



## Research Article

# Evaluation of serum levels of irisin and nesfatin-1 in patients with migraine without aura

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### Abstract

**Objectives:** Migraine is a chronic neurological disorder. A number of cytokines have been linked to the pathogenesis of migraine. This is a preliminary assessment to determine and analyze the serum levels of irisin and nesfatin-1 in patients with migraine without aura.

**Methods:** A total of 80 participants, 40 patients who had been diagnosed with migraine without aura (10 men, 30 women) and 40 healthy controls (10 men, 30 women), were included in the study. The serum irisin and nesfatin-1 parameters were investigated using blood samples drawn from the patient and control groups.

**Results:** The mean serum irisin level was  $16.87 \pm 14.66$  ng/mL in the migraine group and  $17.33 \pm 17.18$  ng/mL in the healthy controls. No significant p value was determined ( $p=0.470$ ), but the level was slightly lower in the migraine group. The mean nesfatin-1 level was  $4.71 \pm 5.96$  mmol/L in the migraine group and  $4.13 \pm 5.41$  mmol/L in the healthy controls ( $p=0.19$ ), again revealing a small but statistically insignificant difference. In addition, there was no statistically significant difference according to age group, visual analog scale score for pain, body mass index, or length of disease duration.

**Conclusion:** Although no statistically significant differences were observed, the present study is believed to be the first to provide insight on the serum levels of irisin and nesfatin-1 in migraine without aura patients.

**Keywords:** Headache, irisin, migraine, nesfatin-1

Migraine is defined as a neurovascular disorder with neurogenic inflammation and contractile dysfunction of the cranial blood vessels [1]. It is a headache disorder that is accompanied by different combinations of neurological and autonomic disorders [2]. Clinically, there are 2 classic types of migraine: with and without aura. Migraine without aura is the most frequent form of primary headaches (60-80% of all migraines). The clinical symptoms of migraine without aura include pulsating pain, pain on at least one side of the head, sensitivity to sound and light, and vomiting and/or nausea [3]. Migraine attacks decrease quality of life (QoL), and may also cause a fiscal burden for individuals and organizations due to medical expenses. Inadequate treatment can lead to more frequent migraine attacks and more disruption for the sufferers.

According to the World Health Organization (WHO), migraine is a cause of labor loss as a result of the headache pain and distress (ranking 19<sup>th</sup> for men and 12<sup>th</sup> for women) [4].

Many theories for the pathophysiology of migraine have been proposed. According to a neurovascular theory, migraine headaches demonstrate vascular changes in secondary neuronal activation. As a result of neuronal events, blood vessels in pain-sensitive structures expand and lead to more trigeminal nerve activation and pain [2]. The exact pathology of migraine has yet to be fully understood. In 1 novel study, it was proposed that cytokines and some neuropeptides may have an important role in the pathogenesis of migraine [5]. Recent research has focused on the association between mi-

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graine and neuropeptides. One of the newly identified peptide hormones, irisin, is composed of 112 amino acids and weighs ~12 kDa [6, 7]. It should be noted that irisin affects autocrine, paracrine, and endocrine hormones. Several studies have found that irisin can be identified in the skeletal muscles, adipose tissue, kidneys, neural cells, ovaries, myocardial and smooth muscles, endothelium, liver, and pancreas [8, 9]. Also, recent observations have demonstrated that irisin has been detected at high levels in the brain, including the Purkinje cells of the cerebellum. Although the hormone irisin is mainly synthesized from muscle tissue, studies have shown the presence of irisin in the neuronal areas of rats [9, 10]. The physiological and hormonal effects of irisin still remain incompletely explained.

Nesfatin-1 has a molecular weight of 9.7 kDa and is composed of 82 amino acids [11]. This newly discovered neuropeptide has antioxidant and antiapoptotic properties and plays a significant role in neurodegenerative damage and cerebrovascular events [12]. Nesfatin-1 has been found to be expressed mostly in the limbic system, the cortical nuclei, the dorsal motor nucleus of the vagus nerve, and the preganglionic sympathetic and parasympathetic neurons of the spinal cord [13]. One study concluded that nesfatin-1 plays a role in emotional and psychological events, such as panic disorder and chronic stress [14]. The present study is a preliminary assessment to determine serum irisin and nesfatin-1 levels in migraine without aura patients and examine whether these data could help with the identification or evaluation of the disease.

