Research Article

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Serum adropin, clusterin, hemokinin-1, and kisspeptin levels in patients with migraine

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Abstract

Objectives: Currently, there are no specific biomarkers available for migraine diagnosis. So, we aimed to measure serum levels of adropin, kisspeptin, hemokinin-1, and clusterin in patients with migraine for diagnostic purposes.

Methods: The study included 150 participants who were divided into three groups: 50 migraine patients with aura, 50 migraine patients without aura, and a control group of 50 healthy individuals. Participants were selected from those who visited the neurology department between March 2021 and January 2022 and were diagnosed according to the International Headache Society criteria. The study was conducted according to the Standards for the Reporting of Diagnostic Accuracy Studies. Serum levels of adropin, clusterin, hemokinin-1, and kisspeptin were measured using enzyme-linked immunosorbent assay (ELISA) kits.

Results: Serum levels of adropin, clusterin, and kisspeptin did not show significant differences between migraine patients and the control group. However, hemokinin-1 levels in migraine patients with aura were significantly higher than those in the control group ($p<0.01$). The cut-off value for hemokinin-1 was determined to be 0.55 ng/L (69.0 % sensitivity and 64.8 % specificity). No significant correlations were found between sociodemographic data, clinical data, and the serum levels of kisspeptin, hemokinin-1, clusterin, and adropin among patients with migraine with aura. Additionally, there was a significant difference in hemokinin-1 levels when comparing migraine patients with aura to those without aura ($p<0.01$).

Conclusions: Our study showed that hemokinin-1 levels were higher in migraine patients with aura when compared to the control group. Further investigations are needed to confirm this topic.

Keywords: adropin; clusterin; hemokinin-1; kisspeptin; migraine

Introduction

Migraine is commonly defined as a neurophysiological disease characterized by neurogenic inflammation and dysfunction of the cranial blood vessels [1]. The global migraine prevalence was determined as 15 %, while in Türkiye, migraine affects approximately 16.4 % of the population [2]. The diagnosis of migraine is made clinically following the criteria proposed by the International Headache Society (IHS). Recently identified biomarkers may contribute to the diagnosis and grading of migraine.

The precise causes and mechanisms behind migraine are not yet completely understood but various theories have been proposed. These include vascular theories, neurogenic inflammation, and cortical spreading depression as a form of depolarization, as well as theories involving serotonin and cytokines. Recent studies have shown that neuropeptides and cytokines play significant roles in the development of migraine and the occurrence of migraine-related headaches [3].

As a neuropeptide, adropin plays a crucial role in various physiological functions, including metabolic homeostasis, physical activity, and motor neuron coordination. Additionally, it has paracrine and autocrine effects in peripheral tissues. Adropin was recently shown to be significantly involved in the progression of several nervous system

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disorders, such as bipolar disorder, paralysis, schizophrenia, Huntington's disease, Alzheimer's disease, and Parkinson's disease [4]. Clusterin is widely found in the brain and shows increased expression during cellular stress events. Studies suggest that clusterin is associated with neuropathies that involve abnormal cell death or proliferation [5]. Hemokinin-1, a member of the tachykinin family, was first identified in B lymphocytes. It has various roles in the immune, central nervous, and cardiovascular systems and its physiological effects include pain modulation, hematopoietic cell progression, vasodilation, and inflammation [6]. As a neuropeptide, kisspeptin is encoded by the KISS1 gene and is released from the hypothalamic nucleus. Kisspeptin is predominantly located in specific areas of the brain, such as the arcuate nucleus and the hypothalamic anteroventral periventricular nucleus [7].

Investigating novel biomarkers could enhance our understanding of mechanisms related to migraines and may provide valuable information for diagnosis. In the literature, there is no information regarding the relationships between clusterin, hemokinin-1, and kisspeptin levels and migraine. So, we aimed to measure and evaluate serum levels of adropin, clusterin, hemokinin-1, and kisspeptin in migraine patients with and without aura for diagnostic purposes.

Materials and methods

This cross-sectional study was conducted at Necmettin Erbakan University, Faculty of Medicine Hospital and received approval from the Non-Invasive Clinical Research Ethics Committee of Necmettin Erbakan University Medicine Faculty (Decision No: 2018/1485). The research was conducted in accordance with the Standards for the Reporting of Diagnostic Accuracy Studies (STARD). In line with the principles of the Declaration of Helsinki, written informed consent was obtained from all participants before beginning the study.

