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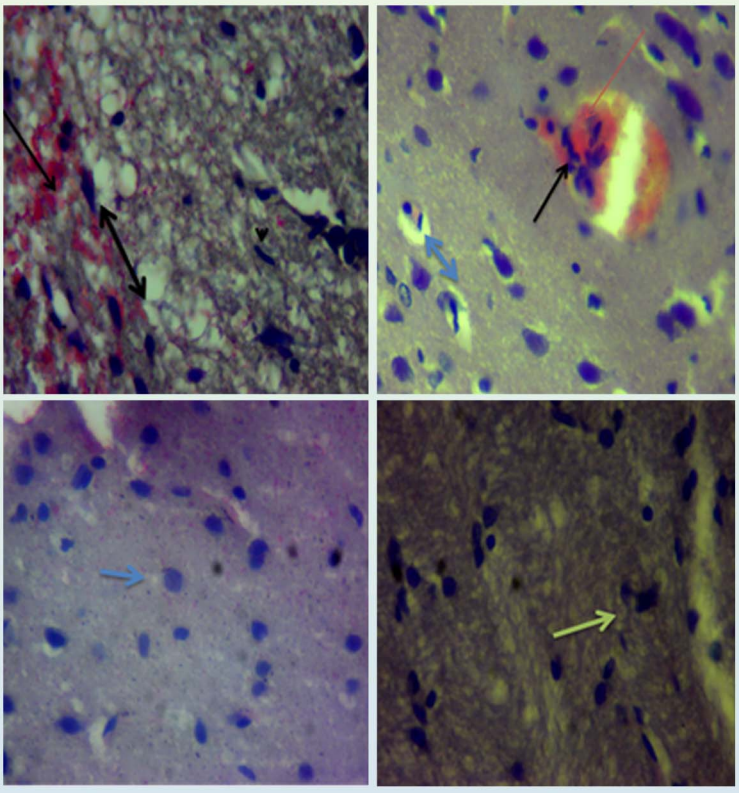

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AIM AND SCOPES
Journal of Cellular Neuroscience and Oxidative Stress is an online journal that publishes original research articles, reviews and short reviews on the molecular basis of biophysical, physiological and pharmacological processes that regulate cellular function, and the control or alteration of these processes by the action of receptors, neurotransmitters, second messengers, cation, anions, drugs or disease.

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C- Interaction Between Oxidative Stress and Ion Channels in Neuroscience
(Effects of the oxidative stress on the activation of the voltage sensitive cation channels, effect of ADP-Ribose and NAD^+ on activation of the cation channels which are sensitive to voltage, effect of the oxidative stress on activation of the TRP channels in neurodegenerative diseases such Parkinson's and Alzheimer's diseases)

D- Gene and Oxidative Stress
(Gene abnormalities. Interaction between gene and free radicals. Gene anomalies and iron. Role of radiation and cancer on gene polymorphism)

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Keywords
Ion channels, cell biochemistry, biophysics, calcium signaling, cellular function, cellular physiology, metabolism, apoptosis, lipid peroxidation, nitric oxide, ageing, antioxidants, neuropathy, traumatic brain injury, pain, spinal cord injury, Alzheimer's Disease, Parkinson's Disease.

RESEARCH ARTICLE

J Cell Neurosci Oxid Stress 2020;12(1): 914-921.

Antioxidant and cytokine levels in plasma of patients with attack and non-attack periods

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Abstract

Oxidative stress and inflammation are two possible mechanisms in the etiology of patients with migraine. However, there are conflicting data between reactive oxygen species and cytokine generation in patients with migraine. The current study aimed to determine the cytokine, oxidant, and antioxidant levels in plasma of migraine patients with attack and non-attack periods.

In the current study, we used control (n=30), patients with attack (n=30), and passive (n=30) periods. In the plasma samples of control and patients, we measured lipid peroxidation (MDA), glutathione (GSH), glutathione peroxidase (GSHPx), vitamin A, vitamin E, β-carotene, and cytokine (IL-1β, IL-6 and TNF-α) levels in the plasma of control and patients with migraine. The GSH, GSHPx, and vitamin E levels were low in the patients with non-attack period as compared to control subject, although MDA levels were high in the patients with non-attack period. The concentrations of vitamin A and β-carotene did not differ in the control and patient groups. The levels of IL-1β, IL-6 and TNF-α were higher in the non-attack group than in the control. In addition, the levels of cytokines were further increased in the attack group as compared to control and non-attack groups. In conclusion, we found signs of inflammation and oxidative stress in the plasma of migraine patients suggesting that this headache form might relate with inflammatory and oxidative stress pathways.

