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The Role of Oxidative and Nitrosative Stress in Migraine Patients

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Abstract

This research aimed to explore the potential involvement of oxidative stress in the onset of migraines. The primary objective was to assess the concentrations of malondialdehyde (MDA), which serves as an indicator of oxidative stress, as well as nitric oxide (NO), a marker for nitrosative stress, and asymmetric dimethylarginine (ADMA), an indicator of endothelial dysfunction. Ninety (90) participants were recruited in this research work from the neurology department's outpatient headache clinic at Al Jumhury Teaching Hospital in Erbil city, the study consisted of (60) patients and (30) as controls. In the migraine group, there were (45) females and (15) males, while the control group was comprised of (20) females and (10) males with age and sex matching. The study was granted ethical approval by the Human Research Ethics Committee (HREC) at the Department of Biology, College of Science, Salahaddin University-Erbil, on February 6th, 2022.The study showed that the migraine patients had significantly greater levels of MDA, NO and ADMA than the control group. Additionally, the number of headache days experienced per month by migraine patients was positively correlated with the serum concentrations of MDA, NO, and ADMA. Specifically, as the frequency of monthly headache days increased, levels of the oxidative stress markers MDA and NO, as well as the endothelial dysfunction marker ADMA, also tended to be higher.

Keywords: Migraine, oxidative stress, nitrosative stress, MDA, NO, ADMA.

دور الإجهاد التأكسدي والنتروزي في مرضى الصداع النصفي

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الخلاصة

تهدف الدراسة إلى التحقيق في الدور المحتمل لإلجهاد التأكسدي في تطور الصداع النصفي. كان الهدف الرئيسي للدراسة هو قياس مستويات *malondialdehyde (MDA)* ، وهي عالمة لإلجهاد التأكسدي ، وأكسيد النيتريك*(NO)* ، وعالمة لإلجهاد النترزي وثنائي ميثيل أرجينين غير المتماثل*(ADMA)* باعتباره عالمة خلل وظيفي في البطانة . تضمن البحث *(90)* تسعين مشاركا من عيادة الصداع الخارجية التابعة لقسم االعصاب في مستشفى الجمهورية التعليمي في مدينة أربيل, 60 مريضا (45انثى و 15 ذكر)في مجموعة الصداع النصفي، بينما تألفت المجموعة الضابطة من 30 مشاركا *(*20 أنثى و 10 ذكور*)* مع مطابقة العمر والجنس. حصلت الدراسة على الموافقة الأخلاقية من قبل لجنة أخلاقيات البحث البشري (*HREC*) في قسم الأحياء ، كلية العلوم ، جامعة صلاح الدين – أربيل ، في 6 شباط 2022. اظهرت الدراسة أن مرضى الصداع النصفي

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لديهم مستويات أعلى بكثير من *MDA* و *NO* و *ADMA* من المجموعة الضابطة. بالإضافة إلى ذلك ، كان عدد أيام الصداع التي يعاني منها مرضى الصداع النصفي شهريا مرتبطا بشكل إيجابي بتركيزات مصل *MDA* و *NO* و *ADMA*. على وجه التحديد ، مع زيادة تواتر أيام الصداع الشهرية ، تميل مستويات علامات الإجهاد التأكسدي *MDA* و *NO* ، بالإضافة إلى علامة الخلل البطاني *ADMA* ، إلى أن تكون أعلى.

1. Introduction

Migraine is a prevalent neurological disorder that is commonly observed in developed countries, with an incidence of around 10-12% worldwide. Women experience migraines more frequently, with an incidence rate 2-3 times higher than that in men. Migraine episodes typically commence between the ages of 20 and 40 years. Migraine is characterized by episodes of unilateral throbbing headaches, vomiting, nausea and photo- and phonophobia. The duration of these symptoms ranges from 4 to 72 hours [1]. Migraine is a chronic neurovascular disorder that is highly prevalent and considered to be a leading cause of disability. Migraines have a significant negative impact on public health due to their high prevalence and incapacitating symptoms [2]. Episodic migraine and chronic migraine are the two basic kinds of migraine that are commonly recognized having less than 15 migraine-related headache days per month is known as an episodic migraine. Medical professionals can diagnose and treat migraine patients more successfully by using these distinctions. Contrarily, chronic migraine is characterized by more than 15 headache days per month, with at least 8 of those days displaying migraine features or responding to triptans, for at least three months [3]. When there exists a disparity between the activity of reactive oxygen species (ROS) and the body's capacity to counteract them with antioxidants, oxidative stress may ensue. This can result in harm to the cell membrane, encompassing microdamage, as well as DNA damage and the deactivation of proteins. As a result, the harmful effects of oxidative stress can impact various aspects of cellular function and lead to negative health outcomes [4]. Oxidative stress occurs when there is an imbalance between the production of reactive nitrogen species or ROS and the body's antioxidant defence systems [5]. Initially, an adaptive response occurs in the form of induction of antioxidant production. However, when antioxidant depletion occurs, cellular injury and dysfunction can follow. Therefore, oxidative stress can lead to detrimental effects on cells and tissues [6]. Free radicals from oxygen are extremely reactive substances that can harm biological molecules. Living things' proteins, nuclear DNA, and lipids are all vulnerable to harm from these radical species. Oxidative stress is the term used to describe the harm ROS bring to biological cells [7]. Neuronal damage can result from ROS, regardless of whether they are produced internally or externally [8]. By many influences such as diet, environment, behavior, and medication, brain tissue is continuously exposed to oxidative damage throughout a person's life. Hence, oxidative stress is key in the emergence of a variety of neurological conditions, including migraine [9].

