Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Clinical Research

J. Exp. Clin. Med., 2019; 36(1): 1-8
doi: 10.5835/jecm.omu.36.01.001

Thiol disulfide homeostasis as oxidative stress marker in migraine patients

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ARTICLE INFO

Article History
Received 12 / 07 / 2019
Accepted 21 / 10 / 2019
Online Published Date 04 / 12 / 2019

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Keywords:
Aura
Migraine
Oxidative stress
Thiol disulfide

ABSTRACT

Migraine is a very common disease. Annual prevalence of migraine in our country is reported as 16.4%. Oxidative stress is assumed to play a role in the pathophysiology of migraine. In many recent studies conducted on individuals with migraine, serum Oxidative Stress Index (OSI), Total Antioxidant Status (TAS), Total Oxidant Status (TOS) values were analyzed and it was indicated that the balance shifts towards oxidative direction. Thiol-disulfide homeostasis, which is an oxidative stress marker, was described in recent years and has been shown to have vital importance on cellular functions. In the light of this information, we aimed to examine the role of oxidative stress in pathogenesis of migraine disease with new biomarkers. The study was conducted on 36 cases of 24 patients (17 female, 7 male; mean age: 40.54±11.60) followed up with a migraine diagnosis and 12 people in the healthy control group with similar age and sex (10 female, 2 male; mean age: 38.17±10.80). Total thiol (μmol/L), native thiol (μmol/L) and disulfide level, disulfide/native thiol, disulfide/total thiol, native thiol/total thiol ratios were quantified in the patient and control groups. In the migraine group with aura, reduced ratio and thiol oxidation reduction ratio values were high and oxidized thiol ratio values were low (p = 0.010, 0.015, 0.048). This study focused on thiol-disulfide hemostasis, a new and reliable indicator in determining oxidative stress which is held responsible for the pathophysiology of migraine.

1. Introduction

Migraine is a very common disease characterized by moderate-severe throbbing headache attacks accompanied by nausea and/or vomiting, photophobia and phonophobia (Stewart et al., 1992; IHS, 2013). It is usually unilateral and its symptoms get worse with physical activity. One-year prevalence rate of migraine among adults in our country is reported as 16.4% (Ertas et al., 2012).

Oxidative stress is defined as the damage caused by reactive oxygen types (hydroxyl radical, superoxide radical and hydrogen peroxide) on organic molecules and cells (Blokhina et al., 2003; Valko et al., 2007). Oxidant–antioxidant balance disorders underlie several types of acute and chronic diseases of the central nervous system. It is believed that oxidative stress plays a role in the pathogenesis of migraine (Eren et al., 2015). In many recent studies conducted on individuals with migraine, serum Oxidative Stress Index (OSI), Total Antioxidant Status (TAS), Total Oxidant Status (TOS) values are analyzed and the results indicate that balance shifts towards oxidative direction (Alp et al., 2010; Oz et al., 2010; Yılmaz et al., 2011a; 2011b).

Thiols are a class of organic compounds known as mercaptans containing sulfhydryl (-SH) group, which has a critical role in preventing the development of any oxidative stress condition in cells (Tuncel et al., 2008). They eliminate reactive oxygen species (ROS) and other free radicals by enzymatic and non-enzymatic mechanisms and are an important component of the antioxidant cascade (Sen et al., 2000). When oxidative protein damage occurs, protein carbonyl levels increase, while protein thiol levels decrease (Caderas, 1989). It is important to measure total thiol levels in order to evaluate the excessive formation of free radicals (Hu, 1994).

Thiols cause formation of disulfide forms by oxidative reacting through oxidants. When oxidative stress increases, mixed disulfides are formed between thiols and protein thiol groups, however this formation is reversible. Dynamic thiol/disulfide homeostasis plays a role in cell signal mechanisms, transcription factors, enzymatic activation regulation, apoptosis and signal transmission, antioxidant protection and detoxification (Pasaoglu et al., 2004; Kayacan et al., 2018).

