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Research Article

Investigating the Role of Oxidant-Antioxidant Balance in the Etiology of Migraine

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Abstract

Aim: Migraine, a prevalent neurovascular disorder, is marked by repetitive headache episodes. Its complex etiology encompasses biochemical, genetic, and environmental influences, but its exact pathophysiology remains elusive. Recent studies have hinted at a link between migraine and oxidative stress. Hence, this study sought to delve into the correlation between migraine, oxidative stress markers, and lipid profiles.

Material and Method: This case-control study involved 60 adult migraine patients from Dicle University's Neurology Department in Diyarbakır, Türkiye, observed between 2009 and 2010. The control group was age- and gender-matched healthy individuals. Parameters like malondialdehyde (MDA), paraoxonase-1 (PON-1), total antioxidant capacity (TAC), and lipid constituents such as total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were measured in both groups.

Results: Migraine sufferers, particularly those with aura, had significantly elevated MDA levels compared to controls ($p<0.05$). Conversely, TAC and PON-1 levels were notably lower in the migraine population, suggesting an imbalance in their oxidant/antioxidant systems ($p<0.05$). Lipid analysis showed heightened TC, LDL-C, and TG in migraine patients, while HDL-C was diminished, with marked differences in subgroups ($p<0.05$).

Conclusion: The surge in MDA and the decline in TAC and PON-1 levels insinuate that oxidative stress plays a pivotal role in migraine's pathophysiology. The lipid profile alterations in migraineurs highlight potential cardiovascular concerns. Comprehensive cohort studies are essential to confirm these findings and understand the intricate ties between migraine, oxidative stress, and metabolic indicators. This research underscores oxidative balance's potential significance in migraine pathogenesis, emphasizing the need to consider oxidative stress in migraine management and prevention strategies.

Keywords: Migraine disorders, oxidative stress, malondialdehyde, aryldialkylphosphatase, lipids, cardiovascular diseases

INTRODUCTION

Migraine is a common neurovascular disease accompanied by several clinical features such as headache, nausea, and photophobia (1). Approximately 12%-16% of the general population, primarily women, suffers from migraine (2). Although many biochemical, genetic, and environmental factors have been suggested to play a role in the pathogenesis of migraine, the exact pathogenesis is still unclear (3-5). However, recent studies increasingly suggest that oxidative stress may play a central role in migraine's pathophysiology.

Oxidative stress refers to a shift in the antioxidant/oxidant balance in the direction of oxidants. Overproduction of reactive oxygen species causes damage to cells, organs, and even the entire body (6). Malondialdehyde (MDA), the product of lipid peroxidation, has been used to assess oxidative status in various conditions, such as respiratory distress, cardiovascular problems, neuroinflammatory disorders, and cancer (7). Paraoxonase-1 (PON-1), a key antioxidant chemical, has anti-inflammatory and antiatherosclerotic characteristics, preventing low-density lipoprotein (LDL) and high-density lipoprotein (HDL) from oxidation (8-10). Total antioxidant capacity (TAC), an integrated parameter of detectable antioxidants, reflects the synergistic interaction of all antioxidants in serum or plasma (11).

Several studies have reported changes in oxidative stress marker levels in migraine patients, suggesting a possible relationship between oxidative damage and migraine. In a

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recent study, proteomics analysis revealed inflammatory and oxidative stress markers in the plasma of migraine patients during pain episodes, suggesting their use as potential disease biomarkers (12). Another study reported that botulinum toxin type-A (BoNT/A) treatment improved plasma oxidative stress biomarker levels, further confirming the role of oxidative stress in chronic migraine (13). Additionally, a study on the status of inflammatory and anti-inflammatory markers in migraine patients concluded that MDA, an oxidative stress marker, and other inflammatory markers may act as potential risk factors for migraine (14). On the other hand, other studies did not find any significant difference between migraine patients and healthy control subjects in oxidative stress marker levels (15-18). Hence, the exact nature of the complex relationship between oxidative stress and migraine remains unclear. Therefore, more comprehensive studies that will provide a deeper insight into the multifaceted role of oxidative stress in migraine are needed.