Malondialdehyde (MDA) is regarded as a crucial biomarker for assessing levels of total lipid peroxidation and as a sign of free radical damage brought on by oxidative stress. MDA, a byproduct of lipid peroxidation, is widely used to measure the body's level of oxidative stress. Since free radicals and other ROS can harm cells and tissues, their presence indicates that they are being produced. As a result, monitoring MDA levels is a helpful method for determining the degree of oxidative stress present in the body [10]. MDA is an organic molecule that occurs naturally and can be utilized as a predictor of oxidative stress [11].

Nitric oxide (NO) is a type of neurotransmitter that is non-adrenergic and non-cholinergic. It is involved in processing painful impulses and sensitizing sensory nerves that surround blood vessels. Superoxide anions and NO react quickly because of the unpaired electrons in their outer orbits. The effective half-life and biological effects of NO are decreased by this

interaction's quick radical/radical reaction [12]. Tissue damage can result from the interaction of NO and peroxynitrite, a free radical that produces superoxide [13]. Previous research show that migraines and increased levels of oxidative stress may be related. High levels of oxidative stress have been linked to migraines in recent studies, particularly those that concentrated on children, adolescents, and women. As a result, migraines and elevated oxidative stress are probably related [14].

Asymmetric dimethylarginine (ADMA), an endogenously generated inhibitor of nitric oxide synthase (NOS), and its pathogenic effects have become crucial components of the biology of the NO pathway [15]. Importantly, ADMA can negatively impact the cellular and mitochondrial function of the target organs in addition to causing endothelial dysfunction [16].

The goals of this study involved quantifying the serum levels of nitric oxide (NO), malondialdehyde (MDA), and asymmetric dimethylarginine (ADMA) within both the migraine and control groups. Additionally, the study aimed to establish any potential correlations between the levels of MDA, NO, and ADMA with the frequency of monthly headache episodes.

2. Materials and Methods

2.1 Study population

This study took place between July 2022 and January 2023. Participants were recruited from the outpatient headache clinic at the Department of Neurology in Al Jumhury Teaching Hospital, located in Erbil, Iraq. The hospital's ethics committee approved recruitment of patients from this clinic for the study. This study included a total of 90 participants, with 60 patients and (30) as healthy controls. The migraine group consisted of 45 females and 15 males, while the control group contain of (20) females and (10) males, matched with age and sex.

Inclusion criteria: Participants meeting the inclusion criteria had a confirmed diagnosis of migraine without aura by an experienced neurologist using the International Classification of Headache Disorders (ICHD)-3 beta criteria [17]; They also had a minimum one-year history of migraine, were between the ages of (20 to 50 years) old, had discontinued any treatment for migraine management for at least three months before the study, and provided written consent to participate.

Exclusion criteria for the study included participants with coronary artery disease, menstrual irregularities, diabetes mellitus, Bechet’s disease, a history of drug allergy, severe hypertension, pregnancy, systemic or psychiatric diseases, liver or kidney dysfunction, seizure disorders, malignancies, and glaucoma. Additionally, individuals who were unwilling to participate in the study were excluded based on the predetermined exclusion criteria.

2.2 Sociodemographic

The participants were requested to fill out a sociodemographic questionnaire, gathering information on body mass index (BMI in kg/m^2), age (in years), current medications, medical background, and educational background. The neurologist will also gather information on the characteristics of migraine headaches, such as their monthly frequency and duration. The purpose of this data collection is to explain and understand the characteristics of migraine in the study population.

2.3 Collection of samples and measurements

To obtain blood samples, venous blood was drawn from the participants' antecubital vein and put into separator gel tubes. After 20 minutes, the tubes were centrifuged for 10 minutes at 5000 rpm to separate the serum from other blood components. The serum samples were then kept and stored at a temperature of -20°C until they were ready to be measured.