Thiol-disulfide homeostasis is identified as an oxidative stress marker in recent years and shown to have vital importance on cellular functions (Jones et al., 2009). Thiol is a term used for compounds containing sulfur, and the sulfur in its content is a very significant element for biological environments as it is also contained in amino acids, proteins and other biomolecules (Atmaca, 2004). According to a study conducted on healthy individuals, thiol protein groups constitute 52.9% of total antioxidant capacity in serum (Erel, 2004). Thiols, known as strong antioxidants, modulate glutathione-related antioxidant enzymes and remove free radicals from the environment (Atmaca, 2004; Eren et al., 2015). Studies report that dynamic thiol-disulfide homeostasis is associated with antioxidant protection, detoxification (Biswas et al., 2006), apoptosis (Circu et al., 2010), regulation of enzymatic activity and cellular signal mechanisms in the organism (Erel et al., 2014), as well as many diseases such as diabetes (Matteucci et al., 2010), chronic kidney disease, liver disorders (Rodrigues et al., 2012), cardiovascular diseases (Kundi et al., 2015) and stroke (Bektas et al., 2016).

In the light of this information, we aimed to investigate thiol disulfide hemostasis as a new marker for oxidative stress, which is assumed to be involved in the pathophysiology of migraine.

2. Materials and methods

Patient selection

The study was conducted on 36 cases of 24 patients (17 female, 7 male; mean age: 40.54±11.60) followed up with migraine diagnosis and 12 people in the healthy control group with similar age and sex (10 female, 2 male; mean age: 38.17±10.80). Patients with malignancy and systemic diseases, smokers, pregnant and lactating women, and patients who took any medication in the last 15 days were not included in the study.

Demographic characteristics of the patients were collected. Migraine patients were evaluated based on whether they had auras or not, whether they were in the ictal or interictal period, number of painful days per month, number of attacks per month and their life quality with EQ5D (with activity, self-care, ordinary, pain, anxiety, index and EQ5D VAS sub-groups).

Ethical committee approval of the study was obtained from Sakarya University Faculty of Medicine Ethical Committee. Informed consent was taken from the patients and control groups. All researchers hereby confirm the ethical standards of the Helsinki Declaration.

Blood samples

In pre-analytic period

In order to ensure that the samples in the tubes are in good contact with silica particles, the tubes were gently turned upside down 5-6 times and were never shaken.

Biochemical parameters

Blood serum analyses were performed by a fully automated Beckman Coulter AU 680 (serial no: 2016024580, Koutou-ku, Tokyo, Made in Japan) auto-analyzer. Rel Assay Diagnostics brand kit was used in the study. Samples were subjected to re-centrifuge (micro centrifuge) process as instructed in the kit insert. Total thiol (μmol/L) and native thiol (μmol/L) measurements in serums and the total measurements of thiols were recorded, and thiol/disulfide balance was determined.

Total thiol level (μmol/L) (TTL), native thiol level (μmol/L) (NTL) and disulfide level, disulfide/native thiol, disulfide/total thiol, native thiol/total thiol ratios were determined for the patient and the control groups. In this study, dynamic thiol-disulphide homeostasis in the serum samples was identified by an automated method recently developed by Erel et al. (2014). Total thiol (–SH+–S–S–) and native thiol (–SH) concentrations in the samples were measured by using Ellmann's and modified Ellmann's reagent. Native thiol content value was subtracted from the total thiol content value, and half of this difference gave the amount of dynamic disulphide bonds (–S–S). In addition, the (–S–S–) x 100 / (–SH), (–S–S–) x 100 / (–SH+–S–S–), and –SH x 100 / (–SH+–S–S–) ratios were calculated by using these parameters.

Analytical recovery

The percent recovery of the novel method was determined by adding 200 μM oxidized glutathione to the plasma samples. The mean percent recovery was 98–101%.

