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Assessment of Advanced Oxidation Protein Products and Some Biochemical Parameters in Iraqi Patients with Migraine

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Abstract

The molecular mechanisms of migraine, a complex neurological disease, are yet unknown. The pathogenesis of migraine is thought to be influenced by oxidative stress. The presented work aims to evaluate the fasting blood sugar (FBS), advanced oxidation protein product (AOPP), homeostasis model assessment of insulin resistance (HOMA-IR), insulin, lipid profile, triglyceride-glucose index (TyG), copper, magnesium, vitamin D, potassium, and B12 vitamin in patients with migraine. The studied groups were divided into two groups: Group 1 (G1) is the healthy control group (HC) (n=50, males n=21/ females n=29). Group 2 (G2) consisted of patients with episodic migraine (n=50, males n=9/ females n=41). Results had shown that patients who have migraine had increased significance P <0.01 of AOPP, FBS, insulin, TyG, HOMA-IR, triglyceride (TG), total cholesterol (TC), very low-density lipoprotein (VLDL-C), high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C), copper, and potassium. Compared with control group, migraine patients had a decreased significance $P < 0.01$ in magnesium, vitamin B12, and vitamin D3. A negative correlation has been seen between AOPP and magnesium, vitamin B12, and vitamin D3. Meanwhile, the AOPP and other metrics have a positive correlation. In conclusion, several biochemical parameters show significant associations with migraine. This study demonstrates a significant increase in insulin resistance, lipid profile, AOPP, MDA, copper, and potassium levels in migraine patients, alongside a significant decrease in magnesium, vitamin B12, and vitamin D3 levels. Furthermore, a negative correlation was found between AOPP and magnesium, vitamin B12, and vitamin D3, while a positive correlation existed between AOPP and other biochemical

Keywords: Advance oxidation protein products, oxidative stress, insulin resistance, lipid profile, migraine.

منتجات أكسدة البروتين المتقدم وبعض المؤشرات البايوكيميائية في المرضى العراقيين المصابين بالشقيقة تقييم

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الخلاصة:

الميكانيكية الجزيئية للشقيقة كمرض عصبي معقد غير معروف لحد الان. الهدف من العمل الحالي هو تقييم سكر الدم الصائم, منتجات أكسدة البروتين المتقدم, تقييم مقاومة الانسولين, الانسولين, ملف الدهون,

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محتوى الكلوكوز–الدهون الثلاثية, النحاس, المغنيسيوم, فيتامين د, بوتاسيوم و فيتامين ب 12 في مرضى الشقيقة. مجاميع الدراسة قسمت الى مجموعتين, المجموعة الاولى مجموعة السيطرة و تتكون من50 من الاشخاص الاصحاء (29 أناث و 21 ذكور)., المجموعة الثانية تتكون من 50 من مرضى الشقيقة العرضي (41 أناث و 9 ذكور)., النتائج تشير الى ان مرضى الشقيقة لديهم زيادة معنوية في منتجات أكسدة البروتين المتقدم, سكر الدم الالصائم, الانسولين, محتوى الكلوكوز–الدهون الثلاثية, مقاومة الانسولين, الدهون الثلاثية, الكوليستيرول الكلي, البروتيمات الدهنية واطئة الكثافة جدا, البروتينات الدهنية العالية الكثافة, البروتيمات الدهنية الواطئة الكثافة, النحاس والبوتاسيوم. مقارنة مع مجموعة السيطرة, مرضى الشقيقة لديهم نقصان معنوي في المغنيسيوم, فيتامين د و فيتامين ب 12. اضا هنالك علاقة عكسية بين منجات أكسدة البروتين المتقدم و المغنيسيوم, فيتامين د 3 و فيتامين ب 12.بينما هنالك علاقة موجبة بين منتجات أكسدة البروتين المتقدم و بقية المؤشرات الاخرى. الاستنتاج:بعض المؤشرات الكيموحيوية لها تأثير معنوي على صداع الشقيقة. في الدراسة الحالية هنالك زيادة معنوية في مقاومة الانسولين, ملف الدهون, منتجات أكسدة البروتين, مالون داي الديهايد, النحاس والبوتاسيوم. بينما هنالك قلة معنوية في المغنيسيوم, فيتامين ب 12 و فيتامين د. ايضا هنالك علاقة عكسية بين منتجات أكسدة البروتين والمغنيسيوم, فيتامين ب 12 و فيتامين د, بينما هنالك علاقة أيجابية بين منتجات أكسدة البروتين و بقية المؤشرات.

Introduction

Migraine is a syndrome that can appear in both non-neurological and neurological ways. It ranks as the sixth most common disability cause worldwide. As time goes on, migraine steadily rises to the top, impacting 11% of the adult global population's mental and physical well-being and substantially impairing individual quality of life, health, and economic and social advancement [1]. According to Mohanad *et al*., [2], visual abnormalities are the most commonly reported. Medication used for preventing migraine attacks, such as lamotrigine, is usually started in the case when migraine attacks with aura occur. Aura may worsen a migraine-related stroke, which is an episode of cerebral ischemia accompanied by neurological deficits [3]. In spite of a great deal of research on migraine pathophysiology, the specific molecular cause of the anomalies that cause migraine is still unknown [2]. Oxidative stress, defined as disturbances in the production-degradation balance of the ROS, is emphasized heavily in the proposed theories [3-5]. This process consequently leads to a number of illnesses, such as ischemic stroke, atherosclerosis, and reduced kidney function [6]. Recently, the start of neuroinflammatory and neurodegenerative disorders regarding the central nervous system (CNS), like multiple sclerosis, Alzheimer's and Parkinson's diseases, has also been associated with migraine headaches [6]. The hypothesis that oxidative stress is experienced by migraineurs was explored for many years. [2] An increase in the concentration of chemicals that interact with thiobarbituric acid was observed in patients who have migraines with aura and who do not experience attacks. Increased cell inflammation, apoptosis and necrosis, chromosomal aberration, base-damage to DNA, double- and single-stranded breaks in DNA, cross-links between DNA and proteins, collagen structure, lipid membrane, and mitochondrial function can all result from this. Numerous illnesses, which include cancer, chronic kidney disease, chronic obstructive lung disease, cardiovascular diseases and neurological diseases, are known to be affected by oxidative stress.

Advance oxidation protein products (AOPPs) are cross-linked proteins containing di-tyrosine that are produced when proteins react with chlorinated oxidants (HOCl/OCl−) and are a new type of marker for oxidative stress [7]. Compared to children/adolescents and adults, plasma levels of AOPPs are substantially higher in the elderly [8]. By activating nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, AOPPs could cause redox imbalance and ROS production [9]. Since proteins make up the biggest group of such molecules, oxidation stress has a negative impact on cellular macromolecules. ROSs, as well as chloraminated oxidants, primarily hypochlorous acid (HClO), induce oxidative damage to the plasma

proteins during an oxidative stress state. This damage results in di-tyrosine cross-linking, which in turn produces AOPP [10]. The aim of the present study is to evaluate AOPP as a biomarker for oxidative stress and its correlation with some biochemical parameters.

