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The Association Between Neuropsychological Function with Serum Vitamins A, D, and E and hs-CRP Concentrations

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Abstract

Vitamin status and the presence of subclinical inflammation may affect cognitive performance and behavior. We have investigated the relationship between serum fat soluble vitamins (vitamins A, D, and E) and inflammatory markers with aggression and cognitive abilities, in a population of healthy adolescents. A cross-sectional study of 940 adolescent girls was performed. Serum concentrations of vitamins A, D, and E, hs-C-reactive protein (hs-CRP), and antibody titers to Hsp27 (anti-Hsp27) were measured. Hematological indices including lymphocyte, neutrophil, platelet counts, and red blood cell distribution width (RDW) were evaluated. Neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and RDW to platelet ratio (RPR) were calculated. A Cognitive Abilities Questionnaire and the Buss-Perry Aggression Questionnaire were applied to assess cognitive performance and aggression, respectively. There was a positive correlation between serum vitamins A with vitamins D and E, as well as between serum hs-CRP with serum vitamin E. Linear regression analysis showed that serum vitamin D, hs-CRP, anti-Hsp27, and RDW were significantly associated with aggression score. Furthermore, serum vitamin E, hs-CRP, anti-Hsp27, NLR, and RPR were significantly associated with cognitive ability score. Inflammatory processes may affect cognitive performance and behavior. Prospective studies are warranted to determine the potential of targeting antioxidant and inflammatory pathways for the treatment of psychological disorder.

Keywords Inflammation · Vitamin E · Cognitive ability · Aggression · Neutrophil

Introduction

Vitamin A (all-trans retinol) is a fat-soluble micronutrient which is converted to retinoic acid in the body and acts as a transcriptional regulator and potentiate candidate for neuromodulation (Suchankova et al. 2013). Vitamin E (α-tocopherol) is a powerful antioxidant, which can prevent oxidative damage of cells (Ortega et al. 2002). The precursors of vitamins A (Vit A) and E (Vit E) have protective effects against oxidative stress (Jiménez-Jiménez et al. 1999; Mecocci et al. 2002). Vitamin D (Vit D; calciferol) is a steroid hormone that is obtained from dietary sources or through the action of ultraviolet B (UVB) radiation on 7-dehydrocholesterol in the skin (Nowson et al. 2012). It has previously been shown that the status of vitamins A, D, and E is associated with cognitive performance in elderly subjects

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(Ortega et al. 2002; Przybelski and Binkley 2007; Rinaldi et al. 2003).

There is growing evidence that inflammatory pathways might affect cognitive function and aggression (Wang et al. 2013). High-sensitivity C-reactive protein (hs-CRP) is a sensitive marker of systemic low-grade inflammation (Pearson et al. 2003). Serum CRP values in the blood are usually very low, but rise rapidly during inflammation. Higher serum values of hs-CRP have been associated with impaired cognition (Joseph et al. 2015; Mecocci et al. 2002; Ravaglia et al. 2005; Teunissen et al. 2003; Wium-Andersen et al. 2013; Yaffe et al. 2003). In population-based studies, a higher serum hs-CRP has been related to poor memory (Komulainen et al. 2007; Teunissen et al. 2003) and global cognitive performance (Ravaglia et al. 2005; Tilvis et al. 2004; Yaffe et al. 2003). But, in some other studies, no significant relationships between hs-CRP and cognition have been reported (Dik et al. 2005; Weuve et al. 2006). Some studies have reported that inflammatory markers, such as serum CRP, were positively associated with anger, aggression, and hostility scores (Marsland et al. 2008) in psychiatric individuals with personality disorder (Coccaro 2006) and in intermittent explosive disorder patients (Coccaro et al. 2015).

Oxidative stress occurs due to the physiological imbalance between pro-oxidant and antioxidant species which disturbs limbic neuroarchitecture and function (Choi and Rothman 1990; Rahal et al. 2009). One of the important outcomes of oxidative stress is induction of the expression and release of intracellular proteins such as heat shock proteins (Hsps). The overexpression of Hsps under stressful conditions is part of the cell protective mechanisms (Pourghadamyari et al. 2011).