Linearity

The linearity of the native thiol measurement was the same as that of Ellman's reagent assay. Serial dilutions of the glutathione solution were prepared. The upper limit of

the linearity for the native thiol measurement was 4000 µM. Linearity of the total thiol measurement was also dependent on the amounts of $NaBH_4$ and formaldehyde concentrations. Serial dilutions of the oxidized glutathione solution were also prepared. The upper limit of the linearity for the disulphide measurement was 2000 µM. Dilution of plasma samples did not affect the novel assay.

Lower detection limit

The detection limit of the assay was determined by evaluating the zero calibrator 10 times. The detection limit, defined as the mean value of the zero calibrator + 3 standard deviations (SDs), was 2.8 µM (X).

Analytical sensitivity

As the slope of the calibration line, analytical sensitivity was found to be 7.9 × 10–4 Absorbance/Amount, [A × (µM)–1].

Interference

It was found that hemoglobin, EDTA, citrate and oxalate did not interfere with the assay, but bilirubin negatively interfered with the assay. Lipemic and uremic plasma samples did not interfere with the assay. Plasma and serum samples were used as samples.

Precision

To determine the precision of the novel assay, we assayed three levels of plasma pools. The plasma pool with high disulphide levels was obtained from the samples of patients with diabetes mellitus. The plasma pool with medium disulphide levels was obtained from the samples of healthy persons. The plasma pool with low disulphide levels was obtained from the samples of patients with urinary bladder cancer. Percent coefficient variation (%CV) was 4 ($\bar{X}$= 29.12 and σX=1.2) for high levels, 5 ($\bar{X}$= 16.03 and σX = 0.79) for medium levels and 13 ($\bar{X}$= 7.15 and σX = 0.98) for low levels.

Storage

Storage at 4°C for 1 day led to a 7% decrease in the native thiol amount and 170% increase in the disulphide amount (total thiol, native thiol and disulphide levels of fresh and stored plasma samples were 391 µmol/L, 357 µmol/L, 17 µmol/L and 391 µmol/L, 333 µmol/L, 29 µmol/L, respectively). Plasma native thiol, total thiol and disulphide concentrations were not affected by storage at –80°C for 3 months.

Statistical analysis

NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) was used for statistical analyses. Descriptive statistical methods (mean, standard deviation, median, frequency, and ratio) as well as Shapiro Wilks test and box plot graphs were used for the evaluation of the suitability of variables to normal distribution. Kruskal Wallis test was used for intergroup comparisons of parameters which do not indicate normal distribution, Dunn test was used for post-hoc evaluations, Mann Whitney U test was used for evaluations based on groups. Fisher's Exact test and Fisher-Freeman Halton test was used for comparison of qualitative data. Results were evaluated to be within a confidence range of 95% and a significance level of $p<0.05$.

3. Results

Demographic characteristics of cases are given in Table 1. Aura was observed in 50% (n=12) of migraine cases. With regards to the number of painful days per month, the ratio of cases with 1-5 days/month was 16.7% (n=4), 5-15 days/month was 54.2% (n=13), over 15 days/month was 29.2 % (n=7). There were 5 patients (20.8%) who had 1-3 attacks per month and 19 patients (79.2%) who had 3 or more attacks per month (Table 2).

Table 1. Evaluation of demographic characteristics by groups (Migraine (with/out aura) and Control).

