

## Assessment of the Antioxidants Blood Levels of Migraine Patients in Erbil City

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### Abstract

Migraine is a prevalent chronic condition that is often characterized by recurrent incapacitating headache attacks and related symptoms. The aim of this study was to assess the levels of several significant antioxidants, including catalase (CAT), superoxide dismutase (SOD), thioredoxin (TRX), and glutathione peroxidase 1 (GPX1), in migraine patients. Ninety participants were recruited from the outpatient headache clinic of the neurology department at Al Jumhury Teaching Hospital in Erbil City for this study. In this study, there were 60 patients with migraine and 30 controls. Among the migraine group, there were 45 female and 15 male participants, while the control group consisted of 20 female and 10 male participants, with matching in terms of age and sex. According to study results, both male and female migraine patients had significantly lower levels of enzymes superoxide dismutase (SOD) and glutathione peroxidase 1 (GPX1) compared to the control group. Additionally, female migraine patients had significant lower levels of catalase (CAT) compared to the control group. In male migraine patients, catalase (CAT) also showed lower levels compared to control group, but the difference was not statistically significant. On the other hand, thioredoxin (TRX) showed lower levels in both female and male migraine patients, but the difference was not statistically significant compared to the control group. In both females and males, a negative correlation was found between the frequency of headache-related days per month and the serum concentrations of superoxide dismutase (SOD), with a correlation coefficient of -0.3543 for females and -0.6089 for males.

**Keywords:** Migraine, Antioxidants, CAT, SOD, GPX1, TRX.

### تقييم مستويات مضادات الأكسدة في الدم لمرضى الصداع النصفي في مدينة أربيل لانه عثمان محمود<sup>\*1</sup>، كامران عبدالرحمن<sup>1</sup>

قسم الكيمياء ، كلية العلوم ، جامعة صلاح الدين - أربيل ، أربيل ، إقليم كردستان ، العراق

#### الخلاصة

الصداع النصفي هو حالة مزمنة منتشرة تتميز غالبا بنوبات الصداع المتكررة المعجزة والأعراض ذات الصلة. ان الغرض من هذه الدراسة هو لتقييم الآثار المحتملة لمضادات الأكسدة على الصداع النصفي. ان الهدف الرئيسي من الدراسة هو قياس تراكيز العديد من مضادات الأكسدة المهمة ، مثل الكاتالاز (CAT) ، ديسموتاز الفائق الأكسيد (SOD) ، ثيوريدوكسين (TRX) والجلوتاثيون بيروكسيديز 1 (GPX1). شارك في الدراسة تسعين شخصا من العيادة الخارجية لقسم الأعصاب في مستشفى الجمهورية التعليمي في مدينة أربيل . في هذه الدراسة ، كان هناك 60 مريضا يعانون من الصداع النصفي و 30 شخص كمجموعة ضابطة. من بين مجموعة المرضى بالصداع النصفي ، كان هناك 45 مشاركة من الإناث و 15 من الذكور ، في حين تألفت المجموعة الضابطة من 20 مشاركة من الإناث و 10 من الذكور ، مع المقارنة من حيث العمر والجنس. وفقا لنتائج الدراسة ، كان لدى كل من مرضى الصداع النصفي من الذكور والإناث مستويات منخفضة جدا من إنزيمات SOD و GPX1 مقارنة بالمجموعة الضابطة. بالإضافة إلى ذلك ، كان لدى مرضى الصداع النصفي الإناث مستويات قليلة ملحوظة CAT مقارنة بالمجموعة الضابطة. في مرضى الصداع النصفي الذكور ، أظهر CAT أيضا مستويات أقل مقارنة بالمجموعة الضابطة ، لكن الفرق لم يكن ذا دلالة مقارنة بالمجموعة الضابطة. من ناحية أخرى ، أظهر TRX مستويات أقل في كل من مرضى الصداع النصفي من الإناث والذكور ، لكن الفرق لم يكن ذا دلالة إحصائية مقارنة بالمجموعة الضابطة. في كل من الإناث والذكور ، تم العثور على ارتباط سلبي بين تكرار الأيام المرتبطة بالصداع في الشهر وتركيزات ديسموتاز الفائق (SOD) في المصل ، مع معامل ارتباط 0.3543 للإناث و 0.6089 للذكور.

