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Evaluation of the oxidative and inflammatory profile of patients with migraine

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ABSTRACT

Among one of the most commonly seen and primary headaches is migraine. Oxidative stress and inflammation is discussed to be implicated in the pathogenesis of migraine. However, further knowledge about this issue is necessary because data are in part controversial and the possible underlying mechanisms remain inconclusive to date. To evaluate and compare the oxidative and inflammatory profile of patients with migraine 47 volunteers were divided into 3 groups: 15 women with chronic migraine (WCM); 17 women with episodic migraine (WEM) and 15 men with migraine (MM) and enrolled in this study.Total antioxidant status; the enzymatic activity of the antioxidant agents Catalase (CAT), Glutathione S-transferase (GST) and Superoxide Dismutase (SOD); oxidative stress markers malondialdehyde (MDA) and carbonylated proteins; blood count and neutrophil/lymphocyte ratio; uric acid, c-reactive protein and cholesterol total and fractions were determined in pacients with migraine in the interictal phase. The group male participants (MM) displayed a reduction in total antioxidant status, as well as a lower value for antioxidant enzymes, but had no significant alterations in markers related to damage by oxidative stress compared to women. These findings suggest that there is a difference in the oxidative profile between the sexes among migraine patients. This may allow a better understanding of patients profile with different migraine phenotypes and identify new markers that might help understanding the pathophysiology and migraine patient management.

Keywords: Headaches; migraine; oxidative stress; neutrophil/lymphocyte ratio

1 INTRODUCTION

Headache can be considered as one of the most prevalent neurological disorders today, and it is rare to find someone free from a headache episode (Fernández-de-las-Peñas *et al.* 2014). Headaches are considered one of the 12 most common complaints in primary care services (Steiner *et al.* 2018).

Migraine is one of the most common types of headache (Stovner *et al.* 2007) and, due to its high prevalence, estimated in 15 to 18% of the global population, (Silberstein *et al.* 2017) it has a great negative socioeconomic impact, being an important cause of work absenteeism and impairment of quality of life (Abu Bakar *et al.*, 2016). It is the third most prevalent clinical condition and the seventh specific cause of disability in the world (Vos *et al.* 2015).

Other factors are related to the onset of migraine attacks (Charles 2017). Omitting meals, excessive caffeine intake or deprivation of it, stress, ingesting foods rich in nitrates or glutamate, fatty cheeses, chocolate, red wine, sleep deprivation or excessive sleep are often identified as triggers of migraine (Odegard *et al.* 2010; Engstrom *et al.* 2013; Oh *et al.* 2014; Song *et al.* 2016).

Several studies have been conducted with the aim of clarifying the pathophysiology involved in migraine. Cortical depression, neurogenic inflammation, and dysfunction in cranial vascular contractility may be involved in its genesis (Neri *et al.*, 2015, Borkum, 2016, Goadsby, 2012).

In addition to these factors, oxidative stress has been related to several types of headache (Vurucu, Karaoglu, Paksu, Yesilyurt, Oz, Unay, Akin, 2013; Cordero, Cano-Garcia, Alcocer-Gómez, De Miguel, Sánchez-Alcázar, 2012; Neyal *et al.*, 2013), including with migraine (Eren, Dirik, Neselioglu, Erel, 2015).

Tissue damaging free radicals produced as a result of metabolic and physiological processes are normally neutralized by enzymatic and non-enzymatic antioxidant systems. The balance may become a state of oxidative stress due to either increased free radical production, or a deficiency in antioxidant defense mechanisms (Geyik, Altunisik, Neyal, Taysi, 2016). Oxidative stress can damage lipid

membranes, nucleic acids, proteins and extracellular matrix components, including proteoglycans and collagens (Rajendran *et al.*, 2014).

Alterations of mitochondrial oxidative metabolism may play a role in the pathophysiology of migraine. In addition, there is strong evidence linking migraine to a variety of comorbid disorders, including cardiovascular disease and stroke, in which oxidative stress appears to be an important underlying mechanism (Pizza *et al.*, 2015).