Malonaldehyde (MDA) level was measured using the Lipid Peroxidation (MDA) Assay Kit from Abbexa (abx096010, UK) and a microplate reader system. The MDA in the sample was combined with thiobarbituric acid (TBA) to form MDA-TBA, which was quantified calorimetrically at a wavelength of 532 nm. The data were presented in µmol/ml. NO was measured using the Nitric Oxide Assay Kit from Abbexa (abx298829, UK) and a microplate reader system. The dye reagents reacted with NO, producing an absorption maximum of 550 nm. The intensity of the colour was directly proportional to the concentration of NO. The results were expressed in µmol/ml. ADMA was measured using Asymmetrical Dimethylarginine ELISA Kit from Abbexa (abx574122, UK) and this kit is based on a competitive enzyme-linked immunosorbent assay technique (ELISA). The data were presented in ng/ml.

3. Statistical analysis:

To present the data, the mean and standard error of the mean (SEM) were used. The importance of the difference of various means has been tested with the use of the students-t-test for the differences between 2 independent means and the importance of the difference of different has been tested with the use Pearson correlation. Statistical significance has been taken under consideration whenever the P value has been ≤0.05. GraphPad Prism software was used to conduct the statistical analysis.

4. Results

The study revealed that the migraine group had 45 (50%) women and15 (16.6%) men and in the control group, there were 20 (22.2%) women and 10 (11.1%) men. It was found that the mean age of women with migraine was 34.78 years, while men had a mean age of 35.40 years. In the control group, the mean age of women was 32.85 years and men had a mean age of 33.4 years. The mean BMI (kg/m^2), the women with migraine was 26.63 and, while men with migraine had a mean BMI of 26.06. in the control group, the mean BMI (kg/m^2) of women was 25.31. While men had a mean BMI (kg/m^2) of 25.7. In addition, the results indicated that there were no significant differences in age or BMI between the migraine and control groups, as indicated by a p-value greater than 0.05 as shown in Table 1.

Table 1: Characteristics of the participants in the study

Variable	Patient (n=60)	Control (n=30)	*p*-value
Number of Women (%)	45 (50%)	20 (22.2%)	
Number of Men (%)	15 (16.6%)	10 (11.1%)	
Average Female Age (Year)	34.78	32.85	NS
Average Men Age (Year)	35.40	33.4	NS
Women's Average BMI (kg/m^2)	26.63	25.31	NS
Men's average BMI (kg/m^2)	26.06	25.70	NS

NS: Non-Significant

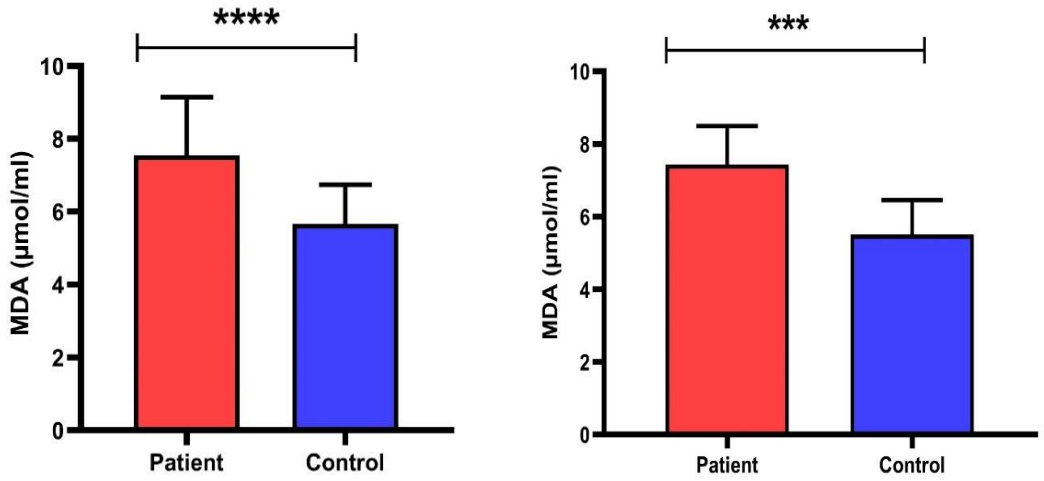
Table 2 and Figure 1 were presented data about MDA concentrations in two studied groups: the migraine and control groups. The highest mean MDA concentrations were recorded in the migraine group, with values of 7.552 ± 0.237 and 7.438 ± 0.273 µmol/ml for

females and males, respectively. In contrast, the control group had the lowest MDA concentrations, with values of 5.662 ± 0.242 and 5.511 ± 0.299 µmol/ml for females and males, respectively. The difference in MDA concentrations between the two studied groups were statistically significant with (P=0.0001).

