

# FREQUENCY OF 25-HYDROXY VITAMIN D DEFICIENCY IN PATIENTS WITH MULTIPLE SCLEROSIS

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## ABSTRACT

**OBJECTIVE:** To determine the frequency of 25-hydroxy vitamin-D deficiency in patients with multiple sclerosis (MS).

**METHODS:** This cross-sectional study was conducted at Civil Hospital Karachi, Pakistan from January to December 2019. One hundred and sixty five diagnosed cases of MS of either gender, aging 20-55 years, not taking vitamin-D supplements, steroids and could go outside in the sun were selected through non-probability consecutive sampling technique. Patients having history of rickets, parathyroid disease, chronic liver or renal diseases were excluded. Blood sample was taken to measure 25-hydroxyl vitamin D<sub>3</sub> levels. A level of <20 ng/ml was considered as vitamin-D deficient. Logistic regression analysis was used to identify determinants.

**RESULTS:** Out of 165 MS patients, 106 (64.24%) were females, 66 (40%) had income between PKR 10000-25000, 51 (30.9%) were illiterate and 12 (7.3%) had graduate level education. Majority (n=101; 61.21%) had relapsing-remitting MS. Mean age of enrolled participants was 32.92±8.19 years and mean duration of MS was 2.17±0.84 years. Ninety-nine (60%) patients had history of adequate sun exposure. Vitamin-D deficiency in MS patients was 55 (33.3%). Female patients with MS had 2.9 times more likely to be vitamin-D deficient compared to male patients (95% CI: 1.3-6.5). Vitamin-D deficiency in MS patients having no or primary level education patients was recorded in 38 (69.1%) patients as compared to 17 (31.9%) case having secondary or higher education (p-value=0.046).

**CONCLUSION:** Vitamin-D deficiency is common in MS patients. Females and less educated MS patients are at a higher risk of being vitamin-D deficient.

**KEY WORDS:** Multiple Sclerosis (MeSH); Risk (MeSH); Vitamin D (MeSH); Vitamin D Deficiency (MeSH); Educational Status (MeSH); Socioeconomic Factors (MeSH); Female (MeSH); Male (MeSH).

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## INTRODUCTION

Multiple sclerosis (MS) is a diverse disease with fluctuating clinical and pathologic features reflecting various pathways to tissue injury.<sup>1</sup> Natural elements seem to speculate a crucial role in the development of MS. These consist of viral infections, geographic latitude, place of birth, sunlight exposure. Vitamin D deficiency is one of the substantial risk factors for MS.<sup>2</sup> Low levels of vitamin D have shown to not only influence the disease onset in an individual but also

influence the frequency of relapses in patients with MS.<sup>3</sup> 25-hydroxy (25-OH) vitamin D effect is mainly mediated by pro-differentiating, anti-proliferative, and anti-inflammatory characteristics. 25-OH vitamin D regulates immune expression of major histocompatibility complex class II as well as co-regulatory receptors on antigen-presenting cells. Thus, 25-OH vitamin D deficiency may worsen the MS.<sup>4</sup>

Notably, MS is more frequent in higher latitudes, where daylight is of lower intensity. The literature reveals latitude

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inclination in MS frequency. There is a strong relationship between increased body exposure to daylight leading to appropriate levels of vitamin D and decreasing the risk of MS in individuals.<sup>5</sup> The relationship of disease activity with vitamin D levels in MS patients has been assessed, the patients having a higher level of vitamin D having less relapse rate while patients with lower vitamin D levels having higher percentage of functional impairment.<sup>6,7</sup>

Therapeutic goals in MS are reducing relapses and maintaining an acceptable quality of life, an appropriate level of vitamin D help in achieving therapeutic goals, and balance vitamin D addition as adjunctive therapy is recommended in patients with MS.<sup>8</sup> As we are a population having higher rates of 25-OH vitamin D deficiency, despite adequate sun exposure as compared to rest of the world due to increased pigmentation, use of sunblock or purdah.<sup>9</sup>

The findings of this study help us in establishing the frequency of vitamin deficiency in patients suffering from MS; it may also help us later in planning further studies regarding its role in building cost-effective protocols for disease prevention and examining whether they related to the risk of advancement of disease in MS. Therefore, we planned this study to determine the frequency of 25-OH vitamin D deficiency in patients with MS in our local population.