In this context, this study was carried out to comparatively assess the plasma levels of MDA, PON-1, TAC, and lipid profile in individuals with and without migraine with a view to clarifying the potential role of oxidant/antioxidant balance in migraine.

MATERIAL AND METHOD

Study Design and Ethical Considerations

This research was designed as a forward-looking, case-control study. Approval for the study protocol was obtained from the ethics committee of Dicle University, Diyarbakır, Türkiye, prior to initiation (Approval No: 14-26.05.12). The conduct of this study adhered to the ethical guidelines outlined in the Declaration of Helsinki. All participants provided their consent through signed, written informed consents.

Population and Sample

The research focused on adult individuals (over 18 years of age) diagnosed with migraine, monitored at the Dicle University, Diyarbakır, Türkiye's Faculty of Medicine, Neurology Department's outpatient clinic from 2009 to 2010. Migraine typically presents as repeated episodes of severe headaches that can last from 4 to 72 hours and are often exacerbated by everyday physical activities. Symptoms frequently accompanying migraines include nausea, vomiting, visual disturbances, and heightened sensitivity to light and sound (1). Migraine auras are characterized by reversible focal neurological symptoms involving visual, sensory, speech, and/or motor problems that develop gradually and usually precede the headache phase (19).

Consecutive patients between the ages of 20 and 50 who were diagnosed with migraine (with or without aura) by an experienced neurologist according to the International Classification of Headache Disorders version 3 Beta (ICHD-3 beta) criteria (1) had at least two migraine attacks per month, did not smoke or drink alcohol, were taking regular medication in the last one month before the study at the minimum, and gave their consent to participate in the study were included in the study.

On the other hand, patients with major psychiatric or neurological disorders who had a history of pregnancy, breastfeeding, or menopause and have used any medication that may affect the levels of oxidant/antioxidant markers in the last month were excluded from the study.

In the end, 60 migraine patients who met the study inclusion criteria were included in the patient group (Group 1). Group 1 was divided into two subgroups: those with aura (Group 1a) (n=32) and those without aura (Group 1b) (n=28). The control group (Group 2) consisted of 30 age- and gender-matched healthy individuals with no personal or familial history of migraine or other headache disorders and who applied to the neurology outpatient clinic for other reasons during the study period.

Data Collection

Venous blood samples were taken to assess patients' serum MDA, PON-1, and TAC levels and lipid profiles. Blood samples were collected from all participants into heparinized tubes between 08:00 a.m. and 09:00 a.m. after fasting overnight. Blood samples were maintained in gel biochemistry tubes for 30 minutes, centrifuged at 3500 x g for 5 minutes to separate plasma, labeled, and promptly stored at -80°C until testing.

Lipid peroxidation was spectrophotometrically assessed in blood plasma using a 2-thiobarbituric acid-reactive substance (TBARS) assay (20) (Shimadzu UV-160, Cayman Chemical Company). MDA equivalents were used to calculate the TBARS levels. Tetramethoxypropane (TMP; 1, 1, 3, 3) was selected as the standard. The resulting data were presented in terms of µmol/L plasma.

PON-1 enzyme activity was assessed using the Rel Assay Diagnostics PON enzyme test kit (Abbott Architect c16000 clinical chemistry analyzer). The activity of PON-1 towards paraoxon was measured spectrophotometrically at 412 nm (21). The enzyme activity in one micromole of p-nitrophenol produced in one minute was measured at 37°Cusing17 100 M^{-1} cm^{-1} as the molar extinction coefficient.

The plasma TAC level was assessed using the Rel Assay Diagnostics test kit and spectrophotometer (Abbott Architect c16000 clinical chemistry analyzer). The technique used for measuring plasma TAC levels employs a fully automated method, as formulated by Erel (22). his method is predicated on the discoloration of the typically more resilient 2,2'-azino-bis (3-ethylbenz-thiazoline-6-sulfonic acid) radical cation by antioxidants. The findings are expressed in terms of millimoles of Trolox equivalent per liter.