Besides that, evidences of sex differences in the epidemiology, clinical features and pathophysiology of migraine already exists and possible sex differences in the oxidative and inflammatory profile of migraine should be more investigated (Kjersti *et al*; 2017). If oxidative stress and inflammation indeed represent key events in the pathophysiology of migraine and, therefore, are appropriate therapeutic targets, further knowledge about this issue may contribute to the understanding of the cause and complications of migraine and may be essential for the development of new therapeutic approaches.

2 MATERIALS AND METHODS

2.1 Patient inclusion

Our cross-sectional study recruited individuals from an ambulatory of the Federal University of Viçosa, Minas Gerais, Brazil. The total number of patients attended in the period from July to November of 2018 with the diagnosis of migraine who fulfilled the International Classification of Headache Disorders (beta version - 2013) criteria was included in the study.The subjects, aged 18 to 61 years, were divided into three groups: (1) women with chronic migraine (WCM) n = 15; (2) women with episodic migraine (WEM) n = 17; and (3) men with migraine (episodic or chronic) (MM) n = 15. The study was approved by local ethics committee and all participants gave their written informed consent.

Exclusion criteria were: patients with comorbidities that interfere with the oxidative stress and the inflammatory profile (chronic diseases such as neoplasias, infections, collagenoses and other autoimmune diseases; other inflammatory processes, chronic renal insufficiency, chronic obstructive pulmonary disease, atherosclerotic vascular disease (coronary disease, stroke, peripheral artery disease), recent postoperative, allergies in activity, post-acute recent illness, recent post-hospitalization, pregnant women, and patients taking corticosteroids or immunosuppressants).

2.2 Collection of blood samples from patients

A blood sample was always obtained in the attack-free period between migraine attacks (interictal phase). Blood samples were centrifuged and the serum stored at -80 °C.

2.3 Biochemical analysis

Quantification of uric acid, C-reactive protein (CRP) and blood counts were performed using commercial kits following manufacturer's instructions (Labtest). Blood counts were performed in an automated impedance counting system. Concentration of blood proteins was performed according to Bradford (1976) using bovine serum albumin as standard.

Plasma TAS (total antioxidant status) was measured using fully automated colorimetric assay developed by Erel (2004) based on measurements of the OH radicals. Catalase (CAT) activity was assayed by measuring the rate of decrease of H2O2 absorbance at 240 nm (Aebi 1984). Estimation of serum glutathione-S-transferase (GST) was carried out as reported by Habig *et al.* (1974). Superoxide dismutase (SOD) activity was assayed by measuring the inhibition of adrenaline auto-oxidation, as described by Bannister and Calabrese (1987). As an index of lipid peroxidation, we used the formation of thiobarbituric acid reactive substances

(TBARS) during an acid heating reaction (Draper and Hadley,1990). Briefly, the samples were mixed with 1 ml of TCA 10% and 1 ml of thiobarbituric acid 0.67%, then heated in a boiling water bath for 15 min. TBARS were determined by the absorbance at 535 nm. All the results were normalized by the protein content (Lowry *et al.* 1951). The oxidative damage to proteins was assessed by the determination of carbonyl groups based on the reaction with dinitrophenylhydrazine (DNPH), as previously described (Levine *et al.* 1990). Briefly, proteins were precipitated by the addition of 20% trichloroacetic acid (TCA) and redissolved in DNPH and the absorbance read at 370 nm.

2.4 Statistical analysis

The analyzed variables displayed a normal distribution in the Shapiro-Wilk test, therefore, the One Way Anova parametric test was performed for multiple comparisons. The results were expressed as mean ± standard deviation. Spearman's distribution and correlation was performed between total antioxidant status (TAS) and oxidative markers. Statistical significance was considered at $p < 0.05$. Analyses were performed using the GraphPad Prism 7.0 program (GraphPad Software, Inc. San Diego, CA, USA).

3 RESULTS

In the present study, 47 volunteers were divided into 3 groups: 15 women with chronic migraine (WCM) with mean age of 36,3 years ± 9.6 years; 17 women with episodic migraine (WEM) with mean age of 25,7 years ± 6.5 years and 15 men with migraine (MM), with a mean age of 23,8 years ± 4.4 years, seeking to analize possible sex differences in the oxidative and inflammatory profile of migraine. Other socio-demographic characteristics of the volunteers are summarized in Table 1.