Study design and data source

A total of 150 participants were enrolled in the study, including 50 healthy individuals without any metabolic disease and 100 migraine patients (50 with aura and 50 without aura), between March 2021 and January 2022. The diagnosis of migraine (with and without aura) was confirmed using the IHS diagnostic criteria and was clinically assessed by a neurologist. The patient and control groups consisted of men and women (sex-matched) between the ages of 18 and 65 years. The exclusion criteria for all groups included hypertension, renal insufficiency, diabetes, peripheral vascular diseases, cerebrovascular diseases, metabolic syndrome, and psychotic disorders. The control group comprised healthy volunteers without any headache complaints and/or history of migraine. None of the patients had used medications before participating in the study. The data collected from the patients included information on sex, age of onset, frequency, duration, and localization of migraine pain. Other assessed factors included the severity of pain and accompanying symptoms such as phonophobia, vomiting, photophobia, and nausea, as well as changes in pain related to physical activity, triggers, perpetuating factors, and details of psychiatric and social histories.

The functional status of the migraine patients was assessed using the Migraine Disability Assessment (MIDAS) questionnaire and a visual analog scale (VAS). The MIDAS quantifies headache-related disability over a prior 3-month period and correlates with physician evaluations of the severity of illness. Scores for this questionnaire are categorized as follows: scores of 5–10 points signify little or no disability, 11–20 points indicate moderate disability, and>20 points reflect severe disability. The VAS score was used to determine the severity of pain, with VAS scores of 1–3 points indicating mild headache pain, scores of 4–6 points indicating moderate pain, scores of 7–8 points indicating severe pain, and scores of 9–10 points indicating extremely severe pain [8].

Peripheral venous blood collection

After clinical evaluation by an expert physician, fasting venous blood samples of 10 mL were obtained in the morning hours from the migraine patients of both groups in a pain-free/interictal period and from members of the control group. These samples were drawn in serum tubes (BD Vacutainer® SST™ Tubes, Ref. No: 367955, Lot No: 9127605, 5.0 mL/13 × 100 mm) and centrifuged at 1500 × *g* (rcf) and 4 °C for 7 min. The obtained sera were transferred to Eppendorf tubes (2 mL) and stored at −80 °C until analysis.

Biochemical measurements

The kits employed for biochemical analysis utilize sandwich enzyme-linked immunosorbent assay (ELISA) technology. With an anti-sample antibody, a pre-coated 96-well plate was used. A biotin-conjugated anti-sample antibody served as the detection antibody. First, 100 µL of sample mixture was added to each well (50 µL of standard, 40 µL of sample, and 10 µL human sample antibody). The plate was covered with a sealer and incubated for 60 min at 37 °C. After incubation, unbound conjugates were removed using a wash buffer.

Subsequently, 100 µL of the biotinylated detection antibody was added to each well and the plate was incubated at 37 °C for an additional 1 h. Following another wash to remove unbound conjugates, 100 µL of horseradish peroxidase-streptavidin was added and the plate was incubated at 37 °C for 30 min. After a final washing, 90 µL of 3,3,5,5-tetramethylbenzidine substrate solution was added and the plate was incubated for 10 min at 37 °C. To stop the reaction, 50 µL of stop solution was added.

Absorbances were read with a microtiter plate reader at 450 nm within 10 min after adding the stop solution (ELx800™, BioTek Instruments, USA). The concentration of biomarkers in the samples was determined by constructing a standard curve. Serum levels of adropin were determined using an adropin ELISA kit (Bioassay Tech Lab, China; Cat-N: E3231Hu, sensitivity: 2.49 ng/L, measurement range: 5–1000 ng/L). Clusterin levels were measured using a clusterin kit (Bioassay Tech Lab, China; Cat-N: E1189Hu, sensitivity: 0.31 ng/mL, measurement range: 0.5–300 ng/mL). Hemokinin-1 levels were measured with a tachykinin 4/hemokinin-1 kit (MyBioSource, USA; Cat-N: MBS2602776, sensitivity: 0.5 ng/mL, measurement range: 0.156–10 ng/mL). Kisspeptin-1 levels were determined using a kisspeptin-1 kit (Bioassay Tech Lab, China; Cat-N: E3122Hu, sensitivity: 12.14 ng/L, measurement range: 20–1500 ng/L).