Keywords: Antioxidants; Cytokine; GSH; Migraine; Oxidative stress.

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List of Abbreviations;

***GSH**, reduced glutathione; **GSHPx**, glutathione peroxidase; **H_2O_2**, hydrogen peroxide; **IL**, interleukin; **IL-1β**, interleukin 1beta; **IL-6**, interleukin 6; **MDA**, malondialdehyde; **ROS**, reactive oxygen species; **SDU**, Suleyman Demirel University; **TNF-α**, tumor necrosis factor alpha*

Introduction

Migraine is characterized with unilateral and recurrent pain. It is interesting that 2% of adult and children over all the world suffers from migraine attacks (Diener et al. 2015). Incidence of migraine attacks has a high rate in women (5% to 25%) compared with men (2% to 10%). The disease has been mostly observed between 18 and 44 ages in the women (Yeh et al. 2018). Etiology migraine has not been fully clarified yet. However, there are possible molecular pathways in the etiology of migraine (Kowalska et al. 2016; Magalhães et al. 2018). Oxidative stress and inflammation have main roles within the pathways of migraine induction (Bulboacă et al. 2020). Hence, antioxidant treatments are popular in the treatment of migraine treatment (Goschorska et al. 2020).

Oxidative stress is induced excessive generation of reactive oxygen species (ROS) such as superoxide and hydroxyl radicals. The excessive generation of ROS has harmful effects in lipids, proteins, and nucleic acids of cellular membranes (Halliwell et al. 1992; Nazıroğlu 2007). Mitochondria play a central role in generation of ATP in body cells and neurons (Li et al. 2016). It is well-known that mitochondria have main roles in the generation of ROS (Dong et al. 2017). It was obliviously indicated that mitochondria acted a main role in the pathogenesis of migraine (Li et al. 2016; Dong et al. 2017). ROS are scavenged by enzymatic and non-enzymatic antioxidants. The non-enzymatic antioxidants include glutathione (GSH), β-carotene, vitamin A, and vitamin E. Vitamin E scavenges hydroxyl radicals in the lipid phase of cells (Halliwell et al. 1992; Nazıroğlu 2007). The enzymatic antioxidants include glutathione peroxidase (GSHPx), catalase, and superoxide dismutase. Hydrogen peroxide (H_2O_2) is converted into water by the GSHPx and catalase. Limited data indicate that there are low levels of the vitamin E, catalase, GSH, and GSHPx in blood of human and experimental animals with migraine (Vurucu et al. 2013; Aytaç et al. 2014; Bütün et al. 2015; Nazıroğlu et al. 2015). However, the enzymatic and non-enzymatic antioxidant levels in plasma of patients with moderate and severe intensity migraine have not been clarified yet.

In addition to the excessive ROS generation in migraine, cytokine generations such as interleukin (IL)-1beta (IL-1β) and IL-6 are responsible in the etiology of migraine (Oliveira et al. 2017a; Oliveira et al. 2017b). As a member of cytokines, tumor necrosis factor-alpha (TNF-α) is a key marker in the neuronal physiological process and progression of migraine (Sarchielli et al. 2006; Yücel et al. 2016; Martami et al. 2018). In addition to the increase of TNF-α during migraine progression, TNF-α generation was increased in patients with the severe intensity migraine (de Roos et al. 2017). Cytokine generations are induced in patients with migraine by excessive generation of ROS (Grinberg et al. 2013). Hence, inhibition of the migraine-induced ROS generation by antioxidant markedly decreases the cytokine generations (Shim et al. 2016). However, there are several conflicting results on the cytokine levels in the plasma of migraine. For example, it was more recently reported that the plasma levels of TNF-α and IL-1β were not differ between control and patients with vestibular migraine (Karaaslan et al. 2020). There was no difference on the plasma levels of TNF-α, IL-1β, and IL-6 in the women with episodic migraine (Oliveira et al. 2017a). Hence, the levels of IL-1β, IL-6, and TNF-α in the plasma of patients with moderate and severe intensity migraine might further clarify by additional studies. This is a main subject of the current study.