**TABLE I: SOCIODEMOGRAPHIC CHARACTERISTICS PATIENTS WITH MULTIPLE SCLEROSIS (N= 165)**

Characteristics	Variables	N	Percentage (%)
<b>Gender</b>	Male	59	35.76%
	Female	106	64.24%
<b>Age in Group</b>	< 35 years	98	59.39%
	≥ 35 years	67	40.61%
<b>Monthly income (PKR)</b>	< Rs. 10,000	60	36.36%
	Rs. 10,000 to 25,000	66	40.00%
	> Rs. 25,000	39	23.64%
<b>Education Level</b>	Illiterate	51	30.91%
	Primary	48	29.09%
	Secondary	33	20.00%
	Intermediate	21	12.73%
	Graduation	12	7.27%
<b>Types of Multiple Sclerosis v/s total number of patients</b>	Primary progressive	16	9.70%
	Secondary progressive	39	23.64%
	Progressive-relapsing	9	5.45%
	Relapsing-remitting	101	61.21%
<b>Types of Multiple Sclerosis with deficiency of Vitamin D</b>	Primary progressive	4	2.42%
	Secondary progressive	19	11.52%
	Progressive-relapsing	2	1.21%
	Relapsing-remitting	30	18.18%

**METHODS**

The study was conducted in the Department of Neurology, Civil Hospital, Karachi, Pakistan from 1<sup>st</sup> Jan 2019 to 31<sup>st</sup> Dec 2019. The patients within the age group of 20 to 55 were selected by using non-probability consecutive sampling technique. McDonald criteria was used to diagnose MS.<sup>9</sup> Those patients were taken into consideration who were not using any drug or supplement having vitamin D & steroids. In this study, all those patients were excluded who had physical disability, rickets or parathyroid disease, chronic liver disease or chronic renal disease, history of stroke, vasculitis, pregnant females and patients having any co-morbid like ischemic heart disease, diabetes or hypertension.

For this study, we calculate sample size of 165 by using WHO sample size calculator by prevalence as 30%, margin of error as 7% and confidence interval of 95%.<sup>10</sup> Patients were enrolled in this study after getting consent from patients or

caretaker. A 3 ml of whole blood sample was taken and was analyzed for 25-OH vitamin D3 levels by using Immunodiagnostic Systems (IDS)-iSYS 25(OH)DS (Immunodiagnostic Systems Ltd, Boldon, United Kingdom) at local facility. 25-OH vitamin D levels of less than 20 ng/ml was considered deficient. MS was classified into different types according to McDonald criteria. Sun exposure was defined as time exposed in the sun between 10 am and 3 pm for at least 20 minutes or more for at least 4 days a week in the past one year or more was labeled as adequate.<sup>11</sup> The data were recorded on predesigned questionnaire. The overall analyze and comparison evaluated by using IBM-SPSS version 23 & Microsoft Excel and shown through appropriate tables, graphs, and their percentages. Level of significance also determined by using 95% confidence interval and p values are obtained.

**RESULTS**

The total number of studied patients was 165 out of which 59 (36%) were

male and 106 (64%) were female. The mean age of overall studied patients was 32.92±1.25 years, whereas the mean age of male patients was 30.81±1.87 years and female patients was 34.08±1.64 years. The basic demographic characteristics of patients having MS are presented in Table I.

Frequency of 25-OH vitamin D deficiency in patients suffering from MS compared by different factors like age, gender, educational status, monthly income, type of MS, sun exposure and duration of MS was done.

The results of these factors that are associated with deficiency of vitamin D are presented in Table II.

In female patients, the frequency of vitamin D deficiency suffering from MS was 42 (76.4%) compared to 13 (23.6%) cases among male patients (p value=0.025).