		Groups		Test values
		Migraine (n=24)	**Control (n=12)**	**P**
Age (year)	Min-Max (Median) Mean±SD	19-68 (40) 40.54±11.60	20-51 (40) 38.17±10.80	Z:-0.185 [d] ***0.853***
Sex	**Female** **Male**	17 (70.8) 7 (29.2)	10 (83.3) 2 (16.7)	χ^2:0.667 [c] ***0.685***
Height (meter)	Min-Max (Median) Mean±SD	1.5-1.8 (1.65) 1.65±0.09	1.5-1.8 (1.63) 1.62±0.08	Z:-0.774 [d] ***0.439***
Weight (kg)	Min-Max (Median) Mean±SD	42-120 (74) 74.50±19.66	45-94 (61) 66.17±15.20	Z:-1.226 [d] ***0.220***
BMI (kg/m²)	Min-Max (Median) Mean±SD	18.6-42.9 (26.2) 27.22±6.60	20.3-33.5 (23.17) 24.87±4.36	Z:-0.889 [d] ***0.374***
	Normal **Overweight** **Obese**	10 (41.7) 8 (33.3) 6 (25.0)	9 (75.0) 1 (8.3) 2 (16.7)	
Education	**Primary School** **High School** **University**	10 (41.7) 8 (33.3) 6 (25.0)	4 (33.3) 1 (8.3) 7 (58.3)	χ^2:4.303 [b] ***0.113***
Exercise	**No** **Regular** **Irregular**	12 (50.0) 7 (29.2) 5 (20.8)	3 (25.0) 2 (16.7) 7 (58.3)	χ^2:4.664 [b] ***0.122***
Chronic Disease	**No** **Yes**	21 (87.5) 3 (12.5)	12 (100.0) 0 (0.0)	χ^2:1.636 [c] ***0.536***
Menstruation Age (n=26)	Min-Max (Median) Mean±SD	11-16 (13) 13.06±1.39	12-15 (12.5) 13.00±1.25	Z:-0.274 [d] ***0.784***
OCD (n=26)	**Yes** **No**	3 (18.8) 13 (81.3)	1 (10.0) 9 (90.0)	χ^2:0.362 [b] ***1.000***

[b] Fisher Freeman Halton Test [c] Fisher's Exact Test [d] Mann Whitney U Test
OCD: Oral Contraceptive Drug

Table 2. Clinical features of migraine patients.

Aura	**No**	12 (50.0)
	Yes	12 (50.0)
Frequency of aura (day per month)	**1-5**	4 (16.7)
	5-15	13 (54.2)
	≥15	7 (29.2)
Number of attacks (day per month)	**1-3**	5 (20.8)
	≥3	19 (79.2)

In the comparative evaluation of the control group, and the migraine groups with and without aura, no statistically significant difference was found based on the groups in EQ-5D scale "Activity", "Self-Care" and "Ordinary" sub-dimensions (p>0.05). A statistically significant difference was found in the "pain" sub-dimension (p=0.025; p<0.05). Incidence of pain was significantly higher in cases of migraine with and without aura, compared to cases of the control group (p=0.027; p=0.030; p<0.05). In "Anxiety/Depression" sub-dimension of EQ-5D scale, a statistically significant difference was found for the incidence of anxiety/depression (p=0.006; p<0.05). The rate of anxiety/depression incidence in migraine with aura group was significantly higher compared to the control group (p=0.004; p<0.01). A statistically significant difference was found between the EQ-5D index measurements (p=0.004; p<0.01). According to the paired comparison results conducted to determine the difference; EQ-5D index values of migraine groups with and without aura were found significantly lower compared to the cases of the control group (p=0.010; p=0.001; p<0.05) (Table 3).

A statistically significant difference was found between EQ-5D VAS measurements of cases based on groups (p=0.006; p<0.01). According to the paired comparison results conducted to determine the difference; EQ-5D VAS value of migraine group with aura was found significantly lower, compared to the cases of migraine group without aura and control group (p=0.019; p=0.005; p<0.05) (Fig.1).

In Table 4, TTL, NTL, Disulfide, Reduced ratio, oxidized thiol ratio and thiol oxidation reduction ratio values are shown in accordance with the groups.