In the current study, we tested the levels of GSH, GSHPx, β-carotene, vitamin A, and vitamin E in the patients with attack and non-attack periods. In addition, we analyzed the IL-1β, IL-6, and TNF-α in the plasma of patients with attack and non-attack periods. By the results, we aimed to clarify involvement of antioxidant/oxidant and cytokine levels in the etiology of patients with attack and non-attack periods.

Material and Methods

Control and patients

Approve of the current study was taken from the Clinical Human Ethical Committee of Suleyman Demirel University (SDU), Isparta, Turkey. Thirty female control and patients with migraine were quarried in accordance with the guidelines of the Clinical Human Ethical Committee of SDU (Protocol Number: 2020/47. Date: 06.03.2020). The age limits of the patients and control subjects were kept between 18 and 60 years old. The study was conducted at the BSN Health, Analyses, Innovation, Consultancy, Organization, Agriculture and Industry Ltd (Göller Bölgesi Teknokenti, Isparta, Turkey). The patients enrolled in the study were selected from the Departments of Emergency Medicine of SDU,

and they had a previous diagnosis of migraine. A migraine was diagnosed according to the classification of the most recent diagnostic criteria of International Headache Disorders accepted by the World Health Organization (WHO) and World Neurology Federation (WNF).

The exclusion criteria for the patients were the presence of inflammatory disease, fibromyalgia, cancer, ischemic heart disease, stroke, hyperlipidemia, diabetes mellitus, pregnancy or hypertension.

Thirty healthy control subjects were also included, and informed consent was obtained from all the participants. There were no inflammation and antioxidant treatments in the patients and controls for 6 months. Demographic characteristics, clinical information, physical examination findings, and laboratory tests were recorded for all the subjects included in the study.

Study groups and preparation of plasma samples

We used two main groups as control and migraine. The migraine groups were divided into two subgroups as non-attack and attack groups. Baseline blood samples were obtained from the migraine patients with passive attack and control groups (n = 30 in each). Then blood samples from the active patient groups with migraine attacks were obtained again (n=30). Blood from the control and patients were taken into tubes with anticoagulant (EDTA). Plasma samples were obtained from the whole blood samples by centrifugation (at 1000 g for 5 min).

Lipid peroxidation (MDA) measurement in the plasma of control and patients with migraine

Malondialdehyde (MDA) concentrations in the plasma samples were measured according to the method of Placer et al. (1966) as described in a previous study (Sahin et al. 2011). Briefly, the plasma sample was mixed 1 ml of 20% TCA and 0.5% TBA mixture. After boiling (at 95 °C for 20 min), cooling, and centrifugation procedures of the mixture, supernatant off the mixture was transferred to a clean tube. The absorbance pink color in the supernatant was spectrophotometrically (Cary 60 UV-Vis, Santa Clara, California, USA) detected at 532 nm. The data of MDA in the samples were expressed as μmol/g protein. Total protein levels in the plasma samples were measured by using Lowry's method as described in a previous study (Bütün et al. 2015).

Analyses of reduced glutathione (GSH) level and glutathione peroxidase (GSHPx) activity

The GSH level of the plasma samples were detected at 412 nm using the method of Sedlak and Lindsay (1968). In the method, the -SH groups can mediate by the reduction of 5, 5′-dithiobis-2- nitrobenzoic acid into 2-nitro-5-thiobenzoic acid. The data of GSH concentration were indicated μmol/g protein unit.

GSHPx activity in the plasma samples was assayed at 37 ºC according to the method of Lawrence and Burk (1976). The decrease of GSHPx was recorded at 412 nm against blank in the spectrophotometer (Cary 60 UV-Vis). The activity of GSHPx was expressed as IU/ g protein.

β-carotene, vitamin A and vitamin E analyses in plasma of control and patients with migraine

Concentrations of vitamin A and vitamin E in the plasma samples were determined by spectrophotometrically (Cary 60 UV-Vis) according to methods of Desai (1984). The vitamin A and E were extracted from the plasma samples with hexane and the levels were monitored 325 nm and 532 nm, respectively. The levels of β-carotene in plasma samples were determined according to the method of Suzuki and Katoh (1990). The data of β-carotene in hexane was measured at 453 nm in a spectrophotometer (Cary 60 UV-Vis). The data of β-carotene, vitamin A, and E were expressed as μmol/l of plasma.

