Association of Serum Levels of Vitamin D and E with Markers of Nlrp3-inflammasome Pathway in Patients with Multiple Sclerosis

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Abstract

Objective: Multiple sclerosis (MS) is an autoimmune inflammatory disease that predominantly damages myelin in the central nervous system. Many diseases' mechanisms and progressions have been hypothesized to include "sterile inflammation" (SI) triggered by oxidative stress. In this context, the inflammatory process occurs in the absence of an infectious agent. Inflammasomes are complexes composed of multiple proteins that play a vital role in regulating the inflammatory processes including the SI. Antioxidants are substances that include vitamins that eliminate oxidative stress in living organisms. However, the exact role of antioxidant vitamins in association with inflammasome has not been examined in MS. Therefore, in this study we aimed to investigate the possible association between inflammasome markers (interleukin-18 (IL-18), interleukin-1 beta (IL-1β), and NLRP3 (nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3)) levels and antioxidant vitamins (vitamin D and E) in MS disease. ***Methods:*** A total of 100 patients with MS and 100 healthy controls participated in this study. Blood samples were collected and then analyzed by enzyme-linked immunosorbent assay (ELISA) for IL-18, IL-1β, NLRP3, vitamin D, and E. ***Results:*** Patients with MS had significantly higher levels of IL-18, IL-1 β, and NLRP3 compared to the control group. An inverse correlation was observed between serum NLRP3 and vitamin D. Moreover, a significant negative correlation existed between IL-1 β and vitamin E. ***Conclusions:*** This study shed light on the link between inflammasome activation and decreased levels of antioxidant vitamins in patients with MS. Hence, inflammasome markers may serve as future potential biomarkers of MS.

Keywords: sterile inflammation; inflammasome; vitamin D; multiple sclerosis; vitamin E

Introduction

Multiple sclerosis (MS) is a central nervous system (CNS) neurodegenerative disease characterized by both autoimmune and inflammatory effects. It is the most widespread chronic inflammatory CNS disorder, impacting 2.5 million people globally.[1] Phenotypes of MS are not distinguishable from one another. Therefore, MS can only be diagnosed with a combination of physical findings, imaging examinations, and laboratory assays. One of the most useful diagnostic methods for MS is magnetic resonance imaging (MRI).[2] Multiple sclerosis patients have a wide variety of symptoms; nevertheless, ataxia, cognitive impairment, and visual loss are the most often reported.[2] The complex etiology of MS may be the reason for such varied symptoms.

There are four distinct clinical characteristics associated with MS: clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS). RRMS is the most common form of MS, representing 85% of all patients diagnosed with MS, and it is defined by a sudden increase in the intensity of illness activity and symptoms subsequently remissions.[3] Over 70% of individuals with RRMS will eventually transition to SPMS after 20 years.[3] The onset of SPMS resembles that of PRMS; however, the symptoms of SPMS continue to deteriorate with time.[4] The symptoms of patients with PPMS worsen over time and never improve. PRMS is an uncommon type of illness characterized by a steady deterioration of symptoms over time.

It is still unclear the etiology and pathogenesis of MS disease. However, neurodegeneration arising from inflammatory demyelination due to peripheral immunological activation is increasingly being recognized as a contributing factor.[5] Inflammatory lymphocytes, macrophages, and activated microglia infiltrate the affected area early in the illness process. This is followed by the overproduction of inflammatory mediators, which causes demyelination and axonal conduction block, ultimately resulting in neurological disability.[6]

Neuroinflammation is primarily triggered by the innate immune response, but if this response becomes dysregulated, it can have detrimental consequences for the central nervous system (CNS).[7] In this context, sterile inflammation is a kind of inflammation free of infectious organisms, but rather by inflammatory inducers linked to tissue damage occur.[5] The inflammasomes are important for detecting types of stress signals called damage associated molecular patterns (DAMPs). These DAMPs have a role, in controlling the body's immune response and were first identified in CNS, where they regulate inflammation after spinal cord injuries.[7]

