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The correlation Between Vitamin D Metabolite Levels With Relapse Rate And Disability In Multiple Sclerosis

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Abstract

Background: Multiple sclerosis is a major cause of disability in young adults. Vitamin D is a potent immunomodulator and the protective effect of Vitamin D on multiple sclerosis is supported by the reduced risk associated with sun exposure and use of Vitamin D supplements. Moreover, high circulating levels of Vitamin D have been associated with lower risk of multiple sclerosis. **Objectives**: The aim of this study is to clarify the relationship between vitamin D metabolite level and disability and relapse rate in multiple sclerosis**. Methods:** Fifty four Multiple sclerosis patients fulfilling McDonald's criteria and 70 controls matched in age, sex and same geographical areas,35 (64.8 %) patients were with relapsing remitting type,9 (16.6 %) patients were primary progressive type and 10 (18.6 %) patients were secondary progressive type. For the control group, 28 of them were with non-MS demyelinated neurological diseases including 18 with chronic inflammatory demyelinating polyneuropathy, 6 were Gillian Barrie syndrome and 4 were acute demyelinating encephalomyelitis, and the remaining forty two were apparently healthy controls. All multiple sclerosis patients and controls are subjected to assessment of 25(OH) D serum level by RIA. **Results:** very high statistically significant difference between patients and controls, also very high statistically significant negative correlation in all patients, and disability and relapse rate .

Conclusion: There is an important role of vitamin D in outcome of multiple sclerosis and the relapsing rate of the relapsing remitting type

Keywords: multiple sclerosis,vitamin D,relapse,disability

1. Introduction

In the Multiple sclerosis (MS) is a major cause of disability in young adults. The social costs associated with MS are high because of its long duration, the early loss of productivity, the need for assistance in activities of daily living and the use of immunomodulatory treatments and multidisciplinary health care.[1] Multiple sclerosis is not considered a hereditary disease. However, a number of genetic variations have been shown to increase the risk of developing the disease.[2,3] Although genetic susceptibility explains the clustering of MS within families, it cannot fully explain the geographical variations in MS frequency and the changes in risk that occur with migration, which support the action of strong environmental factors. Different environmental factors, both of infectious and non infectious origin have been proposed as risk factors for MS,[4] among these, vitamin D status, as vitamin D is a potent immunomodulator, and several studies have shown that administration of the biologically active 1, 25-dihydroxyvitamin D prevents experimental autoimmune encephalomyelitis (EAE) onset and progression in mice.

Also the protective effect of Vitamin D on multiple sclerosis is supported by the reduced risk associated with sun exposure and use of Vitamin D supplements. Moreover, high circulating levels of Vitamin D have been associated with lower risk of multiple sclerosis.[5] Moreover, a newly identified gene-environment interaction between vitamin D and the main MS-linked HLA-DRB1*1501 allele and evidence showing that vitamin D levels are significantly lower in patients with MS as compared to controls. Direct genomic signaling by active vitamin D (1,25(OH)2) occurs through the vitamin D receptor (VDR), which is present in multiple cells of the immune system as well as in neurons and glial cells in the human brain. Activation of the VDR by vitamin D stimulates a shift from pro-inflammatory T-helper cell-1 (Th1) responses to anti-inflammatory T-helper-2 (Th2) responses.[5,6,7,8,9]. Serum concentration of 25(OH) D is the best indicator of vitamin D status, it reflects vitamin D produced cutaneously and that obtained from food and supplements and has a fairly long circulating half-life of 15 days. However, the circulating 1,25(OH)2D is generally not a good indicator of vitamin D status because it has a short half-life of 15 hours and serum concentrations are closely regulated by parathyroid hormone, calcium, and phosphate. Levels of 1,25(OH)2D do not typically decrease until vitamin D deficiency is severe.[10,11]