Cytokine measurements in the plasma samples of control and patients with migraine

For cytokine measurements in the plasma samples, the plasma was assayed according to the protocol provided with the ELISA kit (Human IL-1β, IL-6, and TNF-α kits, R&D Systems, Minnesota, USA) (Dogru et al. 2019). The absorbance changes were recorded at 450 nm by ELISA microplate reader (Infinite Pro200). The data were expressed as pg/ml.

Statistical analysis

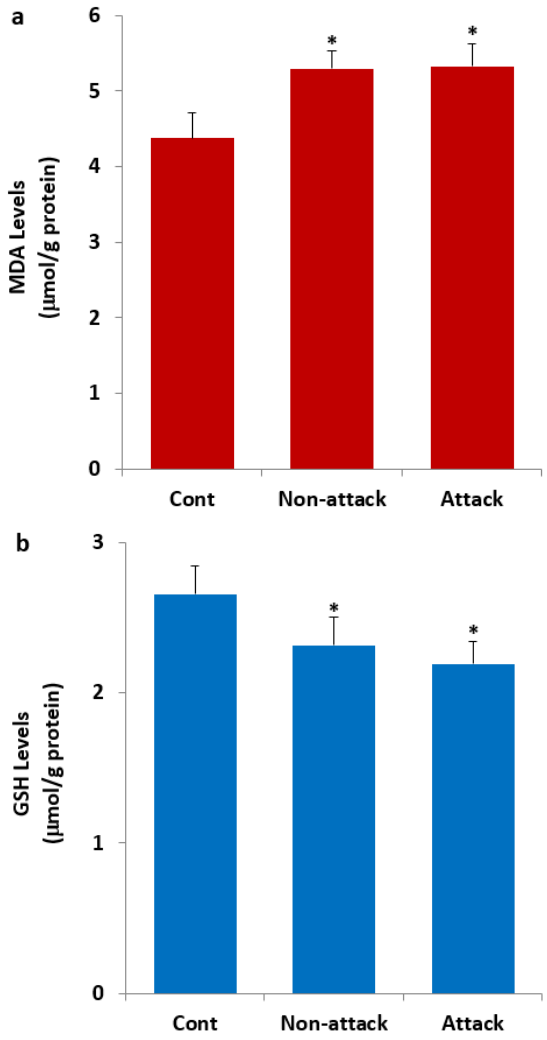
Results were expressed as mean ± standard deviation (SD). Presence of statistical significances were detected by a Least Significant Difference (LSD) test. For detecting level of significance values, a Student's t test was used. Statistically significant values were those with a P value ≤ 0.05. Statistics were conducted using SPSS

Statistical program (17.0, SPSS Inc. Chicago, Illinois, USA).

Results

Plasma MDA level was increased in the patients with migraine, although GSH level was decreased in the patients

As shown in Figure 1a, MDA level was markedly ($p \leq 0.05$) increased in the non-attack group as compared to control group, although its level was further increased in attack group as compared to the non-attack group ($p \leq 0.05$). As shown in Figure 1b, GSH concentration and GSHPx activity were markedly ($p \leq 0.05$) decreased in the non-attack group as compared to control group ($p \leq 0.05$). Importantly, we found that MDA levels were increased the intensity of migraine, although GSH concentrations and and GSHPx activity were decreased by the intensity of migraine.



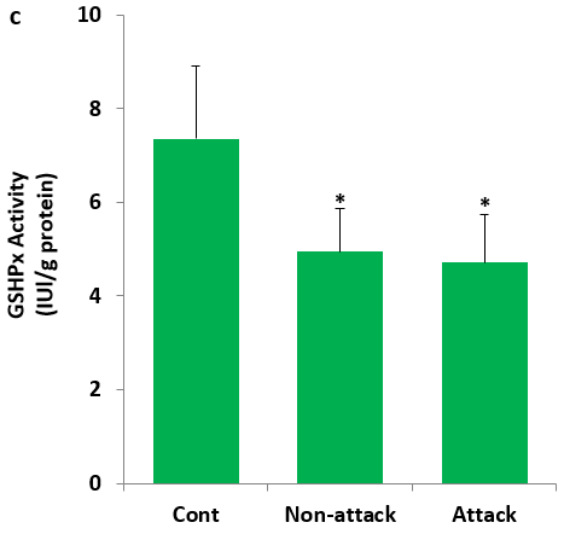


Figure 1. **The levels of lipid peroxidation (MDA), reduced glutathione (GSH), and glutathione peroxidase (GSHPx) in plasma of control and patients with attack and non-attack periods**. (Mean ± SD and n=30). The levels of MDA (**a**), GSH (**b**), and GSHPx (**c**) were measured by using the spectrophotometer. (*p≤0.05 vs control (Cont) group).