The study measured various biochemical parameters, namely total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol

(HDL-C), and triglycerides (TG). These assessments were conducted using established methods on an Abbott Architect c16000 clinical chemistry analyzer.

The study's primary and secondary outcomes were determined as migraine patients' oxidant/antioxidant levels and lipid profiles and the differences, if any, between migraine patients (with and without aura) and control subjects in oxidant/antioxidant levels and lipid profiles, respectively.

Statistical Analysis

The post-hoc power analysis revealed the statistical power of the independent two-sample t-test featuring the MDA values of Group 1a and the control group (Table 1) as 99%. In addition, the post-hoc power analysis revealed the statistical power of the independent two-sample t-test featuring the MDA values of Group 1b and the control group (Table 1) as 99%.

Given the sample size, these data suggest that our study featured adequate statistical power to detect the differences observed in MDA values between the migraine subgroups and the control group. The analysis was performed using the "statsmodels" library in Python (version 3.8.5).

For the analysis of our collected data, we utilized the SPSS 24.0 software suite (IBM Corp., Armonk, NY, U.S., 2016), a widely recognized tool for advanced statistical analysis. To ensure the robustness of our results, we first verified the normal distribution of our continuous data using the Kolmogorov-Smirnov test. This step is crucial as the normality of data can influence the choice of statistical tests and the validity of their outcomes.

Our continuous variables were then represented as mean±standard deviation (SD) for clarity and ease of interpretation. In contrast, categorical variables were presented in terms of frequencies (n) and percentage (%) values, providing a comprehensive overview of the distribution of our data.

To compare categorical data, we employed Pearson's chi-square test, a standard method for understanding associations between categorical variables. We also utilized Levene's F-test to ensure the homogeneity of variances across our datasets.

Depending on the results of our preliminary tests and the nature of our data, we chose the most appropriate statistical tests for comparison. In the analysis of continuous variables, the study utilized either one-way analysis of variance (ANOVA) or the Kruskal-Wallis test, contingent upon the data distribution. ANOVA was applied for data that followed a normal distribution, whereas the Kruskal-Wallis test was used for data that did not. In cases of pairwise comparison, the selection between the student's t-test and the Mann-Whitney U test was also based on whether the data was normally distributed or not.

To validate the robustness of our results, each test was executed with a 95% confidence interval. A two-sided p-value of less than 0.05 was deemed indicative of statistical significance, aligning with the common benchmark in numerous scientific investigations.

RESULTS

Upon examining the baseline data, no notable disparities were observed in the anthropometric and demographic attributes across the groups. A detailed breakdown of the laboratory findings for each group can be referenced in Table 1.

Table 1. Laboratory data in all subjects by groups and subgroups

Results*	Group 1 (Patient) (n=60)		Group 2 (Healthy control) (n=30)	p1	p for ANOVA	p-values**		
	Group 1a (n=32)	Group 1b (n=28)				p2	p3	p4
Oxidative and antioxidative parameters								
MDA	6.7±0.52	3.96±0.56	2.56±0.11	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
PON-1	106.5±13.1	103.6±10.2	143.9±12.2	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.348
TAC	1.05±0.14	1.07±0.09	1.22±0.05	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.520
Lipid profile								
COL	-	-	-	**<0.001**	**<0.001**	>0.05	>0.05	**0.007**
HDL-C	40.2±9.4	49.9±9.2	40.6±7.8	**<0.001**	**<0.001**	0.856	**<0.001**	**<0.001**
LDL-C	114.7±15.5	98.0±13.1	85.1±26.0	**<0.001**	**<0.001**	**<0.001**	**0.022**	**<0.001**
TG	155.3±37.6	113.4±29.5	113.1±44.5	**<0.001**	**<0.001**	**<0.001**	0.976	**<0.001**

