

## Association between Sun Exposure, Vitamin D Intake, Serum Vitamin D Level, and Immunoglobulin G Level in Patients with Neuromyelitis Optica Spectrum Disorder

### Abstract

**Background:** Neuromyelitis optica spectrum disorder (NMOSD) is a central nervous system inflammatory disorder in which immunoglobulin G (IgG) autoantibodies possibly play a pathogenic role against the aquaporin-4 water channel protein. Vitamin D may modulate B-cell function and decrease the IgG synthesis and may play a role in NMOSD as a crucial factor. The aim of this study was to investigate the relation between Vitamin D intakes from food, Vitamin D intake from sunlight exposure, blood Vitamin D levels, and IgG-neuromyelitis optica (NMO) level in serum of patients with NMOSD and NMO. **Method:** In this cross-sectional study, food Frequency Questionnaires (FFQ) and Sun Exposure Questionnaire (SEQ) were completed to evaluate of vitamin D intakes from food and sun light exposure. Moreover, serum levels of 25(OH) vitamin D3 and IgG-NMO were assessed in patients with NMOSD and NMO. **Results:** We assessed IgG-NMO levels in 29 patients with NMOSD that nine patients ( $n = 31\%$ ) were positive and for the rest it was negative. Sunlight exposure scale ( $P = 0.01$ ) and 25(OH) D3 ( $P = 0.04$ ) in IgG-NMO-negative patients were significantly more than patients with positive IgG-NMO. Age, gender, and latitude were not confounder variables. A positive significant correlation was observed between the sun exposure scale and serum levels of 25(OH) D3 in all participants ( $r = 0.747$ ,  $P \leq 0.001$ ). **Conclusions:** Physiological variation in Vitamin D may apply a significant effect on IgG-NMO synthesis in patients with NMO. Vitamin D may have significant role in pathogenesis of NMOSD and NMO.

**Keywords:** Immunoglobulin G, neuromyelitis optica spectrum disorder, Vitamin D

### Introduction

Neuromyelitis optica spectrum disorder (NMOSD) or Devic's syndrome is a relapse disease of the central nervous system (CNS) that basically affects the optic nerves and spinal cord.<sup>[1]</sup> Based on the reports of epidemiological and population-based studies, the prevalence of neuromyelitis optica (NMO) is between  $<1/100,000$  and  $44/100,000$  in Europe and North America.<sup>[2-6]</sup> In more than 90% of patients, NMOSD is an unpredictable relapsing illness with the optic neuritis (ON) attacks, myelitis, or both.<sup>[7]</sup> The most abundant water channel in the CNS is aquaporin-4 (AQP4), which is limited to astrocytes and ependymal cells and located at glial-pial and glial-endothelial interfaces and surrounds Ranvier nodes and paranodes, adjacent oligodendroglia loops, and synapses.<sup>[8]</sup>

In recent years, scientists and clinical neurologists have recognized a highly

specific serum immunoglobulin G (IgG)<sup>[9]</sup> autoantibody (NMO-IgG) targeting the most affluent astrocytic water channel AQP4 as a key biomarker for this disorder.<sup>[10-13]</sup> In general, NMO is recognized as an IgG-mediated autoimmune astrocytopathy. Before discovering this antibody, NMOSD was misclassified as multiple sclerosis (MS). NMO-IgG is basically involved in the pathogenesis of NMO spectrum disorders.<sup>[14]</sup>

Vitamin D3 is a prohormone made by the action of ultraviolet (UV) on 7-dehydrocholesterol in skin. It is metabolized to 25-hydroxyvitamin [25(OH)] D3 in liver and then is changed to the biologically active form 1,25-dihydroxyvitamin [1,25(OH)2] D3 in kidney. The main role of Vitamin D in human is to regulate the bone homeostasis and calcium metabolism. Furthermore, it is also vital for activating immune defense systems and preventing the

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10.4103/ijpvm.IJPVM\_45\_16

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**How to cite this article:** Shaygannejad V, Maljaei MB, Saraf-Bank S, Mirmosayyeb O, Maracy MR, Askari G. Association between sun exposure, Vitamin D intake, serum Vitamin D level, and immunoglobulin G level in patients with neuromyelitis optica spectrum disorder. *Int J Prev Med* 2018;9:68.