Table 2: Presents the Mean ± S.E. values for both the patient and control groups

Variable	Patient	Control		Patient	Control	
	Female (n=45)	Female (n=20)		Male (n=15)	Male (n=10)	
	Mean± SE	Mean± SE	*P* -value	Mean± SE	Mean± SE	*P* -value
MDA (µmol/ml)	7.552 ± 0.237	5.662 ± 0.242	<0.0001	7.438 ± 0.273	5.511 ± 0.299	0.0001
NO (µmol/ml)	1.362 ± 0.108	0.799 ± 0.107	0.0005	1.382 ± 0.148	0.774 ± 0.082	0.0018
ADMA (ng/ml)	27.08 ± 2.300	12.93 ± 1.856	<0.0001	15.42 ± 1.294	9.942 ± 1.356	0.0080

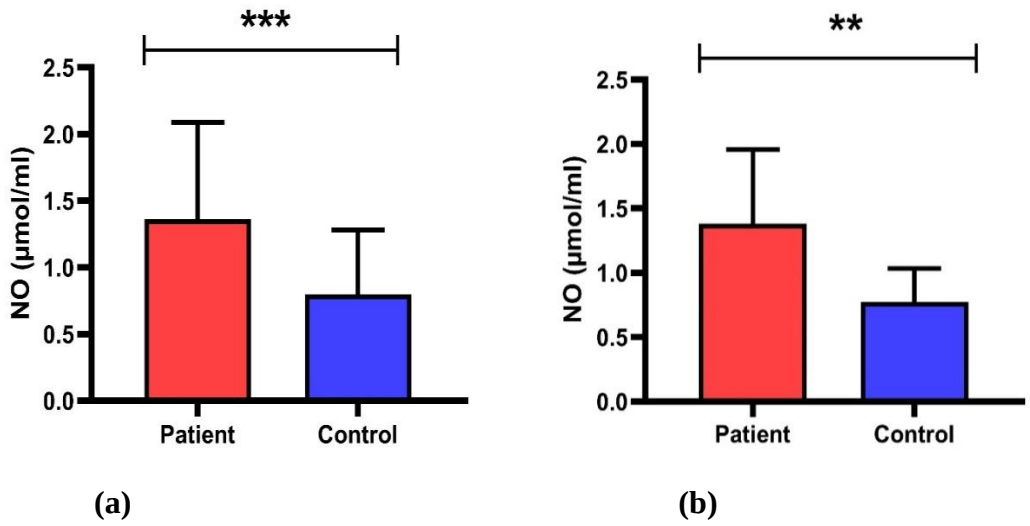
MDA: Malondialdehyde. NO: Nitric oxide. ADMA: Asymmetric dimethylarginine. Statistical significance level p <0.05.



(a) **(b)**

Figure 1: Serum malondialdehyde (MDA) (µmol/ml) levels in both patients and control groups (a) Female and (b) Male

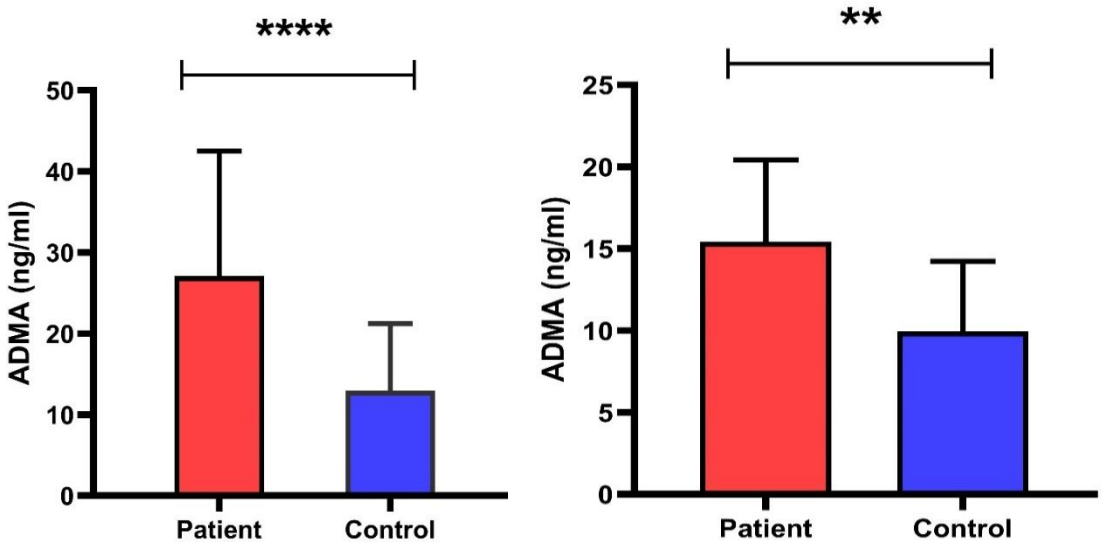
The findings indicated that the migraine group exhibited the highest average levels of NO concentration, with values of 1.362 ± 0.108 µmol/ml for females and 1.382 ± 0.148 µmol/ml for males. Conversely, the control group had the lowest NO concentrations, with values of 0.7996 ± 0.107 µmol/ml for females and 0.774 ± 0.082 µmol/ml for males, as shown in Table 2 and Figure 2. Statistical analysis revealed a significant difference in NO concentrations between the migraine and control groups (P=0.0018).