الكلمات المفتاحية : الصداع النصفي ، مضادات الأكسدة ، CAT ، SOD ، GPX1 ، TRX.

### Introduction

Migraine attacks have a negative effect on productivity and quality of life in both personal and

social environments. It was also discovered that migraineurs have a significantly higher prevalence

of panic and anxiety disorders than the general population. Stress, too much or too little sleep, hormones, neuroendocrine imbalances, inflammation, oxidative stress, and unhealthy diet and allergenic foods have all been identified as migraine triggers <sup>(1)</sup>. Migraines are a common neurological disorder that is frequently seen in developed nations. A 2-3 times higher incidence rate in women than in men indicates that women are more frequently affected. In most cases, migraines begin between the ages of 20 and 40. Unilateral throbbing headaches, vomiting, nausea, photo- and phonophobia, and throbbing headaches are symptoms of migraine. These symptoms can last from four to seventy-two hours <sup>(2)</sup>. Around 14.4% of people worldwide are thought to get migraines, with women experiencing them at a rate of 18.9% and males at a rate of 9.8% <sup>(3)</sup>.

A considerable majority of people under the age of 50 suffer from migraines, which are a prevalent neurological condition that significantly impairs individuals and places a heavy strain on society. It is characterized by paroxysmal attacks with head discomfort, nausea, and heightened sensitivity to light, sound, and movement <sup>(4)</sup>. For a migraine attack to be considered a chronic migraine (CM), which is defined as a headache that happens more than 15 days a month, it must last at least eight days for more than three months. Episodic migraine is the presence of migraines on less than 15 days per month (8 days of an episode) <sup>(5)</sup>. Antioxidants' physiological function is to stop chemical processes, particularly those caused by free radicals, from harming the cellular components. The ability of antioxidants to function as free radical scavengers is what gives them their protective characteristics <sup>(6)</sup>. The complex antioxidant defense system in human cells is made up of the enzymes catalase (CAT), superoxide dismutase (SOD), glutathione reductase, and glutathione peroxidase (GPX), as well as some low molecular weight antioxidants including vitamins, glutathione, ascorbate, tocopherol, cysteine, and thioredoxin <sup>(7)</sup>.

The body has evolved a variety of natural antioxidant defense systems, both enzymatic and non-enzymatic. In addition to several endogenous enzymes including catalase, glutathione peroxidase, and glutathione reductase, the non-enzymatic defense mechanism also consists of vitamins C and E and reduced glutathione. The initial line of defense against reactive oxygen species (ROS) is provided by the essential endogenous antioxidant enzyme SOD, which converts superoxide radicals into H<sub>2</sub>O<sub>2</sub> <sup>(8)</sup>. The body's supply of antioxidant molecules comes from both endogenous and external sources, and the body's antioxidant defense system is a very complicated biochemical architecture made up of many enzymes and scavenger molecules <sup>(9)</sup>. The TRX system is essential for neutralizing ROS and

shielding cells from free radical damage. In this system, the TRX protein serves as a hydrogen donor and is reduced by the thioredoxin reductase enzyme, which uses NADPH to enhance its functions <sup>(10)</sup>.

In this study, we were interested in comparing the serum levels of the patients with migraine and control groups for SOD, CAT, GPX1, and TRX, and investigated any possible associations between SOD, CAT, GPX1, and TRX levels and the frequency of monthly headache episodes.

## Materials and Methods

### Study population

The outpatient clinic unit of the department of neurology at Al Jumhury Teaching Hospital in Erbil served as the study's recruitment site from July 2022 to January 2023. The Hospital Ethics Committee approved the study's protocol. With 60 patients with migraine and 30 controls, there were a total of 90 participants in the study. The control group contained 20 females and 10 males that were age- and sex-matched, whereas the migraine group had 45 females and 15 males.

Inclusion criteria: Participants who met the inclusion criteria had an experienced neurologist confirm their diagnosis of migraine without aura using the International Classification of Headache Disorders (ICHD)-3 beta criteria <sup>(11)</sup>; They also had a minimum of one year of migraine history, were between the ages of 20 and 50, had stopped taking any medication for migraine management for at least six months before the study, and gave written consent to participate.