Subjects and methods

Subjects

To accomplish the study's objectives, 100 apparently control subjects and patients who visited Bab Al-Sharqi-Baghdad's Neurological Hospital between December 2023 and March 2024 have been included in the study. They have been divided into two main groups, as follows: patients with episodic migraine group 2 (G2) (n=50, males n=9/ females n=41) and the apparently healthy control group (HC) (n=50, males n=21/ females n=29) group 1 (G1). Blood samples were taken from the patients after they agreed to undergo some appropriate medical tests.

Determination of fasting blood sugar

Fasting blood sugar was determined using a kit manufactured by LABORA (Spain)

Determination of Serum Insulin

Serum Insulin was determined using a sandwich ELISA kit manufactured by Abcam, (Italy).

Determining homeostasis model assessment of insulin resistance (HOMA-IR)

HOMA-IR was calculated using the following formula (fasting insulin x fasting glucose (mg/dL))/405 or (fasting insulin x fasting glucose (mmol/L))/22.5 [11].

Body Mass Index (BMI) determination

BMI is computed as follows: weight (kg) divided by height (m^2) [3].

Determining serum total cholesterol (T. chol)

Total cholesterol was determined using a kit manufactured by LABORA (Spain) [12].

Determining the serum HDL-c

HDL-c level was determined using a kit manufactured by Biosystem (Spain) [13].

Serum triglycerides (TG) determination

Triglyceride was determined using a kit manufactured by LABORA (Spain) [14].

Serum very low-density lipoprotein (VLDL-C) determination

VLDL was calculated using the following formula [0.2xTG (mg/dl)] [15].

Serum low-density lipoprotein cholesterol (LDL-c) Determination

Serum LDL was calculated using Friedewald's equation· LDL-c =T.Chol. – (VLDL-c + HDL-c) [15].

Measurement of serum malondialdehyde (MDA)

The Buege and Aust method was used in order to determine the concentration of MDA in serum. MDA functions as an appropriate peroxidation reaction index and is created when poly-unsaturated fatty acids break down. To estimate MDA, thiobarbituric acid (TBA) was used; it reacted with TBA to produce a pink color that was measured at λ_{max} 535 nm [16].

Measurement of advanced oxidation protein products (AOPP)
Principle

Based on Witko-Sarsat *et al*., [17], which had been modified by Kalousovf *et al*., [18], AOPP determination (i.e., certain products of oxidation with specific absorbance) have been based upon spectrophotometric detection, and AOPP content was expressed in chloramines-T equivalents.

Determination of serum copper

Using Dibrom PAESA techniques and quantitative colorimetry, the content of serum copper was determined [19].

Determination of serum potassium

The turbidometric method is used to quantify potassium. The AGAPPE (Chem CHEK) kit measures the amount of turbidity photometrically at 578 nm, which is proportional to the potassium content [20].

Determination of serum magnesium

Magnesium is determined using the AGAPPE (Chem CHECK) colometric kit. In an alkaline solution, magnesium and xylidyl blue combine to generate a colorful compound. The amount of magnesium in the sample determines how intense the color becomes [21].

Determination of vitamin D3 and B12

The automated analyzer Roche Elecsys/Cobas-Bioprom was used to measure vitamin D3 and B12 levels.

Calculation of triglyceride-glucose index

The triglyceride-glucose index was calculated with the use of the formula: (TG [mg/dL] ×glucose [mg/dL]/2) [22].

Statistical analyses

SPSS for Windows, v. 27, has been used for conducting data analyses. The information has been displayed as mean ± standard deviation (SD). The study parameters were examined to see if they followed the gaussian distribution using the Shapiro-Wilk normality test. Pearson's analysis of correlation was utilized to examine the degrees of relationship. It has been determined that a $p<0.05$ value is significant [23].

Results and discussion

Description of studied groups

One hundred individuals were collected and then distributed to 2 groups: healthy controls (HC), patients who suffer from migraine; divided into males and females. Table 1 shows significant differences in gender and body mass index (BMI). There is a significant increase in BMI (Kg/m^2) $P < 0.01$ in migraine patients group (MP) (28.68 ± 4.69) compared with the healthy control group (HC) (22.99 ± 3.45).

Table 1: Distribution of groups, gender, age, and body mass index (BMI).

Groups	No.	Gender	Age mean ± SD (Years)	BMI mean ± SD (Kg/m^2)
Patients group (MP)	50	♀ 9 ♂ 41	32.64 ± 8.52	28.68 ± 4.69
Healthy control group (HC)	50	♀ 21 ♂ 29	28.72 ± 7.51	22.99 ± 3.45
P value		P < 0.001	P > 0.050	P < 0.001

P < 0.001: significance, *P* > 0.050: no significance

Additionally, the preceding table shows gender disparities of significance: the MP group (female 41/male 9) and the HC group (female 29/male 21). Ashkenazi *et al*., [24] claim that migraine sufferers have a sexual dimorphism and that estrogen and women's menstrual cycles are related to migraine symptoms. Thus, the majority of patients in our study are female. Numerous researchers have examined the correlation between BMI and migraine headache severity, duration, disability, and frequency, but the results have been inconsistent. Abdominal obesity (AO) and total body obesity (TBO) were linked to a higher frequency of migraine headache attacks, according to population-based studies, which included 4290 migraineurs; however, this conclusion was only applicable to women under the age of 50 [25]. A different Chinese population survey (300 migraineurs out of 1327 main headache patients) revealed that BMI significantly affected headache frequency, yet not headache duration or intensity [26]. A cross-sectional study conducted by Winter *et al*., [27] included 9195 women who were experiencing migraine attacks at the time and came to the same conclusion. The next processes could account for the relationship between migraine headaches and BMI: Obesity itself is a pro-inflammatory condition by the increase of the circulating cytokines levels, calcitonin gene-related peptide (CGRP), one of the important migraine mediators, is elevated in obese individuals [28]. Additionally, leptin and adiponectin are adipokines released mainly from the subcutaneous adipose tissue, and might have nociceptive characteristics in themselves. Even though they might decline during episodes, migraineurs' levels of adiponectin and leptin are both higher in between attacks. According to Mohammed and Zaki [28], there is a positive correlation between raised levels of leptin and pro-inflammatory cytokines IL6 and TNFa, which have been observed to be elevated in migraines [29]. Migraine prevention medications, which have been utilized in the preventive treatment of migraines, might be one of the potentially contributing reasons for the changes in BMI. Like obesity, migraines were reported to be a factor of risk for cardiovascular disorders and stroke [28].

Fasting serum glucose and related parameters

Levels of FBS and insulin for the two studied groups were measured, and then HOMA-IR and triglyceride-glucose index (TyG index) parameters were calculated and compared, as shown in Table 2. There were increased significance differences $P < 0.001$ in FBS, insulin, HOMA-IR and TyG index in migraine patients group (MP) (171.56 ± 33.91, 32.83 ± 10.52, 13.90 ± 5.09 and 24884.46 ± 7031.36 respectively) compared with healthy control group (HC) (91.56 ± 9.25, 11.63 ± 2.18, 2.63 ± 0.56 and 10780.85 ± 1282.18 respectively).

