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Prooxidant-antioxidant balance in relapsing-remitting multiple sclerosis patients

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Abstract

Background: Multiple sclerosis (MS) is a demyelination disorder of the central nervous system (CNS), which is believed to be associated with oxidative stress. Therefore, researchers try to find reliable biomarkers to monitor the disease and predict its prognosis. Cholesterol and lipids in the myelin sheath are vital for nerve cells. Serum low-density lipoprotein (LDL) is susceptible to lipid peroxidation induced by oxidative stress. This study aimed to evaluate oxidative stress markers in the serum of patients with relapsing-remitting MS (RRMS) and examine their correlation with lipid markers.

Methods: A total of 18 MS patients (14 women and 4 men) and 18 healthy subjects (matched by age and sex) were enrolled in this cross-sectional study. The serum samples were collected in both relapsing and remitting phases. The prooxidant-antioxidant balance (PAB), malondialdehyde (MDA), and oxidized LDL (oxLDL) were measured as markers of oxidative stress.

Results: The mean age of participants was 29.21 (22-42) years. In the comparison between the patient and control groups, the most differences were increased levels of PAB in the patient group ($P < 0.05$), no difference between relapsing and remitting phases ($P = 0.995$), increased MDA levels in the relapsing phase ($P = 0.013$)—but no change in the remitting phase ($P = 0.068$), no difference in LDL and oxLDL levels in the patient group ($P > 0.05$), and MDA, LDL, and oxLDL levels did not have any significant correlation with PAB ($P > 0.05$).

Conclusion: High levels of oxidative stress markers were present in both phases of the disease. Lipid peroxidation markers (such as MDA) increased in the acute phase, but oxLDL did not change. Also, there was no significant correlation between oxidative stress and cholesterol markers.

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Introduction

Multiple sclerosis (MS), the most prevalent disability in young adults, is a chronic, autoimmune disorder of the central nervous system (CNS), which is characterized by oligodendrocyte loss, inflammation, demyelination, and axonal injury (1). Multiple sclerosis can manifest in various forms, such as primary progressive MS (PPMS), relapsing-progressive MS (RPMS), secondary progressive phenotypes MS (SPMS), and relapsing-remitting MS (RRMS, which is the most prevalent form [80% of all cases]) (2, 3). In MS patients, myelin in the CNS is destroyed, and the survival of myelin-producing oligodendrocytes is compromised (4). Progressive destruction of myelin and degradation of its component proteins may further fuel the autoimmune response (5). As myelin consists of 70% of lipids, human serum lipoproteins are implicated in the transportation of lipids, modulation of membrane lipid distribution, and regulation of signal transduction in the CNS (6, 7). Under normal conditions, high levels of high-density lipoproteins (HDL) and low-density lipoproteins (LDL) are present in the CNS to transport across the brain-blood barrier (BBB) (8, 9). Although dyslipidemia may contribute to inflammatory processes, it leads to the generation of adhesion molecules and the recruitment of leukocytes. The recruitment of immune cells beyond the activated endothelium of the BBB is critical in MS pathogenesis (10, 11). Existing evidence on oxidative stress and its clinical involvements suggests that the formation of free radicals (which leads to oxidative stress) plays a role in the pathogenesis of neurodegeneration (12). In a healthy condition, prooxidants and antioxidants remain in a balance status (13). The respiratory chain, inflammatory cells, and mitochondria are among the causes of free radical production (14). Oxidative stress is an imbalance status between prooxidants and antioxidants in favor of prooxidants. It hurts cellular ingredients, including proteins, lipids, and DNA (15, 16).

Reactive oxygen species (ROS)-induced peroxidation of biological molecules, particularly lipoproteins, is involved in the pathogenesis of MS (17). The CNS is sensitive to oxidative stress because of the brain's high oxygen consumption, rich lipid content, and lack of antioxidant agents (18, 19). The precise role of oxidative stress in MS patients requires further investigation.

Based on this background and considering the limited data available on oxidative stress agents' role, including ROS and malondialdehyde (MDA), we aimed to evaluate the serum level of oxidative agents and their correlation with oxidized lipids in RRMS patients.