Inflammasomes consist of multi-protein complexes that exist in the cytosol and are composed of an upstream sensor nucleotide-binding oligomerization domain-like receptors NOD-like (NLR) protein, a middle protein called an apoptosis-associated speck-like protein with a CARD (ASC), and a downstream caspase-1 effector protein.[8] After being stimulated by various microbial or damage-associated molecular patterns, the nucleotide-binding oligomerization domain-like receptors assemble into an inflammatory complex that triggers the autocatalytic cleavage of caspase-1, transforming proinflammatory cytokines interleukin-1β (IL-1β) and interleukin-18 (IL-18) into their mature and dynamic forms.[8] Many studies have indicated that autoimmune diseases are associated with strong expression and activation of inflammasome and its downstream effectors, including caspase-1, IL-1β, and IL-18. Furthermore, activating the inflammasome has been identified as a risk factor for developing and progressing autoimmune diseases.[9]

The presence of a discrepancy between the accumulation and production of reactive oxygen species (ROS) within cells and tissues, and the biological system's detoxification process to remove them, is known as oxidative stress. The latter, in turn, triggers the activation of the inflammasome pathway through a process of priming.[10]

ROS created by the brain tissues can modulate synaptic and non-synaptic neuro-inflammation communications, contributing to neurodegeneration and loss of memory.[11] Multiple activators of NLRP3 cause an upsurge in mitochondrial ROS generation, and the activation of inflammatory pathways dependent on NLRP3 is suppressed by preincubation with certain antioxidants.[12]

Antioxidant vitamins such as vitamin D and α-tocopherol (αT) which is the predominant form of vitamin E play a crucial role in terminating cellular damage caused by free radicals.[13] The significance of these vitamins in the pathophysiology of MS has been investigated in depth.[14, 15] Conversely, it was shown that the generation of inflammatory markers can reduce antioxidant vitamins.[16] However, the exact role of antioxidant vitamins in association with inflammasome has not been investigated in MS. In addition, the impact of vitamins D and E on the NLRP3 inflammasome pathway in MS has been independently studied. Studies have demonstrated that vitamin D levels are capable of suppressing NLRP3 inflammasome activation and downstream IL-1β signaling.[17, 18] Regarding vitamin E, it has been found that vitamin E analogues suppress the NLRP3 inflammasome and protect against inflammation.[19]

To the best of our knowledge, no prior studies have evaluated the combined influence on important inflammatory mediators such as IL-18, IL-1β, and NLRP3. This gap in the literature highlights the novelty and importance of our work. Therefore, in this study we aimed to determine any possible association between inflammasome markers (IL-18, IL-1β, and NLRP3) levels and antioxidant vitamins (vitamin D and E) in MS disease.

Methods

The study was approved by the Institutional Review Board (IRB) (Ref.: 162/132/2020) at King Abdullah University Hospital (KAUH) and Al-Bashir Hospital (IRB no. 4718, 21/3/2022). Informed written consent was obtained from all subjects before participating in the study. One hundred patients with MS who have been referred to private and public neurology clinics were enrolled in this study. The MS subjects were divided into two groups depending on their MS subtype: relapsing-remitting MS RRMS (n = 30) and progressive MS (which included both primary and secondary subtypes, n= 70).

The MS inclusion criteria were included: subjects between 18-70 years of age, neurologist confirmed diagnosis of MS according to revised McDonald criteria,[20] and ability to give written consent. Patients diagnosed with chronic diseases other than MS, such as diabetes mellitus, kidney diseases, and cardiovascular disease, were excluded from this study. The Control group involved one hundred non-MS subjects who were volunteers from Jordan University of Science and Technology (JUST). The age, sex, and body mass index (BMI) were matched between the control and MS groups.

For each subject, a 10 mL venous blood sample was taken in a plain tube without a clot activator (AFCO, Jordan). Blood samples were centrifuged at 3000 ×g for 10 minutes to separate and collect the serum and frozen at -80 °C until analysis.

All serum samples were subjected to ELISA analysis to determine the levels of NLRP3 (intra-assay coefficient of variation <8%; inter-assay coefficient of variation <10%) (MyBioSource, USA, Cat No. MBS917009), IL-1β (intra-assay coefficient of variation 2.8-8.5%; inter-assay coefficient of variation 4.1-8.4%) (R&D Systems, USA, Cat No. DLB50), IL-18 (intra-assay coefficient of variation <4%; inter-assay coefficient of variation <7%) (R&D Systems, USA, Cat No. QK318), vitamin E (α-tocopherol) (intra-assay coefficient of variation <10%; inter-assay coefficient of variation <12%) (MyBioSource, USA, Cat No. MBS2700403), and vitamin D) (intra-assay coefficient of variation <10%; inter-assay coefficient of variation <12%) (MyBioSource, USA, Cat No. MBS580159) as per the manufacturer's instructions. The ELx800 Microplate Reader (BioTek Instruments, Winooski, VT, USA) was utilized to determine the absorbance at 450 nm.