Exclusion criteria: Participants with coronary artery disease, irregular periods, a history of drug allergies, severe hypertension, pregnancy, diabetes mellitus, Behçet's disease, systemic or psychiatric problems, dysfunctional liver or kidneys, seizure disorders, malignancies, and glaucoma were excluded from the study.

### Sociodemographic

A sociodemographic questionnaire were given to the participants, and it would ask questions about their body mass index (BMI), age, current medications, past medical conditions, and education. The length and frequency of migraine headaches monthly would also be gathered by the neurologist. Data collection was carried out in order to gain a deeper understanding of the attributes of migraines.

### Collection of samples and measurements

Blood samples were obtained by drawing venous blood from the participant's antecubital vein and placing it into separator gel tubes. The tubes were centrifuged at 5000 rpm for 10 minutes after 20 minutes to separate the serum from other blood components. Serum samples were maintained at a temperature of -20°C, ready to be measured at any time. CAT was measured using Human Catalase

(CAT) ELISA Kit from Abbexa (abx572370, UK) and This kit's technology is based on a sandwich enzyme-linked immunosorbent assay. The data were presented in ng/ml. SOD was measured using the Superoxide Dismutase (SOD) Assay Kit from Abbexa (abx096009, UK) and a microplate reader system. SODs reduce superoxide concentration and therefore lower the rate of NBT-formazan formation. NBT-formazan concentrations can be determined by measuring the absorbance at 560 nm. The results were expressed in U/ml. GPX1 was measured Human Glutathione Peroxidase 1 (GPX1) ELISA Kit from Abbexa (abx253783, UK), and the sandwich enzyme-linked immunosorbent assay technique acts as the basis for this kit. The data were presented in pg/ ml, and the TRX was measured Human Thioredoxin / TRX (TXN) ELISA Kit from Abbexa (abx252296, UK), the kit is known as an enzyme-linked sandwich immunosorbent assay. The data were presented in ng/ml.

**Statistical analysis**

The data were presented using the mean and standard error of the mean (SEM). To determine

how the variables were correlated, unpaired t-tests and Spearman correlation analysis were utilized. A significance level of 0.05 was employed to evaluate statistical significance. The statistical analysis was completed using the Graph Pad Prism program.

**Results and Discussion**

According to the study, there were 45 (50%) women and 15 (16.6%) men in the patient with migraine group and 20 (22.2%) women and 10 (11.1%) men in the control group. According to the study, women and men with migraines were on average 34.78 years old and 35.40 years old, respectively. The mean ages of the women and men in the control group were 32.85 and 33.4 respectively. Women with migraines had a mean body mass index (BMI) of 26.63, whereas men with migraines had a mean BMI of 26.06. In the control group, women had a mean BMI of 25.31 and men had a mean BMI of 25.70. A p-value larger than 0.05 in Table (1) indicates that the findings showed no significant differences in BMI or age between the migraine and control groups.

**Table 1. Characteristics of Migraine Patients**

Variable	Patient (n=60)	Control (n=30)	p-value
Women (%)	45 (50%)	20 (22.2%)	
Men (%)	15 (16.6%)	10 (11.1%)	
The average age of women (Year)	34.78	32.85	NS
The average age of men (Year)	35.40	33.4	NS
Average BMI (kg/m <sup>2</sup> ) for Women	26.63	25.31	NS
Average BMI (kg/m <sup>2</sup> ) for men	26.06	25.70	NS

NS: Non-Significant

Table (2) and Figure (1) present data on CAT concentrations in two groups: patient with migraine and control groups. The lowest mean CAT concentrations were recorded in the migraine group, with values of 1.441 ± 0.030 and 1.388 ± 0.036 (ng/ml) for females and males, respectively. In contrast, the control group had the highest CAT

concentrations, with values of 1.814 ± 0.104 and 1.520 ± 0.075 (ng/ml) for females and males, respectively. In comparison with the male migraine patients, the difference in CAT concentrations between the two groups was statistically significant in female migraine patients.