Neutrophil/lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), red blood cell distribution width (RDW), and RDW to platelet ratio (RPR) are also easily measurable, and noninvasive parameters of systemic inflammation derive directly from complete blood count (CBC). Several studies have reported an association between increased level of these markers and cerebrovascular and cardiometabolic diseases (Dik et al. 2005).

Because of the paucity of data regarding the association of antioxidant and systemic inflammation with cognitive performance and aggression, the present study was conducted to evaluate fat-soluble vitamins and low-grade inflammation in relation with cognitive abilities and aggression in healthy adolescent girls.

Methods

The study involved 940 adolescent girls, who were recruited between January and April 2015 in the cities of Mashhad and Sabzevar, in northeastern Iran. Participants were selected using a randomized clustering method. Written consent was signed by the girls and their parents. The ethical committee of Mashhad University of Medical Sciences approved the study.

Blood Collection and Biochemical Measurements

Fasting blood samples were collected in morning after a 12-h overnight fast. The samples were immediately centrifuged to separate serum. Serum 25(OH) vitamin D level was determined using an electrochemi-luminescence method (ECL, Roche, Basel, Switzerland). Serum hs-CRP was quantified by commercial kits (Pars Azmun, Tehran, Iran) and the BT-3000 auto-analyzer (Biotechnica, Rome, Italy).

Serum levels of Vit A (all-trans retinol) and Vit E (α-tocopherol) were measured by isocratic high-performance liquid chromatography (HPLC) (Driskell et al. 1982). Briefly, 250 μL ethanol was added to 250 μL serum and vortex for 5 s. After that, 500 μL n-hexane was added to supernatant, vortex, and centrifuged at 1000*g* for 1 min. Supernatant was evaporated under nitrogen gas, and the residue was reconstituted in 200 μL methanol. Twenty-five microliters of the solution was injected to the HPLC column at a flow rate of 1.5 mL/min. Methanol was applied as the mobile phase and was detected at 294 nm using UV detector (Waters 486, Milford, MA, USA).

Neutrophil counts, lymphocyte counts, red blood cell distribution width (RDW), and platelet counts were measured as part of the automated CBC using an auto hematology analyzer (Sysmex K-800). After that, NLR, PLR, and RPR were calculated for each case.

Neuropsychological Assessment

Cognitive Abilities The Cognitive Abilities Questionnaire (CAQ) comprised 30 items, each of which was scored on a five-point Likert scale (1–5). Higher scores indicate better cognition performances (Nejati 2013).

Aggression Status The Persian version of Buss-Perry Aggression Questionnaire (BPAQ) which has 29 items with a five-point Likert scale (1–5) was used to assess symptom severity aggression. Higher scores represent a more aggression status (Motevalian et al. 2011).

Statistical Method

Data were evaluated for normality using the Kolomogorov-Smirnov test. Correlation between vitamins and inflammatory markers was assessed using Pearson correlation analysis. Subjects' level of serum Vit A, Vit D, Vit E, hs-CRP as well as NLR, PLR, and RPR was divided into tertiles. One-way analyses of variance (ANOVA) and post hoc Tukey's test were used to test for any significant differences in aggression and cognitive ability scores between tertile groups. Univariate and

multivariate analysis was performed using linear regression model to determine the relationships between cognitive abilities and aggression scores and various variables including Vit D, Vit E, hs-CRP, RDW, NLR, PLR, and RPR. The $P < 0.05$ was considered statistically significant.

Results

The mean age of the participants was 14.56 ± 1.52 years (range 12–18 years). Their clinical characteristics are shown in Table 1.

The correlation between the serum fat-soluble vitamins and serum concentrations of the inflammatory markers was performed using Pearson correlation analysis (Table 2). Correlation analysis showed a positive correlation between serum Vit D with Vit A and Vit E ($r = 0.155$, $p = 0.031$, and $r = 0.237$, $p = 0.001$, respectively), as well as hs-CRP with Vit E ($r = 0.300$, $P = 0.001$). Furthermore, RPR was significantly correlated with RDW and PLR ($r = 0.379$, $p < 0.001$, and $r = -0.492$, $p < 0.001$). RDW also positively correlated with anti-hsp27 ($r = 0.122$, $p = 0.04$).

Compared with participants in the lowest serum Vit D tertile, participants with higher levels of serum Vit D appeared to have a lower aggression score (Table 3). Compared with subjects in the lowest serum Vit E tertile, subjects with higher levels of serum Vit E had a higher cognitive ability score ($p < 0.05$).