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pathologies of immunological disease.<sup>[15]</sup> By recognizing the Vitamin D receptor (VDR) on lymphocytes, the immunological importance of Vitamin D was detected for the first time.<sup>[16,17]</sup> Previous studies have investigated the effects of Vitamin D on human adaptive immune cells and showed an expression of the nuclear VDR as well as Vitamin D-activating enzymes in both T- and B-cells.<sup>[18]</sup> Vitamin D prevents B-cell sudden proliferation and differentiation and therefore reduces Ig secretion. Moreover, Vitamin D affects sudden increase of T-cell and maturation which results in reduction in the amounts of T-cells with the phenotypes of Th1 and Th17.<sup>[15,19]</sup> Many studies have revealed that Vitamin D levels are low in patients with autoimmune disorders, such as MS, systemic lupus erythematosus, rheumatoid arthritis, and type 1 diabetes.<sup>[20]</sup> Moreover, Vitamin D levels have been reported to be associated with illness disability or activity in these disorders.<sup>[21-23]</sup>

To the best of our knowledge, association between sun exposure, Vitamin D intake, serum Vitamin D level, and IgG-NMO levels in patients with NMOSD has not been examined. Therefore, the aim of this study was to examine the association between sun exposure, Vitamin D intake, and serum levels of 25(OH) D and NMO-IgG in newly diagnosed patients with Devic's syndrome.

## Methods

### Study design and patients

The present research is a cross-sectional study carried out in Isfahan, Iran, in June 2015 that was approved by the Ethics Committee of Isfahan University of Medical Sciences (Project Code: 393886). Sixty-three patients with newly diagnosed NMOSD and NMO with magnetic resonance imaging assessment of spinal cord were recruited from MS clinic in Ayatollah Kashani Hospital of Isfahan University of Medical Sciences, Isfahan, Iran. Inclusion criteria included having NMOSD, lack of medical comorbidities, or any other basic chronic illnesses. Exclusion criteria were using cholecalciferol, calcium, multivitamin, mineral supplementation, or Vitamin D-fortified foods during the past 3 months and lived in other city with different latitude. Thirty-four patients excluded from the study because they consumed cholecalciferol and were living in other city with different latitude. A 49-item semi-quantitative food frequency questionnaire was used for the assessment of dietary intake, particularly calcium and Vitamin D intake. Food intake frequency over the past 3 months was reported in day, week, or month. Calcium content of foods was calculated from Nutritionist 4 software published by N-squared computing (FIRM) modified for Iranian foods, and reliability and relative validity were surveyed in the previous study.<sup>[24]</sup> Vitamin D was calculated based on the "provisional table on the Vitamin D foods' content" released by the United States Department of Agriculture.<sup>[25]</sup>

### Sunshine exposure assessment

Average sunshine exposure was measured using a questionnaire to quantify the amount of time patients spent in the sun and other sun-related habits during the past 3 months of the patients' recruitment. The questions were about the amount of time that patients spent outdoors, time spending outdoors, wearing sunscreen, sun protection factor, type of clothing, and the skin pigment. It was a modified version of the sun exposure questionnaire made by Glanz *et al.*,<sup>[26]</sup> and it was used in previous study in Iran.<sup>[9]</sup>

The score of sun index was determined as hours that were spent under sun exposure during the week, sun-protective behaviors (i.e., clothing and sunscreen use), and patients' skin color. Possible scores ranged from 4 to 14. Higher scores showed higher sunlight exposure. The sun scores were examined regarding their relationship to serum Vitamin D levels.

### Clinical characteristics

All 29 participants were Iranian and had been living in Isfahan city since their birth (latitude: 26°42'N). We collected demographic and clinical characteristics of participants such as sex and age, body mass index (BMI), illness duration, the first clinical sign, and history of other autoimmune disease. Patients were stable in remission and experienced no attack and did not take any pulse therapy during the past 3 months. All of the patients have received a low dose of oral prednisolone and/or oral azathioprine as maintenance therapy.