Table 1 – Socio-demographic characteristics of the volunteers (N = 47)

Sex	**Female**		**Male**
Groups	WCM	WEM	MM
N	15	17	15
Mean age	36 years and 4 months (SD=± 9,6 years)	25 years and 7 months (SD = ± 6,5 years)	23 years and 8 months (SD = ± 4,4 years)
Race/color		White = 65,95%	
Schooling		Complete upper course = 46,81%	
Single/married		Single = 76,65%	
BMI (mean)	25,1 (SD =±4,6)	22,9 (SD =±3,7)	24,3(SD =±3,5)

The majority of subjects self-declared to be of the white race, with complete superior course and singles. All declared to be non-smokers.

No significant difference was observed in the quantification of the blood cell types analyzed in blood count and leukogram between the three groups; there was no difference in the neutrophil/lymphocyte ratio (RN/L) (Table 2).

Table 2 – Hematological analysis of the studied groups (n = 47)

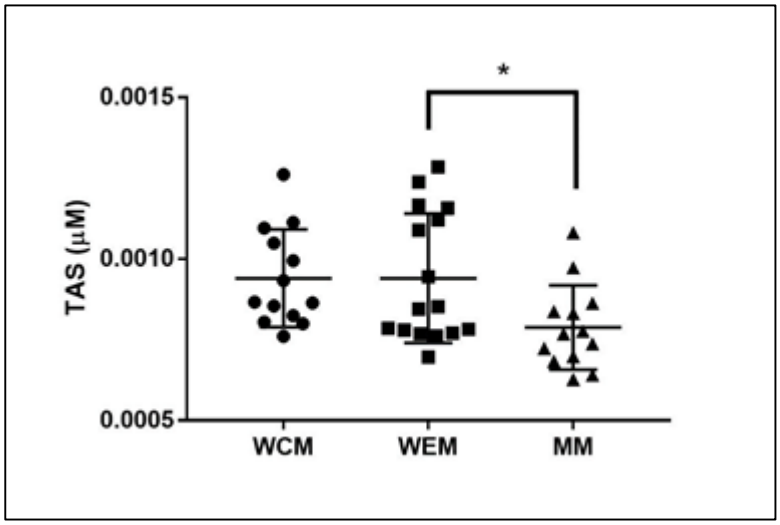
	WCM (n = 15) mean ± SD	**WEM (n = 17) mean ± SD**	**MM (n = 15) mean ± SD**
Leukocytes (mm^3) - (10^3)	5,8 ± 1,3	6,4 ± 2,3	5,7 ± 1,4
Lymphocytes (mm^3) - (10^3)	2,0 ± 0,4	2,2 ± 0,6	2,0 ± 0,4
Neutrophils (mm^3) - (10^3)	3,2 ± 1,0	3,8 ± 1,7	3,3 ± 1,0
Eosinophils (mm^3) - (10^3)	0,1 ± 0,03	0,2 ± 0,15	0,1 ± 0,07
Monocytes (mm^3) - (10^3)	0,4 ± 0,08	0,4 ± 0,17	0,3 ± 0,08
RN/L	1,59	1,74	1,67

SD = standard deviation; RN/L = neutrophil/lymphocyte ratio

No significant differences were detected in the quantification of the inflammatory marker PCR and on cholesterol, total and fractions, among the 3 groups (data not shown).

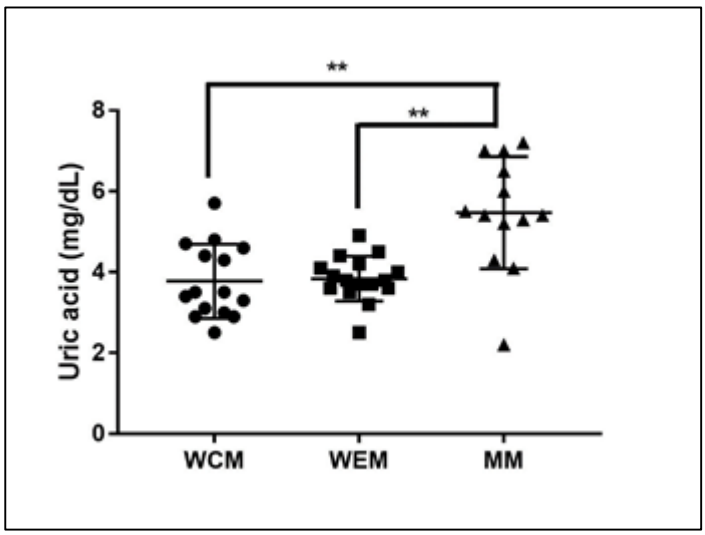
For the evaluation of the oxidative profile in the patients' serum, the total antioxidant status by iron reduction (TAS) was initially determined. It was verified that the group of men (MM) presented total antioxidant capacity significantly lower than the group of women with episodic migraine (WEM). Although the difference observed between the group of women with chronic migraine (WCM) and men (MM) was not significant, its value was close to statistical significance: p = 0.0630 (Fig. 1).

