



# The Possible Role of Apelin and Sirtuin 1 in Migraine Pathogenesis

## *Apelin ve Sirtuin 1'in Migren Patogenezindeki Olası Roller*

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### Abstract

Migraine is recognized as a neurovascular and neuroinflammatory condition. The demonstration of temporary demyelinating lesions in brain parenchyma caused different thoughts about the pathogenesis of migraine other than the pain process. *In vitro* studies –emphasizing the occurrence of this situation through neuroinflammation – have led us to hypothesize that as an adipocytokine member, apelin, and an epigenetic regulator, sirtuin 1 (SIRT1) may have a possible role in the pathogenesis of migraine. We measured these molecules' serum levels with ELISA. The serum levels were not significantly changed in subgroups, so a direct correlation in the pathogenesis of migraine could not be shown, but levels in the migraine group had drawn our attention. SIRT1 and apelin may increase migraine attacks to compensate for the probable neurodegeneration. This initial study speculated that SIRT1 and apelin may have a role in migraine pathogenesis that needs to be clarified.

**Keywords:** Apelin; Migraine; Neurodegenerative diseases; Neuroimmunology; Sirtuin 1 (SIRT1)

Migraine is a neurovascular and neuroinflammatory condition. The reason for the characteristic pain of migraine is the sensitization of the primary afferent nociceptive neurons that innervate intracranial and related vessels after the cortical spreading depression occurs. The real mechanism of this activated meningeal nociception remains unclear, but local sterile inflammation has been accused in this process.<sup>[1,2]</sup> Moreover, the demonstration of temporary demyelinating lesions in the brain parenchyma *in vitro* models caused different thoughts about the nature of this disease.

SIRT1 (sirtuin 1) has a protein deacetylase and adenosine diphosphate (ADP)-ribosyl transferase activity.<sup>[3]</sup> It promotes axonal elongation and dendritic branching during neuronal development. These have an essential role in the generation of memory via effecting the synaptic plasticity in hippocampal neurons. Sirtuin regulates feeding behavior and circadian rhythm of hypothalamic functions. Also, SIRT1 has some epigenetic effects on metabolic regulation and vascular protection.<sup>[4]</sup> Apelin is the endogenous ligand for the apelin receptor (APJ) that is expressed at the surface

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of several organs. It is a key regulator in a normal glucolipid metabolism, also playing a potential role in obesity, insulin resistance, controlling water, and food intake.<sup>[5]</sup>

Whether migraine creates a neurodegenerative process remains a controversial subject; we hypothesize that apelin and SIRT1 molecules may have a possible role in this pathogenesis.

## Materials and Methods

### Study Design and Data Analysis

Thirty patients were accepted in this study who had applied to Gazi University, Faculty of Medicine, Neurology Department between 2014 and 2015 years. Patients have been diagnosed as having migraine according to The International Classification of Headache Disorders, 3rd edition beta version (ICHD–III beta), and patients who had systemic comorbidity especially inflammatory conditions, obesity, and severe cardiac pathologies were excluded from this study.

In the migraine group, 22 patients had episodic migraine and 8 had chronic migraine. Four patients had migraines with aura, and 26 had migraines without aura. Furthermore, 12 patients were in an attack period, and 18 were in an attack-free period at the time blood samples were obtained. All patients with migraine with aura were also in the episodic migraine group. The mean disease duration of the patients after diagnosis was 5.6 years. At the time of sampling, all patients have received treatment. The treatment that had been received by chronic migraine patients were amitriptyline, propranolol, duloxetine, topiramate, nonsteroidal anti-inflammatory drugs, and triptans; and the treatments received by episodic patients who had less than three attacks in a month were only nonsteroidal anti-inflammatory drugs and triptans. Furthermore, 20 healthy volunteers, with similar age and gender compared to the migraine group, were included in this study as a control group.

The study was approved by the ethics committee of Keçiören Training and Research Hospital (No. 891 dated 24.06.2015). All individuals who were included in the study were informed about the study and their written consents were obtained.

### Experimental Procedure

Ten cubic centimeters (cc) peripheric blood samples were obtained from patients and healthy volunteers. Serum parts were separated by centrifugation at 3000 rpm for 5 min. Serum samples were stored at  $-70^{\circ}\text{C}$  until analysis. Quantitative measurement of serum SIRT1 and apelin was done with ELISA technique. After standard medium con-

**Table 1.** Comparison with mean values of apelin and sirtuin 1 with gender

	Female (n=31)	Male (n=19)	p
Apelin (pg/ml)	1048.3	961.7	0.610
Sirtuin 1 (ng/ml)	5.4	4.9	0.312

taining SIRT1 and apelin antibodies were diluted, serum samples were added to the wells, incubated at room temperature for 2.5 h, washed, and then incubated with biotin antibody for 1 h. After washing, streptavidin was added, left for 45 h, and washed again, and one-step reagents (Bioassay Technology Laboratory® Human SIRT1 and Apelin Kit, Shanghai, China) were added and incubated for 30 min. The concentrations of SIRT 1 and apelin were determined spectrophotometrically. Absorbance values at 450 nm were determined using an ELISA reader.