2. Patients and Methods

According to line of treatment 43 (79.7 %) patients were treated by corticosteroids, 7 (13 %) patients treated by disease modifying drugs other than corticosteroids, 3 (5.5 %) patients received combined treatment in the form of corticosteroids and another disease modifying agent, and one (1.8 %) patient received no specific treatment. The following patients were excluded from the study: Patients with decreased serum albumin, or receiving anticonvulsants, those with advanced renal disease, mal-absorption syndrome, end-stage liver disease, smoking, and patients received vitamin D. The control were divided into 2 subgroups: (A) including 28 patients with demyelinting neurological diseases other than MS including 18 patients with Chronic Inflammatory Demyelinting Polyradiculoneuropathy (CIDP), with a mean duration ± SD of 4.2±0.9 year and the diagnosis confirmed by neurophysiological studies and no significantly related cervical MRI findings, 6 patients with Gillian Barrie Syndrome (GBS), with a mean duration ± SD of (5±1.3) week, diagnosed clinically and supported by neurophysiologic studies and CSF findings and 4 patients with ADEM Acute Disseminated Encephalomyelitis (ADEM), with a mean duration ± SD (4.5 ± 1.3) months, diagnosed clinically and supported by brain MRI, and subgroup (B) including 42 healthy subjects. The patients were subjected to a full medical history taking, full neurological examination, and assessment of the patient disability state using the Expanded Disability Status Scale (EDSS). All participants (cases and controls) were underwent CBC, liver and renal function tests, stool analysis, serum albumin and assessment of the Serum vitamin D (25 hydroxyvitamin D) which was done using the Radio-Immune-Assay (RIA) performed in the Hormone assay unit, National Institute Center at Cairo to study the relationship between serum level of 25 hydroxyvitamin D and clinical MS severity, disability as expressed by EDSS-score and MS subtypes. Data were collected and statistically analyzed. Statistics were done by computer using Epi - info. Software, version 6.04. A word processing, data base and statistics program (WHO, 2001).

3. Results

In this study, regarding the 25(OH) D serum levels and gender of the patients and controls, we found the results showed in table (1):

Table (1): 25(OH) D serum levels and gender of the patients and controls

		Sex	(OH)D mean ± SD	P value
Case group		F	33 ± 21	0.8
		M	34.3 ± 24.4,	
controls	Diseased	F	54.1 ± 17.2	0.5
		M	49.3 ± 19.7,	
	Healthy	F	49.4 ± 11.4	0.000
		M	86±11.4	

Relation of 25(OH)D levels to sex difference appear to be with no statistical significance in both MS and control groups, but with very high statistical significance in healthy control and be of low levels in females.

There is a mild positive correlation (Correlation Coef= 0.1), between duration of illness in years and disease severity as expressed by EDSS with no statistical significance, as shown in table (2):

Table (2): relation between duration of illness in MS and EDSS

Disease duration	EDSS	Correlation Coef.	P value
3.8±2.9	4.09±1.9	0.1	0.45

As regard comparison of 25(OH)D serum levels between case and control groups, the result showed in table (3)

Table (3): The serum level of 25(OH)D in the case and control groups.

	Patient group (MS) 25(OH)D , Mean ± SD: 33.3 ± 21.7	
Comparative group	Diseased control, 25(OH)D , Mean ± SD: 52.7 ± 17.7	Healthy control, 25(OH)D , Mean ± SD: 59.9 ± 21.4
P value	0.000	0.000

Very high statistical significance between the patient and control groups and appear to be lower in case group.

The comparison of 25(OH)D levels and status in both case and control groups subtypes, the results showed in table (4).

Table (4):25(OH)D serum level and status in different groups

group type// Item	Subtypes	number	25 (OH) Mean±SD	P value	25(OH) D status:		
					deficient	Insuff.	Norm.
Patient group (MS)	Total	54	33.3±21.7	0.016	21	22	11
	RRMS	35	39.3±23.6		10	14	11
	PPMS	9	19.6±7.4		6	3	0
	SPMS	10	25.2±14.6		5	5	0
					P 0.000	0.000	0.000
Diseased control	Total	28	52.7±17.7	0.000	0	14	14
	CIDP	18	59.5±1.8		0	14	4
	GBS	6	42.7±10.7		0	0	6
	ADEM	4	78.4±11.1		0	0	4
					P ———	---	0.7

Healthy control	42	59.9±21.4	0	22	20
			P	0.000	

For comparison of 25(OH)D levels between each MS subtypes and control group (healthy and diseased), the results shown in table (5).

Table (5) Comparison of 25(OH)D levels in each MS subtypes to controls:

MS subtype	RRMS (39.3±23.6)		PPMS (19.6±7.4)		SPMS (25.2±14.6)	
Comp. group	Diseased control	Healthy control	Diseased control	Healthy control	Diseased control	Healthy control
25(OH)D, mean ± SD	52.7±17.7	59.9±21.4	52.7±17.7	59.9±21.4	52.7±17.7	59.9±21.4
P value	0.3	0.0001	0.0001	0.0001	0.0002	0.0001

Twenty five (OH)D levels is significantly lower in MS subtypes compared to the controls.