Figure 1 – Total antioxidant status (TAS) in the serum of women with chronic migraine. WCM (n = 15), women with episodic migraine; WEM (n = 17) and men with migraine; and MM (n = 15)



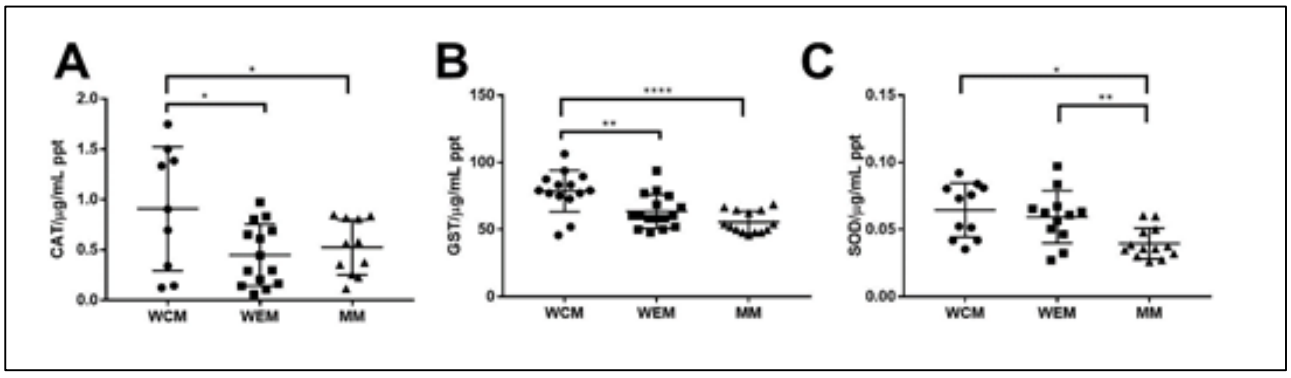
Uric acid is an important antioxidant. The group of men had higher mean uric acid values than the groups composed by women, which was expected since the reference values for males are higher (Fig. 2).

Figure 2 – Quantification of serum uric acid in patients with migraine. Serum uric acid values in women with chronic migraine. WCM (n = 15), women with episodic migraine; WEM (n = 17); and men with migraine MM (n = 15). ** p ≤ 0.01 One-way ANOVA



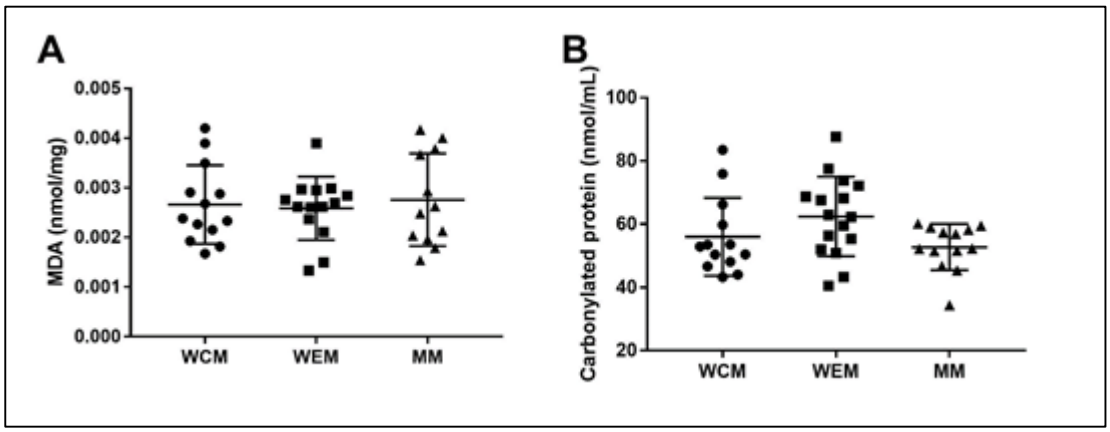
Subsequently, the enzymatic activity of the antioxidant agents Catalase (CAT), Glutathione S-transferase (GST) and Superoxide Dismutase (SOD) were determined. The CAT and GST detections were significantly higher in the WCM group compared to the WEM and MM group (Fig. 3A and B). However, SOD detection was significantly increased in the two groups of women compared to the group of men (Fig. 3C).