(a) **(b)**

Figure 2: Serum nitric oxide (NO) (µmol/ml) levels in both patients and control groups (a) Female and (b) Male

The results also predicted that the highest mean ADMA concentrations were obtained in the migraine group, with values of 27.08 ± 2.3 and 15.42 ± 1.294 ng/ml for females and males, respectively, while the lowest ADMA concentrations were found in the control group, with values of 12.93 ± 1.856 and 9.942 ± 1.356 ng/ml for females and males, respectively as represented in Table 2 and Figure 3. Statistical analysis revealed a significant difference in ADMA concentrations between the migraine and control groups (P=0.008).



(a) **(b)**

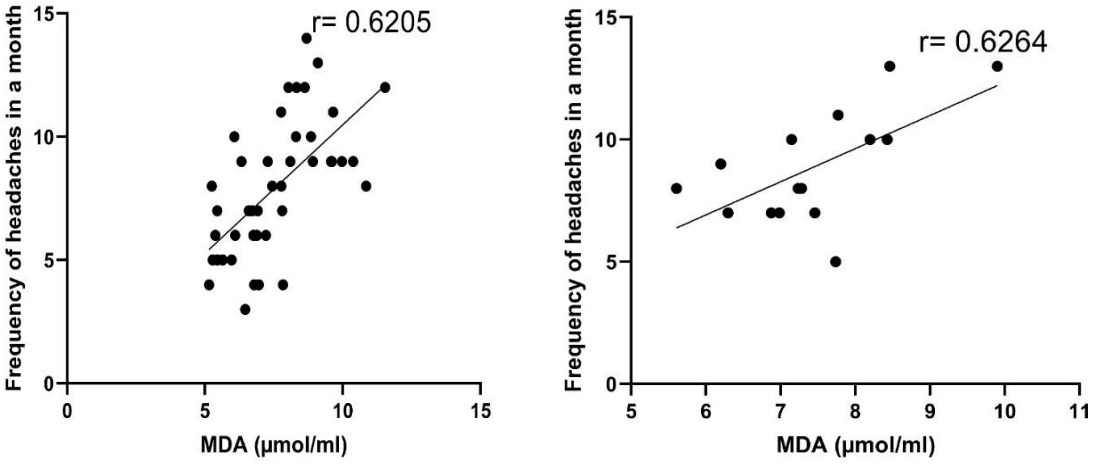
Figure 3: Serum asymmetric dimethylarginine (ADMA) (ng/ml) levels in both patients and control groups (a) Female and (b) Male

According to these findings of the Pearson correlation analysis was found a significant moderate positive correlation was observed between the levels of MDA and the frequency of monthly headaches experienced ($r=0.6205$, $p<0.0001$) among female patients, also, there was a moderate positive correlation between the levels of MDA and the frequency of headaches experienced in a given month ($r=0.6264$, $p<0.0125$) among male patients, as presented in Table 3 and Figure 4.

Table 3: Correlation between malondialdehyde and frequency of headaches in a month in patient groups.