Statistical analysis

The sample size was determined using G*Power version 3.1.9.7 software, following the methodology of Kang [9]. The parameters were set as follows: the probability of type I error (α) was 0.05, the effect size was 0.4, critical f was 1.438, degrees of freedom (df) were 197, and the non-centrality parameter λ was 32. Consequently, a total sample size of 146 participants was needed to achieve a statistical power (1–β) of 78 %.

Statistical analysis was conducted using IBM SPSS Statistics 21.0 (IBM Corp., USA). Kolmogorov-Smirnov tests were used to assess the normality of the data. The normally distributed variables of age, clusterin, hemokinin-1, disease duration, VAS score, and MIDAS score were expressed as mean ± standard deviation (SD). The non-normally distributed variables of adropin and kisspeptin were expressed as median (25th–75th percentiles). One-way analysis of variance (ANOVA) tests were conducted for variables with normal distribution and Kruskal-Wallis tests were conducted for non-normal distribution. Post hoc analyses were performed with the Tukey HSD test to conduct multiple pairwise comparisons after the ANOVA test. Chi-square (χ^2) tests were used for categorical variables. Correlation analysis was performed using Pearson and Spearman correlation. Area under the curve (AUC) values, cut-off scores, and sensitivity and specificity values were used to assess the discrimination ability of the biomarkers. Youden's index was used to determine optimum cut-off values. Values of $p<0.05$ were considered statistically significant.

Results

This study included 100 patients diagnosed with migraine (50 with and 50 without aura) and 50 healthy individuals as a control group. The mean age of patients with aura was 40.6 ± 9.6 years and that of patients without aura was 37.5 ± 7.3 years, while the mean age of the control group was 38.6 ± 7.9 years. The clinical and sociodemographic data of the patients are presented in Table 1. The serum levels of adropin, clusterin, and kisspeptin in the migraine patient groups showed no differences when compared to those of the control group. However, the serum levels of hemokinin-1 in the migraine patient with aura were higher when compared to the control group ($p<0.01$) (Table 1). A positive correlation has been found between age-disease duration ($r=0.69$, $p<0.01$), and clusterin-kisspeptin ($r=0.57$, $p<0.01$).

The mean MIDAS score was found to be 3.00 ± 0.84 and the VAS score was 2.95 ± 0.21 in the group of patients with aura. Among migraine patients without aura, the mean MIDAS score was 3.03 ± 0.61 and the VAS score was 2.96 ± 0.19. The cut-off and AUC values of adropin, clusterin, hemokinin-1, and kisspeptin levels for the group of migraine patients with aura are given in Table 2. While there was no difference in adropin, clusterin and kisspeptin between migraine with aura and without aura groups, a significant difference was determined in hemokin-1 levels ($p<0.01$) (Table 3). The results of the post hoc test ANOVA demonstrated a significant difference in hemokinin-1 levels between migraine with aura, without aura, and control groups ($p<0.01$). Furthermore, no significant difference in clusterin levels were determined between migraine with aura, without aura, and control groups. The flowchart of the study is described in Figure 1. Comparisons of serum adropin, clusterin, hemokinin-1, and kisspeptin levels between migraine patients (with aura and without aura) and the control group are shown in Figure 2.

Discussion

Although hemokinin-1 levels were elevated in migraine patients with aura, there were no significant differences in the levels of kisspeptin, hemokinin-1, clusterin, and adropin

Table 1: Comparison of adropin, clusterin, hemokinin-1, and kisspeptin levels between migraine patients (with aura/without aura) and control group, with related sociodemographic and clinical data.