Table 2: Mean ± SD of fasting glucose and insulin along with the obtained HOMA-IR and TyG index parameters in serum of two studied groups.

Parameters	Patients group (MP) mean ± SD	Healthy control group (HC) mean ± SD	*P* value
FBG (mg/dl)	171.56 ± 33.91	91.56 ± 9.25	P < 0.001
Insulin (µIU/ml))	32.83 ± 10.52	11.63 ± 2.18	P < 0.001
HOMA-IR	13.90 ± 5.09	2.63 ± 0.56	P < 0.001
Glucose-triglyceride index (TyG)	24884.46 ± 7031.36	10780.85 ± 1282.18	P < 0.001

P < 0.001: significance difference

One crucial area of research interest is the disruption of glucose metabolism in migraineurs. According to a recent paper that has been carried out by Cross *et al*., [1] migraine is an adaptive reaction in those with imbalanced brain energy metabolism who are genetically prone. Insulin resistance (IR) and migraine were found to be substantially correlated in the current investigation; the IR group experienced a much higher frequency of

IR compared to the normal control group. Similar to this, [29] used HOMA-IR to test IR in migraine research. However, only two earlier investigations discovered a link between IR and migraine. However, as an alternative to the HOMA-IR approach, several research studies have produced results comparable to those of other IR assessment approaches [1]. It is hypothesized that IR affects homeostatic as well as inflammatory responses to insulin, changes neuronal and glial cell receptor modulation, or impairs neurotransmitter release at the brain level. According to [30], all of such pathways are speculative ideas that explain how migraine is related to IR as well as metabolic syndrome.

Mona *et al*., [30] recommended a thorough assessment for altered glucose metabolism in migraine patients as a result of these findings. Numerous techniques, including insulin-sensitizing medications, exercise, and dietary changes, have been developed to treat IR or hyperinsulinism [30].

Both metabolic syndrome as well as migraine are common and costly diseases. Although the two illnesses coexist, it is unknown how the two processes are related to one another. IR may play a part in the comorbidity of vascular disease and migraine, as two studies revealed that patients with migraines have reduced insulin sensitivity [31]. Therefore, a major metabolic role in the correlation between migraine and several comorbidities might be played by IR. Hyperinsulinemia is related to a 5.67-fold increased incidence of migraine in the case of comparing the highest and lowest quartiles of HOMA [31]. In a larger group that includes 84 migraine patients, [32] showed that following the oral glucose tolerance test (OGTT), both insulin and glucose were significantly higher ($p < 0.001$) in patients than in healthy individuals [31]. More recently, a number of clinical studies have established that patients who have both episodic and chronic migraines frequently have IR [31]. According to another study, patients who have episodic migraines had normal sensitivity to insulin, while those who have chronic migraines had considerably higher levels of IR [31]. Serum levels of calcitonin gene-related peptide (CGRP) have been shown to rise throughout migraine attacks [33], increasing the sensitivity of the trigeminal system. In addition to its involvement in migraines, research on animals showed that CGRP also affects the production of glucagon as well as insulin [31]. Since CGRP is a neuropeptide that is released in sensory nerves linked to glucose metabolism and has a critical impact on the pathogenesis of migraines, elevated plasma insulin levels in migraine patients may be induced as well by this neuropeptide. Additionally, migraine frequency is decreased and prevented by CGRP antagonism mediated by receptor antagonists or monoclonal antibodies [34].
According to Kruth *et al*., [39], there is a correlation between migraine and IR. There has been a linear link between TyG IR and migraine [35]. The triglyceride glucose index is utilized to measure IR.

Lipid profile in the studied group

Serum TC, TG, and HDL-c were measured for all patients, then LDL and VLDL were calculated. The results were compared to healthy individuals, and the results are shown in Table 3. There was a significant increase ($P < 0.001$) in TC, TG, HDL-C, VLDL-C, and LDL-C (290.38 ± 64.84, 289.12 ± 52.69, 55.84 ± 7.06, 57.82 ± 10.54 and 291.10 ± 64.03 respectively) in migraine group (MP) compared with healthy control group (HC) (200.68 ± 29.08, 176.66 ± 41.77, 46.88 ± 7.15, 47.10 ± 2.92 and 235.72 ± 22.62 respectively).

Table 3: Mean ± SD of Lipid profile in serum of studied groups.

Parameters	Patients group (MP) mean ± SD	Control group (HC) mean ± SD	*P* value
Cholesterol (mg/dl)	290.38 ± 64.84	200.68 ± 29.08	P < 0.001
Triglyceride (mg/dl)	289.12 ± 52.69	176.66 ± 41.77	P < 0.001
HDL-C (mg/dl)	55.84 ± 7.06	46.88 ± 7.15	P < 0.001
LDL-C (mg/dl)	291.10 ± 64.03	235.72 ± 22.62	P < 0.001
VLDL-C (mg/dl)	57.82 ± 10.54	47.10 ± 2.92	P < 0.001

$P < 0.001$: significance difference

Twelve percent of people worldwide are affected by the widespread and incapacitating condition known as migraine. 13% of Americans are estimated to get migraine attacks very frequently. According to some recent research, blood lipid levels might have an impact on the severity as well as the frequency of migraine attacks [36]. The aforementioned problems highlight how crucial it is to investigate the correlation between such metabolic abnormalities and cardiovascular diseases as controllable risk factors. Consistent with our findings, other recent research has demonstrated that the frequency and intensity of migraine attacks are correlated with serum lipid levels and that migraineurs have a higher prevalence of dyslipidemia compared to the general population. An increase in oxidized LDL-C was linked to a 7.93-fold greater incidence of migraine, according to Elif and Gizem, who found an increase in LDL-C and oxidized LDL-C cholesterol in migraineurs who have normal weight [37]. According to Wenjing *et al*., [38], migraines with aura had a higher mean total cholesterol level in their group than in the normal population, and they were also more likely to have an inadequate level of cholesterol profile.

According to Farhad *et al*., [36], those who suffer from migraines, particularly those with aura, have a higher chance of developing cardiovascular disease than people who do not. In a separate investigation, the lipid profile parameters of both healthy and episodic migraineurs were assessed. The results showed a strong correlation between migraines and levels of VLDL and total cholesterol [36]. Based on a 2008 study that has been carried out by Kruth *et al.,* [39], migraines are strongly associated with both the elevated cardiovascular disease risk and their adverse variables. According to Kruth *et al*., [39], there has been a statistically significant increase in total cholesterol, apoprotein B-100, non-HDL cholesterol, and C-reactive protein in migraine group when compared to non-migraine controls in this cohort analysis that included 5,087 women. All of these research' findings agree with the findings of our investigation. The disruption in serum lipid levels as an etiological factor, which our study confirmed, is one of the significant elements in all of these investigations.

According to Mohammed *et al.,* [40], the migraine group had significantly higher mean levels of serum total cholesterol and LDL cholesterol compared to the non-migraine group. Additionally, [41] found that the migraine group had significantly higher LDL and total cholesterol. In patients with migraines, [42] discovered a significant correlation between triglycerides and total cholesterol. BMI is a straightforward metric to determine and has a strong correlation with body fat. In people who have IR, hyperinsulinemia and a higher BMI are significant contributors to increased VLDL production, TC, elevated TG levels, and smaller, dense LDL particles [43].