Statistical analyses were performed with GraphPad Prism 9 (GraphPad Software, San Diego, CA). Student t-test was used to identify whether significant differences existed in serum NLRP3, IL-18, IL-1β, α-tocopherol, and vitamin D levels between control and patients with MS. Additionally, between RRMS and progressive MS groups. The value of Pearson's correlation coefficient (r) was used to determine the correlations between vitamins (D and E) and inflammasome markers (NLRP3, IL-18, and IL-1β). The experimental data in the current study are reported as means ± standard error of the mean (SEM). $P < 0.05$ was considered statistically significant.

Results

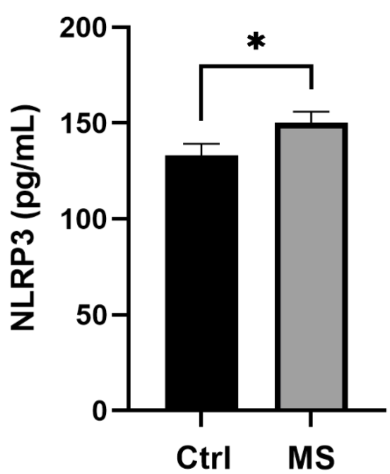
A total of 100 patients with MS and 100 controls were enrolled in the study. The two groups were matched for age, gender, and body mass index (BMI). Table 1 displays demographic and clinical data of patients with MS and control. Serum NLRP3 and IL-1β levels indicated a significant increase in patients with MS (150.10 pg/mL and 9.82 pg/mL; respectively) compared to control (133.30 pg/mL, p=0.04 and 3.90 pg/mL, p= 0.0008; respectively) (Figure 1A and 1B). Moreover, IL-18 showed a significant increase among individuals diagnosed with MS as compared with the control group (229.20 pg/mL, 197.30 pg/mL, respectively, p =0.02) (Figure 1C). Interestingly, vitamin D showed a significant increase in patients with MS compared to the control (27.47 ng/mL and 19.01 ng/mL respectively, p<0.0001) (Figure 2A). In contrast, α-tocopherol (vitamin E) showed a significant decrease in patients with MS compared to the control (27.64 μg/mL and 35.82 μg/mL, respectively, p=0.006) (Figure 2B).

Table 1. Clinical and demographic data of enrolled MS patients and healthy control

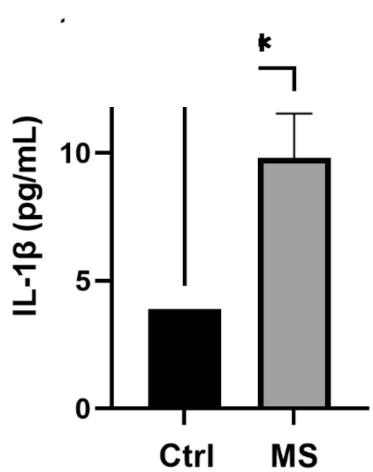
Demographic and clinical characteristics	MS (*n*=100)		Control (*n*=100)		
	Mean	**SEM**	**Mean**	**SEM**	**p-value**
Age (years)	36.45	1.05	34.65	0.29	0.10
Gender (F/M) [a]	68/32	NA	67/33	NA	0.88
BMI (kg/m^2)	27.48	1.87	27.85	0.33	0.83
IL-18 (pg/mL)	229.20	10.91	197.30	9.10	0.02*
Vitamin D (ng/mL)	27.47	1.39	19.01	0.89	<0.0001*
TCPa (µg/mL)	27.64	1.73	35.82	2.39	0.006*
NLRP3 (pg/mL)	150.10	5.70	133.30	5.98	0.04*
IL-1β (pg/mL)	9.82	1.72	3.90	0.00	0.0008*

