shown a correlation between vitamin D and MS. MS patients have been observed to have low vitamin D.[6,7] It has been also shown that MS patients have a lower prevalence of non-melanoma skin cancer and actinic damage, both of which are cause by sun-exposure.[4] The prevalence of MS is directly related to latitude.[4] It is hypothesized that MS is more prevalent in the northern hemisphere because of the shorter days, colder temperatures, and less sunlight, which all attribute to less daily sunlight exposure in these areas. Therefore, these populations get less exposure to vitamin D. In the United States, patients have a higher prevalence of MS, compared to the southern hemisphere of the US. These observations gives a strong reason to believe that there is a relationship between vitamin D and MS.

However, there is still uncertainty as to whether or not vitamin D decreases MS relapse rates and the possible mechanism by which vitamin D may be producing effects in MS patients. Relapse is defined as any neurological deficit such as weakness, paralysis, tingling, numbness, blurry vision, ataxia, or balance problems which last for at least 24 hours occurring at least 30 days after the pervious relapse. Some studies have shown that there is an inverse relationship between serum 25-hydroxyvitamin D levels and the rate of relapses in MS patients, as well as a predictor of MS activity and progression.[8,10] Vitamin D supplementation has been shown to decrease the number of relapses and disease severity.[6,11,12] It is thought that the relationship between vitamin D and MS is due to the effects that vitamin D has on the inflammatory response of the immune system. 1,25 dihydroxyvitamin D has been suggested to have an effect the upregulation of T-cells.[8,9] It has been demonstrated that vitamin D inhibits CD4+ T cell proliferation, enhances IL-10 and inhibits IL-6 and IL-17, and induces CD4+CD25+ FoxP3+ regulatory T cells through an IDO-mediated pathway.[9] Still other studies have not shown these positive results with vitamin D supplementation, as well as other studies that are limited by a small sample size.[7,12] More research needs to be continued to solidify the effects that vitamin D has on MS patients. It is hypothesized that MS patients who are taking vitamin D will have a lower recurrence of relapse when compared to MS patients who are not taking vitamin D.

Methods

A retrospective chart review and cross sectional study was performed. The patient population came from all MS patients of the Palmetto Health-USC Neurology group. A patient list was collected via ICD-9 340 and ICD-10 G35 code from January 1st 2015 to March 26th 2017. Patient's charts were reviewed from January 1st 2015 to March 26th 2017. The patients' name, date of birth, and medical record number were collected and each patient was given a new serial number to conceal their identity. Patient's charts were reviewed for confirmation of their identity, MS diagnosis using 2010 McDonalds criteria for MS, and MS diagnosis date. Patients with CIS, RRMS, SPMS, PPMS, and PRMS were all included. Male and female patients from the age of 18 to 99 of all races were included.

For each patient the following information was collected:

- The patient's age, race, gender
- On vitamin D or not
- Had a relapse or no
- Number of relapses

Statistical Analysis

- Chi-square test: Performed to compare vitamin D and MS relapse.
- Mann-Whitney test: Performed to compare the number of relapses for patients that were on vitamin D and not on vitamin D.

Results

Patient Demographics

230 patients were collected, 157 patients were reviewed, 100 patients had confirmed identities and a diagnosis date before January 1st 2015 were confirmed. The patient demographics and clinical characteristics are shown in table 1.

Table 1: Patient Demographics (N=100)

Variables	Not on vitamin D (N=62)	On vitamin D (N=38)
Age (years)[a]	34.6 ± 10.5	39.2 ± 11.9
Race (%)		
White	41.9	57.9
Black	51.6	39.5
Other	6.5	2.6
Gender (%)		
Male	27.4	28.9
Female	72.6	72.1
Baseline EDSS[b]	1.0, 0-8	.50, 0-7
MS Type (%)		
CIS	1.6	0
RRMS	91.9	94.7
SPMS	6.5	0
PPMS	0	5.3

[a] mean ± SD
[b] median, range

Chi-square Test

The cross sectional analysis showed that 38 patients were on vitamin D (6 of whom had a relapse) and 62 were not on vitamin D (19 of whom had a relapse), as seen in figure 1. 18.75% of patients on vitamin D had a relapse and 44.19% of patients not on vitamin D had a relapse. The chi-square test showed an association between vitamin D and MS relapses that was not statistically significant $\chi 2$ (1, N = 100) = 2.04, p =.15, odds ratio= 0.42, 95% CI [0.15 to 1.19], as seen in table 1.