Tissues, cells, body proteins, organs, lipids, and DNA can all be damaged by oxidative stress. Neurological disorders, such as migraine headaches, might develop as a result of injury to neurons. The spectrum of injury includes both chronic and acute inflammatory reactions in addition to an abundance of free radicals. According to [1], trigeminal nerve afferents might be stimulated by neurogenic inflammation, cellular extravasation, mast cell activation,

vasodilatation, and the production of pro-inflammatory mediators, which could contribute to symptom sensitization in migraineurs.

In the current study, there was an increase in HDL-C in migraine group compared to the control group. This finding is in agreement with Mattiuzzi and Cervellin [44], while Winsvold *et al.,* [45], clarifies decreased HDL-C in migraine patients.

Association of some elements with migraine

Table 4 shows significant differences in some elements in migraine patient group compared to healthy controls. There was increased significance $P < 0.001$ in copper and potassium in migraine patients group (MP) (190.32 ± 72.47 and 4.96 ± 1.13 respectively) compared with healthy control group (HC) (83.86 ± 21.30 and 3.48 ± 0.58 respectively). In contrast, there was a significant decrease ($P < 0.001$) in magnesium in patients' group (1.60 ± 0.25) compared with the control group (2.41 ± 0.54).

Table 4: Mean ± SD of copper, potassium, and magnesium in the studied group.

Parameters	Patients group (MP) mean ± SD	Control group (HC) mean ± SD	*P* value
Copper (mg/dl)	190.32 ± 72.47	83.86 ± 21.30	P < 0.001
Potassium (mmol/L)	4.96 ± 1.13	3.48 ± 0.58	P < 0.001
Magnesium (mg/dl)	1.60 ± 0.25	2.41 ± 0.54	P < 0.001

$P < 0.001$: significance difference

Micronutrients from the diet play a crucial role in supporting many metabolic processes. Maintaining a regular human metabolism requires potassium. It is the principal cations in cellular structures that are essential to preserving the typical shape and functionality of cells. According to the current research, potassium might have an impact on migraine. A 1950s study found that those who experienced migraines had higher than normal amounts of potassium and sodium in their urine, suggesting a possible link between such electrolytes and migraine pathogenesis. The link between migraine and salt has been the main subject of subsequent studies [46]. Migraine's pathophysiological processes are yet unknown. According to a number of studies, migraines occur when the body's antioxidant capacity is insufficient to combat oxidative stress [1]. Research indicates that the preventive effect of dietary potassium on endothelial cells may be able to avert oxidative stress-induced vascular damage [47].

According to Peng, migraines are typically thought of as neurovascular sensory threshold illnesses [48]. A number of substances have been shown to trigger migraines in human trials; the most common one is cephalic artery dilatation [49], which is followed by the activation of vascular smooth muscle ATP-sensitive potassium (KATP) channels [50].

The consequences of Mg-Ca imbalances on the neurological system can be divided into at least two categories. One of the most significant ions in cellular/mitochondrial energy fluctuations is magnesium. In addition to participating in a variety of enzymatic processes, it also keeps cell membrane equilibrium, affecting permeability and lowering the risk of spontaneous depolarization. It impacts the peripheral nervous system's excitability and nerve conduction. Proper glutamatergic communication in CNS is made possible by the appropriate cellular storage of this element, which is thought to be crucial for protecting neurons from excitotoxicity as well as oxidative stress [51].

It seems clear that migraine and magnesium shortage are related. Yet, there had been insufficient evidence to support a firm recommendation for this treatment based on the findings of numerous research on the impact of intravenous magnesium compounds in migraine patients. This may be because little is known about the correlation of Mg problems in migraine with the disease's clinical history, the frequency and severity of episodes, and gender and age index. Finding research that might objectify such clinical observation depending on a trustworthy statistical analysis of migraine patients' demographic and clinical data, as well as in comparison to healthy people, is challenging in both older and more contemporary literature. This study attempts to address this issue [51]. The backdrop of migraine symptoms can just be partially explained by cortical spreading depression (CSD) and, in certain situations, cerebral flow reduction throughout an attack [51]. The pathogenesis of migraine, particularly its aura, may be caused by a self-propagating wave of temporary post-cranial depression. The findings of Vinogradova's research [52] and Van Harreveld's study [51] from previous years suggest that an increase in extra-cellular potassium concentration or long-term depolarization of neurons linked to excessive Ca-dependent glutamate release could be the triggering factor. It is not impossible that both elements might exist at the same time. At the same time, cortical depression could be initiated in part by the structure of N-methyl-D-aspartate (NMDA) receptor, which is implicated in the release of glutamate. This receptor requires a healthy metabolism of magnesium as well as calcium to function, and changes in ion concentration could have an impact on the induction of cortical depression. Magnesium interacts with the NMDA receptor, which is one of its primary roles in the neurological system. The magnesium ion shields the cell from an uncontrollably high calcium ion inflow by blocking the calcium channel in the NMDA receptor. Thus, hypomagnesemia may increase excitotoxicity and glutamatergic neurotransmission, which in turn may cause oxidative stress. Low magnesium levels in migraine patients' platelets have been shown to be linked to an increase in cyclic AMP levels, yet not to cyclic GMP levels. According to Boska *et al.,* [53], the release of neurotransmitters that cause vasomotor abnormalities throughout the early stages of migraine and the development of cortical depression (CSD) are likely correlated with the amounts of those substances. Hypomagnesemia might also lessen the spinal centers' gating of nociceptive signals, which is likely directly linked to the headache experienced during a migraine attack. It is thought that aberrant glutamatergic neurotransmission is directly linked to neurological conditions like migraine, epilepsy, and chronic pain [54].

Parameters related to oxidative stress

The significant differences in oxidative stress parameters measured in this investigation are displayed in Table 5. A significant increase ($P < 0.001$) was observed in AOPP and malondialdehyde (MDA) in the MP group (30.93 ± 8.27 and 30.86 ± 8.29, respectively) in comparison with the HC group (30.93 ± 8.27 and 15.32 ± 5.60, respectively).

Table 5: Level of MDA and AOPP in the studied groups.

