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The effect of oxidative stress on the etiopathogenesis of primary dysmenorrhea

Primer dismenore etiyopatogenezinde oksidatif stresin etkisi

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ÖZ

Amaç: Bu araştırmanın amacı, primer dismenoresi olan hastalarda serum oksidatif stres belirteçleri ve antioksidan enzim düzeylerini karşılaştırarak oksidatif stresin dismenore etyopatogenezine etkisini araştırmaktır.

Yöntemler: Hastanemiz kadın hastalıkları polikliniğine başvuran primer dismenoresi olan 38 kadın ve dismenoresi olmayan 21 kadın çalışmaya dahil edildi. Çalışmaya alınan kadınların her birinden siklusun 3. ve 21. gününde kan örneği alındı. Paraoksonaz (PON), Arilesteraz (ARES) ve Stimulated Paraoksonaz (SPON) serum düzeylerine bakıldı. PON, ARES ve SPON düzeyleri hasta ve kontrol grupları arasında ve her grup içinde siklusun 3. ve 21. gününde karşılaştırıldı.

Bulgular: Çalışmamızda hasta ve kontrol grupları arasında yaş ortalamasında anlamlı fark bulundu. Menarş yaşı, düzenliliği ve süresi açısından anlamlı fark gözlenmedi. Menstrüel siklusun 3. ve 21. günlerinde bakılan ARES, PON ve SPON düzeylerinde hasta ve kontrol grupları arasında anlamlı fark bulunmadı.

Sonuç: Çalışmamızın sonuçlarına göre, hasta ve kontrol grupları arasında siklusun 3. ve 21. günlerinde bu belirteçlerin düzeylerinde anlamlı bir fark bulunmadı. Buna dayanarak, oksidatif ve antioksidan belirteçlerin dismenore etiyopatogenezinde doğrudan yer almadığını veya siklustan bağımsız etki ettiğini düşünmekteyiz.

Anahtar Kelimeler: primer dismenore, oksidatif stres, paraoksonaz, arilesteraz

ABSTRACT

Aim:The aim of this research is to investigate the effect of oxidative stress on the etiopathogenesis of primary dysmenorrhea by comparing serum oxidative stress markers and antioxidant enzyme levels

Methods:A total of 38 women with primary dysmenorrhea and 21 women without dysmenorrhea who applied to our hospital's gynecology clinic were included in the study. Two blood samples were taken from each of the women included in the study, on the 3rd day and the 21st day of their menstrual cycle. The serum levels of Paraoxonase (PON), Arylesterase (ARES), and Stimulated Paraoxonase (SPON) were examined. PON, ARES, and SPON levels were compared between the patient and control groups, as well as within each group, on the 3rd and 21st days of menstrual cycles.

Results: In our study, a significant difference was found in the mean age between the patient and control groups. No significant differences were observed in terms of age at menarche, regularity, and duration. No significant differences were found in the ARES, PON, and SPON levels examined on the 3rd and 21st days of the menstrual cycle between the patient and control groups.

Conclusion:According to the results of our study, there was no significant difference in the levels of these markers between the patient and control groups on their respective menstrual cycle days. Based on this, we believe that oxidative and antioxidant markers are not directly involved in the etiopathogenesis of dysmenorrhea or they exhibit cycle-independent effects.

Keywords: Dysmenorrhea, Oxidative Stress, Paraoxonase, Arylesterase

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INTRODUCTION

Dysmenorrhea is one of the most common causes of pelvic pain in women of all ages and races (1). Results ranging from 45% to 90% have been reported in studies conducted on the prevalence of dysmenorrhea. The variations in results can be attributed to differences in pain perception related to dysmenorrhea, societal differences and the assessment criteria of pain perception (2). Dysmenorrhea is evaluated as primary and secondary. Primary dysmenorrhea refers to menstrual pain that is not associated with organic pathology. According to a study by Rodrigues AC et al., it was reported that 65% of adolescents and young adults had limitations in their daily activities due to dysmenorrhea (3). Studies conducted on female adolescents and young women report the prevalence range of primary dysmenorrhea from 20% to 90% in Turkey (4,5). Although the treatment of dysmenorrhea varies, including conservative treatment, medical treatment, physical therapy and rehabilitation, there is no definitive treatment method that has proven effective for all women (6,7). While the etiopathogenesis of primary dysmenorrhea remains uncertain, studies have shown increased levels of prostaglandins (PGF2α, PGE2) and vasoactive mediators in the endometrium and menstrual blood. The increased levels of PGF2α in the endometrium during the secretory and menstrual phases, specifically, stimulate uterine contractions and reduce uterine blood flow. It is believed that the resulting uterine hypoxia and ischemia contribute to menstrual pain (8,9).