Table 1 Biochemical and hematological characteristics of participants ($n = 940$)

Biochemical parameters	
Serum Vit A (μmol/L)	5.48(1.81–11.31)
Serum Vit D (μmol/L)	19.22(12.57 ± 31.70)
Serum Vit E (μmol/L)	4.52(2.86–5.80)
Serum hs-CRP (mg/L)	0.97(0.50–1.85)
Serum anti-Hsp27(OD)	0.25 ± 0.17
Hematological indices	
WBC(10^9 cells/L)	6.49 ± 2.31
Neutrophil(10^{12} cells/L)	55.0 ± 10.21
Lymphocyte(%)	36.5 ± 8.8
RBC(%)	4.97 ± 0.79
Platelet (10^6/L)	259.3 ± 6.8
RDW(%)	13.08 ± 1.59
NLR	1.66 ± 0.89
PLR	6.87 ± 3.41
RPR	0.062 ± 0.029

Data presented as median (IQR) or mean ± SD

High sensitivity C-reactive protein (hs-CRP), white blood cell (WBC), red blood cell (RBC), red blood cell distribution width (RDW), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), red blood cell distribution width to platelet ratio (RPR)

Subjects with highest tertile of serum hs-CRP were found to have higher aggression and lower cognitive ability scores compared to those in the lowest serum hs-CRP tertile ($p < 0.05$). Cases with lowest tertile of NLR and RPR demonstrated higher cognitive abilities compared to lowest tertile ($p < 0.05$). Individuals with highest tertile of RDW showed higher aggression score compared to lowest tertile (Table 3).

Individuals with the highest tertile of anti-hsp27 revealed lower cognitive abilities and higher aggression compared to subjects with lowest serum anti-hsp27 tertile ($p < 0.001$) (Table 3).

Univariate and multivariate linear regression analysis was performed to assess the relationship of cognitive abilities and aggression scores with clinical variables in Table 4. This revealed that serum Vit D, hs-CRP, anti-hsp27, and RDW were significant factors in the multivariate model associated with aggression score. Furthermore, serum Vit E, hs-CRP, NLR, anti-hsp27, and RPR were significant factors in determining the cognitive abilities score.

Discussion

Serum Vit D was found to be related with aggression score, and serum Vit E was associated with cognitive abilities in this cross-sectional study. However, serum levels of Vit A were not related with either. The existing data in this area are limited.

Various oxidative mechanisms including the monoamine oxidase activity and the formation of free radicals have been proposed to be involved in the degeneration of neurons (Group 1993). Rinaldi et al. found that plasma Vit E are low in mild cognitive impairment (MCI) and Alzheimer's disease (AD) (Rinaldi et al. 2003). A prospective cohort study found that high dietary intake of Vit E may be related with a lower risk of AD (Engelhart et al. 2002). However, no relationship was found in patients with Parkinson's disease (PD) (Behl et al. 1992). A Cochrane review by Mgekn et al. reported that Vit E treatment does improve features of MCI (Isaac et al. 2008). In animal models, alpha-tocopherol decreased the degeneration of hippocampal cells post cerebral ischemia (Isaac et al., 2008) and increased the recovery of motor function subsequent spinal cord injury (Anderson et al. 1988).

Both 25-hydroxylase and 1-α hydroxylase enzymes are present in the central nervous system (CNS) (Przybelski and Binkley 2007). The nuclear Vit D receptor has been found in main areas of the brain which is regulating behavior (Lee et al. 2009). Vit D was found to promote cognitive function in rats through anti-inflammatory and antioxidant characteristics (Liu et al. 2015). The beneficial effect of Vit D on cognitive function was found in animal and in vitro experiments (Bourre 2006; McCann and Ames 2008). Additionally, active Vit D produced in neurons could affect cognitive function and behavior. Several clinical studies have shown a positive

Table 2 Correlation matrix between the fat-soluble vitamins and inflammatory markers using spearman correlation analysis