Parameters	Patients group (MP) mean ± SD	Control group (HC) mean ± SD	Probability
MDA (µmol/L)	62.87 ± 15.10	30.93 ± 8.27	P < 0.001
AOPP (µmol/L)	30.86 ± 8.29	15.32 ± 5.60	P < 0.001

According to the presented work, there may be two main causes of the pathophysiology of migraine headaches: an increase in oxidants or a decrease in antioxidants. As a result, we identified AOPP and MDA as the markers for oxidative stress activation [55]. As far as we are aware, this is the first study to look at the correlation between migraine as well as oxidative stress in a sample of Iraqi people. Overall, our findings showed that oxidant

levels are up and antioxidant defenses are lowered in migraine attacks, indicating a shift in the oxidative-antioxidative balance in favor of oxidative condition. The outcomes support our theory and are in line with previous research. In comparison with controls, migraine patients' blood has been found in multiple studies to have higher amounts of MDA, a byproduct of oxidative damage to lipids [56]. Plasma levels regarding MDA as well as total antioxidant capacity, have been found to be elevated in migraine patients by Gupta *et al.,* [57]. An imbalance between ROS formation (free radicals) and antioxidant defenses is referred to as oxidative stress. Damage to proteins, nucleic acids, lipids, and cell membranes may ensue [2]. According to Suat *et al*.,[58], free radicals are thought to be the cause of oxidative stress, which might contribute to migraine pathogenesis. An increasing number of academics are looking into the function that oxidative stress plays in migraine [59]. Recent research has demonstrated that lipid peroxide, a migraine trigger, and migraine attacks cause increased oxidative stress levels in patients who have migraine [60]. The paraoxonase (PON) levels of the patient and the control group did not differ, according to Yigit *et al*., [61]. It was found that whereas PON levels were comparable in the two groups, migraine patients without aura had higher activity compared to the control group [62]. It was demonstrated that patients with migraine without aura had a lower PON ($p < 0.05$) than the controls. Within migraine patients, our study reveals significant increases in MDA and AOPP levels along with a reduction in the GSH and paraoxonase activity when compared with healthy controls [63]. Patients who have migraine have been reported to have elevated levels of serum AOPPs. The purpose of this research was to evaluate the theory that AOPPs cause oxidative stress, which causes migraines in turn. Oxidative stress causes albumin to react with chlorinated oxidants, resulting in the formation of AOPPs, which are protein products that include di-tyrosine and are cross-linked. As oxidative stress markers, AOPPs are mostly used, although some research suggests that they may also have a pathogenic function in prostate cancer and play a role in ROS formation and vascular inflammation [64]. Since they stimulate neutrophils, monocytes, and T lymphocytes, AOPP were described as both a novel class of inflammatory mediators as well as ultrasensitive markers regarding oxidative stress. ROSs overproduction under pathological situations is well documented to impair endothelial functions and is thought to be a contributing component to vascular dysfunction [65,66].

Association of vitamin D3 and B12 in the studied group

In the research group, Table 6 displays the significance of vitamin B12 and D3 variations. There has been a reduction in significance $P < 0.001$ in vitamin D3 and B12 (14.10 ± 3.73 and 26.79 ± 8.71 respectively) in migraine patients group (MP) compared with healthy control group (HC) (29.37 ± 6.14 and 84.03 ± 17.68 respectively).

Table 6: Level of D3 and B12 in the studied groups.

Parameters	Patients group (MP) mean ± SD	Control group (HC) mean ± SD	*P* value
Vitamin D_3 (ng/ml)	14.10 ± 3.73	29.37 ± 6.14	P < 0.001
Vitamin B_{12} (pg/ml)	26.79 ± 8.71	84.03 ± 17.68	P < 0.001

$P < 0.001$: significance difference

Recently, there has been discussion about the significance of vitamin D in neurovascular disorders [66]. Because of the limited number of studies, inconsistent findings, and dearth of large-scale clinical trials assessing the benefits of the supplementation of vitamin D in migraine headaches, the exact cause of vitamin D deficiency and migraine headaches is still not known [67]. The current investigation found that, in comparison to controls, patients with migraine headaches had much lower serum levels of 25(OH) vitamin D. The incidence of autonomic symptoms, phonophobia/photophobia, allodynia, aura, and treatment resistance

was reported to be much higher in migraine patients who have vitamin D deficiency compared to those who have normal vitamin D levels. These outcomes were generally in line with several recent investigations. In contrast to controls, Wheeler found that patients who have persistent migraines had much lower serum levels of vitamin D. According to his research, 25.9% of patients who have chronic migraine had a serum vitamin D level between 20 and 30ng/mL. In comparison, 14.8% of patients had a level below 20ng/mL.13. Furthermore, Togha *et al*., discovered that those with serum 25(OH) D levels below 20ng/mL had an 80–83% decreased chance of experiencing a migraine headache compared to these with levels between 50 and 100 ng/mL of vitamin D [68]. Comparable results have been reached by Togha *et al*., [69], who have discovered that supplementing with vitamin D significantly resulted in the reduction of the frequency as well as duration of migraine headache attacks in patients who have migraines compared with those receiving a placebo. However, neither the vitamin D group nor the placebo group had a statistically significant pattern of change over time in terms of migraine intensity, pressure thresholds, or migraine-related symptoms that include nausea, aura, allodynia, and photo/phonophobia [69]. It was found that there is no correlation between the severity of migraine headache attacks as well as the plasma level of vitamin D, which is in contrast to our findings [70]. Several theories have been put up on the causative correlation between vitamin D deficiency and migraines. Among these was the low magnesium levels in the serum of patients who were vitamin D deficient. It's interesting to note that research has shown a favorable correlation between magnesium and 25(OH)-vitamin D concentrations in serum. It is well-recognized that magnesium deficiency contributes to the pathogenesis of migraine, particularly menstrual migraine. The symptoms of migraine headaches were significantly reduced once the magnesium deficiency was corrected [71]. The anti-inflammatory properties of vitamin D, which might influence the neuro-inflammatory response linked to migraine, offer an additional explanation for the link between vitamin D deficiency and migraines. Numerous investigations showed that vitamin D, at physiological levels, could inhibit the production of pro-inflammatory cytokines, like interleukin-6 and tumor necrosis factor-α.31The synthesis of anti-inflammatory cytokine IL10 is increased by vitamin D. Furthermore, the manufacture of inducible nitric oxide synthase that produces nitric oxide (NO), could be inhibited by vitamin D in its active form, 1,25(OH)2D [30,2]. Trigeminal ganglion neurons produce and release calcitonin gene-related peptide (CGRP), which in turn induces nitric oxide (NO) release. Therefore, it could result in a positive feedback loop that strengthens and sustains the trigeminal ganglion's inflammatory processes. Meningeal nociceptor sensitization occurs as a result of this throughout migraine attacks [72]. When combined, such results could provide an explanation for the correlation between migraine and vitamin D deficiency; nevertheless, the exact mechanism underpinning vitamin D's real participation in the pathogenesis of migraine is yet unknown. One finding from our research has been that serum vitamin B12 levels in patients with migraines have been comparatively lower in comparison to those in the group of healthy controls. According to Bottini *et al*., [73], migraineurs' levels of vitamin B12 were normal. Nonetheless, low vitamin B12 levels were discovered in both our study and the research by Acar *et al*., [74]. Vitamin B12 insufficiency can develop at the cellular level even if serum levels have been normal, according to Fenech [75], who also observed that patients with serum vitamin B12 levels < 300pmol/L experienced damage to DNA in their blood cells. Additionally, they stated that the levels of vitamin B12 must be maintained at or above 300 pmol/L [75]. Our findings further supported the need to assess for vitamin B12 insufficiency in migraine patients and provided evidence in favor of vitamin B12 therapy to reduce pain frequency.

Pearson correlation of advanced oxidation protein products

The relationship between AOPP and the other biochemical parameters was examined using Pearson correlation (Table 7).