In MS patients having no or primary level education patients, the frequency of 25-OH vitamin D deficiency was recorded in 38 (69.1%) patients as compared to

**TABLE II: COMPARISON OF FACTORS ASSOCIATED WITH 25-OH VITAMIN D DEFICIENCY & MULTIPLE SCLEROSIS (N=165)**

Factors		Vitamin D Deficiency				Total (n=165)		P-value against Chi-Square (x <sup>2</sup> ) test	P-value against Univariate analysis
		Deficient (n=55)		Not deficient (n=110)					
		n	%	n	%	n	%		
Gender	Male	13	23.6%	46	41.8%	59	35.8%	0.025	0.022
	Female	42	76.4%	64	58.2%	106	64.2%		
Age (years)	< 35	32	58.2%	66	60.0%	98	59.4%	0.867	0.824
	≥ 35	23	41.8%	44	40.0%	67	40.6%		
Monthly income (PKR)	< 10,000	25	45.5%	35	31.8%	60	36.4%	0.229	0.132
	10,000-25,000	19	34.5%	47	42.7%	66	40.0%		
	> 25,000	11	20.0%	28	25.5%	39	23.6%		
Educational Status	Illiterate	20	36.4%	31	28.2%	51	30.9%	0.298	0.046
	Primary	18	32.7%	30	27.3%	48	29.1%		
	Secondary	10	18.2%	23	20.9%	33	20.0%		
	Intermediate	6	10.9%	15	13.6%	21	12.7%		
	Graduation	1	1.8%	11	10.0%	12	7.3%		
Types of Multiple Sclerosis	Relapsing-remitting	30	54.5%	71	64.5%	101	61.2%	0.124	0.295
	Secondary progressive	19	34.5%	20	18.2%	39	23.6%		
	Primary progressive	4	7.3%	12	10.9%	16	9.7%		
	Progressive-relapsing	2	3.6%	7	6.4%	9	5.5%		
Duration of Multiple Sclerosis	< 2 years	36	65.5%	75	68.2%	111	67.3%	0.728	0.727
	> 2 years	19	34.5%	35	31.8%	54	32.7%		
Sun Exposure	Adequate	25	45.5%	41	37.3%	66	40.0%	0.318	0.315
	Inadequate	30	54.5%	69	62.7%	99	60.0%		

17 (31.9%) case having secondary, intermediate or graduation level patients (p value=0.046).

## DISCUSSION

Our study reveals the frequency of vitamin D deficiency in patients suffering from MS was 33.3%. Now, this is a well-established fact that vitamin D deficiency is fairly common in patients with MS with an impact on disease progression, relapse, and other morbidities. The result reflects sunlight exposure and limited outdoor activities due to limitations may be responsible but therapeutic strategies to overcome vitamin D deficiency need to be addressed. Generally, vitamin D supplementation seems to be reasonable for all MS.<sup>12</sup> In female patients, the frequency of vitamin D deficiency suffering from MS was significantly high as compared to males. The findings are

similar to many other studies.<sup>13,14</sup> Pakistan is having the highest prevalence rate of vitamin-D deficiency in South East Asia.<sup>15</sup> In the general population, 57-58% of women reported having vitamin-D deficiency.<sup>16,17</sup> Our study shows a high percentage of vitamin-D deficiency in women with MS as compared to the general population. The majority of our female patients are in the fertile age group, and female with MS face many challenges in form of different comorbidities. The known MS comorbidities like depression, anxiety, and migraines are also related to vitamin D deficiency.<sup>18</sup>

Our study did not find effect modification of age, income, type of MS, and adequate exposure to sunlight on 25-OH vitamin D levels in patients with MS. Generally, the high financial status and better social

conditions have a positive impact on health. There is less and inconsistent data available for an association between high socioeconomic status and expanded risk for MS. There are few pieces of evidence that shows a few signs of a stronger effect but the results are variable and firm outcomes are inconvenience.<sup>19</sup>

In our study, vitamin D deficiency in MS patients was significantly higher in less educated as compared to highly educated patients (p-0.046). In another study, the higher level of education was related to lower chances of MS (p-0.001) in comparison to patients with lower educational levels.<sup>20</sup> The lower educational level could be a reason for an obscure vulnerability that is significant for the etiology of MS.