## Materials and Methods

Eighty participants were included into the study in 2 groups: Migraine without aura patients (10 men, 30 women) and healthy subjects (10 men, 30 women). All of the participants were categorized in 10-year age groups from 20 to 59 years. The patients and healthy subjects had no metabolic diseases before the study. The exclusion criteria included any known history of headache disorder, endocrinopathy, cardiovascular disease, psychiatric disorder, cerebrovascular disease, neurological disorder, and the use of anti-inflammatory or steroid drugs, or anti-hypertensive medication. The patient data were obtained through self-reported questionnaires. The group of healthy controls was composed of participants with no migraine or headache complaints. Migraine without aura is the most frequent form of primary headache. Migraine without aura patients who were between migraine episodes were selected from individuals admitted to the neurology department of Konya Education and Research Hospital between March and December 2018. The migraine patients were diagnosed by an experienced neurologist according to the diagnostic criteria of the International Headache Society (IHS) (3rd edition, beta version).

According to the IHS, the diagnostic criteria of migraine without aura are at least 5 headache attacks lasting 4-72 hours with/without treatment and at least 2 of the following a)

pulsating quality, b) unilateral or bilateral location, c) pain intensity that is moderate to severe, and d) increased pain with physical activity (daily routine activity), as well as the experience of either vomiting and/or nausea, or phonophobia or photophobia during the headache. A visual analog scale (VAS) was used to assess pain intensity in the migraine without aura patients with a rating from 0 (no pain) to 10 (worst pain). Body mass index (BMI) was calculated as weight (kg) divided by the square of the height (m<sup>2</sup>) according to the WHO BMI classification (Technical Report Series 854). The duration of migraine without aura was determined by a single neurologist based on the patient questionnaires and clinical examination. Blood samples (10 mL) drawn from each patient were transferred to biochemistry tubes in order to evaluate the serum nesfatin-1 and irisin levels. The samples were separated after coagulation, centrifuged at 3000 rpm for 10 minutes, and stored in deep freeze at -80°C until the run time. The serum levels of irisin and nesfatin-1 were measured using enzyme-linked immunosorbent assay (ELISA) kits.

This study was approved by the ethics board of the Meram Faculty of Medicine of Necmettin Erbakan University in Konya, Turkey (approval number: 2018/1337-68) and conducted based on the principles of the Declaration of Helsinki. Written, informed consent was obtained from each participant prior to the study.

### Measurement of serum irisin and nesfatin-1

Serum irisin levels were measured using ELISA kits (Human Irisin ELISA Kit, catalog no: 201-12-5328; Shanghai Sunred Biological Technology, Shanghai, China). The analytical sensitivity, assay range, and intra-assay and inter-assay variation rates were 0.157 ng/mL, 0.2-60 ng/mL, <10%, and <12%, respectively. Serum nesfatin-1 levels were also measured using ELISA kits (Human NES 1 ELISA Kit, catalog no: 201-12-4341; Shanghai Sunred Biological Technology, Shanghai, China). The analytical sensitivity was 0.113 mmol/L, the assay range was 0.2-35 mmol/L, the intra-assay variation was <10%, and the inter-assay variation was <12%. The kit manufacturer's instructions were followed throughout all of the analyses. The absorbance of the samples was measured at 450 nm and recorded using a microplate reader (ELx800; BioTek Instruments, Winooski, VT, USA).

### Statistical analysis

The statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). Differences between the migraine without aura patients and the healthy controls were evaluated with the Mann-Whitney U test. The data were expressed as mean±SD (X±SD). One-way analysis of variance and the Kruskal-Wallis tests were used for age categories, VAS and BMI scores, and disease duration. The results were accepted as statistically significant at p<0.05.

## Results

A total of 80 participants were recruited according to the exclusion criteria. As shown in Table 1, the mean serum level of irisin was  $16.87 \pm 14.66$  ng/mL in the migraine without aura group and  $17.33 \pm 17.18$  ng/mL in the healthy group. No significant p values were determined ( $p=0.470$ ), but the irisin level was lower in the migraine group. The mean level of nesfatin-1 was 4.71 mmol/L in the migraine group and 4.13 mmol/L in the healthy group. While no significant p values were determined ( $p=0.191$ ), the nesfatin-1 level was slightly higher when compared with the healthy subjects. The BMI scores were not statistically significant ( $p=0.136$ ) (Table 1).