Table 7: Pearson correlation analysis of AOPP in group MP.

Parameters	AOPP Pearson's correlation	Probability (2-tailed)
FBG	0.634	P < 0.0010
Insulin	0.646	P < 0.0010
HOMA-IR	0.654	P < 0.0010
Glucose-triglyceride index	0.577	P < 0.0010
Cholesterol	0.551	P < 0.0010
Triglyceride	0.543	P < 0.0010
HDL-C	0.458	P < 0.0010
LDL-C	0.279	P < 0.0010
VLDL-C	0.342	P < 0.0010
Copper	0.545	P < 0.0010
Potassium	0.471	P < 0.0010
Magnesium	-0.481	P < 0.0010
MDA	0.602	P < 0.0010
Vitamin D_3	-0.685	P < 0.0010
Vitamin B_{12}	-0.680	P < 0.0010

Table 7 shows a negative correlation of AOPP with magnesium, vitamin D3, and vitamin B12. At the same time, there is a positive correlation between AOPP and other parameters.

Conclusion

In the present study, we conclude there is an increased significance of advanced oxidation protein products, insulin resistance, lipid profile, MDA, copper and potassium. In contrast there is a decrease in the significance of magnesium, vitamin B12 and vitamin D3. Additionally, AOPP has been found to negatively correlate with magnesium, vitamin B12, and vitamin D3. While the AOPP and other metrics have a positive correlation in the migraine patients.SO advance oxidation protein products may be biomarker for migraine.

Ethical clearance

The Research Ethical Committee at scientific research by ethical approval of the environmental and health as well as higher education and scientific research ministries in Iraq.

Conflict of interest

None

Reference

[1] E. C. Gross, M. Lisicki, D. Fischer, P. S. Sándor, and J. Schoenen, "The metabolic face of migraine – from pathophysiology to treatment," *Nature ReviewsNeurology,* vol. 15, no. 8, pp. 471–487, 2019.

[2] S. Mohanad, Al-Fayyadh, H. I. Kefah, and J. R. Ali, "Migraine and plant antioxidant," *University of Thi-QarJournal of Science*, vol. 10, no. 1, pp. 1–10, 2023.

[3] N. Frank, "Body mass index," *Nutrition Today*, vol. 50, no. 3, pp. 1–4, 2015.

[4] S. Mohanad, Al-Fayyadh, and A. W. Shatha, "Effects of Red Cabbage and Garlic Extracts on Oxidative Stress Induced by Fumonisin B1," *Iraqi Journal of Science*, vol. 62, no. 6, pp. 1850–1861, 2021.

[5] M. Goschorska, I. Baranowska-Bosiacka, I. Gutowska, E. Metryka, M. Skórka-Majewicz, and D. Chlubek, "Potential role of fluoride in etiopathogenesis of the Alzheimer's Disease," *International Journal of Molecular Sciences, vol*. 19, no. 12, p. 3956, 2018.

[6] A. Aboonabi, R. R. Meyer, I. Singh, "The association between metabolic syndrome components and the development of atherosclerosis," *Journal of Human Hypertension*, vol. 33, no. 8, pp. 844–855, 2019.

[7] M. Cristani, A. Speciale, A. Saija, S. Gangemi, P.Minciullo, and F. Cimino, "Circulating advanced oxidation protein products as oxidative stress biomarkers and progression mediators in pathological conditions related to inflammation and immune dysregulation," *Current Medicinal Chemistry*, vol. 23, no. 38, pp. 3862–3882, 2016.

[8] M. Maciejczyk, A. Zalewska, and J. R. Ladny, "Salivary antioxidant barrier, redox status, and oxidative damage to proteins and lipids in healthy children, adults, and the elderly," *Oxidative Medicine and Cellular Longevity*, Article ID 4393460, 2019.

[9] S. Y. Zhu, J. S. Zhuang, Q. Wu, Z. Y. Liu, Z. Y. Liao, and S. G. Luo, "Advanced oxidation protein products induce pre-osteoblast apoptosis through a nicotinamide adenine dinucleotide phosphate oxidase-dependent, mitogen-activated protein kinases-mediated intrinsic apoptosis pathway," *Aging Cell*, vol. 17, no. 2, e12764, 2018.

[10] C. Diana, S. Villalpando, A. Cleto, A. Aguilar, and G. Gómez, "Advanced oxidation protein products and their relationship with cardiovascular risk factors in young apparently healthy people," *Clinical Investigations in Arteriosclerosis*, vol. 29, no. 5, pp. 209–215, 2016.

[11] T. M. Wallace, J. C. Levy, D. R. Matthews, "Use and abuse of HOMA modeling," *Diabetes Care*, vol. 27, no. 6, pp. 1487–1495, 2004.

[12] W. Richmond, "Determination of cholesterol by enzymatic method," *Clinical Chemistry*, vol. 19, no. 8, pp. 1350–1356, 1973.

[13] M. Burstein, "Measurement of lipid profile," *Lipid Research*, vol. 11, no. 4, pp. 583–588, 1970.

[14] P. Fossatti and S. Prencipel, "Determination of triglycerides by enzymatic method," *Clinical Chemistry*, vol. 28, no. 10, pp. 2077, 1982.

[15] W. T. Friedewald, R. I. Levy, M. Wite, and D. S. Fredrickson, "Estimation of the concentration of low-density lipoprotein cholesterol in plasma without the use of preparative ultracentrifuge," *Clinical Chemistry*, vol. 18, no. 6, pp. 499–502, 1972.

[16] J. A. Buege and S. D. Aust, "Microsomal lipid peroxidation," *Methods in Enzymology*, vol. 52, pp. 302–310, 1978.

[17] V. Witko-Sarsat, M. Friedlander, C. Capeillere-Blandin, T. Nguyen-Khoa, A. Nguyen, J. Zingraff, P. Jungers, and B. Deschamps-Latscha, "Advanced oxidation protein products as a novel marker of oxidative stress in uraemia," *Kidney International,* vol. 49, no. 4, pp. 1304–1313, 1996.

[18] M. Kalousovf, T. Zima, V. Tesař, J. Äkrha, S. Ätõpek, "Determination of advanced glycation end-products and advanced oxidation protein products," *Klinische Biochemie und Molekularbiologie*, vol. 10, no. 1, pp. 11–16, 2002.

[19] A. Abe, S. Yamashita, A. Noma, "Measurement of serum copper," *Clinical Chemistry*, vol. 35, no. 3, pp. 552–554, 1989.

[20] D. S. Young, "Clinical Chemistry Principles and Techniques," 2nd Edition, Waveland Press, Inc., 1974.

[21] D. S. Young, "Effects of disease on clinical laboratory tests," 4th Edition, AACC Press, 2001.

[22] F. Guerrero Romero, L. E. Simental Mendia, M. Gonzalez Ortiz, E.Martinez Abundis, M. G. Ramos Zavala, and S. O. Hernandez Gonzalez, "The product of triglycerides and glucose, a simple measure of insulin sensitivity: comparison with the euglycemic–hyperinsulinemic clamp," J*ournal of Clinical Endocrinology & Metabolism*, vol. 95, no. 7, pp. 3347–3351, 2010.