We did not find a significant association between adequate sun exposure and

vitamin D deficiency in MS. Time of adequate sun exposure itself has a direct effect on MS without vitamin D level also. Present adequate sun-exposure does not reflect what the patient's vitamin D level was in the past.<sup>21</sup> Vitamin D is most likely to have protected effects, evidence support that low-level vitamin D levels in MS patients cause worsening of symptoms. We don't have obvious proof of the effect of vitamin-D on disease progression but literature reveals that lower vitamin-D levels are more prevalent in MS.<sup>22</sup> These patients have increased susceptibility to osteoporosis and autonomic dysfunction. Studies are supporting the association of low bone-mass density with inflammatory and neurodegenerative processes of MS and other co-morbidities like depression and fatigue. Addressing these issues may reduce the risk of osteoporosis, autonomic dysfunction and most importantly the progression of MS leading to improved quality of life in these patients.<sup>23</sup> Therefore, 25-OH vitamin D levels should be determined, and if deficiency is found, should be treated.

### LIMITATION OF THE STUDY

MS is a rare disease with low prevalence rate compared to many other neurological disorders. The number of patients are low so it will be difficult to generalize the results. We need more studies in other parts of the country to confirm the trend and to look at vitamin D levels during relapses as well as remission and with duration of sunlight exposure.

### CONCLUSION

The overall frequency of vitamin D deficiency in patients suffering from MS was 33.3%. Frequency is high in female MS patients as compared to general population. Apparently, literacy affects vitamin D deficiency, but we need further studies to confirm these trends.

### REFERENCES

1. Voet S, Prinz M, van Loo G. Microglia in central nervous system inflammation and multiple sclerosis pathology. *Trends Mol Med* 2019;25(2):112-23. <https://doi.org/10.1016/j.molmed.2018.11.005>
2. Kocovska E, Gaughran F, Krivoy A, Meier UC. Vitamin-D deficiency as a

potential environmental risk factor in multiple sclerosis, schizophrenia, and autism. *Front Psychiatry* 2017; 8:47. <https://doi.org/10.3389/fpsy.2017.000477>