*Mean±SD values, **p-values are for One-way ANOVA or Kruskal Wallis in three group comparisons, P values are for Student t-test or Mann Whitney U test in two groups comparisons. p1: Group 1 and Group 2, p2: Group 1a and Group 2, p3: Group 1b and Group 2, p4: Group 1a and Group 1b. Group 1a: Migraine with aura, Migraine without aura, Group 2: Control, MDA: Malondialdehyde, PON-1: Paraoxonase-1, TAC: Total antioxidant capacity, COL: Total cholesterol, LDL-C: Low-density lipoprotein, HDL-C: High-density lipoprotein, TG: Triglyceride

When assessing oxidative stress markers, a pronounced increase in MDA levels was evident in both migraine subgroups when juxtaposed with the control group (Group 2) ($p<0.05$). Conversely, antioxidant markers, specifically TAC and PON-1 levels, were discernibly diminished in migraine patients relative to the controls ($p<0.05$). Delving into the lipid profiles, it was observed that TC, HDL-C, LDL-C, and TG concentrations were markedly elevated in patient groups (Group 1) compared to Group 2 ($p<0.05$).

A deeper dive into the subgroups revealed that MDA concentrations were notably higher in the migraine patients with aura (Group 1a) than their counterparts without aura (Group 1b) ($p<0.05$). However, no discernible differences were found between these subgroups concerning TAC and PON-1 levels. In terms of lipid concentrations, the comparison of Group 1a and Group 1b revealed significantly higher TC, LDL-C, and TG levels in Group 1a ($p<0.05$). While no significant disparity was found between Group 1a and the control group in terms of HDL-C levels ($p>0.05$), Group 1b exhibited higher HDL-C levels when compared to both Group 1a and the control group ($p<0.05$).

For a visual representation of the distribution of MDA, PON-1, and TAC levels across groups, please refer to Figure 1. Similarly, Figure 2 provides a graphical depiction of the distribution of TC, LDL-C, HDL-C, and TG levels among the groups.