Parameter	Migraine group (with aura/without aura)	Control group	p-Value
Gender (male/female)	50/50	25/25	–
Age (mean)[b] (with aura) mean ± SD	40.6 ± 9.6	38.6 ± 7.9	0.29
(Without aura)	37.5 ± 7.3	38.6 ± 7.9	0.37
Adropin (ng/L)[a] (with aura) median, (25th–75th percentile)	100.2 (72.5–155.6)	88.9 (26.5–311.7)	0.26
(Without aura)	91.9 (73.9–238.2)	88.9 (26.5–311.7)	0.11
Clusterin (ng/mL)[b] (with aura) mean ± SD	89.8 ± 39.1	91.9 ± 44.1	0.32
(Without aura)	96.9 ± 35.6	91.9 ± 44.1	0.35
Hemokinin-1 (ng/mL)[b] (with aura) mean ± SD	0.57 ± 0.25	0.37 ± 0.21	<0.01
(Without aura)	0.36 ± 0.29	0.37 ± 0.21	0.09
Kisspeptin (ng/L)[a] (with aura) median, (25th–75th percentile)	335.8 (242.9–624.7)	378.4 (318.8–574.3)	0.36
(Without aura)	380.3 (270.4–631.2)	378.4 (318.8–574.3)	0.14
Disease duration (year)[b] (with aura) mean ± SD	15.6 ± 6.8		
(Without aura)	12.4 ± 3.2		
VAS (attack severity)[b] (with aura) mean ± SD	2.95 ± 0.21		
(Without aura)	2.96 ± 0.19		
MIDAS (disability)[b] (with aura) mean ± SD	3.00 ± 0.84		
(Without aura)	3.03 ± 0.61		

MIDAS, migraine disability assessment score; VAS, visual analog scale; [a]Kruskal Wallis test (expressed as median (25th–75th percentile); [b]one-way ANOVA test (expressed as mean ± SD).

Table 3: Comparison of adropin, clusterin, hemokinin-1, and kisspeptin levels between migraine patients with and without aura groups.

Parameter	Migraine patients with aura	Migraine patients without aura	p-Value
Adropin (ng/L)[a] Median, (IQR)	100.2 (83.1)	91.9 (164)	0.81
Clusterin (ng/mL)[b] mean ± SD	89.8 ± 39.1	96.8 ± 35.6	0.92
Hemokinin-1 (ng/mL)[b] mean ± SD	0.57 ± 0.25	0.36 ± 0.29	<0.01
Kisspeptin (ng/L)[a] median, (IQR)	335.8 (1228)	380.3 (360)	0.55

[a]Kruskal Wallis test (median); [b]one-way ANOVA test (mean ± SD); IQR, interquartile range.

and without aura) exhibited no disability and reported only mild pain.

Recent studies have shown that neuropeptides play a role in the development of migraine and the occurrence of migraine-induced headaches. Migraine can cause headaches and recurrent attacks, which are associated with the dural neurogenic inflammation involved in the pathogenesis of migraine. Neurogenic inflammation events are well-described pathophysiological conditions that entail the secretion of potent vasoactive neuropeptides [10].

Many neuropeptides play important roles in neurovascular and degenerative diseases such as multiple sclerosis, Alzheimer's, dementia, and Parkinson's. As a polypeptide, adropin has a remarkable role in inflammation and different metabolic processes. It is assumed that adropin may also play a significant role in age-related cerebrovascular diseases and it is reported to be involved in the development of central nervous system disorders such as

Table 2: Cut-off and AUC values of adropin, clusterin, hemokinin-1, and kisspeptin in migraine patients with aura.

Parameter	AUC 95 % Confidence interval Lower-upper bound	Cutt-off	Sens (%)	Spec (%)	PPV	NPV	p-Value
Adropin (ng/L)	0.57 (0.48–0.66)	91.5	56.0 %	51.2 %	76.9 %	59.3 %	0.16
Clusterin (ng/mL)	0.51 (0.40–0.61)	85.5	58.1 %	59.4 %	68.7 %	66.4 %	0.89
Hemokinin-1 (ng/mL)	0.26 (0.18–0.34)	0.55	69.0 %	64.8 %	82.1 %	63.5 %	<0.01
Kisspeptin (ng/L)	0.44 (0.34–0.54)	381.7	54.0 %	53.7 %	67.2 %	58.6 %	0.19

AUC, area under curve; Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predicive value.

when compared to the control group. There was a significant difference in hemokinin-1 levels when compared to migraine patients with and without aura groups. The MIDAS and VAS scores indicated that the migraine patients (with schizophrenia, stroke, and bipolar disorder [11]. Moreover, serum levels of adropin were found to be decreased in multiple sclerosis patients [12]. In the study conducted by Algul et al. [13], however, it was determined that serum