Gender	Parameters	Pearson correlation (r)	*P*-values
Female	MDA (µmol/ml)	0.6205	<0.0001
Male	MDA (µmol/ml)	0.6264	0.0125

MDA: Malondialdehyde. Statistical significance level p <0.05



(a) **(b)**

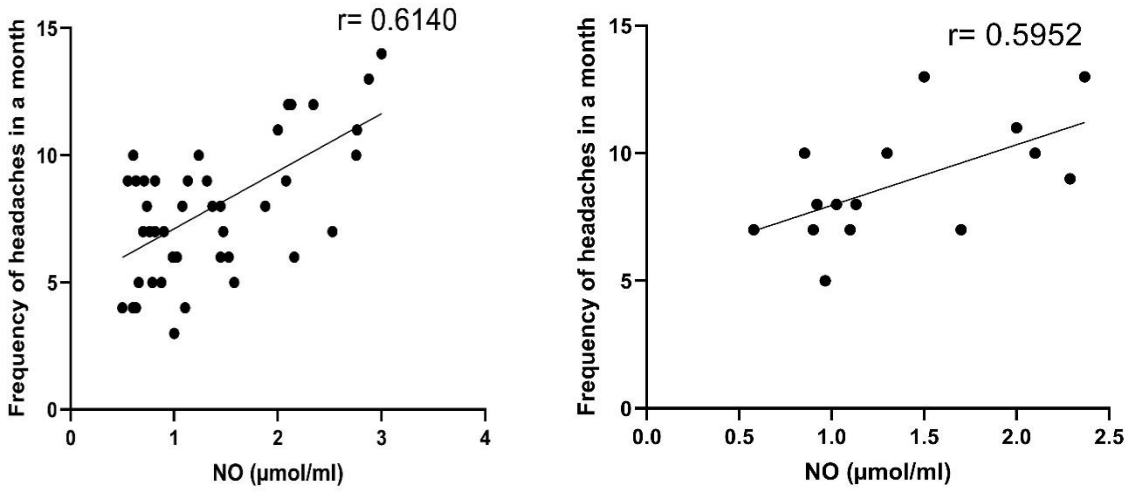
Figure 4: Correlation between serum MDA (µmol/ml) in patients and frequency of headaches in a month (a) Female and (b) Male

The findings also indicated a moderately strong positive correlation between NO levels and monthly headache frequency in female migraine patients. A Pearson correlation analysis showed that as nitric oxide concentrations increased, so did the number of headaches experience per month (r=0.6140, p<0.0001). This suggests that higher NO levels were associated with a greater number of monthly headache episodes among the female migraine participants. The levels of NO and the number of headaches experienced in a month showed a moderately positively correlated in male patients (r=0.5952, p=0.0192), as shown in Table 4 and illustrated in Figure 5.

Table 4: Correlation between nitric oxide and frequency of headaches in a month in patient groups

Gender	Parameters	Pearson correlation (r)	P-values
Female	NO (µmol/ml)	0.6140	<0.0001
Male	NO (µmol/ml)	0.5952	0.0192

NO: Nitric oxide. Statistical significance level p <0.05



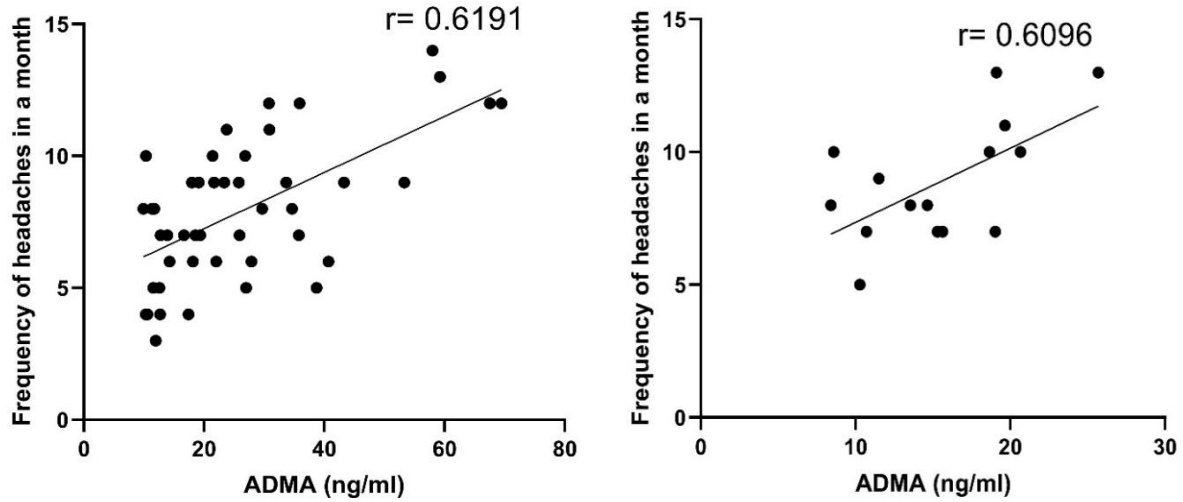
(a) **(b)**

Figure 5: Correlation between serum NO (µmol/ml) in patients and frequency of headaches in a month (a) Female and (b) Male

In addition, the study resulted that the ADMA levels and the number of headaches experienced in a given month were discovered to have a moderately positive correlation (r= 0.6191, p<0.0001) in female patients, according to the findings of the Pearson correlation analysis. The levels of ADMA and the number of headaches experienced in a month are moderately positively correlated in male patients (r=0.6096, p=0.0158), as shown in Table 5 and illustrated in Figure 6.