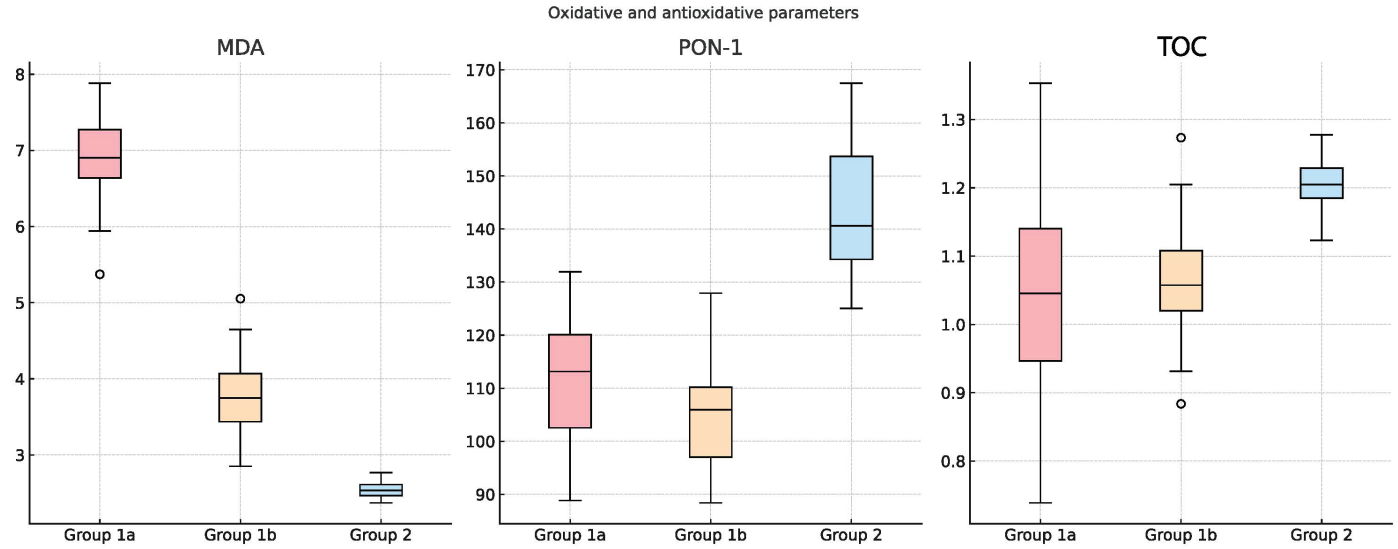

Figure 1. MDA, PON-1, and TAC levels across patient groups: Migraine with aura, migraine without aura, and control. MDA; malondialdehyde, PON-1; paraoxonase-1, TAC; total antioxidant capacity

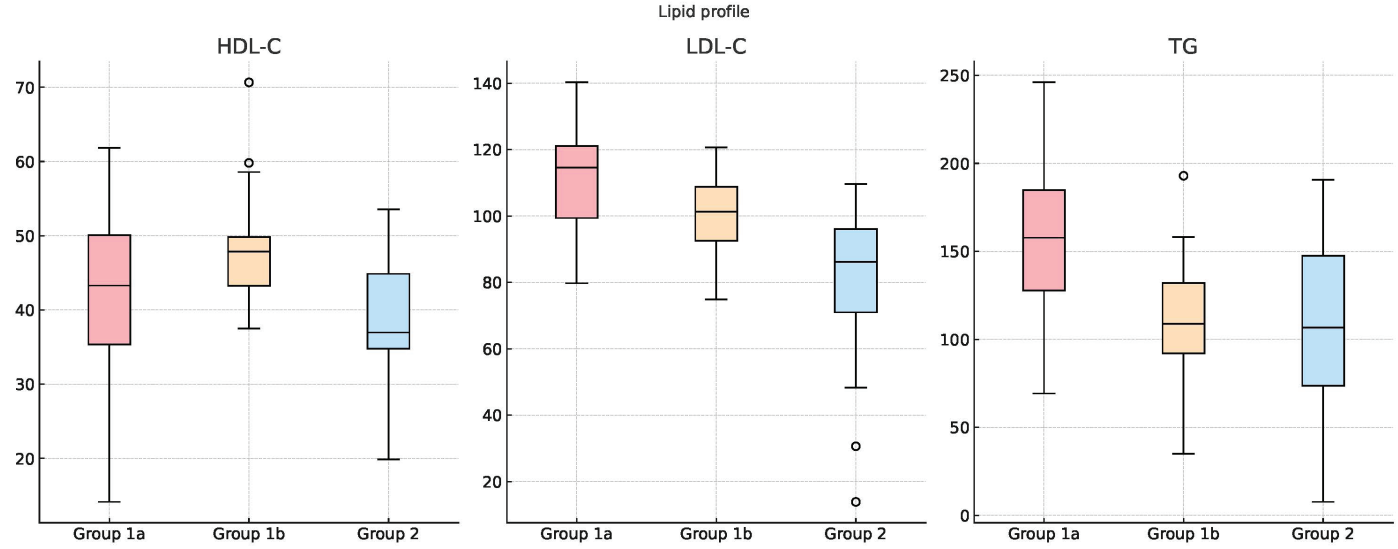

Figure 2. Analysis of the lipid profiles LDL-C, HDL-C, and TG levels among the patient groups: Migraine with aura, migraine without aura, and control. LDL-C; low-density lipoprotein, HDL-C; high-density lipoprotein, TG; triglyceride

DISCUSSION

The comparison of serum levels of specific metabolic markers, including MDA, PON-1, and TAC, between migraine patients and healthy individuals revealed a significant increase in serum levels of oxidative stress markers, particularly MDA, in migraine patients, especially in those with aura. These findings were accompanied by

decreased antioxidant activity, as evidenced by reduced PON-1 and TAC levels.