*MS: Multiple sclerosis; F/M: Female and Male; BMI: Body mass index; IL-18: Interleukin-18; TCPa: Alpha-Tocopherol; NLRP3: nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3; IL-1β: Interleukin-1 beta. [a] Reported as the number of subjects in each group. Values are reported as mean ± SEM. *P < 0.05 between control and MS using Student's t-test and Chi-square.*

A)



B)



C)

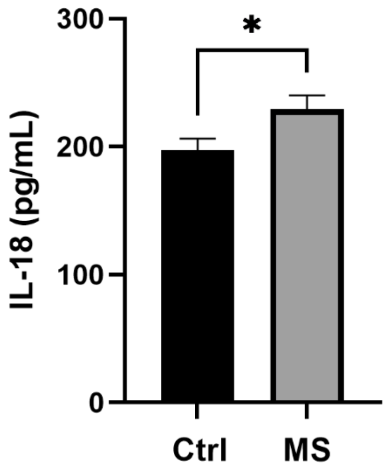


Figure 1. Comparison between serum levels of inflammasome markers in patients with MS and control groups. A) NLRP3, B) IL-1β, and C) IL-18. The results are reported as the mean ± SEM. *P< 0.05, **P< 0.01, ***P<0.0001.

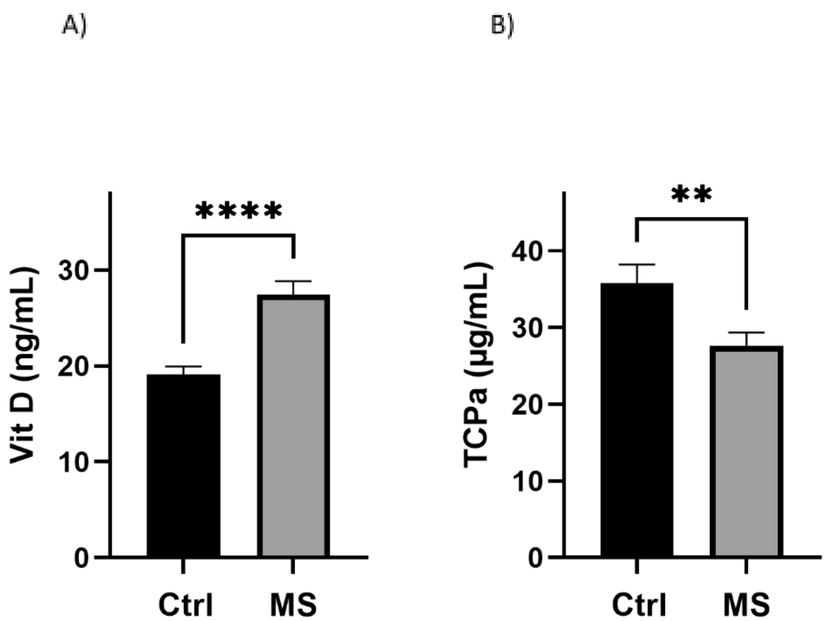


Figure 2. Comparison between serum levels of vitamins in patients with MS and control groups. A) vitamin D, and B) TCPa. The results are reported as the mean ± SEM. **P< 0.01, ***P<0.0001.

NLRP3, IL-1β, IL-18, vitamin D, and α-tocopherol serum levels were not significantly different between patients with RRMS and progressive MS (Table 2).

Table 2. Demographic and clinical data of recruited patients with RRMS and progressive subtypes.

Items	RRMS	progressive MS	p-value
Cases (n)	30	70	-
Age (years)	37.45 ± 1.78	35.9 ± 1.26	0.50
Gender (F/M)	21/9	47/23	0.78
BMI (Kg/m^2)	25.43 ± 0.94	28.6 ± 2.84	0.42
IL-18 (pg/mL)	232.2±22.56	227.9±12.34	0.86
Vitamin D (ng/mL)	24.84±2.84	28.53±1.54	0.22
TCPa (µg/mL)	29.55±3.78	26.78±1.83	0.46
NLRP3 (pg/mL)	142.9±9.04	152.8±7.12	0.42
IL-1β (pg/mL)	11.44±2.73	9.13±2.12	0.54