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

Variable	Patient		P-value	Control		P-value
	Female (n=45)	Female (n=20)		Male (n=15)	Male (n=10)	
	Mean± SE	Mean± SE		Mean± SE	Mean± SE	
CAT (ng/ml)	1.441 ± 0.030	1.814 ± 0.104	0.0023	1.388 ± 0.036	1.520 ± 0.075	NS
SOD (U/ml)	220 ± 2.392	292.6 ± 3.73	<0.0001	209.1 ± 2.42	287.6 ± 3.53	0.0003
GPX1 (pg/ml)	230.0 ± 3.91	315 ± 1.64	0.0056	255.3 ± 3.63	319.3 ± 2.89	0.0150
TRX (ng/ml)	5.409 ± 0.276	6.392 ± 0.427	NS	3.285 ± 0.315	3.927 ± 0.145	NS

CAT, Catalase. SOD, Superoxide dismutase. GPX1, Glutathione Peroxidase 1. TRX, Thioredoxin. SE, Standard error. NS, no significant differences. Statistical significance level p <0.05.

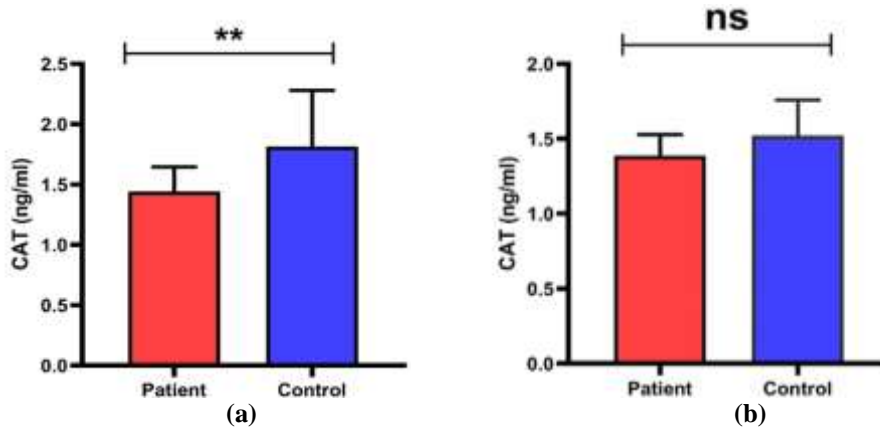


Figure 1. Serum Catalase levels in both patient and control groups (a) Female and (b) Male

The highest mean SOD concentrations were recorded in the control group, with values of  $292.6 \pm 3.73$  and  $287.6 \pm 3.53$  U/ml for females and males, respectively, while the lowest SOD concentrations were found in the migraine group, with values of

$220 \pm 2.392$  and  $209.1 \pm 2.42$  U/ml for females and males, respectively as shown in Table (2) and Figure (2). Statistical analysis revealed a strongly significant difference in SOD concentrations between the migraine and control groups.

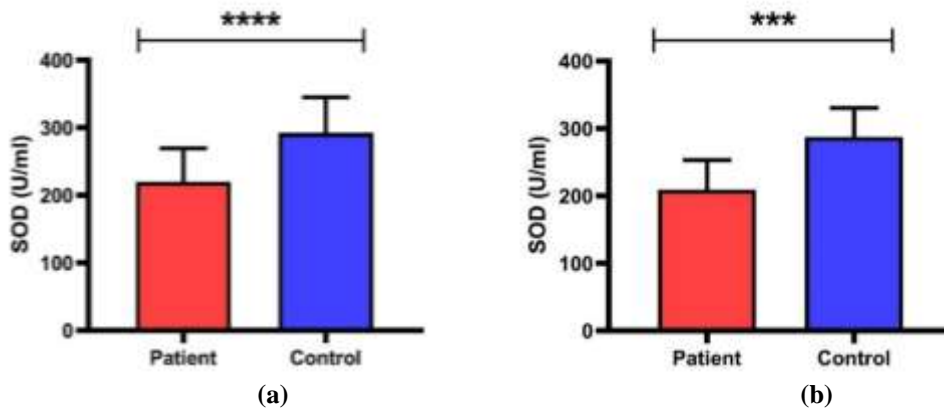


Figure 2. Serum Superoxide dismutase levels in both patient and control groups (a) Female and (b) Male

The highest mean, GPX1 concentrations were recorded in the control group, with values of  $315 \pm 1.64$  and  $319.3 \pm 2.89$  pg/ml for females and males, respectively, while the lowest GPX1 concentrations were found in the migraine group, with values of  $230.0 \pm 3.91$  and  $255.3 \pm 3.63$  pg/ml

for females and males, respectively as showed in Table (2) and Figure (3). GPX1 concentrations were significantly different between the patient with migraine and control groups according to statistical analysis.