There are numerous studies in the literature on oxidative stress markers in migraine. Dini et al. (13) reported that chronic migraine and medication overuse headaches were associated with a diminished antioxidant capacity, suggesting an imbalance in antioxidant processes in migraine patients. In parallel, in this study, the serum levels of oxidative and antioxidant stress markers, particularly MDA, were found to be significantly elevated in migraine patients than in healthy control subjects. In contrast, Bernecker et al. (23) did not find any significant difference in MDA levels between migraine patients and control subjects. Nevertheless, they reported increased levels of 4-hydroxy-2-nonenal (HNE), another lipid peroxidation biomarker.

PON plays a pivotal role in the plasma antioxidant system by providing protection against oxidative damage. Several studies, such as those by Yıldırım et al. (24) and Cakina et al. (25), reported significantly reduced PON activity in migraine patients compared to control subjects, whereas others, such as those by Eren et al. (18) did not find any significant difference in PON activity between migraine patients and control subjects. These discrepancies suggest the complexity of oxidative stress mechanisms in migraine.

Measurement of antioxidants individually can be challenging due to their interactive nature. Thus, TAC and the oxidative stress index (OSI) are often used to reflect the synergistic interaction of all antioxidants in serum or plasma. Eren et al. (18) did not observe significant differences in TAC and OSI levels between migraine patients and control subjects. On the other hand, Tripathi et al. reported decreased TAC levels in migraine patients after preventative therapy (26). Similarly, in our study, the TAC levels were significantly lower in both migraine subgroups compared to the control group.

Migraine has been associated with various cardiovascular risk factors, including lipid metabolic abnormalities. Kurth et al. (27) investigated the relationship between elevated lipid profile levels and cardiovascular diseases in a cohort of primarily non-reproductive aged women with migraines. They found that women with a history of migraine had a marginally increased risk of elevated TC and LDL-C levels. Similar findings have been reported in the literature (28-30). Tana et al. (28) observed a positive correlation between cholesterol levels and migraine severity and frequency. The study also suggested that migraine prophylaxis might reduce the levels of lipid parameters. Although the precise link between lipid profile and migraine severity has not been thoroughly documented, increased endothelial dysfunction, oxidative stress, and inflammation in migraine patients might contribute to an unfavorable lipid profile (28). Uygur-Kucukseymen et al. (30) found that migraine patients without aura had higher lipid levels, suggesting that migraine pathophysiology might be associated with elevated lipid levels. Moreover, different migraine characteristics, such as aura, were unrelated to lipid metabolism. Consistent with these findings, our study observed significant changes in lipid profiles among migraine patients. We found significantly elevated levels of TC, LDL-C, HDL-C, and TG in migraine patients compared to healthy controls. The HDL-C levels in migraine patients without aura were augmented compared to those with aura, aligning with the findings of Uygur-Kucukseymen et al. (30). Additionally, TG levels were comparable between healthy controls and migraine patients without aura. Although, LDL-C levels are considered an indicator of cardiovascular risk in migraine patients with aura, conflicting findings in the literature warrant the need for further large-scale studies to clarify the subject.

Limitations of the Study

The relatively small sample size may be deemed the study's primary limitation, considering that it might have amplified the observed differences. Larger scale studies are needed to elucidate the differences between migraine subgroups further. In addition, the study's case-control design may be deemed another limitation of the study as it precluded establishing causality.

CONCLUSION

In conclusion, this study's findings indicated the significant elevations in serum levels of oxidative markers, particularly MDA, in migraine patients, particularly those with aura, and the concomitant decrease in the serum levels of antioxidant markers, PON-1 and TAC. These results suggest the potential role of oxidative balance in the pathophysiology of migraine, warranting further research to elucidate the implications of the changes in oxidative stress marker levels in migraine-related neuroinflammation.

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Conflict of interest: *The authors have no conflicts of interest to declare.*

Ethical approval: *This research was structured as a forward-looking, case-control study. Approval for the study protocol was secured from the ethics board of Dicle University, Diyarbakır, Türkiye, before the commencement of the study (Approval No: 14-26.05.12). The study's execution was in line with the ethical standards outlined in the Declaration of Helsinki. Every participant in this study provided their agreement in the form of signed, written informed consent.*

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