### Laboratory procedures

25(OH) D was assessed with LIAISON® (LIAISON® 25 OH Vitamin D TOTAL Specimen Diluent Set, REF 310602) method at the Milad Laboratory in Isfahan. This method is a direct competitive chemiluminescence immunoassay for quantitative determination of total 25(OH) D in serum. During the first incubation, 25(OH) D is separated from its binding protein and binds to the specific antibody in the solid phase. The tracer is added after 10 min (Vitamin D linked to an isoluminol derivative). After 10 min of incubation, the unbound material is removed with a wash cycle. Subsequently, the beginner reagents are added to initiate a flash chemiluminescent reaction. The light signal is measured by a photomultiplier as relative light units and is inversely proportional to the 25(OH) D concentration present in calibrators, controls, or samples.

The anti-AQP4 test was conducted at the Milad Laboratory in Isfahan. Anti-AQP4 antibodies (AQP4) were determined in the patients' serum by indirect immunofluorescence (EUROIMMUN IIFT, Germany) on a cell line which had been molecular biologically modified (AQP4 transfected cells) to produce large

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quantities of AQP4. Biochip slides containing AQP4-transfected cells and nontransfected cells (EU-90) were incubated with diluted patient's samples. In the positive reactions case, specific antibodies of the classes IgA, IgG, and IgM would bind to the antigens. In the second step, the attached antibodies are stained with fluorescein-labeled anti-human antibodies and became visible with the fluorescence microscope.

### Ethics statement

Written informed consent was obtained from all the participants. This study was approved by School of Nutrition and Food Sciences, Isfahan University of Medical Sciences (Ethic Code: 393886).

### Statistical analysis

Normal distribution of variables among IgG-NMO positive and negative participants was determined by Shapiro-Wilk test. All variables including sun exposure scale, Vitamin D intake, and 25(OH) D<sub>3</sub> levels were normally distributed. Independent sample *t*-test was applied to compare the means of variables between IgG-NMO positive and negative groups. Pearson's correlation test was used to assess the association between sun exposure scale, Vitamin D intake, and 25(OH) D<sub>3</sub> levels among all the participants and in subgroups of IgG-NMO positive and negative patients. All values were presented as mean (standard deviation [SD]). Statistical analyses were performed using SPSS version 20 published by IBM Corp, Armonk, New York. *P* < 0.05 was considered statistically significant.

### Results

General characteristics of participants are demonstrated in Table 1. According to the presented data, age, sex, BMI, weight, disease duration, and disease diagnosis had no significant differences between NMO-IgG positive and negative group.

Mean ± SD of sun exposure scale, Vitamin D intake, and serum levels of 25(OH) D<sub>3</sub> is shown in Table 2. NMO-IgG-negative participants had significantly higher scores of sun exposure and 25(OH) D<sub>3</sub> levels in comparison with NMO-IgG-positive participants. Furthermore, the participants with negative

NMO-IgG consumed marginally higher amounts of Vitamin D compared to NMO-IgG-positive participants.

Table 3 shows the results of Pearson's correlation test between studied variables and serum levels of 25(OH) D<sub>3</sub>.

### Discussion

This study suggests that negative patients had higher scales of sun exposure, dietary Vitamin D, and serum levels of 25(OH) D<sub>3</sub> in comparison with NMO-IgG-positive participants. In addition, there was a significant direct association between scales of sun exposure and serum concentrations of 25(OH) D<sub>3</sub> among all the participants (*n* = 29), which was the first report of the association between the NMO-IgG levels and sun exposure scale, dietary Vitamin D, and serum levels of 25(OH) D<sub>3</sub>, determined among patients with NMOSD and NMO.