3. Runia TF, Hop WC, de Rijke YB, Buljevac D, Hintzen RQ. Lower serum vitamin D levels are associated with a higher relapse risk in multiple sclerosis. *Neurology* 2012;79(3):261-6. <https://doi.org/10.1212/WNL.0b013e31825fdec7>
4. Thouvenot E, Orsini M, Daures JP, Camu W. Vitamin D is associated with degree of disability in patients with fully ambulatory relapsing-remitting multiple sclerosis. *Eur J Neurol* 2015;22(3):564-9. <https://doi.org/10.1111/ene.12617>
5. Mansouri B, Asadollahi S, Heidari K, Fakhri M, Assarzagdegan F, Nazari M, et al. Risk factors for increased multiple sclerosis susceptibility in the Iranian population. *J Clin Neurosci* 2014;21(12):2207-11. <https://doi.org/10.1016/j.jocn.2014.04.020>
6. Harandi AA, Shahbeigi S, Pakdaman H, Fereshtehnejad SM, Nikravesh E, Jalilzadeh R. Association of serum 25(OH) vitamin D3 concentration with severity of multiple sclerosis. *Iran J Neurol* 2012;11(2):54-8.
7. Smolders J, Menheere P, Kessels A, Damoiseaux J, Hupperts R. Association of vitamin D metabolite levels with relapse rate and disability in multiple sclerosis. *Mult Scler* 2008;14(9):1220-4. <https://doi.org/10.1177/1352458508094399>
8. Pierrot-Deseilligny C, Souberbielle JC. Vitamin D and multiple sclerosis: an update. *Mult Scler Relat Disord* 2017;14:35-45. <https://doi.org/10.1016/j.msard.2017.03.014>
9. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2018;17(2):162-73. [https://doi.org/10.1016/S1474-4422\(17\)30470-2](https://doi.org/10.1016/S1474-4422(17)30470-2)
10. Riaz H, Finlayson AE, Bashir S, Hussain S, Mahmood S, Malik F, et al. Prevalence of Vitamin D deficiency in Pakistan and implications for the future. *Expert Rev Clin Pharmacol* 2016;9(2):329-38. <https://doi.org/10.1586/17512433.2016.1122519>
11. Bouillon R. Comparative analysis of nutritional guidelines for vitamin D. *Nat Rev Endocrinol* 2017;13(8):466-79. <https://doi.org/10.1038/nrendo.2017.31>
12. Ferre L, Sferruzza G, Mascia E, Clarelli F, Dalla Costa G, Radaelli M, et al. Baseline vitamin D levels and multiple sclerosis activity in relapsing remitting patients treated with fingolimod. *Neurol Sci* 2016;39(8):1467-70. <https://doi.org/10.1007/s10072-018-3440-0>
13. Shah Z, Wasay M, Chaudhry BZ, Fredrikson S. Multiple sclerosis in Pakistan: Current status and future perspective. *J Neurol Sci* 2020; 418: 117066. <https://doi.org/10.1016/j.jns.2020.117066>
14. Raja V, Afzal N, Roy N, ur Rehman J, Avinash BK. Frequency of Vitamin D Deficiency Among Patients of Multiple Sclerosis in Pakistan. *J Med Health Studies* 2020;1(1):17-22.
15. Siddiqee MH, Bhattacharjee B, Siddiqi UR, Meshbah ur Rahman M. High prevalence of vitamin D deficiency among the South Asian adults: a systematic review and meta-analysis. *BMC Public Health* 2021;21(1):2-18. <https://doi.org/10.1186/s12889-021-11888-1>
16. Shamsi U, Azam I, Shamsi A, Shamsi D, Callen D. Frequency and determinants of vitamin D deficiency among premenopausal and postmenopausal women in Karachi Pakistan. *BMC Womens Health* 2021;21(1):2-8. <https://doi.org/10.1186/s12905-021-01339-9>
17. Syed F, Latif MSZ, Ahmed I, Bibi S, Ullah S, Khalid N. Vitamin D deficiency in Pakistani population: critical overview from 2008 to 2018. *Nutrition Food Science* 2020;50(1):105-15. <https://doi.org/10.1108/NFS-03-2019-0105>
18. Vorobeychik G, Black D, Cooper P, Cox A. Multiple sclerosis and related challenges to young women's health: Canadian expert review. *Neurodegener Dis Manag* 2020;10(2s):1-13. <https://doi.org/10.2217/nmt-2020-0010>

19. Goulden R, Ibrahim T, Wolfson C. Is high socioeconomic status a risk factor for multiple sclerosis? A systematic review. *Eur J Neurol* 2015;22(6):899-911. <https://doi.org/10.1111/ene.12586>
20. Bjørnevik K, Riise T, Cortese M, Holmøy T, Kampman MT, Magalhaes S, et al. Level of education and multiple sclerosis risk after adjustment for known risk factors: The EnvIMS study. *Mult Scler* 2016; 22(1):104-11. <https://doi.org/10.1177%2F1352458515579444>
21. Bartosik-Psujek H, Psujek M. Vitamin D as an immune modulator in multiple sclerosis. *Neurol Neurochir Pol* 2019;53(2):113-22. <https://doi.org/10.5603/PJNNS.a2019.0015>
22. Smolders J, Torkildsen Ø, Camu W, Holmøy T. An update on vitamin D and disease activity in multiple sclerosis. *CNS Drugs* 2019;33(12):1187-99. <https://doi.org/10.1007/s40263-019-00674-8>
23. Sternberg Z. Cardiovascular autonomic dysfunction: link between multiple sclerosis osteoporosis and neurodegeneration. *Neuromolecular Med* 2018;20(1):37-53. <https://doi.org/10.1007/s12017-018-8481-2>

### AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

**MAB:** Conception & study design, drafting the manuscript, approval of the final version to be published

**AA:** Acquisition, analysis and interpretation of data, drafting the manuscript, approval of the final version to be published

**TA:** Study design, drafting the manuscript, critical review, approval of the final version to be published

*Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.*

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Authors declared no conflict of interest

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### DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request



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