Oxidative stress (OS) occurs as a result of an imbalance between reactive oxygen species and other radicals and antioxidants. The formation of free radicals, which are highly reactive and unstable molecules that can occur in the organism under physiological conditions, and the rate at which they are removed by antioxidant systems are in balance. As long as this balance is maintained, the organism is not affected by free radicals. OS is the disruption of this balance in favor of reactive oxygen species (ROS) (10,11).

It is suggested that oxidative stress plays a role in the etiology of ischemia and hypoxia occurring in dysmenorrhea. Studies focusing on the relationship between dysmenorrhea and oxidative stress have gained prominence in recent years. In a study conducted by Kalia et al., although there were signs of oxidative stress in primary dysmenorrhea, no evidence of oxidative stress-related damage was found in patients (12). In contrast, Kaplan et al. found an association between oxidative stress and primary dysmenorrhea in their study (13).

Our aim in this study is to evaluate the paraoxonase and arylesterase enzyme activities in the different phases of menstruation in primary dysmenorrhea, assess the impact of ROS/antioxidant systems on the etiopathogenesis of dysmenorrhea and contribute to the literature in understanding the etiopathogenesis of primary dysmenorrhea. Knowledge of dysmenorrhea pathophysiology will also contribute to the literature in terms of developing effective treatments.

MATERIALS AND METHOD

Our study was planned as a prospective cohort study. A total of 59 women between the ages of 18-49 were included in our study, consisting of 38 female patients who applied to our hospital's gynecology clinic with primary dysmenorrhea and 21 controls without primary or secondary dysmenorrhea. The criteria used for the diagnosis of primary dysmenorrhea were the onset of dysmenorrhea symptoms within 2 years after menarche, the absence of organic pelvic pathology and the pain starting with menstrual bleeding and ending within 48-72 hours (14). Patients with organic gynecological pathologies (such as fibroids, ovarian cysts, adenomyosis), those who had undergone abdominal surgery, and those using intrauterine devices were excluded from the study in both groups. The participants' age, BMI (body mass index), educational status, parity, age of menstruation onset, duration, and regularity were recorded. The pain during menstruation was assessed using the Visual Analog Scale (VAS) pain scale. The blood samples pf the participants were collected on the 3rd (d3) and 21st (d21) days of their menstrual cycle to evaluate paraoxonase and arylesterase enzyme activities. Our study was approved by the ethics committee of our hospital, with decision number 213, on 24.10.2018.

Collection and Preservation of Blood Samples

Venous blood samples were collected from the participants included in the study after an eight-hour fasting period, and within one hour the collected blood samples were centrifuged at 3200 rpm for 10 minutes in order to separate the serum. Serum samples with hemolysis were not included in the study. The separated serum samples were transferred to sterile tubes and stored at -80°C for preservation to investigate PON1 and Arylesterase levels. At the time of the study, all serum samples were studied in the biochemistry laboratory after they were brought to room temperature.

Measurement of paraoxonase enzyme activity

Paraoxonase activity, which is an antioxidant enzyme with lipophilic and hydrophobic properties associated with HDL cholesterol, was measured using the commercial Rel Assay kit. In this method, the paraoxonase enzyme hydrolyzes the substrate paraoxon (O,O-diethyl-O-p-nitrophenylphosphate), leading to the formation of the coloured product p-nitrophenol. The absorbance of the resulting product was monitored at 412 nanometers (nm) in kinetic mode, and the enzyme activity is expressed as U/L.

Measurement of arylesterase enzyme activity

The arylesterase activity of paraoxonase enzyme was also measured using the commercial Rel Assay kit. This test is based on the colorimetric measurement of phenol, which is generated from the hydrolysis of phenyl acetate substrate by the enzyme in the sample. Due to the high levels of enzyme activity, the results are expressed as kU/L.

Statistical Analysis

Descriptive statistics for continuous data include Mean Standard Deviation, Median, Minimum, and Maximum values, while categorical data was presented in percentages. The conformity of the data to the normal distribution was examined using the Shapiro-Wilk test, and the homogeneity of the variances was examined using the Levene test. The T-test was used for the comparison of data showing normal distribution between the experimental and control groups, while the Mann-Whitney U test was employed for the comparison of data that did not exhibit normal distribution. The Chi-Square test and Fisher's Exact test were used for group comparisons of nominal variables (in cross-tabulations). The Repeated Measures Analysis of Vari-

ance was used to examine the differences between the D3 and D21 values in the two groups for data that demonstrated normal distribution and had homogeneous variances. The Wilcoxon Test was used to compare the separate D3 and D21 values within the groups for data that did not conform to normal distribution or had non-homogeneous variances. The Mann-Whitney U test was employed to compare the two groups. Pearson and Spearman's Correlation Coefficients were utilized to examine the relationships between continuous variables. IBM SPSS Statistics 20 software was used for the evaluations, and the statistical significance threshold was set at $p<0.05$. For the study, support was received from the AYBU BAP office with the project number of 5240/2019.