*MS: Multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; F/M: Female and Male; BMI: Body mass index; IL-18: Interleukin-18; TCPa: Alpha-Tocopherol; NLRP3: nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3; IL-1β: Interleukin-1 beta. [a] Reported as the number of subjects in each group. Values are reported as mean ± SEM. *P < 0.05 between control and MS using Student's t-test and Chi-square.*

Table 3 describes the levels of vitamin D and α-tocopherol and their correlations with inflammasome markers (IL-18, NLRP3, and IL-1β). Only NLRP3 had a significant weak inverse correlation with vitamin D levels (r = -0.20, P = 0.02) (Figure 3). Moreover, IL-1β had a significant weak inverse correlation with α-tocopherol levels (r = -0.14, P = 0.04) (Figure 3), while IL-18 was not statistically significant neither with vitamin D nor with a-tocopherol (Table 3).

Table 3. The correlation between vitamin D and TCPa with inflammasome markers (IL-18, NLRP3, and IL-1β).

	Vitamin D		**TCPa**	
Variables	**r**	**p**	**r**	**p**

IL-18	0.07	0.31	-0.03	0.64
NLRP3	**-0.20**	**0.02***	-0.03	0.71
IL-1β	0.08	0.23	**-0.14**	**0.04**

*r: Pearson rank correlation coefficient. *p < 0.05: statistically significant.*

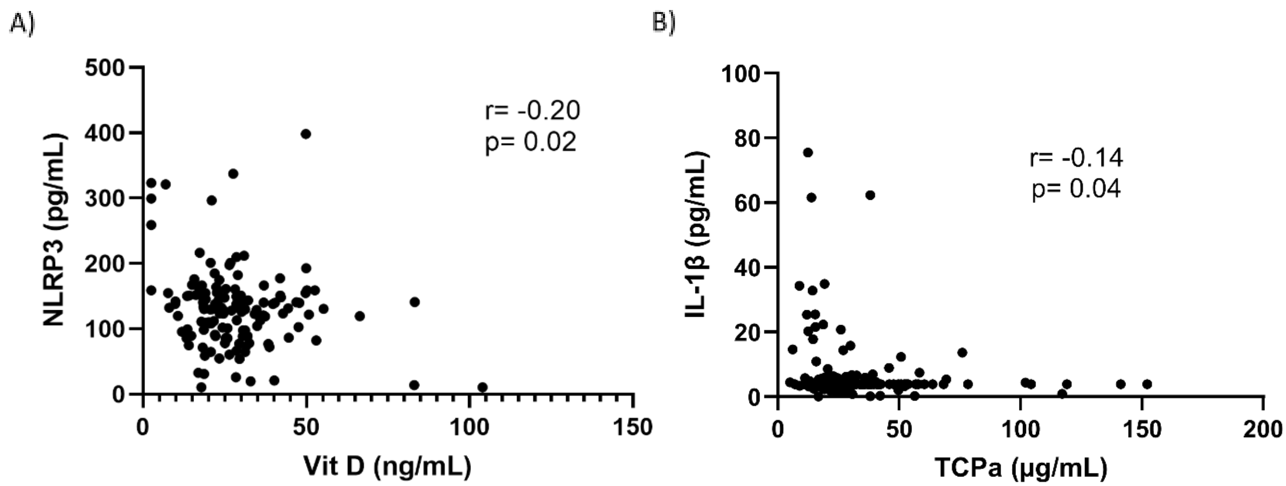


Figure 3. Pearson correlation coefficient comparisons. (A) Comparison between serum levels of vitamin D and NLRP3. (B) Comparison between serum levels of TCPa and IL-1β.

Furthermore, multiple linear regression analysis was applied to assess the influence of covariates (age, sex, and BMI) on dependent variables (vitamin D, TCPa, NLRP3, and IL-1β). No associations between these covariates and dependent variables were detected (Table 4).

Table 4. Multiple linear regression model of covariates (age, gender, and BMI) with vitamin D, NLRP3, and IL-1β as dependent variables.