Table 5: Correlation between Asymmetric dimethylarginine and frequency of headaches in a month in patient groups

Gender	Parameters	Pearson correlation (r)	P-values
Female	ADMA (µmol/ml)	0.6191	<0.0001
Male	ADMA (µmol/ml)	0.6096	0.0158



ADMA: Asymmetric dimethylarginine. Statistical significance level p <0.05

(a) **(b)**

Figure 6 Correlation between serum ADMA (ng/ml) in patients and frequency of headaches in a month (a) Female and (b) Male

5. Discussion

In this study, the serum concentrations of biochemical markers MDA, NO, and ADMA were assessed in both individuals with migraines and those without. The research observed a significant elevation in MDA levels among both male and female migraine patients when compared to the control group without migraines. MDA is a lipid oxidation byproduct that might signify increased amounts of ROS generation and is, therefore, this result consider this marker as a biomarker for assessing oxidative stress [18]. The migraine patient group's MDA levels were found to have significantly increased, which suggests that there was more lipid peroxidation, a major cause of oxidative stress. Polyunsaturated fatty acids, which were found in high concentrations in neuronal membranes, make them particularly sensitive to this form of stress. This result suggests that neuronal loss and oxidative stress may be key factors in the a etiology of migraines [19].

Oxidative stress may play a role in the pathogenesis of migraines, altering the antioxidant-oxidant balance and favoring lipid peroxidation. According to these results, oxidative stress and the body's ability to battle it may contribute to migraine development, including the chronic subtype of the illness [20]. Bockowski, et al. [21] were carried out a study to investigate how lipid peroxidation (MDA) affected migraineurs with and without aura. According to the previous study on children with migraines were found to appear higher levels of MDA when compared with children with no migraines. Other previous stusy conducted by Gupta, et al. [22] ,they compared the levels of oxidative stress in migraineurs, tension headache sufferers, and a control group. Their results showed that people with tension-type headaches and migraine patients had greater levels of MDA when compared with control group. Aytaç, et al. [23] carried out a study on antioxidant status in migraineurs with brain white matter hyperintensities. The results of the study demonstrated that migraine sufferers with brain white matter hyperintensities had reduced antioxidant status and greater levels of MDA. Tuncel, et al. [24] carried out a study to investigate oxidative stress in people with migraines, both with and without aura. The results of the study revealed that MDA levels were increased in migraine patients, both with and without aura, indicating the presence of oxidative stress.

Additionally, the current research showed there was a notable increase in nitric oxide (NO) levels in both males and females with migraines compared to healthy individuals without headaches. NO concentrations were significantly higher in the migraine groups of both genders relative to the control group. This study reinforces that NO is an important signaling molecule in the brain and body, as it revealed differential NO levels between those experiencing migraine attacks and those who did not have the condition [25]. Nitroglycerin (NTG), a NO-donor, is a well-known migraine trigger and has been used extensively in experimental models to cause migraine attacks. Although it has also been proposed that NTG has functions independent of NO, bioactivation in the body is necessary for NTG to create NO [26]. The phenomena of clinical NTG tolerance, which can happen through the generation of peroxynitrite, is usually thought to be caused by the depletion of the bioactivation machinery and the concurrent increase in oxidative stress [27]. The genesis of migraines has been linked to oxidative stress and peroxynitrite production [28]. NO is the smallest signalling molecule and is one of the most significant reactive species molecules. Nitric oxide's increasing production will raise nitro-oxidative stress. The activation of neuronal NOS (nNOS), inducible NOS (iNOS), and endothelial NOS (eNOS), three isoforms of NOS, might result in an increase in NO production [29]. There is growing evidence to suggest that free radical-induced oxidative stress may be involved in the pathogenesis of migraine. The activity

of free radicals in migraine can be linked to NO, which has various effects such as dilating cerebral vessels, acting as a nociceptive neurotransmitter, and playing a key role in the trigeminovascular mechanism of migraine by regulating cerebral blood flow [30]. The potential impact of oxidative stress on headache aetiology is unknown. However, it is thought that elevated levels of ROS, NO metabolites, and pro-inflammatory mediators can result in the oxidation of intracellular molecules (particularly proteins and DNA) and the peroxidation of cell membrane phospholipids, which ultimately disrupts normal cellular function [31].