Figure 3 – Detection of serum enzymatic activity. Evaluation of Catalase (A), Glutationa S-transferase (B) and Superoxide dismutase (C) in serum of women with chronic migraine. WCM (n = 15), women with episodic migraine; WEM (n = 17) and men with migraine; and MM (n = 15). $p \leq 0.05$, ** $p \leq 0.01$, **** $p \leq 0.001$ One-way ANOVA



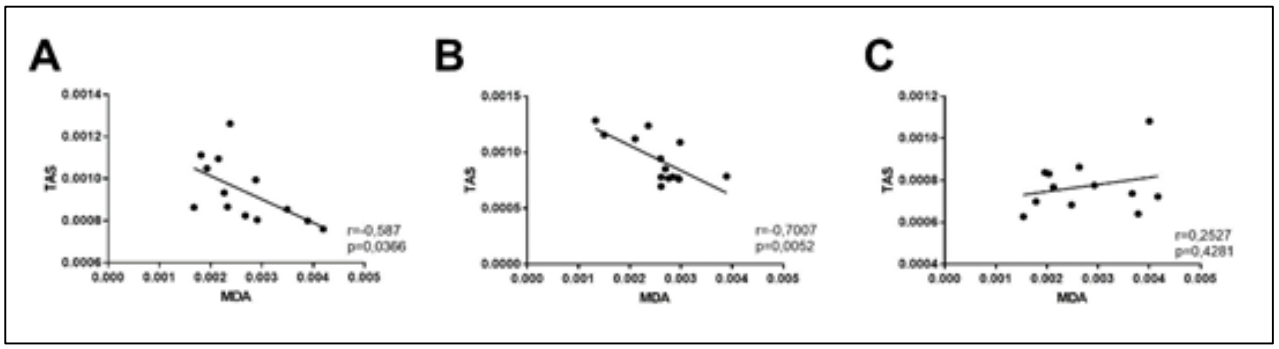
To assess markers of tissue damage resulting from oxidative stress, the lipid peroxidation determined by MDA and the carbonylated proteins were quantified. The mean in the 3 groups show no significant statistical variation for MDA and carbonylated proteins (Fig. 4A and B).

Figure 4 – Quantification of markers of tissue damage. Lipid oxidation evaluation determined by MDA (A) and carbonylated proteins (B) in women with chronic migraine. WCM (n = 15), women with episodic migraine; WEM (n = 17) and men with migraine; and MM (n = 15)



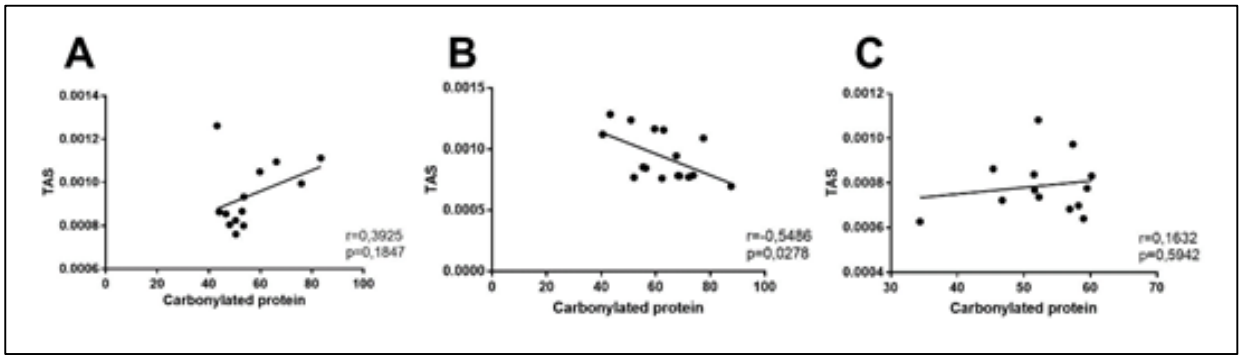
We evaluated the correlation between migraine and the oxidative markers using the Spearman analysis. In the two groups composed of women, a significant inverse correlation was observed between measurements of serum total antioxidant status (TAS) and the marker of oxidative damage evidenced by lipid peroxidation determined by MDA (Fig. 5A and B), interestingly the same relation was not found observed for the male group (Fig. 5C).