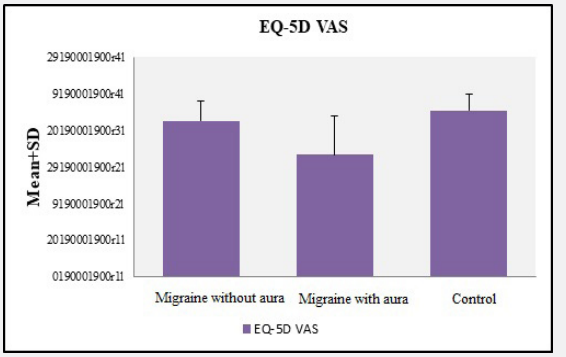

Fig. 1. Distribution of EQ-5D VAS measurements by groups (Migraine with aura, Migraine without aura and Control).

A statistically significant difference was found between the Reduced Ratio measurements of the cases based on groups (p=0.027; p<0.05). Reduced Ratio values of cases in the migraine group with aura were statistically higher than cases in the migraine group without aura (p=0.010; p<0.05). A statistically significant difference was found between Oxidized Thiol Ratio measurements of the cases based on groups (p=0.036; p<0.05). Oxidized Thiol Ratio values of the cases in the migraine group with aura were statistically lower than the cases in the migraine group without aura (p=0.015; p<0.05) (Fig. 2). A statistically significant difference was found between Thiol Oxidation Reduction Ratio measurements of the cases based on the groups (p=0.048; p<0.05). Thiol Oxidation Reduction Ratio values of the cases in the migraine group with aura were statistically higher than the cases in the migraine group without aura (p=0.021; p<0.05) (Fig. 3).

Table 3. Evaluation of EQ-5D scale according to groups (Migraine with aura, Migraine without aura and Control).

EQ-5D		Groups			Test Value	Test Value	Test Value	Test Value
		Without aura[1]	With aura[2]	Control[3]	*p*	p^{1-2}	p^{1-3}	p^{2-3}
Mobility	**No problem in walking**	10 (83.3)	10 (83.3)	12 (100.0)	χ^2:2.292	χ^2:0.000	χ^2:2.182	χ^2:2.182
	Some problem in walking	2 (16.7)	2 (16.7)	0 (0.0)	[b]0.517	[c]1.000	[c]0.478	[c]0.478
Sef care	**No problem**	11 (91.7)	12 (100.0)	12 (100.0)	χ^2:1.874	χ^2:1,043	χ^2:1.043	-
	Some problem	1 (8.3)	0 (0.0)	0 (0.0)	[b]1.000	[c]1.000	[c]1.000	-
Usual activities	**No problem**	12 (100.0)	11 (91.7)	12 (100.0)	χ^2:1.874	χ^2:1.043	-	χ^2:1.043
	Unable	0 (0.0)	1 (8.3)	0 (0.0)	[b]1.000	[c]1.000	-	c1.000
Pain	**No**	5 (41.7)	5 (41.7)	11 (91.7)	χ^2:9.777	χ^2:1.074	χ^2:6.750	χ^2:6.521
	Moderate	7 (58.3)	6 (50.0)	1 (8.3)	[b]0.025*	[b]1.000	[c]0.027*	[b]0.030*
	Extreme	0 (0.0)	1 (8.3)	0 (0.0)				
Anxiety/ Depression	**No**	6 (50.0)	3 (25.0)	11 (91.7)	χ^2:12.169	χ^2:2.683	χ^2:5.042	χ^2:10.531
	Moderate	6 (50.0)	7 (58.3)	1 (8.3)	[b]0.006**	[b]0.240	[c]0.069	[b]0.004**
	Extreme	0 (0.0)	2 (16.7)	0 (0.0)				
EQ-5D index	**Min-Max (Median)**	0.59-1 (0.66)	0.18-1 (0.66)	0.66-1 (1)	χ^2:11.190	Z:-1.089	Z:-2.573	Z:-3.208
	Mean±SD	0.79±0.19	0.65±0.27	0.97±0.10	[a]0.004**	[d]0.276	[d]0.010*	[d]0.001**
EQ-5D VAS (Health state)	**Min-Max (Median)**	60-100 (85)	30-100 (65)	70-100 (90)	χ^2:10.402	Z:-2.353	Z:-1.493	Z:-2.823
	Mean±SD	85.00±10.87	66.67±21.03	90.83±9.00	[a]0.006**	[d]0.019*	[d]0.135	[d]0.005**