The vitamin E concentration was decreased in the plasma of patients with migraine, although the vitamin A and β-carotene concentrations did not change in the patients

The concentrations of vitamin A, β-carotene, and vitamin E as µmol/l were shown in the Figures 2a, b, and c, respectively. Vitamin A concentrations in the control, non-attack, and attack groups were 2.70, 2.66, and 2.62, respectively. However, β-carotene concentrations in the control, non-attack, and attack groups were 1.67, 1.77, and 1.79, respectively. There were no statistical differences on the concentrations of vitamin A and β-carotene in the three groups ($p \geq 0.05$). The concentrations of vitamin E as µmol/l in the control, non-attack, and attack groups were 20.99, 17.94, and 17.69, respectively. The concentration of vitamin E was lower in the attack and non-attack groups than in the control group ($p \leq 0.05$). However, there was no difference on vitamin E concentration between attack and non-attack groups

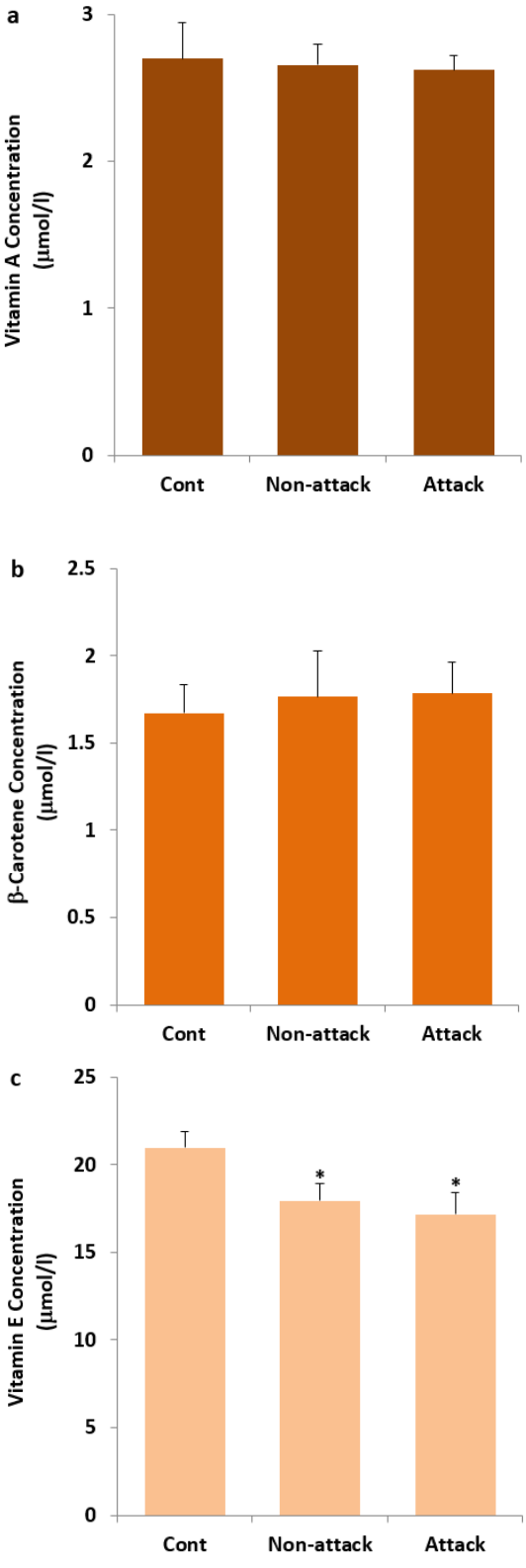
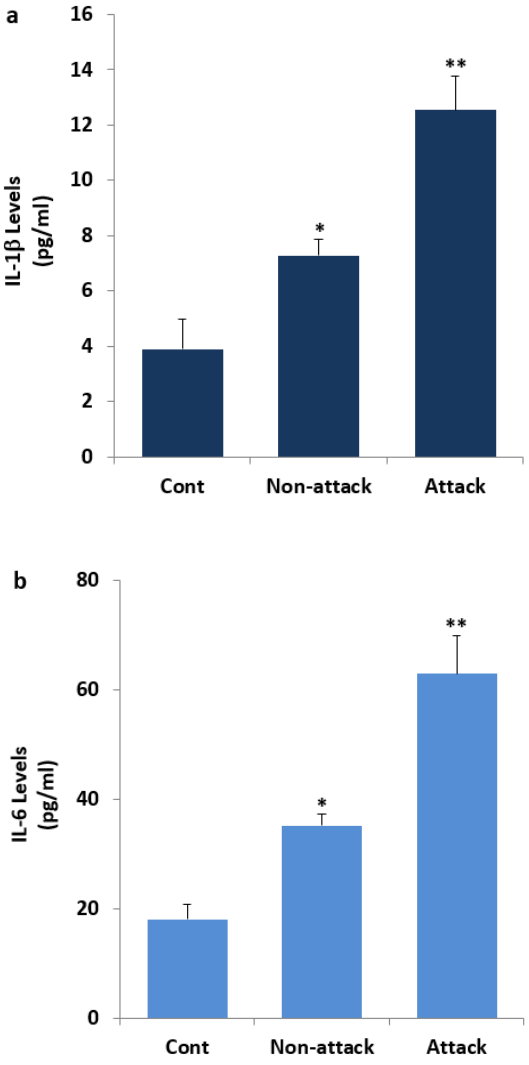