Methods

In this case-control study, after obtaining informed consent, 18 RRMS patients and 18 healthy controls were recruited from Qaem Hospital, Mashhad, Iran. RRMS patients diagnosed to be in an acute phase were referred to Qaem Hospital for corticosteroid therapy. Exclusion criteria were the use of corticosteroids within the past 30 days, presence of infections or fever in the past 30 days, pregnancy, use of vitamin supplements, obesity, diabetes, thyroid dysfunction, and renal disorders. Blood samples (5 mL) were obtained in the relapsing phase before corticosteroid therapy in Qaem Hospital. Plasma was separated from red cells by centrifugation at 2500 rpm and 4 ºC for 15 minutes. Aliquots of the supernatant (0.5-1 mL) were immediately frozen at −20 °C and not thawed until analysis. Three months later, another blood sample was taken from the same patients who were in the remitting phase in the same situation. The control group consisted of 18 healthy individuals from the same geographic area who did not present either clinical or laboratory characteristics of autoimmune, renal, heart, or liver disease. Also, the control subjects reported that they did not use any anti-inflammatory drugs or antioxidant supplements. The patients' nutritional status did not differ from the control group, and none of the subjects were placed on a specific diet (data not shown). Parameters such as age, gender, ethnicity, smoking, and body mass index (BMI) were controlled. The study was performed according to the Helsinki Declaration and approved by the Local Ethics Committee of Mashhad University of Medical Sciences, Iran (code: IR.MUMS.REC.1393.960).

- ***Prooxidant-antioxidant balance method***

The prooxidant-antioxidant balance (PAB) assay uses 2 different reactions: (i) an enzymatic reaction where chromogen TMB is oxidized to a color cation (TMB+) by peroxides and (ii) a chemical reaction. TMB cations are reduced to a colorless composite by antioxidants. The absorbance is compared with the absorbance given by a series of standard solutions that are made by mixing varying proportions (0%-100%) of hydrogen peroxide with uric acid.

A low PAB value means that antioxidants are present at higher concentrations than prooxidants and vice versa. The standard solutions were prepared by the mixture of various proportions (0%-100%) of hydrogen peroxide and uric acid in NaOH. Then, the TMB powder was dissolved in dimethyl sulfoxide (DMSO). For the TMB cation solution preparation, the TMB/DMSO solution was added to the acetate buffer (0.05M buffer and pH = 4.5), followed by the addition of the fresh chloramine T solution. The solution was shaken well and incubated for 2 hours at room temperature in a dark place, after which 25 U of peroxidase enzyme solution was added. This mixture was aliquoted into 1 mL aliquots and stored at –20 ºC. The TMB solution was prepared by adding TMB/DMSO to the acetate buffer (0.05M buffer and pH = 5.8), and the solution was prepared by mixing the TMB cation solution with 10 mL of TMB solution. This working solution was incubated. Samples were mixed with working solution in a 96-well plate and then incubated at 37 ºC for 12 minutes. After incubation, 2 N HCl was added to each well, and the optical density was measured using an enzyme-linked immunosorbent assay (ELISA) reader.

- ***Serum oxidized ldl evaluation***

Oxidized LDL (oxLDL) was measured using an ELISA kit (EASTBIOPHARM, CK-E10869), anti-oxLDL monoclonal antibody FOH1a/DLH3 the capture antibody and an anti-human apolipoprotein B (apoprotein B) monoclonal antibody labeled by horseradish peroxidase.

- ***Malondialdehyde measurement***

Samples were added to the reaction mixture containing phosphate buffer and $FeCl_3$ (pH = 7.4). The reaction was stopped by the addition of 10% trichloroacetic acid (TCA), followed by 0.67% TBA, and the tubes were placed in boiling water for 20 minutes. The tubes were then moved to an ice bath, and the contents were centrifuged for 10 minutes. The amount of MDA formed in each of the samples was assessed by measuring the supernatant's optical density using tetraethoxypropane (TEP) as a standard. The MDA content was expressed as the nmol · mg^{-1} protein.

- ***Serum ldl measurement***

The serum LDL level was measured by a biochemical autoanalyzer (BT3000, Pars Azmoon, Iran) through some enzymatic reaction using cholesterol esterase and peroxidase. The method was performed according to the manufacturer's instructions, and the results were expressed in mg/dL.
Complete blood cell count (CBC) was performed using a Sysmex XS800i hematology analyzer with fluorescence technology (Diamond Diagnostics, USA).