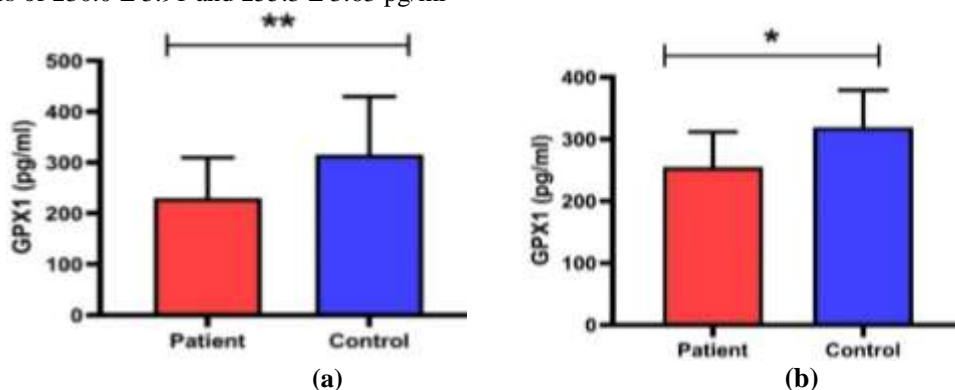
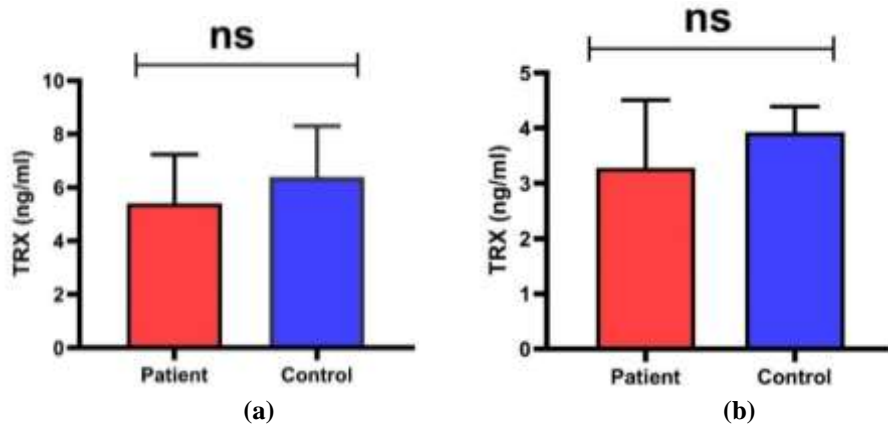


Figure 3. Serum Glutathione Peroxidase 1 levels in both patient and control groups (a) Female and (b) Male

The highest mean, TRX concentrations were recorded in the control group, with values of  $6.392 \pm 0.427$  and  $3.927 \pm 0.145$  ng/ml for females and males, respectively, while the lowest TRX concentrations were found in the migraine group, with values of  $5.409 \pm 0.276$  and  $3.285 \pm 0.315$

ng/ml for females and males, respectively as showed in Table (2) and Figure (4). Statistical analysis showed no significant difference in TRX concentrations between the patient with migraine and control groups.