Figure 5 – Spearman dispersion and correlation (r). Correlation between total antioxidant status (TAS) and serum lipid peroxidation (MDA) in women with chronic migraine. WCM (n = 15), women with episodic migraine; WEM (n = 17) and men with migraine; and MM (n = 15)



Concerning the carbonylated proteins, only the group of women with episodic migraine (WEM) displayed a negative correlation with the total antioxidant status (TAS). (Fig. 6B)

Figure 6 – Spearman dispersion and correlation (r). Relationship between total antioxidant status (TAS) and serum carbonylated proteins in chronic demyelin (A), women with episodic migraine (B) and men with migraine (C).



4 DISCUSSION

Migraine is a frequent form of headache particularly in the third decade of life (Charles 2017). In spite of being considered a benign complaint (Yilmaz 2011), it results in frequent absence from work, significant consumption of medications and changes in the daily life and social activities of the patients (Abu Bakar *et al.* 2016; Dodick 2018).

Eryigit *et al.* (2017) reviewed several studies suggesting that inflammatory processes and oxidative stress are involved in the pathogenesis of migraine.

In order to identify new markers that might eventually help understanding the pathophysiology and migraine patient management, the present study investigated the inflammatory and oxidative profile of 47 volunteers, divided in 15 women with chronic migraine (WCM); 17 women with episodic migraine (WEM), and 15 men with migraine (MM). Most patients self-declared to be of the white race, with complete university degrees and not married.

Participants were selected in a University outpatient clinic, aimed at the care of the academic community, which justifies the predominant schooling, age and race/color, as well as allowing a reliable answers, since they understood well the clinical picture and the questions asked.

No difference was observed in body mass index (BMI) values between the three groups studied, unlike Bahadir *et al.* who in 2013 found significantly lower BMI in the control (healthy) group than in the migraine group.

According to Costa *et al.* (2016), oxidative stress and inflammation are related to the genesis of migraine. Moskowitz and Cutrer (1993) suggested that migraine results from a neurogenic inflammatory reaction, and Turan *et al.* (2011) determined that markers of inflammation may rise during migraine attacks.

Several studies investigated the role of the neutrophil-lymphocyte ratio (N/L ratio) in the diagnosis and treatment of various diseases, including migraine (Gomez *et al.* 2008; Azab *et al.* 2012) as an important marker of inflammation (Demir 2015). Karabulut *et al.*(2016) observed that N/L ration increases as a sign of inflammation during migraine attacks, differently from healthy controls. Eryigit *et al.* (2017), found no statistically significant differences between N/L ratio values in migraine and other groups with primary headache syndromes, similarly to the present results who compared 3 groups of migraine patients with different characteristics.

There was no significant differences between the groups in the red series, but there is an association between hematological disorders, such as anemia and headache, and anemia due to iron deficiency is an important factor related to migraine (Avijgan 2011; Pamuk *et al.* 2015).

Elevated levels of C-reactive protein (CRP) were observed in patients admitted with a migraine crisis, compared to healthy controls (Vanmolkot 2007; Gudmundsson *et al.* 2009), differently from observations of Ceylan *et al.* (2016), in which the levels were increased among those suffering from migraine as compared

to controls. In our study, we found no significant differences in PCR values among the three groups analyzed.