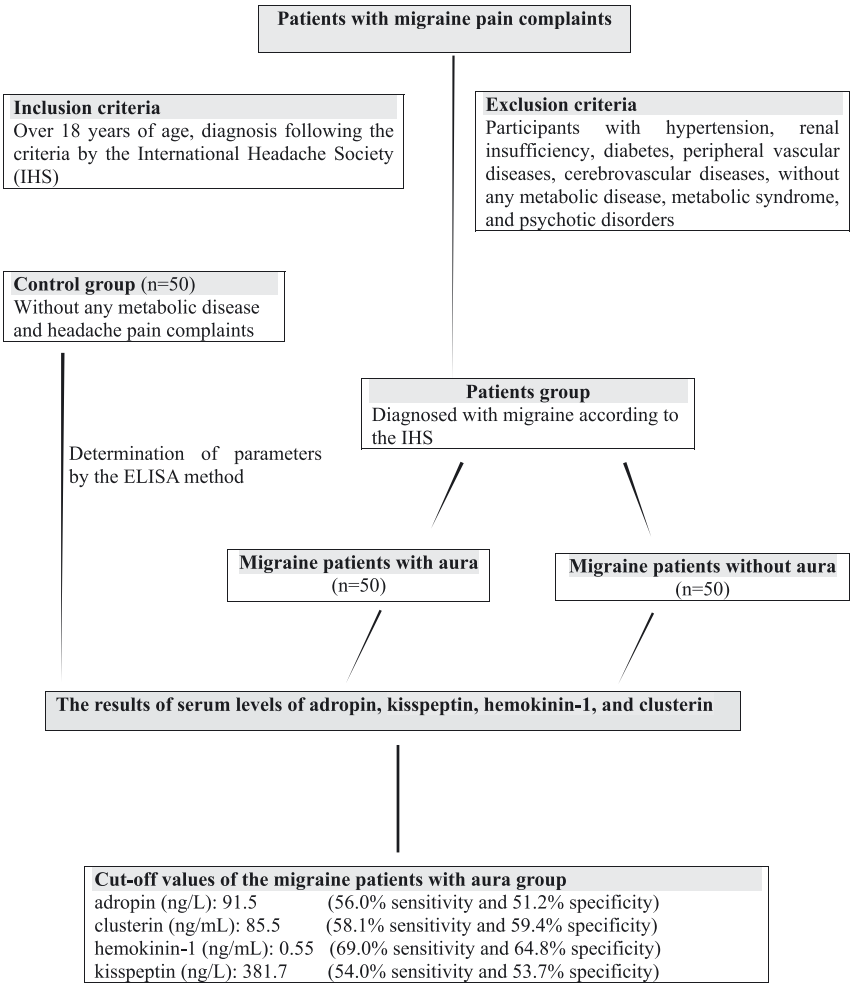

Figure 1: Study flowchart.

adropin levels were not associated with migraine. Similarly, in our study, serum adropin levels in the groups of migraine patients showed no difference when compared to those of the control group.

In vitro investigations have shown that the expression of clusterin is increased in cases of heat shock and oxidative stress. Several studies have determined that clusterin is present at high levels in neuropathies involving abnormal cell death or proliferation, such as Alzheimer's disease and multiple sclerosis [5]. Wang et al. [14] reported that plasma clusterin is associated not only with Alzheimer's disease but also with vascular dementia. Previous studies have also found high levels of clusterin in cases of neurological-based degenerative diseases such as amyotrophic lateral sclerosis and encephalopathies [15]. In addition, a recent study concluded that levels of clusterin in patients with epilepsy were lower compared to the control group [16]. In the present study, there was no significant association between clusterin and the migraine patient groups compared to the controls.

As a pain mediator, hemokinin-1 plays a role in physiological phenomena such as pain modulation, hematopoietic cell progression, vasodilation, and inflammation [17]. A study conducted with mice suggested that hemokinin-1 is a significant pain mediator in inflammatory mechanisms and neuropathic conditions [18]. A previous study indicated that hemokinin-1 may contribute to the inflammatory response involving Th17/Treg 44–45 cells, which play a role in the inflammatory regulation of neurons [19]. Yildirim et al. [20] reported that serum levels of apelin-36, another neuropeptide, were elevated in migraine patients compared to controls. In the present study, serum levels of hemokinin-1 were found to be significantly increased in migraine patients with aura when compared to the control group. However, hemokinin-1 was not correlated with MIDAS or VAS scores in the group of migraine patients with aura.