### Statistical Analysis

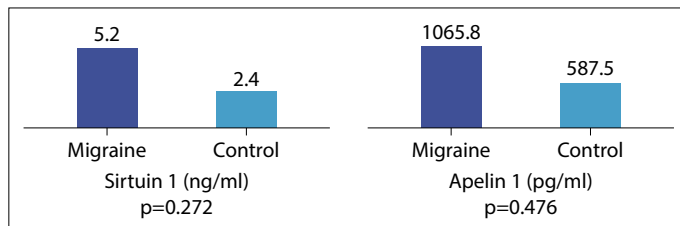
Data analysis was performed by using IBM SPSS 21.0 statistical software package. Data were analyzed using descriptive statistical methods (frequency, percentage, median, min-max) and the comparison of qualitative data with Chi-square and Fisher's and Yates Chi-square (c2). Compliance was assessed by a normal distribution of data Kolmogorov-Smirnov and Shapiro-Wilk tests. A probability (p) value below 0.05 was accepted significant.

## Results

The mean age of our patients was 34.3 years. Apelin values of the participants were  $1,388.0 \pm 1,367.8$  pg/ml, and SIRT 1 levels of the participants were  $5.8 \pm 5.2$  ng/ml. There was no significant difference between sex in migraine groups (Table 1). There were no significant differences between migraine and control groups in serum SIRT1 and apelin levels either ( $p > 0.05$ ) (Fig. 1). Moreover, there was no difference between migraine attack period or attack-free period, episodic migraine, chronic migraine, migraine with aura, and migraine without aura, but still, SIRT1 and apelin levels were found to be higher in migraine groups than in the controls and also even higher in episodic migraine group than in chronic and control groups, respectively (Fig. 2).

## Discussion

Although migraine seems a benign disease, it causes white matter abnormalities on magnetic resonance imaging, also its paroxysmal nature and gives rise to disabilities remind that this disease may have some neurodegenerative features.<sup>[2,6]</sup> In our study, we intended to find



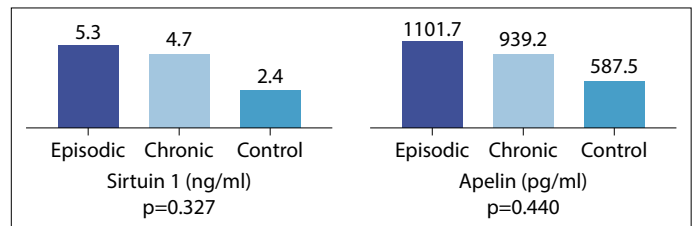
**Figure 1.** Serum apelin and sirtuin 1 levels between migraine patients and control.

some clues about the neurodegeneration process, so we focused on these two molecules.

In this study, there have not been any significant differences between migraine and control groups in serum sirtuin 1 and apelin levels. Moreover, there has not been any difference between migraine attack period or attack-free period and migraine subgroups, but even if the results were insignificant, sirtuin 1 and apelin levels were found to be higher in episodic migraine and in attack periods.

These proteins have been described in various neurological conditions. One of the observations has been suggested that sirtuins may have improved Alzheimer's disease pathology *in vitro*.<sup>[7]</sup> It had been shown that adenosine monophosphate-dependent protein kinase has an effect on amyloid-beta metabolism and provide an anti-amyloidogenic effect.<sup>[8]</sup> The subunit of nuclear factor kappa beta (NF- $\kappa$ B) called RelA/p65 acetylated in Alzheimer's disease and causes amyloid-beta accumulation. Sirtuin 1 deacetylates NF- $\kappa$ B and increases the brain-derived neuroprotective factor. Besides, NF- $\kappa$ B expression increases dramatically in migraine attack period, and peak levels have been seen at the second hour of the attack in previous studies.<sup>[9,10]</sup> However, there has not been any data about whether sirtuin 1 may have deacetylated this protein to cause an endogenous anti-migraine effect or not.

Apelin has been shown to decrease TNF  $\alpha$  and interleukin 1 (IL 1) like inflammatory cytokines, lower N-methyl D-aspartate excitotoxicity, and increase the vascular endothelial growth factor levels in *in vitro* studies. Furthermore, apelin expression, in temporal lobe epileptic patients from the neocortex and the hippocampus and the adjacent cortical area in the rat models, significantly decreased.<sup>[11]</sup> Also, some other studies revealed that apelin inhibits neuronal apoptosis and oxidative stress through inhibiting protein kinase C (PKC), poly adenosine diphosphate-ribose polymerase, and facilitate angiogenesis in inflammatory neurologic conditions.<sup>[11,12]</sup> Therefore, apelin has been investigated for a potential therapeutic agent in neurological conditions.<sup>[13,14]</sup>



**Figure 2.** Serum apelin and sirtuin 1 levels between episodic, chronic migraine patients and control groups.

In this study, it was hypothesized that serum SIRT1 and apelin levels might increase in migraine attacks to compensate for the possible neuroinflammatory and possible neurodegeneration process and might contribute to preventing the demyelinating lesions to become permanent.<sup>[1-5,15]</sup>

This study has several limitations. The most important limitation was the small sample size. Also, the patients were not categorized according to whether they had been received any treatment or not. Treatments that the patients received might have influenced the results either.

## Conclusion

Although the study has important limiting aspects mentioned above, it has been the first human study to elucidate the effect of apelin and SIRT1 in migraine pathogenesis. Results suggest that these molecules are not directly involved in the complex pathogenesis of migraine but elevated levels in the migraine group deserve attention. Considering that migraine has neurodegenerative features, further researches with more independent components such as medications priorly used, attack amount per month, etc. in large-scale studies may confirm these results.

**Peer-review:** Externally peer-reviewed.

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

**Authorship Contributions:** Concept: Cİ; Design: DYC; Supervision: NA; Materials: DYC; Data Collection or Processing: DYC; Analysis or Interpretation: RT; Literature Search: TA; Writing: TA; Critical Review: Cİ.

**Conflict of Interest:** None declared.

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