As regard comparison between 25(OH)D levels and MS severity assessed by EDSS, the results showed in table (6).

Table (6): 25(OH)D levels in relation to EDSS

No. of cases	29 (53.7%) <4	25 (46.3%) ≥ 4	P value
EDSS, Mean ± SD	2.5±0.5	6±1.2	0.000
25(OH)D Mean ± SD	47±14.3	15±4.9	0.000

Very high significant negative relation between 25(OH)D serum levels and disease severity as expressed in EDSS score

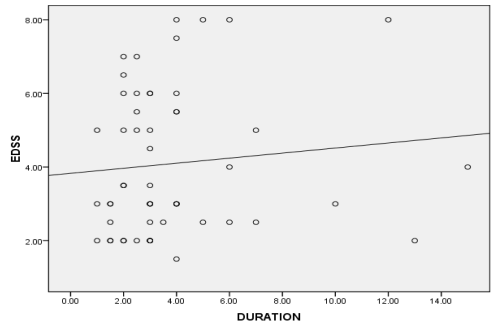
In MS group, RRMS subtype, with 19 patient in relapse and 16 patient in remission, the comparison between 25(OH)D levels in patients during relapse and those during remission, table (7).

Table (7): 25(OH)D levels during relapse and remission

No. of cases	Total (35)	Relapse (n= 19)	Remission (n=16)	P value
25(OH)D Mean ± SD	39.3±23.6	29.5±23.6	31.4±20.9	0.005

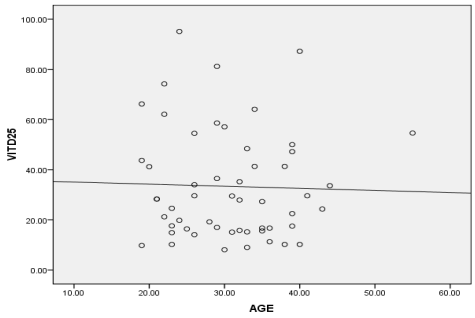
The serum levels of 25(OH)D is significantly lower during relapse than remission.

Figure (1): correlation between MS duration and EDSS



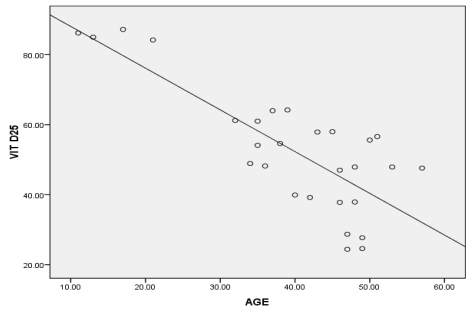
There is mild positive correlation (P=0.45), between duration of illness in years and disease severity assessed by EDSS, with no statistical significance (P=0.45).

Figure (2): correlation between 25(OH) D levels and age of MS patients.



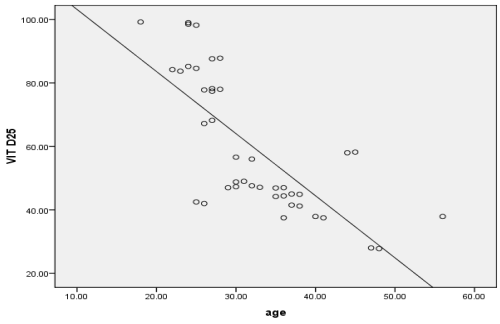
There is a negligible negative correlation between vitamin D levels and age of participants, with no statistical significance (P=0.8).

Figure (3): correlation between 25(OH) D levels and age of diseased controls.



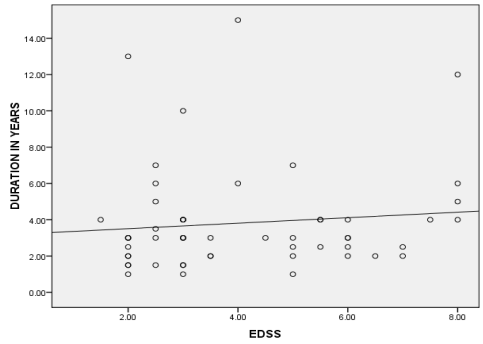
There is a strong negative correlations between vitamin D levels and age of participants, with a very high statistical significance (P=0.000).