Statistical analyses were performed using SPSS version 16 (SPSS Inc, Chicago, IL, USA). Descriptive statistics were used to analyze the data. The distribution of gender, ethnicity, and smoking was analyzed using a chi-square test. Comparisons between control subjects and MS patients were performed using the Mann-Whitney test and independent *t* test for non-parametric and parametric variables, respectively. Comparisons between MS patients in relapsing and remitting phases of the disease were performed using the Wilcoxon test and paired *t* test for non-parametric and parametric variables, respectively. P values less than 0.05 were considered statistically significant.

Results

After neurological examinations, 18 out of 40 individuals were diagnosed with RRMS (45%). The mean age of participants was 29.21 (22-42) years. As expected, the individuals did not differ in any of the controlled parameters. The demographic characteristics of RRMS patients and healthy controls are presented in (Table 1).

Table 1. The characteristics of the relapsing-remitting multiple sclerosis patients and healthy controls

		Controls	RRMS patients	P value
Age	≤20 y	6.0%	5.9%	P > 0.05
	20-30 y	55.0%	47.0 %	
	30-40 y	33.0%	35.3%	
	≥40 y	6.0%	11.8%	
Gender	Male	22.5%	22.2%	P > 0.05
	Female	77.5%	77.8%	

Abbreviation: RRMS, relapsing-remitting multiple sclerosis

The mean PAB value in MS patients was 157.550 ± 52.23 in the relapse phase, 156.766 ± 58.60 in the remission phase, and 118.539 ± 40.66 in healthy controls. The results showed a significantly high serum PAB level in both phases of MS compared with the whole group (Table 2). White blood cell (WBC) count and differentiation in MS patients were compared with healthy controls. In the MS group, the mean WBC count was 7.956 ± 2.006 during the relapse phase and 8.500 ± 2.366 during the remission phase; both values were significantly higher in the MS group than in the control group (6.522 ± 1.577; P < 0.05), but there were no significant differences between the relapse and remission phases of in the MS group (P > 0.05) (Table 3).

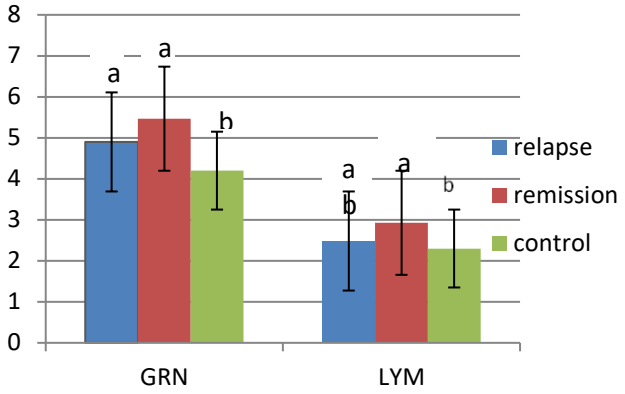

Figure 1. Granulocyte and lymphocyte comparison with controls
(Columns with similar letters are not significantly different)

The Pearson correlation test was used to investigate the correlation of neutrophils, WBC, lymphocytes, and PAB in each study group because both variables follow the normal distribution. There was no significant relationship between neutrophils, WBC, lymphocytes, and PAB (P > 0.05).

The mean count of granulocyte (GRN) was 4.900 ± 1.860 in the relapse phase and 5.467 ± 2.024 in the remission phase, which were significantly higher in the MS group than in the control group (4.200 ± 1.380), but not significant. The mean count of lymphocyte 2.483 ± 0.921 in relapse group and 2.928 ± 0.950 in remission group were not significantly different, and just the remission phase group had a notable difference in comparison with mean of the control group 2.300 ± 0.594 (Figure 1).
The mean MDA level was measured and compared in MS and control groups. Regarding the relapse phase, there was a significant difference in the mean levels of MDA between MS patients (0.314 ± 0.378) and controls (0.119 ± 0.184). However, regarding the remission phase, there was no significant difference in the mean levels of MDA between MS patients (0.218 ± 0.230) and controls (0.119 ± 0.184); in addition, it was not significant between the 2 phases (Table 2). The Spearman correlation test was used to investigate the relationship between MDA and PAB in each of the studied groups; this is because the MDA variable does not follow the normal distribution. There is no significant relationship between MDA and PAB (P > 0.05).