RESULTS

In our study, the mean age of women in the patient group was found to be 24.26±4.91, while in the control group, it was 27.28±4.89. There was a statistically significant difference in the mean age between the two groups (p=0.027). The median VAS score for menstrual pain in the patient group was 8 (6-10), while in the control group, it was 1 (2-0). There is a difference in the VAS scores for menstrual pain between the two groups (p=0.000). The VAS scores for menstrual pain in the patient group were found to be significantly higher compared to those in the control group. There were no significant differences in BMI, age at menarche, and menstrual duration between the patient and control groups. The data is summarized in Table 1.

Table 1: Comparison of menstrual characteristics of women in patient and control groups

	Patient (n=38)	**Control (n=21)**	***p***
Age (year)	24.26±4.91	27.28±4.89	0.027*
BMI (kg/m²)	22.72±3.67	22.28±2.38	0.620
Menstrual cycle			
Menarche age (year)	12.95±1.31	12.86±1.11	0.683
Duration (day)	5.95±1.69	6.33±1.56	0.362
VAS	8.38±1.38	2.00±0.00	0.000*

(VAS= visual analogue scala)While there were no differences observed between the patient and control groups regarding menstrual cycle regularity and having given birth to children, women in the patient group were found to have a lower educational level compared to women in the control group. The data is summarized in Table 2

Table 2: Demographic data of patients

	Total (n=59)	**Patient (n=38)**	**Control (n=21)**	***P***
Education level (n,%)				
Primary	1 (1.7)	0 (0)	1 (2.6)	
High-school	11 (18.6)	0 (0)	11 (28.9)	
Undergraduate	29 (49.2)	7 (33.3)	22 (57.9)	0.000*
Graduate	18 (30.5)	14 (66.7)	4 (10.5)	
Children (n,%)				
Yes	7 (11.9)	4 (19)	3 (7.9)	0.233
None	52 (88.1)	17 (81)	35 (92.1)	
Cycle regularity (n,%)				
Regular	44 (74.6)	17 (81)	27 (71.1)	0.403
Irregular	15 (25.4)	4 (19)	11 (28.9)	

There were no significant differences found in the ARES, PON, and SPON levels measured on D3 and D21 between the patient and control groups. The data is summarized in Table 3.

Table 3: Comparison of Antioxidant levels of patient and control group on the day3 and day21 of menstruation,

	Patient group (n=38)	**Control group (n=21)**	***P***
3rd day of menstrual cycle (d3)			
ARES	177.47±34.13	175.58±25.86	*0.827*
PON	197.11±126.07	184.82±118.19	*0.862*
SPON	598.87±324.32	563.87±355.87	*0.669*
21st day of menstrual cycle (d21)			
ARES	184.93±41.09	180.39±45.03	*0.697*
PON	185.18±116.41	200.40±128.39	*0.716*
SPON	568.25±309.09	557.23±327.08	*0.776*

No differences were observed in the ARES, PON, and SPON levels based on cycle days within the patient and control groups. The data is summarized in Table 4.

Table 4: Comparison of day3 and day21 Antioxidant Levels in Patient group and Comparison of day3 and day21 Antioxidant Levels in Control Group, (ARES=arylesterase), (PON=paraoxonase), (SPON= Stimulated Paraoxonase)

	Patient			**Control**		
	day 3	**day 21**	***p***	**day 3**	**day 21**	***P***
ARES	177.47±34.13	184.93±41.09	*0.299*	175.58±25.86	180.39±45.03	*0.701*
PON	197.11±126.07	185.18±116.41	*0.925*	184.82±118.19	200.40±128.39	*0.339*
SPON	598.87±324.32	568.25±309.09	*0.766*	563.87±355.87	557.23±327.08	*0.848*

DISCUSSION

Dysmenorrhea is frequently observed in menstrual cycles where ovulation occurs and pelvic pathology is not present. Despite its common occurrence, the etiopathogenesis of dysmenorrhea is not fully understood. Certain experimental and clinical studies suggest that increased levels of uterine prostaglandins can lead to increased myometrial tone and subsequent uterine ischemia, which is proposed as the cause of pain (9,15).