**Figure 4. Serum Thioredoxin levels in both patient and control groups (a) Female and (b) Male**

The antioxidative scavenging system, which is engaged in preventing the production of oxidants, is composed of enzymatic and non-enzymatic substances such as glutathione peroxidase, superoxide dismutase, and catalase<sup>(12)</sup>. GPX, which uses glutathione as an electron donor, is a member of another class of antioxidants. They catalyze the conversion of organic hydroperoxides and  $H_2O_2$  into water or the equivalent alcohols<sup>(13)</sup>. GPX1, which is predominately found in glial cells, is the most common GPX in the brain<sup>(14)</sup>. This location could be the reason why glial cells are more resistant to oxidative damage than neuronal cells<sup>(15)</sup>. SOD, one of the most significant antioxidants, is an essential  $O_2$  scavenger. The majority of the superoxide produced is predominantly transformed by SOD into  $H_2O_2$  and then into  $H_2O$ . Myeloperoxidase can further metabolize  $H_2O_2$  to create hypochlorous acid (HOCl), which can then interact with superoxide to create hydroxyl radicals ( $OH\cdot$ ). The Fenton reaction can also produce hydroxyl radicals from  $H_2O_2$ . Moreover, SODs can decrease the oxidative inactivation of NO to stop the creation of ONOO and subsequently endothelial impairment<sup>(16)</sup>. The metalloenzyme family known as SOD, which catalyzes the dismutation of superoxide anions into molecular oxygen and hydrogen peroxide, is a key part of the cellular antioxidant defense system. SOD lowers the quantity of superoxide and prevents NO from breaking down into nitrite and nitrate by scavenging superoxide anions, SOD reduces the amount of superoxide while also preventing NO from degrading into nitrite and nitrate. The antioxidant enzyme SOD is less active in migraineurs than in healthy controls, indicating that oxidative stress is more easily produced in migraineurs and that antioxidant defenses are less effective<sup>(17)</sup>. GPX, SOD, and CAT are all

components of antioxidant defense mechanisms that efficiently eliminate ROS in normal physiological conditions. SOD may even promote the transformation of superoxide radicals into  $H_2O_2$ . The subsequent breakdown of this latter component ( $H_2O_2$ ) into water and oxygen by GPX and CAT prevents the accumulation of ROS. In practically all aerobic species, the antioxidant enzyme CAT converts two  $H_2O_2$  molecules into one oxygen molecule, making it one of the most significant antioxidant enzymes<sup>(18)</sup>. Antioxidants including SOD and GPX are reportedly decreased in migraine sufferers compared to controls, according to research by Bolayir et al.<sup>(19)</sup>. Bockowski et al.<sup>(20)</sup> carried out a study to investigate how lipid peroxidation affected migraineurs with and without aura. According to the study, children with migraines had low levels of SOD than children who did not have migraines. Aytac et al.<sup>(21)</sup> in the study, antioxidant status was examined 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 such as CAT. Togha et al.<sup>(22)</sup> 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 low levels of SOD and CAT. Neri et al.<sup>(23)</sup> conducted a meta-analysis on how oxidative/nitrosative pathways relate to migraine. Their findings demonstrated that the tested subjects' SOD activity was lower than that of the control group.

The results of the Pearson correlation analysis revealed a negative correlation between the levels of SOD and the frequency of monthly headaches experienced. For male patients, the correlation coefficient ( $r$ ) was  $-0.6089$  with a  $p$ -

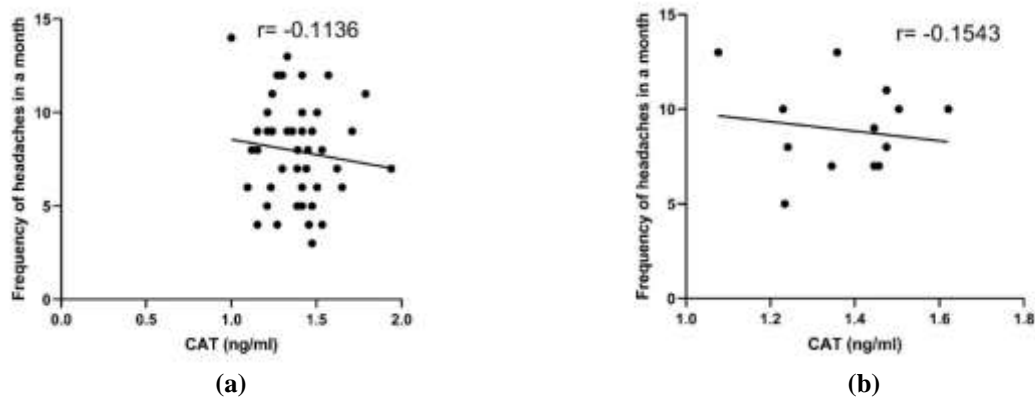
value of 0.0160, indicating a statistically significant negative relationship. Similarly, among female patients, the correlation coefficient was -0.3543 with a p-value of 0.0169, also indicating a statistically negative relationship. These findings were presented in Table (3) and illustrated in Figure (6). The Pearson correlation analysis revealed a negative