In a study by Bahadir *et al.* (2013) total cholesterol (TC) levels were significantly higher in the group with migraine as compared to the control group without migraine. In the present study we did not observe significant variations in the values of cholesterol and fractions among the 3 groups analyzed.

It is known that patients with migraine have lower total antioxidant capacity (Vurucu *et al.* 2013).

It is already known that the sérum of migraine sufferers display a lower total antioxidant capacity (Vurucu *et al.* 2013; Yigit *et al.* 2018). In our study, the total antioxidant status was determined by iron reduction (TAS) in the patients' serum. A lower TAS value was observed in the men group - MM.

Uric acid is an important endogenous antioxidant agent, responsible for about 30% of the antioxidant action capacity in healthy individuals (Geyik *et al.* 2016). In the present study a significantly higher values were observed in the group of men (MM) compared to the two groups of women; however, no values were off the reference value for each sex.

Other serum markers, such as the enzyme catalase (CAT), are predictors of antioxidant capacity (Alp *et al.* 2010). Aytaç *et al.* 2014 and Yigit *et al.* 2018, observed that CAT levels were significantly reduced in patients with migraine compared to healthy controls. In the present study, the group of women with chronic migraine (WCM) presented the highest values of the enzyme catalase (CAT).

Glutathione S-transferases (GSTs) are a family of enzymes responsible for the metabolism of a wide range of xenobiotics and carcinogens (Mannervik 1985) and may represent the first step of a detoxification process leading to the formation of mercapturic acid. In addition, GSTs have a protective role in cells against oxidative stress products (Hayes and Strange 1995). Shukla (2018) showed that GST levels were significantly decreased in migraine patients compared to the control group. In our study, we showed that the group of women with chronic migraine (WCM)

presented the highest values of glutathione S-transferase (GST), as well as that observed for the enzyme catalase (CAT).

A high activity of the enzyme superoxide dismutase (SOD) correlates with better antioxidant power and this prevents oxidation-mediated damage (Ciancarelli *et al.* 2007). According to Borkum *et al.* (2016), lower SOD activity was found in erythrocytes and platelets in migraine sufferers, as well as a lower total antioxidant status, suggesting a greater vulnerability to oxidative stress (Ciancarelli *et al.* 2007). Gupta *et al.* (2009), reported lower levels of SOD in patients with migraine with aura than in patients without aura, suggesting that the migraine subtype may have an effect on the production of oxidants. In the present study, the two groups composed of women, both chronic and episodic migraine, presented higher values of the SOD enzyme in relation to men.

Oxidative stress can modify membrane lipids, nucleic acids, proteins and extracellular matrix components, including proteoglycans and collagens (Geyik *et al.* 2016). To evaluate lipid and protein oxidation and, consequently, oxidative damage to lipids and proteins, we measured the concentration of malondialdehyde (MDA) and carbonylated proteins in serum.

Previous studies found that plasma levels of MDA were significantly elevated in patients with migraine (Gupta *et al.* 2009; Aytaç *et al.* 2014). Similar data were obtained by Yilmaz *et al.* (2011) and by Yigit *et al.* (2018) during migraine attacks. In the present study, in spite of variation in the activity of antioxidant enzymes between men and women, no difference was observed in the markers of damage as evidenced by MDA values.

Another marker of oxidative damage, such as the concentration of carbonylated proteins was not significantly different among the migraine subjects or healrthy controls (Bernecker *et al.* 2011). In the present study, despite the variation in the activity of antioxidant enzymes between men and women, the

mean in the 3 groups showed no significant statistical variation in carbonylated proteins.

In the current study, total antioxidant status (TAS) and damage by active forms of oxygen as measured by lipid peroxidation (MDA) were inversely correlated in groups composed exclusively of females. Likewise, protein carbonylation also showed a negative correlation with total serum antioxidant status, but in this case, only in the group of women with episodic migraine. These findings suggest that there is a difference in the oxidative profile between the sexes among migraine patients.

5 CONCLUSION

In summary, according to the present results, we conclude that the group male participants (MM) displayed a reduction in total antioxidant status, as well as a lower value for antioxidant enzymes, but had no significant alterations in markers related to damage by oxidative stress compared to women. This may allow a better understanding of patients profile with different migraine phenotypes and identify new markers that might help understanding the pathophysiology and migraine patient management.

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