Figure (4): correlation between 25(OH) D levels and age of healthy controls.



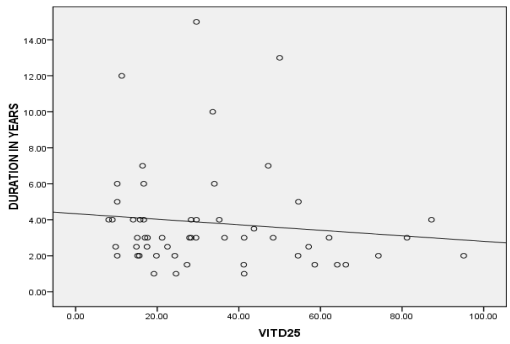
There is a strong negative correlations between vitamin D levels and age of participants, with a very high statistical significance (P=0.000).

Fig. (5) Correlation between disease duration in MS patients and EDSS.



There is a moderate positive correlation between disease duration in MS patients and disease severity assessed by EDSS, with statistical insignificance (P=0.1).

Fig. (6) Correlation between disease duration in MS patients and D levels.



There is a moderate negative correlation between disease duration in MS patients and vitamin D serum levels, with statistical insignificance (P=0.1)

3.3Discussion

In the studied subjects the patients were including 39 female with 25(OH)D mean ± SD of 33 ± 21, and 15 male with 25(OH)D mean ± SD of 34.3 ± 24.4, there was no significant sex difference ,while in the diseased it was high in females than in males. In healthy controls the 25(OH)D levels were less in females than in males. These results are in agreement with El-Ghoneimy, et al[14] who found that no statistically significant difference in vitamin D level between female and male, and not in agreement with the study of Dam et al[15] and the study of Barnes et al[16] who found that women with MS had significantly higher 25(OH) concentrations than men with MS. In the studied patients, the 25(OH)D serum level was lower than that of the controls, these results are in concordance with the study of Correale et al[5] who found that, MS population had lower 25(OH) D than controls, and in concordance with the study of Lucas et al[17] and the study of Lonergan et al[18] who found that there was significantly more patients had low 25(OH)D levels than controls. However the study of Kragt et al[19] reported an inverse relationship between 25 (OH) D and MS in women, also the study of Barnes et al[16] who found that, vitamin D levels were higher only in women with MS, but in our study we found that 25 vitamin D deficiency was evident in both women and men. Regarding to diseases subtypes, 25(OH)D deficiency was more evident in PPMS, compared to SPMS and RRMS, these results are in accordance with Smolders et al[7] who found that circulating levels of 25(OH)D metabolites were significantly lower in the progressive forms of MS when compared to RRMS. But our results were in partial disagreement with Correale et al[5] who found no significant difference when comparing 25(OH)D levels of PPMS patients with healthy controls, but in our study we found that 25(OH)D levels were more deficient in PPMS than other MS subtypes and controls. The serum level of 25(OH)D in the studied patients in relation to disease severity determined by EDSS scale score, there was a very high significant negative correlation in all MS patients, and was being more evident in PPMS and RRMS. These results are in accordance with Bianca Weinstock-Guttman et al[20] and van der Mei et al[21] who found that, lower levels of 25(OH) were associated with higher EDSS and the study of Smolders, et al[7] who found that, 25(OH)D concentrations were inversely associated with disease severity Score. These results are disagree with the study of El-Ghoneimy[14] who found that, there was no statistically significant correlation between 25(OH)D level and disease severity, as assessed by EDSS, but in our study we found that, a very high statistically significant negative correlation between 25(OH)D level and disease severity, as assessed by EDSS, this may be due to exclusion of vitamin D medicated patients in our study. There was a very significant negative correlation between the 25(OH)D serum levels and the relapse rate. This relation is in consistent with the study Smolders et al[7] and Smolders[22] who found that, Serum 25(OH) D levels were associated inversely with relapse rate, also the 25(OH)D serum levels are low during relapse than in remission, these results are consistent with the study of Correale et al[5] who found that, significantly lower levels of both vitamin D metabolites 25(OH)D in patients during exacerbation than patients during remission. Also our results were in accordance with SoiluHanninen[22] who found that 25(OH) D serum levels were significantly lower during acute exacerbations when compared to periods of remission.

5. Conclusion

The serum levels of 25(OH) D are lower in MS patients with a negative correlation when compared to the severity of the disease and to the relapsing rate in the relapsing remitting type.

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