[23] T. Glover and K. Mitchell, "An introduction to biostatistics," 2nd Edition, Waveland Press, Inc., 2008.

[24] A. Ashkenazi and D. S. Silberstein, "Hormone-related headache: pathophysiology and treatment," *Central Nervous System Drugs*, vol. 20, no. 2, pp. 125–141, 2006.

[25] E. S. Kristoffersen, S. Børte, K. Hagen, J. A. Zwart, and B. S. Winsvold, "Migraine, obesity and body fat distribution – a population-based study," *Journal of Headache and Pain*, vol. 21, no. 1, p. 97, 2020.

[26] Q. Liang, X. Huang, S. Wang, and X. Mu, "Association between Body Mass Index and Migraine: A survey of adult population in China," *Behavioral Neurology*, vol. 2018, pp. 1–8, 2018.

[27] A. C. Winter, K. Berger, J. E. Buring, and T. Kurth, "Body mass index, migraine, migraine frequency and migraine features in women," *Cephalalgia*, vol. 29, no. 2, pp. 269–278, 2009.

[28] K. F. Mohammed and N. S. Zaki, "The effect of body mass index on migraine severity in female patients," *Thi-Qar Medical Journal*, vol. 26, no. 2, pp. 45–52, 2023.

[29] R. K. Özcan and S. G. Özmen, "The association between migraine, metabolic syndrome, insulin resistance, and obesity in women: a case-control study," *Sisli Etfal Hospital Journal of Medicine*, vol. 53, no. 4, pp. 395–402, 2019.

[30] A. Mona, H. Mona, M. Rehab, K. Ahmed, A. Salsabil, M. O. Asmaa, H. Aya, and H. Wesam, "The potential impact of insulin resistance and metabolic syndrome on migraine headache characteristics," *BMC Neurology*, vol. 22, no. 1, p. 422, 2022.

[31] R. I. Md and R. N. Dale, "Glucose-related traits and risk of migraine – a potential mechanism and treatment consideration," *Genes*, vol. 13, no. 5, p. 750, 2022.

[32] C. Cavestro, A. Rosatello, G. Micca, M. Ravotto, M. P. Marino, G. Asteggiano, and E. Beghi, "Insulin metabolism is altered in migraineurs: a new pathogenic mechanism for migraine," *Headache*, vol. 47, no. 12, pp. 1436–1442, 2007.

[33] V. Favoni, L. Giani, L. Al-Hassany, G. M. Asioli, C. Butera, I. de Boer, M. Guglielmetti, C. Koniari, T. Mavridis, and M. Vaikjärv, "CGRP and migraine from a cardiovascular point of view: what do we expect from blocking CGRP?" *Journal of Headache and Pain*, vol. 20, no. 1, p. 27, 2019.

[34] M. Hosseinpour, F. Maleki, M. Khoramdad, M. J. Sullman, S. A. Nejadghaderi, A. A. Kolahi, and S. A. Safiri, "Systematic literature review of observational studies of the bilateral association between diabetes and migraine," *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, vol. 15, no. 4, pp. 673–678, 2021.

[35] L. Yao, G. Xiaochuan, Y. Lingmei, and L. Yanming, "The relationship between triglyceride glucose index and migraine: a cross-sectional study from the National Health and Nutrition Examination Survey," *Current Neurovascular Research*, vol. 20, no. 2, pp. 111–118, 2023.

[36] A. Farhad, P. Seyedeh, H. Omid, and S. Behnam, "Frequency of dyslipidemia in migraineurs in comparison to control group," *Journal of Family Medicine and Primary Care*, vol. 8, no. 3, pp. 950–954, 2019.

[37] U. Elif and A. Gizem, "Serum lipid profile in migraine and its association with clinical characteristics," *Neurosurgical Research and Practice*, vol. 45, no. 3, pp. 1–5, 2022.

[38] G. Wenjing, G. Lijie, Z. Yang, W. Kongyuan, C. Ning, and H. Li, "Association between serum lipid levels and severe headache or migraine in representative American population: a cross-sectional study," *Current Neurovascular Research*, vol. 18, no. 4, pp. 333–342, 2021.

[39] T. Kurth, P. M. Ridker, and J. E. Buring, "Migraine and biomarkers of cardiovascular disease in women," *Cephalalgia*, vol. 28, no. 1, pp. 49–56, 2008.

[40] K. F. Mohammed, K. S. Shajal, H. Solaiman, and S. Goutam, "Study of association of serum lipid levels with migraine," *Journal of Enam Medical College*, vol. 10, no. 1, pp. 1–7, 2020.

[41] C. Ren, J.Liu, J. Zhou, J. Liang, Y. Wang, Y. Sun, B. Ma, and Y. Yin, "Lipidomic analysis of serum samples from migraine patients," *Lipids in Health and Disease*, vol. 17, no. 1, p. 22, 2018.

[42] V. Z. Karen, K. K. Jóvyne, B. D. L. F. Jonas, R. A. R. Bruna, C. D. R. P. Vinicius, G. Nilva, and L. O. Claudio, "Association of altered serum vitamin D, glucose, and lipid profiles with headaches in young women: a clinical, cross-sectional study," *Headache Medicine*, vol. 14, no. 4, pp. 214–220, 2023.

[43] V. G. Athyros, K. Tziomalos, A. Karagiannis, and D. P. Mikhailidis, "Dyslipidaemia of obesity, metabolic syndrome and type 2 diabetes mellitus: the case for residual risk reduction after statin treatment," *The Open Cardiovascular Medicine Journal*, vol. 5, pp. 24–32, 2011.

[44] C. Mattiuzzi, G. Cervellin, and G. Lippi, "Epidemiological associations between migraine and lipoprotein (a): a systematic review," *Journal of Thrombosis and Thrombolysis*, vol. 39, no. 1, pp. 113–117, 2015.