correlation between the levels of CAT, GPX1, and TRX, and the frequency of monthly headaches experienced in both female and male patients. However, upon statistical analysis, this correlation was not found to be statistically significant, as shown in Table (3) and Figures 5,7, and 8.

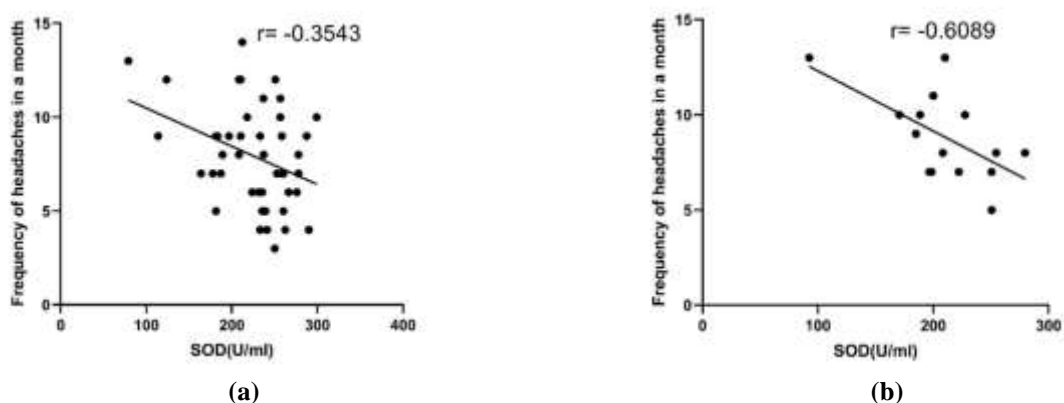
**Table 3. Correlation Study between Antioxidant Parameters and Headaches in Patients**

Gender	Parameters	Pearson correlation (r)	P-values
Female	CAT (ng/ml)	-0.1136	NS
Male	CAT (ng/ml)	-0.1543	NS
Female	SOD (U/ml)	-0.3543	0.0169
Male	SOD (U/ml)	-0.6089	0.0160
Female	GPX1 (pg/ml)	-0.0623	NS
Male	GPX1 (pg/ml)	-0.2341	NS
Female	TRX (ng/ml)	-0.1028	NS
Male	TRX (ng/ml)	-0.0604	NS

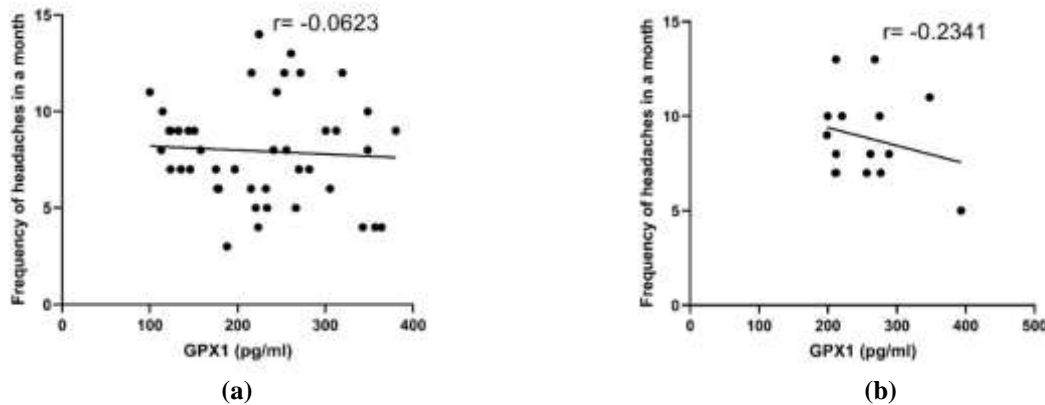
CAT, Catalase. SOD, Superoxide dismutase. GPX1, Glutathione Peroxidase 1. TRX, Thioredoxin. NS, no significant differences. Statistical significance level  $p < 0.05$