Figure 2. The concentrations of vitamin A, β-carotene, and vitamin E in plasma of control and patients with non-attack and attack periods. (Mean ± SD and n=30). The vitamin A (**a**), β-carotene (**b**), and vitamin E (**c**) were measured by using the spectrophotometer. (*p≤0.05 vs control (Cont) group).

Inflammation response increased in the plasma of patients with migraine

To verify whether migraine was associated with the onset of inflammation, we measured the contents of inflammatory cytokines by the ELISA assay kits (R&D Systems), such as IL-1β and IL-6. As shown in Figure 3a and 3b, Non-attack period of migraine resulted in increased levels of IL-1β and IL-6 in the plasma. In addition, the levels of IL-1β and IL-6 were further increased in the attack group as compared to control and non-attack groups ($p \leq 0.05$). We also measured the levels of TNF- α in the plasma of control and patients with migraine using the ELISA kit (R&D Systems). There was a significant increase in TNF-α levels in non-attack group ($p \leq 0.05$) (Figure 3c). In addition, the levels of TNF-α in the plasma samples were further increased in the attack group as compared to control and non-attack groups ($p \leq 0.05$).



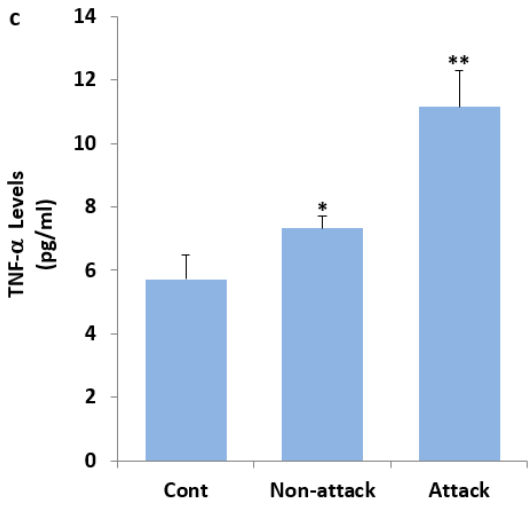


Figure 3. The levels of IL-1β, IL-6, and TNF-α levels in plasma of control and patients with attack and non-attack periods. (Mean ± SD and n=30). The levels of IL-1β (**a**), IL-6 (b), and TNF-α (**c**) levels in the plasma of control and patients with attack and non-attack periods were measured in ELISA by using the commercial kit (R&D Systems). (*p≤0.05 vs control (Cont) group. **p≤ 0.05 vs non-attack group).

Discussion

In the current data, we observed first time that migraine induced the elevation of MDA through down-regulation of GSH, GSHPx, and vitamin E contents the plasma of patients with migraine. In addition, the levels of cytokines were increased related with the intensity of migraine. Hence, oxidative stress and cytokine generation have main roles in the etiology of migraine attacks.