Table 2. The mean levels of prooxidant-antioxidant balance, low-density lipoprotein, oxidized low-density lipoprotein, and malondialdehyde in the multiple sclerosis and control groups.

	MDA	PAB	LDL	oxLDL
	MEAN ± SD	MEAN ± SD	MEAN ± SD	MEAN ± SD
Relapse	0.314 ± 0.378	157.550 ± 52.23	81.89 ± 13.096	3573.978± 2479.016
Remission	0.218 ± 0.230	156.766 ± 58.60	82.17 ± 12.885	3932.897 ± 2745.246
Control	0.119 ± 0.184	118.539 ± 40.66	112.96 ± 31.058	3677.669± 2656.630

Abbreviations: MDA, malondialdehyde; PAB, prooxidant-antioxidant balance; oxLDL, oxidized low-density lipoprotein.

The mean level of LDL in MS patients was 81.89 ± 13.096 in the relapse phase and 82.17 ± 12.885 in the remission phase. Both of these values were significantly higher when compared to the control group (82.17 ± 12.885; P < 0.0001; (Table 2). Mean oxLDL level was 3573.978 ± 2479.016 in relapse group and 3932.897 ± 2745.246 in remission group and 3677.669 ± 2656.630 in control group. None of them did show the significant difference (Table 2).
The Spearman correlation test was used to investigate the relationship between LDL, oxLDL, and PAB in each of the studied groups. There was no significant relationship between LDL, oxLDL, and PAB (P > 0.05).

Table 3. The white blood cell count and its differentiation

	MS patients (relapse)	MS patients (remission)	Control
WBC	7.956 ± 2.006[a]	8.500 ± 2.366[b]	6.522 ± 1.577
GRN	4.900 ± 1.860	5.467 ± 2.024[c]	4.200 ± 1.380
Lymphocyte	2.483 ± 0.921	2.928 ± 0.950[d]	2.300 ± 0.594

a, b, c, and d: a significant difference compared with the control group (independent t test). Abbreviations: MS, multiple sclerosis; WBC, white blood cell; GRN, granulocyte.

Discussion

About 85% of MS patients are diagnosed in the RRMS phase at the time of diagnosis (20). The etiology of MS has been unclear to researchers. Moreover, several studies have been conducted to discover its biochemical, genetic, and immunological aspects. Numerous investigations have introduced oxidative stress as a significant etiology of MS (21-24). Additionally, autoreactive lymphocytes are the primary inflammatory causes in the CNS that begin the disorder process (25). Inflammatory signs were observed in biopsied plaques (including lymphocytes and macrophages) and MS patients' serum (including myelin reactive T lymphocytes) (26). Microglia cells are present in inflammatory situations by releasing cytokines, oxidative products, and free radicals, which are toxic to myelin (27). The inflammation provokes mitochondrial interruption and demyelination and causes neurological diseases (28). Existing evidence shows that mitochondrial dysfunction and oxidative stress are critical factors of common progressive neurological disorders (29). Antioxidants are a promising way of decreasing risk and preventing the disease's progress (30). Oxidative stress results from the prooxidant activity transformation in PAB, an increase in oxidative metabolism, and the failure of antioxidant mechanisms (31). Reactive oxygen species damage lipids, proteins, and nucleic acids and render them to cell death. Their generation elevates through various pathological situations (32). Reactive oxygen species, by its possible role in tissue damage in MS, shows inflammatory responses (33).

Recently, the primary role of ROS involved in MS pathogenesis has been developed, and data prove that free radicals have a vital role in multiple mechanisms underlying MS pathology (34). Although various mechanisms are involved in the demyelination and neurodegeneration in MS, several studies have shown that oxidative stress has a vital role in MS pathogenesis, concerning myelin and oligodendroglia degeneration that ultimately causes neuronal death (35). Notably, high concentrations of prooxidant agents have been found in the serum of MS patients (36). A study has shown a remarkably lower capacity ($P < 0.001$) of total antioxidants in the serum of MS patients compared with healthy subjects (37).