[a]Kruskal Wallis Test [b]Fisher Freeman Halton Test [c]Fisher's Exact Test [d]Mann Whitney U Test *p<0.05 **p<0.01

Table 4. Evaluation of thiol variables according to groups (Migraine with aura, Migraine without aura and Control).

			Groups			Test Value	Test Value	Test Value	Test Value
			Without aura[1] (n=12)	With aura[2] (n=12)	Control[3] (n=12)	*p*	p^{1-2}	p^{1-3}	p^{2-3}
Thiol Values	TTL	Min-Max (Median) Mean±SD	1107-1671 (1335) 1372.67±193.86	938-1644 (1383) 1353.08±174.31	1133-1608 (1393) 1412.67±124.91	χ^2:0.582 [a]0.748	Z:-0.144 [d]0.885	Z:-0.665 [d]0.506	Z:-0.635 [d]0.525
	NTL	Min-Max (Median) Mean±SD	470-633 (516.5) 536.17±63.56	376-601 (512) 499.33±70.31	439-685 (528) 540.5±69.51	χ2:1.613 [a]0.446	Z:-0.983 [d]0.326	Z:-0.144 [d]0.885	Z:-1.185 [d]0.236
	Disulfide	Min-Max (Median) Mean±SD	318.5-522 (41.25) 416.83±64.87	281-521.5 (438.75) 421.18±68.2	347-487.5 (440) 435.5±35.76	χ^2:0.785 [a]0.675	Z:-0.433 [d]0.665	Z:-0.954 [d]0.340	Z:-0.289 [d]0.773
	Reduced Ratio	Min-Max (Median) Mean±SD	37.19-42.46 (39.56) 39.S44±1.79	34.5-41.6 (37.15) 37.62±1.83	34.5-44.08 (38,18) 38.2±2.36	χ^2:7,238 [a]0.027*	Z:-2,570 d0.010*	Z:-1,905 [d]0.057	Z:-0,693 [d]0.488
	Oxidized Thiol Ratio	Min-Max (Median) Mean±SD	28.77-31.41 (30.22) 30.3±0.89	29.96-32.75 (31.37) 31.2±0.79	27.96-32.75 (30.91) 30.9±1.18	χ^2:6.650 [a]0.036*	Z:-2.425 [d]0.015*	Z:-1.905 [d]0.057	Z:-0.577 [d]0.564
	Thiol Oxidation Reduction Ratio	Min-Max (Median) Mean±SD	105.33-147.57 (129.22) 128.16±12.19	105.33-133.81 (117.59) 118.75±6.93	105.33-157.65 (123.53) 124.02±12.97	χ^2:5.384 [a]0.048*	Z:-2.309 [d]0.021*	Z:-1.270 [d]0.204	Z:-1.011 [d]0.312

[a]Kruskal Wallis Test [d]Mann Whitney U Test *p<0.05 TTL: Total Thiol Level NTL: Native Thiol Level

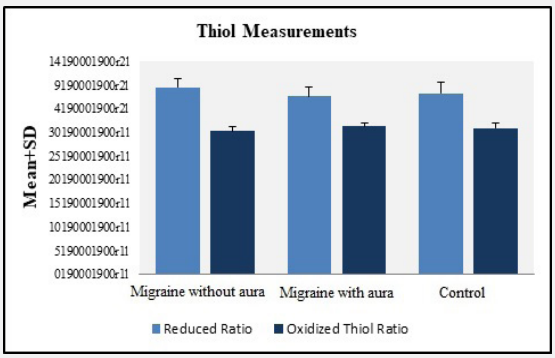

Fig. 2. Distribution of reduced ratio and oxidized thiol ratio measurements according to groups (Migraine with aura, Migraine without aura and Control).