NMOSD and NMO are demyelinating diseases of the CNS with inflammatory lesions that have been seen chiefly in spinal cord and optic nerves.<sup>[27]</sup> Particularly, NMO patients often suffer from recurrent ON and longitudinally wide transverse myelitis (LETMs) that sometimes results in blindness and paraplegia. The discovery of AQP4 antibody (NMO-IgG), the most important laboratory feature, has made it easy to diagnose of NMO from MS. While NMO-IgG was considered only as a biomarker of NMO at first, common fulminant attacks caused investigators suggest NMO-IgG that may be a marker of destructive demyelination rather than an illness-specific biomarker.<sup>[28]</sup>

25(OH) D is the main circulating metabolite of Vitamin D.<sup>[29]</sup> Although the biologically active form of Vitamin D is 1,25(OH) vitamin D<sub>3</sub> that is synthesized in the kidney. It is generally believed that measuring 25(OH) D provides better information regarding the patients' Vitamin D status and therefore it is a useful marker for the recognition of hypovitaminosis.<sup>[29-31]</sup> In general, the presence of VDR is an indicator for cells response to Vitamin D. In addition to osteoblasts, enterocytes, and distal renal tubular cells, it is shown that VDR is found in many other cell types, such as parathyroid gland cells, keratinocytes of skin, colon cells, pituitary gland cells, and ovarian cells. The VDR is also

**Table 1: General characteristics of the study population<sup>a</sup>**

Variables	IgG-NMO positive ( <i>n</i> =9)	IgG-NMO negative ( <i>n</i> =20)	<i>P</i> <sup>b</sup>
Age (years)	30.66±7.176	33.30±8.214	0.41
Gender (%)			
Male	1 (14.3)	6 (85.7)	0.23
Female	8 (36.4)	14 (63.6)	0.23
BMI (kg/m <sup>2</sup> )	22.28±2.32	23.64±2.48	0.17
Weight (kg)	59.44±8.38	62.45±7.59	0.35
Disease duration from the first attack (year)	4.67±2.7	4.15±4.6	0.75
Disease diagnosis (year)	3.11±2.891	2.15±2.66	0.41

<sup>a</sup>All values are presented as mean±SD or (%), <sup>b</sup>*P*-values are obtained from independent sample *t*-test. SD=Standard deviation, IgG-NMO=Immunoglobulin G-neuromyelitis optica, BMI=Body mass index



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widely found in several cell types of the immune system, that is, T-cells, B-cells, monocytes, macrophages, dendritic cells, and natural killing cells.<sup>[16,32-34]</sup> Experimental, epidemiological, and clinical studies have revealed contrary associations between low Vitamin D status and longevity as well as impeding immunosenescence.<sup>[35]</sup>

It seems that Vitamin D may be associated with the human immune dysfunction often originated from geographic variation observations in illness occurrence. In many parts of the world, Vitamin D is principally synthesized in the skin following sun exposure (specifically UV B [UVB] irradiation). Levels of UVB radiation fluctuate strongly according to the distance from the equator (latitude) and time of year. Higher levels of Vitamin D are observed in the following circumstances: a higher radiation intensity (the sun is directly overhead or closer to the equator), in summer, and during the middle of the day. Thus, higher latitude is often considered as the main cause of both lower levels of UV radiation and lower Vitamin D status. Latitudinal gradients, an expression which describes the incidence or prevalence of an illness increases simultaneously with increasing distance from the equator (lower UVB radiation), are applied for MS, type 1 diabetes, autoimmune vasculitis, inflammatory bowel illnesses, and asthma.<sup>[36-40]</sup>

Research on Vitamin D and NMO is infancy. Some studies have shown reduced levels of Vitamin D in patients with NMO or NMOSD.<sup>[41,42]</sup> In another study, the authors have seen an inverse association between levels of Vitamin D and disability in these patients.<sup>[43]</sup>

Although studies about Vitamin D and NMO are low, a large body of studies has been carried out on Vitamin D and MS or other autoimmune illnesses.

**Table 2: Mean±standard deviation values of variables between neuromyelitis optica-immunoglobulin G positive and negative patients**

Variables	IgG-NMO positive (n=9)	IgG-NMO negative (n=20)	P <sup>a</sup>
Sun exposure scale	7.89±1.900	10.30±1.525	0.01
Vitamin D intake	1.28±0.87	2.23±0.81	0.08
25(OH) D3 level	23.44±9.87	32.40±10.225	0.04

<sup>a</sup>P-values are obtained from independent sample *t*-test. 25(OH) D3=25-hydroxyvitamin D3, IgG-NMO=Immunoglobulin G-neuromyelitis optica