Despite the known hypothalamic effects of the kisspeptin hormone, very few studies have explored its physiological effects [21]. It has been reported that kisspeptin is produced in the limbic/paralimbic regions of the brain [22].

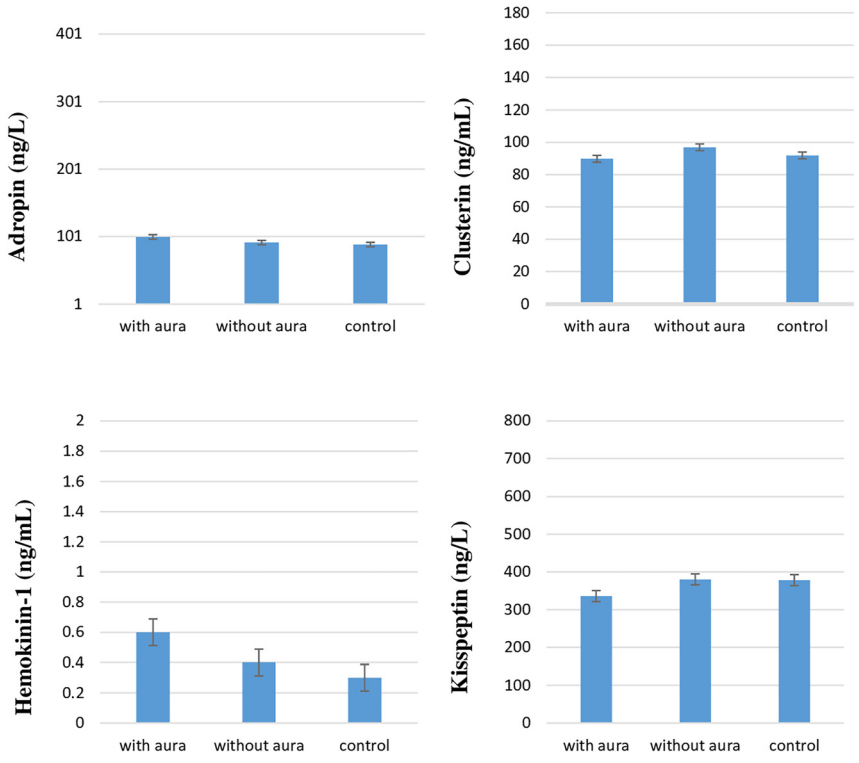

Figure 2: Comparison of serum adropin, clusterin, hemokinin-1, and kisspeptin levels between migraine patients (with aura and without aura) and control group.

Studies have shown that kisspeptin stimulates the hypothalamic-gonadal axis and may alter the release of antioxidant enzymes to protect against oxidative damage [23]. Additionally, kisspeptin has been shown to exert neuroprotective effects against amyloid β-related proteins [24]. In our study, serum kisspeptin levels in the migraine patient groups showed no differences when compared to the control group. When we examined the correlations between sociodemographic data, clinical data, and adropin, clusterin, hemokinin-1, and kisspeptin levels among migraine patients with aura and the control group, we did not find any statistically significant relationships.

In summary, no clinically validated biomarker or laboratory measurement for migraine diagnosis exists today. The present study may contribute new data to the limited information on the relationships between adropin, clusterin, hemokinin-1, and kisspeptin and migraine. Moreover, findings from this study could provide new insights for future investigations on migraine.

Conclusions

As a common and debilitating condition, migraine leads to serious headaches and impacts quality of life, productivity, and healthcare costs for millions of people. In the literature, serum levels of clusterin, hemokinin-1, and kisspeptin have not been previously determined in migraine patients with and without aura. Our study demonstrated that serum levels of hemokinin-1 were increased in migraine patients with aura when compared to the control group. To confirm these results, more comprehensive studies are needed. As a limitation of this study, there is little or no information available regarding the relationships between adropin, clusterin, hemokinin-1, and kisspeptin levels and migraine disease, making it difficult to compare the present results to those of other researchers. The biomarkers analyzed in this study may show different results in populations of migraine patients during migraine attacks, and these possible changes should be investigated in future investigations.

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