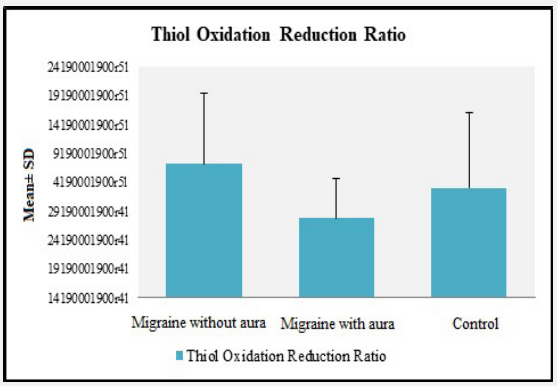

Fig. 3. Distribution of thiol oxidation reduction ratio measurements according to groups (Migraine with aura, Migraine without aura and Control).

Based on ictal or interictal period of the migraine patients and when compared with the control group, no statistically significant difference was found between TTL, NTL, disulfide, reduced ratio, oxidized thiol ratio and thiol oxidation reduction ratio values (p>0.05) (Table 5).

Table 5. Evaluation of melatonin and thiol variables by groups (Interictal, Ictal and Control).

			Groups			Test value
			Interictal (n=18)	Ictal (n=6)	Control (n=12)	p
Thiol Values	TTL	Min-Max (Median) Mean±SD	938-1671 (1382) 1344.22±175.7	1224-1671 (1391.5) 1418.83±200.02	1133-1608 (1393) 1412.67±124.91	χ^2:1.060 [a]0.589
	NTL	Min-Max (Median) Mean±SD	376-631 (512) 511.44±55.97	376-633 (545.5) 536.67±100.83	439-685 (528) 540.5±69.51	χ^2:1.460 [a]0.482
	Disulfide	Min-Max (Median) Mean±SD	281-521.5 (433) 416.39±62.23	318.5-522 (432.25) 426.87±79.05	347-487.5 (440) 435.5±35.76	χ^2:0.853 [a]0.653
	Reduced Ratio	Min-Max (Median) Mean±SD	34.5-42.46 (37.62) 38.19±1.88	37.15-42.46 (39.29) 39.55±2.19	34.5-44.08 (38,18) 38.2±2.36	χ^2:2.329 [a]0.312
	Oxidized Thiol Ratio	Min-Max (Median) Mean±SD	28.77-32.75 (31.19) 30.9±0.94	28.77-31.24 (30.47) 30.28±0.87	27.96-32.75 (30.91) 30.9±1.18	χ^2:2.678 [a]0.262
	Thiol Oxidation Reduction Ratio	Min-Max (Median) Mean±SD	105.33-147.57 (120.61) 123.87±9.95	105.33-147.57 (120.16) 122.22±14.12	105.33-157.65 (123.53) 124.02±12.97	χ^2:0.317 [a]0.853

[a]Kruskal Wallis Test

4. Discussion

It is believed that migraine pathophysiology is related to primary neuronal mechanisms. Under the light of the data presented in recent years, it is suggested that migraine is a neurovascular disease caused by cortically spreading depression, neurogenic inflammation and vasodilatation (Boran et al., 2013; Noseda et al., 2013). Additionally, oxidant-antioxidant balance disorders and resulting oxidative stress is believed to play a role in pathogenesis in migraine as well as many central nervous system diseases (such as epilepsy, stroke, neurodegenerative diseases) (Bockwski et al., 2008; Gruber et al., 2010; Tetik et al., 2010; Méndez-Armenta et al., 2014; Oz et al., 2014; Sharma et al., 2014; Kurt et al., 2017).