Variable		Vit A							
Serum Vit D	r	0.15							
	p	*0.031*	Vit D						
Serum Vit E	r	0.03	0.24						
	p	0.68	*0.001*	Vit E					
Serum hs-CRP	r	− 0.01	− 0.02	0.30					
	p	0.91	0.58	*0.001*	hs-CRP				
Anti-hsp27	r	− 0.13	− 0.08	− 0.16	0.003				
	p	0.22	0.12	0.10	0.95	Anti-hsp27			
RDW	r	− 0.01	− 0.03	− 0.10	− 0.02	0.12			
	p	0.30	0.44	0.27	0.62	*0.04*	RDW		
NLR	r	− 0.04	− 0.06	− 0.06	− 0.06	0.02	− 0.03		
	p	0.70	0.18	0.51	0.20	0.71	0.48	NLR	
PLR	r	− 0.05	− 0.04	− 0.08	− 0.02	0.04	0.01	0.74	
	p	0.58	0.37	0.38	0.64	0.53	0.78	< *0.001*	PLR
RPR	r	− 0.008	− 0.02	− 0.04	− 0.04	0.06	0.38	− 0.04	− 0.49
	p	0.93	0.60	0.70	0.37	0.30	< *0.001*	0.34	< *0.001*

association between memory and mood with serum Vit D levels (Przybelski and Binkley 2007; Wilkins et al. 2006). A systematic review including 37 cross-sectional studies showed that MMSE scores were lower in subjects with lower vitamin D (Balion et al. 2012).

However, other studies on the relationship between Vit D status and cognitive function in humans have been inconsistent (Aung et al. 2007; Jorde et al. 2006; Nes et al. 1988; Wilkins et al. 2006). A cross-sectional study among patients with secondary hyperparathyroidism reported no association between Vit D values and in 14 neuropsychological test performance (Jorde et al. 2006). In a large community-based study, no evidence was found regarding to association between low Vit D levels and disturbed neurocognitive performance (McGrath et al. 2007). The discrepancies between these studies may be due to the use of different cognitive examinations, some of which may be unsuitable for the type of study or patient group and/or the Vit D cellular mechanisms (Buell and Dawson-Hughes 2008). The association between Vit D and cognitive function has not been clearly established and needs further studies.

We have also demonstrated that aggression score is related to serum hs-CRP, anti-hsp27, and RDW, as well as cognitive abilities associated with inflammatory markers including hs-CRP, anti-hsp27, NLR, and RPR. Inflammatory mediators are usually over expressed near region of β-amyloid deposits and neurofibrillary tangles, where it is known to neurodegeneration occurrence (Komulainen et al. 2007; Wang et al. 2013). For many years, an easily measurable and noninvasive marker which might reveal systemic inflammation has been studied. However, there are limited numbers of studies investigating the relationship between inflammatory parameters in cognitive performance of healthy subjects. Hs-CRP is a nonspecific blood protein marker for chronic inflammatory conditions and involved in the immune response. Increased CRP correlated with increased risk of schizophrenia (Wium-Andersen et al. 2013) and PD (Song et al. 2013). Moreover, CRP values have also been found to be related with psychopathology condition (Fan et al. 2007), such as negative manifestation (Garcia-Rizo et al. 2012) and cognitive impairment (CI) (Dickerson et al. 2012), although in two large studies in 4231 elderly women and 1284 older adults, serum hs-CRP concentrations were not related to cognitive function (Dik et al. 2005; Weuve et al. 2006).

Human studies have shown that serum hs-CRP is directly associated with hostility score (Graham et al. 2006; Ranjit et al. 2007), aggressive dispositions (Coccaro 2006; Marsland et al. 2008), and suicidal behavior (Courtet et al. 2015; O'donovan et al. 2013). Suggested mechanisms for the effects of inflammation on behavior include peripheral inflammatory element access to the CNS and affect nerve fibers and/or recruit monocytes and T-lymphocytes to the CNS via high expression of adhesion molecules. In the CNS, inflammatory mediators can affect monoamine neurotransmission, neuroplasticity, and behaviors for example aggression and anxiety (Gibbs et al. 2016).

Physiological and psychological stresses lead to anxiety disorders and trigger drastic alterations at a molecular level in the brain. To negate this stress, the Hsp network attempts to restore the homeostasis of the system. Sriram et al. demonstrated that Hsp90 is an abundant amplified chaperone in neurons that may also serve as a potential biomarker for post-traumatic stress disorder (Sriram et al. 2012).