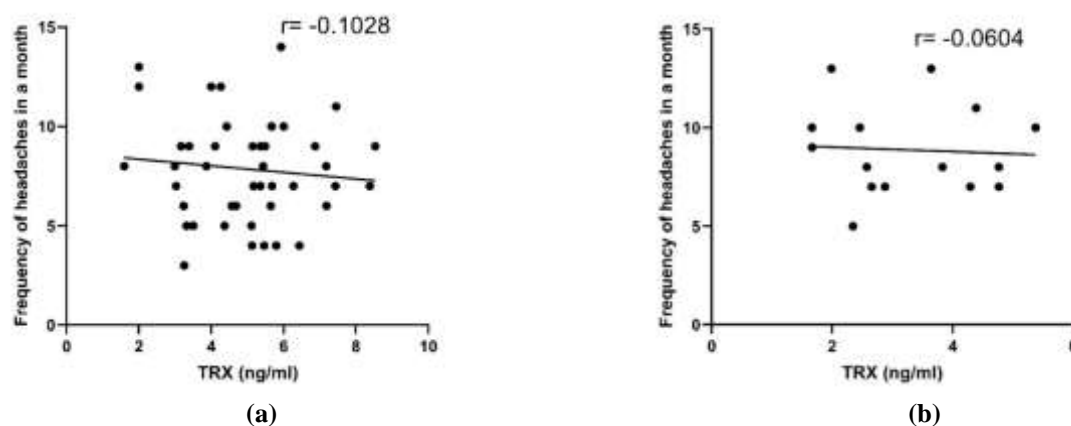
**Figure 5. Correlation between serum CAT in patients and frequency of headaches in a month (a) Female and (b) Male**



**Figure 6. Correlation between serum SOD in patients and frequency of headaches in a month (a) Female and (b) Male**



**Figure 7. Correlation between serum GPX1 in patients and frequency of headaches in a month (a) Female and (b) Male**



**Figure 8. Correlation between serum TRX in patients and frequency of headaches in a month (a) Female and (b) Male**

The findings of the present study, of the Pearson correlation analysis showed that there was a significant negative correlation between the levels of SOD and the frequency of monthly headaches in both male and female patients. This indicates that as the levels of SOD decrease, the frequency of monthly headaches tends to increase. The levels of TRX, CAT, and GPX1 as well as the frequency of monthly headaches experienced by both male and female patients, were found to be negatively correlated by using Pearson correlation analysis. However, statistical analysis did not reveal that this association was statistically significant. Togha et al.<sup>(22)</sup> carried out a case-control study aimed at exploring the oxidant/antioxidant balance in individuals with migraines. The serum concentrations of the two antioxidant enzymes SOD and CAT both exhibited negative relationships with the number of headache days experienced each month ( $r = 0.50$ ,  $P$ -value 0.001) and CAT ( $r = 0.60$ ,  $P$ -value 0.001).

### Conclusions

In conclusion, the findings of this research highlight the potential impact of antioxidants on migraine disease. The study examined the levels of

important antioxidants in migraine patients and in a control group, including SOD, CAT, GPX1, and TRX. The results showed that female and male migraine patients had significantly lower levels of SOD and GPX1 compared to the control group. Female migraine patients also had lower levels of CAT compared to the control group. TRX levels were lower in both female and male migraine patients, but the difference was not statistically significant compared to the control group. These findings suggest that there may be an imbalance in the antioxidant levels in migraine patients. Further research is needed to understand the role of antioxidants in the pathophysiology of migraine.

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### Conflicts of Interest

The authors declare no conflict of interest during this study.

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None

## Ethics Statements

The project has received approval from Salahaddin University-Erbil's Human Research Ethics Committee (HREC), which is located in the biology department of the College of Science.

## Author Contribution

Lana Othman Mahmood: Conceptualization, Methodology, Software, Writing- Original draft preparation, Visualization, Investigation. Kamaran Abdourahman: Supervision, Writing- Reviewing and Editing.

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