In a study, TOS levels of individuals with migraine with aura were found to be higher, while their TAS levels were found to be lower; this data suggested that oxidative/antioxidative balance of individuals with migraine shifted to oxidative direction (Alp et al., 2010). It was suggested that oxidative stress in migraine is related to increased nitric oxide levels (Bockwski et al., 2008). Nitric oxide (NO) causes trigeminovascular activation that plays a role in cerebral vasodilatation at the onset of migraine attacks (Lance, 1993). It is assumed that delayed inflammatory response at durometer, inducible nitric oxide synthase (iNOS) expression, and increase of proinflammatory cytokines such as IL-1 and IL-6 have a role in the pathophysiological mechanism of this activation (Reuter et al., 2001). In a recent study, it was reported that the plasma asymmetric dimethylarginine (ADMA) and NO levels were higher in individuals with migraine compared to healthy groups (Uzar et al., 2011). In the study by Yılmaz et al. (2007), malonaldehyde (MDA), nitrate and nitrite levels among oxidative stress indicators were studied in the thrombocytes of 22 migraine patients without aura and 14 migraine patients with aura during their attack periods, and compared to 36 healthy control cases. The findings illustrated that MDA, nitrate and nitrite levels were higher in migraine patients during the attack periods, compared to the healthy control cases, while there was no difference outside the attack period (Yılmaz et al., 2007).

Tuncel et al. (2018) found that plasma MDA levels and similar superoxide dismutase (SOD) and catalase (CAT) activities were higher in migraine patients compared to the control group. In the study conducted by Erol et al. (2010), SOD, CAT, glutathione peroxidase (GSH-Px) activities known as antioxidants were measured in erythrocytes of children with migraine outside the attack periods. Compared with healthy control cases, SOD activity was found to be similar, while CAT and GSH-Px activities were lower. As the common result of all these studies, it can be suggested that there is a decrease in the activity of antioxidant mechanisms, a shift in the balance towards oxidative direction and development of an oxidative stress environment in individuals with migraine.

In our study, serum disulphide levels were found to be lower in migraine patients compared to the control group (Migraine without aura: 416.83±64.87; Migraine with aura: 421.18±68.2; Control: 435.5±35.76). This situation can be explained by the insufficient number of cases, as well as the studies conducted on antioxidant efficacy of exercise in the literature. While 75% of the patients exercised in our control group, the rate was 50% in the migraine group (Kayacan et al., 2019).

In a study that analyzed the oxidative/antioxidative balance in migraine patients, it was shown that the total thiol levels were low in migraine patients without aura and there was a negative correlation between thiol levels and duration of headache (Alp et al., 2010). In their study conducted on migraine patients, Eren et al. (2015) found that serum TTL in individuals with migraine were lower than those of the healthy control group, whereas TAS, TOS and OSI levels were similar. In the same study, thiol levels were found to be similar between the patients with migraine with and without aura (Eren et al., 2015). In a study conducted on 63 migraine patients, higher TTL and NTL were obtained in comparison to the healthy control group; and as thiols affect the physiological conditions of the organism and they are dynamic molecules in this case, it was concluded that these findings supported the idea that they act like pro-oxidant molecules (Gumusyayla et al., 2016). In our study, reduced ratio and thiol oxidation reduction ratio values were found to be higher and oxidized thiol ratio value was found to be lower in the migraine group with aura (p=0.010, 0.015, 0.048). With these values, we can come to a conclusion in favor of increase in TOS especially in the migraine group with aura, which supports the role of oxidation in pathophysiology of migraine.

This study focused on thiol-disulfide hemostasis, a new and reliable indicator in determining oxidative stress which is held responsible for the pathophysiology of migraine. The reduced ratio, oxidized thiol ratio and thiol oxidation reduction ratio values gave statistically significant results in favor of oxidation, especially in the migraine group with aura, and shed light on the literature. Further studies to be conducted with a larger number of patients will support the presence of oxidative stress in development of migraine.

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