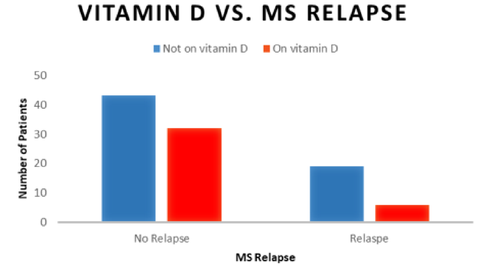

Figure 1. Bar Chart for the cross sectional analysis comparing vitamin D and MS Relapse.

Table 2: Comparison of vitamin D and MS Relapse.

Variable	No Relapse *n* (%)	Relapse *n* (%)	*n*	χ^2-statistic[a] (df)	*P*-value[a]
Off vitamin D	43 (43.0)	19 (19.0)	62	2.04 (1)	0.15
On Vitamin D	32 (32.0)	6 (6.0)	38		

[a] Chi-square test for independence

Mann-Whitney Test

The Mann-Whitney test indicated that the number of relapses were not significantly different for patients on vitamin D (median relapse(s) = 0, range = 0-4) than for patients not on vitamin D (median relapse(s) = 0, range = 0-7) U=1006.00, p = 0.11, as seen in table 3.

Table 3: Comparison of the number of relapses for patients on vitamin D and not on vitamin D.

Variable	Median (range) *n* = 100		*U*-statistic	*P*-value[a]
Number of Relapses	On vitamin D	Not on vitamin D		
	0 (0-4)	0 (0-7)	1006.00	0.11

[a] Mann-Whitney test (2-tailed p-value)

Conclusion

In this retrospective chart review, the relationship between vitamin D and MS relapse was investigated. The results indicate that there is not a statistically significant relation between vitamin D and whether or not patients had a relapse (p = 0.15). The results also indicate that the distributions of the number of relapses for patients on vitamin and not on vitamin D did not differ significantly from one another (p = 0.11).

Our study had negative results unlike previous studies such as the Pierrot-Deseilligny and colleagues study, which showed that 25-OH-D serum level related to a lower relapse rate in RPMS patients after vitamin D supplementation. [11] However, our study looked at patients with all types of MS, not only RRMS patients. As previously stated, other MS types are characterized by having little to no relapses. The fact that 8% of our patients had another type of MS and in particular that 6.5% patients on vitamin D had SPMS, could have very likely skewed our data.

Disease modifying treatments (DMTs) were also not considered in our statistical analysis. The DMTs could have definitely had an impact on the number of relapses the patients had of the two year period. Studies have shown that vitamin D has a positive effect on MS progression. Ascherio and colleagues found that among patients with CIS randomized to early vs late treatment with IFNβ-1b, with higher serum 25(OH)D levels had a lower degree of MS activity, MRI lesion load, brain atrophy, and clinical progression during 5 years of follow-up. [10] The CLIMB study showed that 25(OH)D had an effect on time to relapse and enhancing lesion load for MS patients on IFNβ and Glatiramer Acetate, however, no effect on MS relapse. [14] In our study, however, without knowing when exactly the DMT were started and stopped and the fact that patients changed DMTs within the interval of interest, DMTs were not able to be considered.

It was also seen that 75% of the patients that were reviewed did not have any relapses. It is believed that having so many patients with zero relapses contributed to the fact that the distributions between vitamin D and non-vitamin D patients were not statistically different. This could have been due to a number of factors including patient follow-up, patients going to a different hospital at the time of their relapse, or patients failing to mention a relapse to their physician.

The uncertainty of the patient's vitamin D compliance and levels could have skewed our results and misrepresented the vitamin D patient population. We also did not take into account when the patients started vitamin D, as that was unclear. Rather we took into account whether or not vitamin D was mentioned in the chart during the time interval of interest. When the patients started vitamin D and how long they had been taking vitamin D could have also skewed our results.

The relationship between vitamin D and MS is an area of continued research. Much more research needs done in order to investigate this relationship further and the possible positive effect it could have on MS patients. This study helps us estimate the needed sample size for a future prospective study adjusting for potential confounders. A future prospective study, where many more variables could be controlled and analyzed would be beneficial in investigating this relationship further.

Acknowledgments

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