Table 3 Aggression and cognitive ability scores in the entire group of subjects stratified by tertile of serum vitamins level and inflammatory markers. Comparisons were made using one-way ANOVA and post hoc Tukey's test (for between groups comparisons). αSignificant between tertile 1 and tertile 2. βSignificant between tertile 1 and tertile 3. γ Significant between tertile 2 and tertile 3

	Tertile 1	Tertile 2	Tertile 3	*P* value
Serum Vit A (μmol/L)	0.91 ± 1.03	5.68 ± 1.62	15.57 ± 6.50	*< 0.001* $^{\alpha,\beta,\gamma}$
Aggression	75.49 ± 20.49	76.79 ± 18.47	73.70 ± 18.22	0.641
Cognitive abilities	69.08 ± 17.70	69.66 ± 18.53	69.30 ± 14.39	0.981
Serum Vit D (μmol/L)	10.34 ± 2.37	18.98 ± 2.94	56.09 ± 30.87	*< 0.001* $^{\alpha,\beta,\gamma}$
Aggression	80.70 ± 19.96	73.70 ± 16.61	72.44 ± 20.44	*0.048* $^{\alpha,\beta}$
Cognitive abilities	71.71 ± 17.38	68.95 ± 19.03	68.79 ± 16.93	0.593
Serum Vit E (μmol/L)	2.19 ± 0.73	5.15 ± 0.91	46.8 ± 31.18	*< 0.001* $^{\alpha,\beta,\gamma}$
Aggression	74.34 ± 18.70	77.13 ± 17.22	75.02 ± 20.10	0.741
Cognitive abilities	67.66 ± 14.58	68.03 ± 18.37	74.71 ± 16.30	*0.050* $^{\beta}$
Serum hs-CRP (mg/L)	0.33 ± 0.21	0.99 ± 0.21	3.23 ± 2.16	*< 0.001* $^{\alpha,\beta,\gamma}$
Aggression	68.65 ± 20.37	73.95 ± 18.32	78.42 ± 22.13	*0.039* $^{\beta}$
Cognitive abilities	73.93 ± 20.90	70.02 ± 18.24	62.74 ± 13.12	*0.027* $^{\beta}$
Serum anti-Hsp27	0.09 ± 0.04	0.22 ± 0.04	0.43 ± 0.15	*< 0.001* $^{\alpha,\beta,\gamma}$
Aggression	61.1 ± 11.8	88.5 ± 14.9	81.4 ± 20.7	*< 0.001* $^{\alpha,\beta,\gamma}$
Cognitive abilities	89.64 ± 22.1	84.5 ± 24.7	74.2 ± 24.6	*< 0.001* $^{\alpha,\beta}$
RDW(%)	12.00 ± 0.31	12.47 ± 0.19	14.67 ± 1.93	*< 0.001* $^{\alpha,\beta,\gamma}$
Aggression	70.32 ± 20.07	72.75 ± 16.96	80.39 ± 17.72	*0.049* $^{\beta,\gamma}$
Cognitive abilities	72.34 ± 15.37	73.57 ± 15.14	68.44 ± 18.85	0.386
NLR	0.96 ± 0.19	1.48 ± 0.13	2.50 ± 1.03	*< 0.001* $^{\alpha,\beta,\gamma}$
Aggression	72.12 ± 22.08	73.35 ± 16.49	76.50 ± 16.99	0.575
Cognitive abilities	76.80 ± 20.02	69.53 ± 15.63	67.55 ± 13.28	*0.041* $^{\alpha,\beta}$
PLR	4.12 ± 1.12	6.13 ± 0.39	10.21 ± 3.74	*< 0.001* $^{\alpha,\beta,\gamma}$
Aggression	74.03 ± 17.82	71.85 ± 21.87	76.32 ± 15.56	0.564
Cognitive abilities	72.75 ± 17.88	70.79 ± 17.79	70.58 ± 13.88	0.823
RPR	0.043 ± 0.006	0.054 ± 0.004	0.089 ± 0.036	*< 0.001* $^{\alpha,\beta,\gamma}$
Aggression	75.0 ± 17.80	75.61 ± 16.32	71.90 ± 21.32	0.647
Cognitive abilities	73.84 ± 15.38	74.69 ± 19.01	67.92 ± 14.88	*0.045* $^{\beta,\gamma}$

Table 4 Univariate and multivariate linear regression analysis with cognitive abilities and aggression scores as the dependent variable