Parameters	**Vitamin D**			**TCPa**			**NLRP3**			**IL-1β**		
	Standardized B	***t***	***P value***	**Standardized B**	***t***	***P value***	**Standardized B**	**t**	***P value***	***Standardized B***	***t***	***P value***
Age	-0.007	-0.107	0.915	0.055	0.798	0.426	-0.013	-0.189	0.851	0.012	0.179	0.858
BMI	-0.051	-0.736	0.462	0.040	0.578	0.564	0.014	0.198	0.843	0.125	1.821	0.070
Sex	-0.030	-0.436	0.663	-0.028	-0.409	0.683	-0.094	-1.361	0.175	-0.011	-0.155	0.877

**P-value < 0.05 considered significant*

Discussion

In several diseases, the activation of inflammasomes has been linked to a decrease in levels of antioxidant vitamins. However, this relationship has not yet been explored in the context of MS disease.

Thus, in this study, the association between antioxidant vitamins (D and E) and inflammasome markers (IL-18, NLRP3, and IL-1β) was demonstrated in MS disease.

Our results showed a higher level of IL-18, NLRP3, and IL-1β in patients with MS compared to the control. These results are in line with a previous study by Ardakani *et al.* [21]

Most research has been done on the NLRP3 inflammasome and may be induced by a broad range of stimuli, both microbial and sterile.[22] The activation of inflammasomes which results in the processing and subsequent release of proinflammatory cytokines IL 1β and IL 18 appears to be a factor that contributes to the development and progression of MS.[23] In the animal model of MS, the knockout of NLRP3 gene (NLRP3-/-) in mice showed a significant delay in the disease course and severity.[24]

Unexpectedly, vitamin D levels were lower in the control group than in patients with MS in our study. One probable cause is that the Jordanian population generally has low amounts of vitamin D.[25] However, the vitamin level in both groups was less than the recommended preferred range, as per the endocrine society.[26] Additionally, it is worth noting that vitamin D supplements could contribute to the higher levels observed in patients with MS [27] as our samples were collected non-fasting, which could potentially affect the results.

The results of the study were in alignment with earlier study by Salemi *et al.* showed that α-tocopherol levels were lower in patients with MS than in the control group.[28] Myelin breakdown and axonal degeneration are two hallmarks of MS pathogenesis, and inflammation that characterizes the condition may be influenced by heightened oxidative stress and inflammation.[29] As vitamin E is considered a nonenzymatic antioxidant against free radicals, decreased levels of this vitamin may result from increased oxidative stress during its attempt to reduce inflammation and immune-mediated tissue damage.[30]

In our study, the levels of vitamin D showed a significant weak inverse correlation to NLRP3 levels. In addition, the levels of α-tocopherol were significantly inversely related to IL-1β. It has been suggested that vitamin D and E help in regulating inflammasome indicators. Vitamin D and E are known to suppress the generation of pro-inflammatory cytokines and prevent the activation of the NLRP3 inflammasome in macrophages.[10] It is found that the regulation of NLRP3 inflammasome and interleukin activities is influenced by the status of Vitamin D.[31] Moreover, supplementation of vitamin E decreases levels of IL-1β which is consistent with our results.[32] Some research has linked insufficient vitamin D levels with increased inflammasome marker expression.[33]

Our findings imply that treating MS might be effective by focusing on components of inflammasome. The found inverse correlations between inflammatory markers and antioxidant vitamin levels suggest that control of these processes might be advantageous. Common MS treatment interferon-beta (IFN-β) lowers the expression of Absent in Melanoma 2 (AIM2), an inflammasome sensor linked to IL-1β production, according to earlier studies.[34] Furthermore, antioxidant analogues such as α-tocopherol possibly reduce inflammatory cytokine production and block inflammasome activation.[19]

Limitations of the study include that patients were on medications and supplements, and that caspase-1 as well as antioxidant vitamins, such as C and A, were not measured. Despite such limitations, our study is the first to correlate the inflammasome biomarkers with antioxidant vitamins in MS disease. Studying the inflammasomes in the context of MS disease is important since it might lead to developing more effective diagnostic and monitoring biomarkers in the future. However, further investigations will help verify inflammasome's role and its link with antioxidant vitamins in MS.

Conclusions

The results of the study show a link between inflammasome activity in MS disease. As original findings, the study found a relationship between NLRP3 and IL-1β with nonenzymatic antioxidants (vitamin D and E), respectively. Inflammasome activation is associated with lower levels of antioxidant vitamins in MS disease; these findings may aid in a better understanding of the disease's complicated pathogenic pathways and better management of vitamin levels, which may help in the discovery of potential diagnostic, prognostic, and therapeutic biomarkers for MS patients.

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