In this regard, we aimed to evaluate oxidative stress in MS patients. Moreover, we also conducted these evaluations in the relapsing and remitting phases of the disease to monitor changes between the phases. Our findings showed that the level of oxidative stress did not differ significantly between the relapse and remission phases, although it was significantly higher than healthy controls in both phases. To our knowledge, this is the first study to evaluate oxidative stress in different phases of RRMS.

However, our findings showed that oxidative stress did not have a significant role in MS staging, and current therapies do not affect prooxidant levels. This can predispose patients to more relapses. According to our best knowledge, our study is the first study to measure oxidative stress in different phases of the disease. Several lines of evidence suggest that infiltrated macrophages are among the primary ROS sources in CNS inflammation in patients with MS (38). Infiltrated macrophages lead to neuronal damage via their interaction with lipids, proteins, nucleic acids, and disruption of the membrane integrity of neurons (39). Therefore, high ROS generation is among the most critical ingredients in inflammation and neuronal damage (40, 41).

White blood cells are known as recourses of oxidative stress in inflammatory diseases (42). Here we studied the quantity and differentiation of WBCs to know whether it is correlated with oxidative stress. Our findings showed an increase in WBCs in MS patients compared with healthy controls. However, there was no significant difference regarding WBCs in the relapsing and remitting phases of the disease.

Granulocytes play an essential role in inflammatory diseases. Nevertheless, their role in the pathogenesis of MS is complicated (43). They can play a dual role by omitting damaged myelin particles and secreting growth factors (44). On the other hand, they can adversely affect the disease by producing pro-inflammatory cytokines (45). In our study, the number of granulocytes was more in RRMS patients than in healthy controls. Nevertheless, the difference was significant only in the remitting phase. The granulocyte count was not different in the remitting and relapsing phases of the disease. Histological studies have shown that lymphocytes increase in MS (46). The lymphocyte count is considered to be correlated with axonal injury (47). In our study, even though there were more lymphocytes in MS patients than in healthy controls, the difference was not statistically significant. As mentioned before, there is a hypothesis that peroxidation of lipids by prooxidants can play a role in the pathogenesis of MS. Mariani et al showed that lipid peroxidation products alter cell membrane permeability and induce cell dysfunction (48). Thus, evaluation of these product levels can predict the disease stage. Accordingly, in our study the MDA level, was correlated with PAB in MS patients and healthy individuals. Our results showed that the MDA level was higher in the relapse phase than in the remission phase and control group, and the difference was significant. There was no correlation between MDA and PAB in MS patients, which was in contrast with our expectations.

The oxidization of LDL in serum is involved in the development of multiple disorders, such as Alzheimer and Parkinson diseases (49).

It is proved that an increase in the oxLDL concentration is correlated with the prooxidant level. Our results also showed that measuring dyslipidemia markers, specifically oxLDL and LDL, is more reliably associated with MS and its progression. This supports the hypothesis that pro-inflammatory mechanisms associated with an abnormal lipid profile may contribute to MS progression through processes at the BBB vascular endothelium.

Conclusion

The PAB technique can be useful for the determination of oxidative stress levels in MS patients. High levels of oxidative stress markers are present in both phases of the disease. Lipid peroxidation markers (such as MDA) increased in the acute phase, but oxLDL did not change. Also, there was no correlation between PAB and oxLDL and MDA.

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Ethical statement

The Ethics Committee of the Mashhad university of medical sciences accepted the protocols (Ethic number: IR.MUMS.MEDICAL.REC.1395.375).

Conflicts of interest

The authors have no conflicts of interest to disclose.

Author contributions

All of the authors contributed to the study conception. The Study was designed by Dr Hamidi Alamdari. Material preparation was performed by Dr Isaac Hashemy, data collection and analysis were performed by Sanaz Salaramoli and Samaneh Sabouri. The first draft of the manuscript was written by Sanaz Salaramoli and revised by Samaneh Sabouri. All of the authors commented on previous versions of the manuscript. All of the authors read and approved the final manuscript.

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