**Table 3: Correlation between serum levels of 25-hydroxyvitamin D3 level and studied variables among all participants and neuromyelitis optica-immunoglobulin G positive and negative persons**

	Sun exposure scale <sup>a</sup>	P	Vitamin D intake <sup>a</sup>	P
Total (n=29)	0.747	<0.001	0.170	0.37
IgG-NMO positive (n=9)	0.896	0.001	0.263	0.49
IgG-NMO negative (n=20)	0.599	0.005	0.147	0.53

<sup>a</sup>Pearson's correlation coefficient. IgG-NMO=Immunoglobulin G-neuromyelitis optica

For the first time in 1922, geographical variations were introduced as a potential reason for the association between Vitamin D and human immune dysfunctions as well as MS.<sup>[41]</sup> Regarding the influence of Vitamin D on illness risk, we should differentiate between Vitamin D dependent (Vitamin D supplementation) and independent pathways (Vitamin D produced from sunlight). Limited success in Vitamin D supplementation trials suggests that independent pathway may associate more strongly with illness risk. The incidence of autoimmune encephalomyelitis (EAE) in experimental models (a mouse model for MS) was significantly delayed following chronic irradiation with suberythemal doses of UVB radiation.<sup>[42]</sup> 25(OH) D serum levels were only slightly elevated and remission of illness was not occurred following 25(OH) D oral administration.<sup>[42]</sup> However, the development of EAE was suppressed through hypercalcemia by dietary 1,25(OH)<sub>2</sub> D administration. It was assumed that it was lonely important to illness suppression. TReg-inducing tolerogenic dendritic cells that motivated by UVB irradiation in the skin were required for the amelioration of EAE. Serum 25(OH) D levels and sun exposure have been shown to be independently associated with the CNS demyelination onset in humans as well as brain and spinal cord lesions in people with MS.<sup>[43,44]</sup>

Some involved factors in Vitamin D deficiency are living in north or south latitudes and sun exposure avoidance. Although the prevalence of MS is high in north and south latitudes, the prevalence of MS declines in northern latitudes probably due to adaptation to high Vitamin D-including diets (for instance: oily fish products).<sup>[45,46]</sup> A recent study has revealed that low current Vitamin D status and low past or current sun exposure are independent risk factors for the development of MS and CNS demyelination.<sup>[43]</sup>

A number of biological mechanisms may explain the association between Vitamin D status and MS. VDRs and a VDR-dependent enzyme that is responsible to form the active form of 1,25(OH)<sub>2</sub> D are widely expressed in human brains and are responsible for the formation of the highly active Vitamin D metabolite. Several studies have investigated the effects of Vitamin D on VDR gene transcription in neural cells and have demonstrated that VDRs and Vitamin D are key molecules in developing brain, preventing anxiety, inducing glial-derived neurotrophic factor, and induction of nerve growth factor synthesis.<sup>[47,48]</sup>

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Recently, a study has demonstrated that Vitamin D could also have myelin-protective effects independent of T-lymphocyte activation and infiltration. The high amount of dietary Vitamin D was significantly associated with weaker white matter microglia activation/macrophage infiltration during oligodendrocyte death and demyelination. Moreover, it is revealed that the active metabolic of Vitamin D has immune modulatory affected through inhibiting the differentiation of dendritic cells and desensitization of them to maturing stimuli.<sup>[49]</sup>

## Conclusions

The present study is the first report of association between Vitamin D and IgG-NMO in NMOSD and NMO patients, which shows that Vitamin D may have a major impact on IgG-NMO synthesis in these patients and play an important role in the pathogenesis of NMOSD and NMO. Further studies with larger sample sizes are needed to prove this result.

## Acknowledgments

This study was extracted from M.Sc. dissertation which was approved by School of Nutrition and Food Sciences, Isfahan University of Medical Sciences (Code 393886).

## Financial support and sponsorship

This study was supported by School of Nutrition and Food Sciences, Isfahan University of Medical Sciences, Isfahan, Iran.

## Conflicts of interest

There are no conflicts of interest.

**Received:** 04 Mar 16 **Accepted:** 05 Apr 17

**Published:** 14 Aug 18

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