Oxidative stress has been known as an important factor to promote the migraine-induced pain through increasing the accumulation of mitochondrial ROS (Vurucu et al. 2013; Bütün et al. 2015). Brain has a high rate in oxygen consumption. Hence, the brain is very sensitive to the oxidative stress-induced injury (Halliwell et al. 1992). Mitochondria are main sources of excessive ROS generation in several neurological diseases, including migraine (Borkum 2016). Abnormality in the mitochondria membranes induces excessive generation of ROS in migraine (Li et al. 2016; Dong et al. 2017). The ROS are scavenged by antioxidants such as GSH and GSHPx (Tripathi et al. 2018; Visser et al. 2020). Previous data have displayed that migraine attacks decreased antioxidant mechanisms followed an apparent reduction in the levels of GSH and GSHPx, and elevation in the MDA content in the plasma and brain of experimental animals (Nazıroğlu et al. 2015; Bütün et al. 2015; Oliveira et al. 2017a). However, there are also conflicting results on the MDA, GSH, and GSHPx levels in the blood of patients with migraine (Tuncel et al. 2008; Togha et al. 2019). In the current study, we observed decreased levels of GSH and GSHPx in the patients with migraine, although MDA levels were increased in the plasma of patients.

In addition to the enzymatic antioxidants, there are non-enzymatic antioxidants such as vitamin A, vitamin E, and β-carotene for scavenging the ROS. Vitamin E (α-tocopherol) is a most important antioxidant in the lipid phase of cells. Lipid hyroxyl radicals are scavenged in the lipid phase of body cells by the vitamin E. There is also a direct synergic relationship between vitamin E and GSH. The oxidized form of vitamin E is converted to the normal vitamin E form by the GSH (Packer et al. 2001). Vitamin A (retinol) also serves antioxidant action. β-carotene is a potent precursor of retinol (Halliwell et al. 1992). Vitamin A and β-carotene neutralize peroxyl radicals and singlet oxygen (Olson and Krinsky 1995). Reports of vitamin A, vitamin E, and β-carotene in experimental animals and patents with migraine are conflicting. Decreased concentrations of vitamin A, vitamin E, and β-carotene in the brain of rat with migraine were recently reported (Nazıroğlu et al. 2015; Bütün et al. 2015). However, an absence relationship between migraine risk and the concentrations of vitamin E/ β-carotene in patients was also reported (Cook et al. 2002; Reimund et al. 2005). A protective action of vitamin E treatment against menstrual migraine was reported (Ziaei et al. 2009). In the current data, we observed that the concentration of vitamin E was lower in the patients with migraine as compared to control subject. However, the concentrations of vitamin A and β-carotene did not differ in the control and patient groups.

In addition to the involvement of migraine-induced oxidative stress in the plasma of patients with migraine, cytokine generation has been shown to act important role in the induction of migraine attacks (Oliveira et al. 2017a; Oliveira et al. 2017b; Mahmoudi et al. 2018; Zhao et al. 2020). However, there are also conflicting reports on the cytokine generation in blood of patients with migraine. Therefore, we hypothesized that the cytokine levels have actions in the attacks of migraine. The current results showed that the activation levels of TNF-α, IL-1β, and

IL-6 were markedly increased the plasma of patients with non-attack migraine as compared with the control group. Levels of the cytokines were further increased in the attack group as compared to control and non-attack group. Similarly, the increases of cytokine and TNF-α productions were increased in blood of rats by the migraine induction (Mahmoudi et al. 2018; Zhao et al. 2020). The increase of TNF-α levels in plasma of patients with episodic migraine were reported (Martami et al. 2018). Contrary, it was more recently reported that the plasma levels of TNF-α and IL-1β were not differ between control and patients with vestibular migraine (Karaaslan et al. 2020). There was no difference on the plasma levels of TNF-α, IL-1β, and IL-6 in the women with episodic migraine (Oliveira et al. 2017a).

In summary, current data indicated that the plasma GSH, GSHPx, and vitamin E levels in the patients with attack and non-attack migraine were decreased, although MDA level was increased in the patients. In addition, we found signs of inflammation in the plasma of migraine patients suggesting that this headache form might relate with inflammatory and oxidative stress pathways. There was also a relationship between cytokine generation and migraine attacks.

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Authors' contributions: HHA formulated the present hypothesis and he was responsible for writing the report. DYY was responsible from blood collection. KK was responsible from English editing. Of the manuscript. The analyses in the current study were performed in BSN Health, Analyses, Innovation, Consultancy, Organization, Agriculture Ltd. by technicians.

Declaration of Conflicting Interests

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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