During migraine attacks, oxidative stress can be exacerbated in some ways. These processes include increased mitochondrial energy generation, cellular calcium excess, excitotoxicity of neurons, neuroinflammation, activation of microglia, and activation of neuronal nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [29]. ROS can be produced more than the body's antioxidant defence mechanisms, causing oxidative stress, which has been connected to a range of headache problems, including migraines. Lipids, proteins, and DNA may become harmed by the ensuing oxidative processes [32]. During a migraine, oxidant generation is a complex process that is influenced by a wide range of circumstances. The metabolic changes in the cerebral cortex brought on by intracellular calcium overload during cortical spreading depression, which increases the need for oxygen and may result in oxidative stress, are one of the contributing factors. Local changes in cerebral blood flow that encourage the formation and release of free radicals may also contribute to an accumulation of lipid peroxidation byproducts in the blood. These changes may be to blame for migraineurs' increased susceptibility to oxidative stress [33]. Migraine can also affect mitochondrial biogenesis in the trigeminal nerve, resulting in reduced ATP production and elevated ROS synthesis [34]. Additionally, it has been discovered that ADMA is a marker of oxidative stress and endothelial dysfunction in migraine [35].Uzar, et al. [36] with a previous study were examined the levels of NO and ADMA in migraine sufferers. The results of this study revealed an elevation in levels of NO and ADMA in the group of patients who suffered from migraines. Reyhani, et al. [37] conducted a study on high levels of ADMA, symmetric dimethylarginine, and L-arginine in migraine sufferers. The findings of this study explained that ADMA levels in migraine sufferers were much greater than in the control group. Other study carried out by Ciancarelli, et al. [38] found that the NO levels in the migraine patient group were higher than those in the control group. Also, Yilmaz, et al. [39] reported that the levels of ROS, which might result in the formation of NO metabolites and MDA, may be higher in migraineurs than in healthy individuals. Beside that a meta-analysis conducted by Neri, et al. [40] based on the findings of 19 previous studies examining the relationship between oxidative/nitrosative pathways and migraine, suggested that migraine patients may appear higher levels of oxidative stress compared to controls. Togha, et al. [41] conducted a case-control study to examine the oxidant/antioxidant balance in migraine sufferers. The study's findings showed that compared to the control group, the migraine patient group had higher levels of NO and MDA.

When comparing subjects in this study according gender (female and male patients with female and male controlswith female and male controls), Results showed a greater significance in female migraine patients compared to male patients. Women are reported to experience migraines three times more frequently than males. The different levels of sexual hormones generated by men and women, such as progesterone and estrogens, which are thought to be crucial in the development of the disease, may be the root reason for this gender imbalance [42]. For instance, changes in estrogen levels can precipitate migraines, increasing their frequency during menstruation, perimenopause, and menopause. Hormonal headaches are less common during pregnancy, but after birth, they frequently become worse. Hence, oral contraceptives or hormone replacement treatment may hasten the development of migraines

[43]. During childhood, migraine occurs equally in both sexes, but as adolescence sets in, the incidence in females seems to increase to 2-3 times higher compared to males. In Europe, the risk of developing a migraine over a lifetime is reported to be between 12-28%. Every year, migraines affect around 14-35% of females and 6-15% of males [44].

According to the Pearson correlation analysis, a moderately positive correlation between the number of headaches experienced in a particular month and the concentrations of MDA, NO and ADMA was found. Togha, et al. [41] carried out a case-control study aimed at exploring the oxidant/antioxidant balance in individuals with migraines. The results of this study showed a moderately positive relationship between the frequency of headaches experienced during a given month and the concentrations of NO ($r = 0.62$, P-value< 0.001), and MDA ($r = 0.64$, P-value< 0.001).

Conclusions

In summary, this study provided valuable perspective on how oxidative/nitrosative stress could potentially contribute to migraine development. The findings suggest oxidative stress may strongly influence migraine pathogenesis given the elevated levels of MDA, an indicator of oxidative stress, detected in migraine patients. Additionally, the higher levels of NO, a marker of nitrosative stress, and ADMA, a sign of endothelial dysfunction, found among migraine participants imply oxidative mechanisms could underlie the condition. Therefore, this research furthers the understanding of how oxidative/nitrosative stress may play an important role in the onset and progression of migraine headaches. High correlation between headache frequency and MDA, NO and ADMA levels was found. The findings highlight the need for additional research to better understand the underlying mechanisms linking oxidative stress, nitrosative stress, endothelial dysfunctions and migraines.

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Conflict of interest: According to the authors, there aren't any conflicting interests.

Ethical standards

The Human Research Ethics Committee (HREC) at the Biology Department, College of Science, Salahaddin University-Erbil has approved the study as ethical.

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