Variables	Univariate		Multivariate	
	Aggression B	Cognitive abilities β	Aggression β	Cognitive abilities β
Serum Vit D	0.701*	–	0.709*	–
Serum Vit E	–	0.032*	–	0.034*
Serum hs-CRP	0.124*	− 0.069*	0.125*	− 0.060*
Serum anti-Hsp27	13.38*	− 6.59**	13.40*	− 6.04**
NLR	–	− 0.063*	–	− 0.018*
RPR	–	− 0.116**	–	− 0.092*
RDW	0.181*	–	0.242*	–

Multivariate analysis adjusted for age and BMI

* p value < 0.05

** p value < 0.01

In different stressful events, physiological response leads to rise in neutrophil counts and decrease in lymphocyte counts. Recently, NLR has been introduced as a simple, inexpensive, readily available, and potent marker in several clinical setting. It has also been shown that an increased NLR is correlated with oxidative stress, elevated cytokine production, and higher level of inflammation (Çakır et al. 2015; Seo et al. 2014). Patients with bipolar disorder, AD, schizophrenia, and PD have statistically significantly higher NRL than healthy normal paired controls (Akıl et al. 2015; Çakır et al. 2015; Kuyumcu et al. 2012; Semiz et al. 2014).

PLR is associated with poor prognosis in patients with peripheral arterial occlusive disease and has a key role in atherosclerosis and atherothrombosis. In current study, first we show an association between RPR and cognitive abilities score.

RDW as a marker of heterogeneity in the size of peripheral red blood cells is obtained from the routine CBC test which is usually neglected by clinicians (Sandhaus and Meyer 2002). It has been shown that RDW levels were significantly higher in patients with AD (Öztürk et al. 2013). Although the main mechanism that triggers elevation in RDW levels in such different diseases is understood, it is speculated that inflammation plays a key role in this process. Inflammation might cause elevated RDW values not only by deteriorating iron metabolism but also by suppressing erythropoietin gene expression or suppression proliferation of erythroid progenitor cells or down-expressing erythropoietin receptor expression or decreasing erythrocyte circulatory half-life. By the way, inflammation may involve in anisocytosis from release of immature red blood cells to the circulation (Öztürk et al. 2013).

Our correlation analysis showed a positive correlation of the fat-soluble vitamins: serum Vit D with Vit A and Vit E. Similarly, Chen et al. found the significant correlation between the levels of Vit E and Vit D (Chen et al. 2018). In other study, there was significant linear correlation between Vit D and Vit A (Mata-Granados et al. 2013). But, Gouado and coworker observed significant correlations between serum vitamins A and E (Gouado et al. 2005). Although we do not know the exact reasons for these correlations, Vit D and Vit E both have antigenotoxic and antimutagenic features, and they are both involved in bone metabolism. The relationship between fat-soluble vitamins should be evaluated further in the future.

Also, our result showed hs-CRP significantly correlated with Vit E; also, RPR was correlated with RDW and PLR which are consistent with others (Akıl et al. 2015; Öztürk et al. 2013).

Although we investigated a relatively large number of subjects, the results of this study should be considered in the context of the following limitations. First, due to the cross-sectional design, we could not interpret causal relationships between vitamins and inflammatory mediators with cognitive abilities and aggression. Second, other parameters of immune system function, such as cytokines, were not assessed. Furthermore, our target population was healthy and these results should be confirmed in patients with different type of psychological disorder.

Conclusions

The present study demonstrated that serum Vit D, hs-CRP, anti-hsp27, and RDW are associated with the aggression and serum Vit E, hs-CRP, anti-hsp27, NLR, and RPR were related with cognitive abilities. A better understanding of how oxidative stress and chronic inflammation contributes in cognitive function could provide an important rationale for the prevention and treatment of psychological disorder. Inflammatory processes may be contributed in cognitive performance and behavior. Prospective studies are warranted to determine the therapeutic potential of targeting oxidative stress and inflammatory pathways.

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Writing: G A. F, A B.

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Compliance with Ethical Standards

Ethics Committee Approval The approval of the Ethic Committee of the Mashad University of Medical Sciences was obtained about this study (931188); informed consent: It was taken.

Informed Consent "Informed consent was obtained from all individual participants included in the study."

Conflict of Interest The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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