As seen in Table 2, no significant difference in the mean level of nesfatin-1 or irisin was found between the age groups of migraine patients [nesfatin-1 ( $p=0.070$ ) and irisin ( $p=0.146$ )] and healthy group nesfatin-1 ( $p=0.424$ ) and irisin ( $p=0.248$ ).

The study results also revealed no statistically significant difference in the serum irisin and nesfatin-1 level in terms of the VAS score or disease duration in the migraine without aura group ( $p=0.388$ ,  $p=0.312$ ,  $p=0.555$ , and  $p=0.383$ , respectively) (Table 3).

## Discussion

Migraine is a serious health problem affecting QoL in more than 10% of the general population [15]. Defined as a neo-

**Table 1. Comparison of nesfatin-1 and irisin levels in MWA and healthy groups**

Parameters	MWA group	Healthy group	p
Age (years, mean)	36.74	37.82	0.56
Sex (number)	Men, 10 (%25) Women, 30 (%75)	Men, 10 (%25) Women, 30 (%75)	-
Serum irisin (ng/mL)	Mean: 16.87 n: 40 SD: 14.66	Mean: 17.33 n: 40 SD: 17.18	0.470
Serum nesfatin-1 (mmol/L)	Mean: 4.71 n: 40 SD: 5.96	Mean: 4.13 n: 40 SD: 5.41	0.191
BMI, (kg/m <sup>2</sup> )	$20.91 \pm 0.66$	$22.14 \pm 0.93$	0.139

BMI: Body mass index; MWA: Migraine without aura; SD: Standard deviation.

**Table 2. Comparison of nesfatin-1 and irisin levels according to age categories**

Age categories (years)	MWA group		Healthy group	
	Nesfatin	Irisin	Nesfatin	Irisin
20-29				
Mean	7.48	21.84	24.39	16.24
n	9	9	8	8
SD	7.21	14.74	33.05	14.92
30-39				
Mean	1.68	9.89	30.19	20.20
n	15	15	12	12
SD	1.23	9.59	32.64	13.83
40-49				
Mean	7.22	23.92	18.45	18.18
n	11	11	13	13
SD	7.74	16.14	24.86	22.37
50-59				
Mean	3.30	13.34	28.49	12.07
n	5	5	7	7
SD	4.01	17.22	33.06	15.96
p	0.070	0.146	0.424	0.248

MWA: Migraine without aura; SD: Standard deviation.

**Table 3. Comparison of the levels of nesfatin-1 and irisin according to VAS score and duration of MWA**

VAS scores	Values	df	p
Nesfatin	156.333	152	0.388
Irisin	160.000	152	0.312
<b>Duration of MWA</b>			
Nesfatin	413.333	418	0.555
Irisin	426.000	418	0.383
Number	40		

MWA: Migraine without aura; VAS: Visual analog scale.

vascular disorder, migraine may be associated with different combinations of primary episodic headache disorders [16]. The exact component causing pain in migraine still remains unclear. The majority of migraine sufferers have migraine pain without aura. Clinically, migraine is commonly associated with transient neurological deficits, such as sensitivity to light or sound, throbbing, and vomiting [3].