[45] B. S. Winsvold, K. Hagen, and A. H. Aamodt, "Headache, migraine and cardiovascular risk factors: The HUNT study," *European Journal of Neurology*, vol. 18, no. 4, pp. 504–511, 2011.
[46] X. Lisi, Z. Cong, L. Yan, S. Xiuli, and H. Daifa, "Association between dietary potassium intake and severe headache or migraine in US adults: a population-based analysis," *Nutritional Epidemiology*, vol. 10, pp. 1–8, 2023.
[47] K. Smiljanec, A. Mbakwe, M. Ramos Gonzalez, W. B. Farquhar, and S. L. Lennon, "Dietary potassium attenuates the effects of dietary sodium on vascular function in salt-resistant adults," *Nutrients*, vol. 12, no. 4, p. 1206, 2020.
[48] K. P. Peng, "May A. Migraine understood as a sensory threshold disease," *Pain*, vol. 160, no. 8, pp. 1494–1501, 2019.
[49] L. Pellesi, M. A. Al-Karagholi, B. A. Chaudhry, C. L. Lopez, J. Snellman, J. Hannibal . "Two-hour infusion of vasoactive intestinal polypeptide induces delayed headache and extracranial vasodilation in healthy volunteers," *Cephalalgia*, vol. 40, no. 11, pp. 1212–1223, 2020.
[50] M. Ashina, "Migraine," *New England Journal of Medicine*, vol. 383, no. 19, pp. 1866–1876, 2020.
[51] C. Joanna, S. Elzbieta, D. Wojciech, G. Małgorzata, R. Maria, and D. Izabela, "Migraine and its association with hyperactivity of cell membranes in the course of latent magnesium deficiency—preliminary study of the importance of the latent tetany presence in the migraine pathogenesis," *Nutrients*, vol. 13, no. 12, p. 2701, 2021.
[52] L. V. Vinogradova, "Initiation of spreading depression by synaptic and network hyperactivity: insights into trigger mechanisms of migraine aura," *Cephalalgia*, vol. 38, no. 11, pp. 1177–1187, 2018.
[53] M. D. Boska, K. M. Welch, P. B. Barker, J. A. Nelson, and L. Schultz, "Contrasts in cortical magnesium, phospholipid, and energy metabolism between migraine syndromes," *Neurology*, vol. 58, no. 9, pp. 1227–1233, 2002.
[54] A. Kirkland, G. L. Sarlo, and K. F. Holton, "The role of magnesium in neurological disorders," *Nutrients*, vol. 10, no. 6, p. 730, 2018.
[55] S. H. Areej, A. A. Baydaa, A. M. Osama, and M. H. Abbas, "Assessment of malondialdehyde and soluble α-Klotho serum levels in Iraqi acromegaly patients," *Iraqi Journal of Science*, vol. 65, no. 6, pp. 3008–3014, 2024.
[56] K. Alireza, N. Alireza, G. Abdoreza, A. Zahra, and S. Masoud, "Impaired oxidative-antioxidative balance during migraine attack," *Biomedical Research*, vol. 6, no. 2, pp. 2996–3002, 2019.
[57] R. Gupta, R. Pathak, M. S. Bhatia, and B. D. Banerjee, "Comparison of oxidative stress among migraineurs, tension-type headache subjects, and a control group," *Annals of Indian Academy of Neurology*, vol. 12, no. 3, pp. 167–172, 2009.
[58] C. Suat, Y. Selma, C. P. Cemre, and O. P. Şamil, "Oxidative stress parameters in patients with migraine without aura," *Namık Kemal Medical Journal*, vol. 8, no. 1, pp. 31–35, 2020.
[59] P. Ferroni, P. Barbanti, D. Della-Morte, R. Palmirotta, E. Jirillo, and F. Guadagni, "Redox mechanisms in migraine: novel therapeutics and dietary interventions," *Antioxidants*, vol. 20, no. 12, p. 1144, 2018.
[60] M. Yigit, O.Sogut, and O. Tataroglu, "Oxidative/antioxidative status, lymphocyte DNA damage, and urotensin-2 receptor level in patients with migraine attacks," *Neuropsychiatric Disease and Treatment*, vol. 14, pp. 367–374, 2018.
[61] Y. Eren, E. B. Dirik, S. Neþelioðlu, and Ö. Erel, "Serum lipid profiles, relationship between paraoxonase/arylesterase activity and high-density lipoprotein levels in patients with migraine," *Turkish Journal of Neurology*, vol. 23, no. 3, pp. 117–121, 2017.
[62] N. Yilmaz, O. Aydin, A. Yegin, A. Tiltak, and E. Eren, "Increased levels of total oxidant status and decreased activity of arylesterase in migraineurs," *Clinical Biochemistry*, vol. 44, no. 10–11, pp. 832–837, 2011.
[63] S. Yildirim, S. Akar, M. Kuyucu, A. Yildirim, S. Dane, and R. Aygul, "Paraoxonase 1 gene polymorphisms, paraoxonase/arylesterase activities and oxidized low-density lipoprotein levels in patients with migraine," *Cell Biochemistry and Function*, vol. 29, no. 7, pp. 549–554, 2011.
[64] N. Marta, W. Tomasz, B. Maciej, K. Stefan, R. Piotr, and R. Barbara, "A preliminary evaluation of advanced oxidation protein products as a potential approach to evaluating prognosis in early-stage breast cancer patients and its implication in tumor angiogenesis: a 7-year single-centre study," *Cancers*, vol. 16, no. 5, p. 1068, 2024.

[65] K. Iva, H. Hansjorg, H. Lidija, L. Margarete, and K. Lucija, "Advanced oxidation protein products are strongly associated with the serum levels and lipid contents of lipoprotein," *International Journal of Molecular Sciences*, vol. 25, no. 1, p. 2024.

[66] H. A. Abdulameer and Z. H. Saba, "Assessment of oxidative stress parameters for some of Baghdad city fuel stations workers," *Iraqi Journal of Science*, vol. 64, no. 6, pp. 2669–2680, 2023.

[67] B. Asadi, F. Khorvash, A. Najaran, and F. Khorvash, "Cyproheptadine versus propranolol in the prevention of migraine headaches in children," *Pakistan Journal of Medical Sciences*, vol. 28, no. 2, pp. 309–311, 2012.

[68] A. Celikbilek, A. Y. Gocmen, and G. Zararsiz, "Serum levels of vitamin D, vitamin D-binding protein, and vitamin D receptor in migraine patients from central Anatolia region," *International Journal of Clinical Practice*, vol. 68, no. 12, pp. 1272–1277, 2014.

[69] M. Togha, S. Razeghi Jahromi, Z. Ghorbani Z, Martami F, and S. Sefishahpar, "Serum vitamin D status in a group of migraine patients compared with healthy controls: a case-control study," *Headache*, vol. 58, no. 10, pp. 1530–1540, 2018.

[70] P. Gazerani, R. Fuglsang, and J. G. Pedersen, "A randomized, double-blinded, placebo-controlled, parallel trial of vitamin D3 supplementation in adult patients with migraine," *Current Medical Research and Opinion*, vol. 35, no. 4, pp. 715–723, 2019.

[71] A. Zandifar, S. S. Masjedi, and M. Banihashemi, "Vitamin D status in migraine patients: a case-control study," *BioMed Research International*, vol. 2014, Article ID 514782, 2014.

[72] S. T. Chen and J. W. Wu, "A new era for migraine: the role of calcitonin gene-related peptide in the trigeminovascular system," *Progress in Brain Research*, vol. 255, pp. 123–142, 2020.

[73] F. Bottini, M. E. Celle, M. G. Calevo, S. Amato, G. Minniti, L. Montaldi, and et al., "Metabolic and genetic risk factors for migraine in children," *Cephalalgia*, vol. 26, no. 6, pp. 731–737, 2006.

[74] A. Acar, O. Evliyaoğlu, E. Uzar, Y. Yücel, M. U. Çevik, and I. Güzel, "Serum vitamin B12, folic acid and ferritin levels in patients with migraine," *Turkish Journal of Neurology*, vol. 17, no. 2, pp. 90–95, 2011.

[75] M. Fenech, "Folate (vitamin B9) and vitamin B12 and their function in the maintenance of nuclear and mitochondrial genome integrity," *Mutation Research – Reviews in Mutation Research*, vol. 733, no. 1–2, pp. 21–33, 2012.