Recent studies have proposed that adipo-myokines and some peptides may be linked to the pathogenesis of migraine. Lukacs et al. [5] reported that substance P, nitric oxide, vasoactive intestinal peptide, pituitary adenylate cyclase-activating polypeptide, and calcitonin gene-related peptide have potentially important roles in the regulation of inflammatory mechanisms in patients with migraine. Boström et al. [6] identified a new peptide, irisin, a member of the myokine family. This protein is a cleaved version of fibronectin type-III domain-containing protein 5 (FNDC5), a member of the group of fibronectin type-III repeat containing genes modulated by peroxisome proliferator-activated receptor gamma coactivator 1 alpha [17]. Expressed FNDC5/irisin has been found not only in skeletal muscle muscles, but also in various regions of brain tissue [18]. New studies have shown the presence of FNDC5/irisin protein in the hypothalamus, cerebellum, and spinal cord [19]. Similarly, immunoreactivity of FNDC5/irisin has been observed in neurons, astrocytes, and microglia in brain tissue [20]. The serum level of irisin is regulated by several factors, such as obesity, exercise, diet, pharmacologicals, and some pathological conditions [21]. Irisin was initially defined as a myokine protein [6], but new investigations have revealed that irisin acts as an adipokine [22], as well as a potential neurokinine [23]. It is well documented that irisin plays a notable role in apoptosis and inflammatory and oxidative stress [24]. In a study performed by Bosma et al. [25] it was observed that in mice, FNDC4 (homology with FNDC5) may have an anti-inflammatory influence on macrophages and thus may improve colitis. However, the physiological properties and functional role of irisin in the brain have yet to be fully explained. New studies have noted that the level of irisin may be increased or decreased in many diseases. A study conducted by Ebert et al. [26] reported that the level of serum irisin was lower in chronic kidney disease. Similarly, the serum irisin levels were lower in patients with type 2 diabetes mellitus (DM) [27]. A recent

study has shown that a low level of serum irisin was a possible biomarker in the early prediction of ischemic stroke [28]. Ates et al. [29] demonstrated that the level of irisin was higher in patients with type 1 DM. Our study revealed a minimal decrease in the serum irisin levels in migraine patients compared with the healthy group, although the difference was statistically insignificant ( $p=0.470$ ). In a previous study, the mean serum irisin level of a healthy group was determined to be 3.6 ng/mL [30]. In contrast, the mean serum level of irisin was 17.33 ng/mL in the healthy subjects in our study. New studies have suggested that irisin may have a therapeutic use for some diseases. In a study performed in mice, oral irisin was demonstrated to have a protective effect in the treatment of atherosclerosis [31]. Further studies are needed to clarify this issue.

Several studies have focused on the physiology of nesfatin-1 and its role in different diseases. It has been reported that chronic stress may elevate the plasma levels of nesfatin-1 [32]. Ari et al. [33] concluded that plasma nesfatin-1 levels were increased in patients with major depressive disorder. Several studies have shown that migraine was associated with oxidative mechanisms and affected by oxidative factors [34, 35]. Also, it has been observed that nesfatin-1 had a significant effect on the suppression of brain damage resulting from oxidative mechanisms [12]. Aydın et al. [36] revealed that serum and saliva levels of nesfatin-1 were remarkably higher in patients with epilepsy than those of controls. The human serum and saliva nesfatin-1 levels ( $25.8\pm 5.84$  ng/mL,  $33.5\pm 8.79$  ng/mL, respectively) in untreated epileptic patients were 160 times greater than those of control subjects ( $0.16\pm 0.002$  ng/mL,  $0.21\pm 0.003$  ng/mL, respectively). Interestingly, another study determined that the level of nesfatin-1 was higher in patients with schizophrenia compared with a control group ( $10.51$ - $350.8$  pg/mL,  $4.86$ - $68.91$  pg/mL, respectively) [37]. In our study, a slight increase in the serum level of nesfatin-1 was observed in patients with migraine without aura compared with the healthy group; however, the difference was not statistically significant ( $p=0.19$ ) (Table 1). Xiao et al. [38] determined a level of nesfatin-1 of 5.33 mmol/L in the healthy group, which is similar to the findings observed in our study (5.41 mmol/L).

Distress and disturbances caused by the disruptive symptoms of migraine represent one of the most important problems for patients with migraine and result in elevated social and fiscal burdens on both the individual and national health systems. Currently, only a limited number of biochemical parameters are utilized in the diagnostic process of migraine. The availability of rapid and sensitive biomarkers is important for early diagnosis, prognosis, and treatment of migraine.

## Conclusion

To the best of our knowledge, this is the first study to examine the serum levels of irisin and nesfatin-1 in patients with migraine without aura. We performed the analysis according to the ELISA kit manufacturer's instructions and methods. Nonetheless, there are limitations to the present research. We

did not use a control serum and the present study was performed in only a single province. Therefore, more comprehensive multi-centered research and studies with larger populations are needed to further understand the entity of migraine without aura.

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