Different results have been reported in studies examining the relationship between the prevalence of primary dysmenorrhea and age. In their study, Kaplan et al. found a decrease in the frequency and severity of primary dysmenorrhea with the advance of age (13). Although the prevalence of primary dysmenorrhea decreases with age, it has been reported to be most common in the ages ranging between 20-24 years (16). However, Harlow et al., in their study, concluded that there is no relationship between dysmenorrhea and age (17). In our study, we found that the mean age of women with primary dysmenorrhea was significantly lower compared to the control group. We also observed that dysmenorrhea complaints decreased as the level of education increased. Considering the socioeconomic impact of dysmenorrhea, the concept of pain and the measurement of its severity become crucial. The Visual Analog Scale (VAS) was used to assess pain in our study, and the average pain intensity according to the VAS was determined as 8.38±1.38. We believe that higher levels of education result in the dismantling of existing and/or constructed taboos surrounding menstruation, as well as an increase in awareness. Studies have shown a decline in dysmenorrhea complaints after childbirth(13,18). Gürel et al. stated that there is no relationship between dysmenorrhea and parity or history of miscarriage (19). In our study, we found no significant difference in childbirth rates between women with and without dysmenorrhea.

Psychological factors and prostaglandins are considered to play a role in the etiopathogenesis of dysmenorrhea. The primary prostaglandins, PGF2 alpha and prostaglandin E (PGE), particularly PGF2 alpha, are believed to induce uterine contractions, decrease blood flow, and lead to uterine hypoxia and ischemia, especially during the luteal and menstrual phases of the endometrial cycle, which is thought to contribute to the development of menstrual pain (8,9). The ischemia and hypoxia occurring in dysmenorrhea suggest the involvement of oxidative stress in its etiology.

Oxidative stress occurs as a result of the imbalance between reactive oxygen species and other radicals and antioxidants. It is a consequence of increased free radical formation and/or decreased physiological activity of antioxidant defenses (20). ROS are continuously generated during normal cellular metabolism and are neutralized by the antioxidant defense system. Oxidative stress occurs when there is an imbalance between the production of ROS and the antioxidant defense system, favoring an increase in ROS production (21). Antioxidant molecules such as PON and arylesterase are part of the defense system against free oxygen radicals that occur in the body.

Paraoxonase has two important functions, which are detoxifying organophosphate compounds like paraoxon and hydrolyzing lipid peroxides to prevent the oxidation of LDL. Studies have demonstrated that paraoxonase (PON1), as one of the endogenous free radical scavenging antioxidant systems in the body, eliminates lipid-soluble carcinogenic radicals formed as a result of lipid peroxidation (22-24). It has been noted that the PON1 enzyme not only hydrolyzes paraoxon but also exhibits similar activities such as arylesterase, lactonase, low-level peroxidase, and phospholipase A2 enzymes (25-28). Paraoxonase is known to demonstrate antioxidant and anti-inflammatory properties through lipopolysaccharide inactivation, and it is believed that PON1 activity is inversely proportional to oxidative stress in both serum and macrophages (29).

Basini et al. evaluated the modulation of ROS production in granulosa cells under hypoxic conditions and demonstrated that, in this case, ROS production decreased, while superoxide dismutase and peroxidase production increased (30). Verit et al. investigated the relationship between the endometriosis stage and PON levels, and a significant association was found in the advanced stages of the disease (31).

In recent years, studies have been conducted to investigate the relationship between dysmenorrhea and oxidative stress. In a study conducted by Kaplan et al. it was found that there was an association between oxidative stress and primary dysmenorrhea. In this study, lipid peroxidation, reduced glutathione, glutathione peroxidase, and total antioxidant values were studied in patients with primary dysmenorrhea and they were found to be significantly higher in healthy controls (13). Similarly, Turhan et al., in their study, found that plasma MDA (malondialdehyde) levels were higher in patients with dysmenorrhea than in those without dysmenorrhea (32). MDA is an enzyme that correlates with the degree of lipid peroxidation, which plays a role in lipid peroxidation. The degree of increase in lipid peroxidation products after oxidation is directly proportional to susceptibility to

oxidation. In a study conducted by Dikensoy et al., they also identified higher plasma levels of MDA, nitric oxide (NO), and adrenomedullin (AM) in patients with primary dysmenorrhea (33).

In our study however, no significant difference was found in PON, ARES, and SPON values between the patient and control groups in samples taken during different phases of the menstrual cycle (D3/D21). In a similar study conducted by Demirdöğen et al. evaluating PON activity in pseudoexfoliative glaucoma based on the role of prostaglandins in the etiopathogenesis, no significant differences were found (34). These results suggest that antioxidant enzymes such as ARES, PON, and SPON may not be effective in hypoxia or ischemia caused by prostaglandin release. Similarly, in a study by Kalia et al., although there were signs of oxidative stress in premenstrual syndrome, no evidence of oxidative stress-related damage was found. They suggested that this could be due to the strong antioxidant properties of not only progesterone but also estrogens, which can exhibit a protective and adaptive response against oxidative stress, supported by previous studies (12). We believe that the similar findings in our study may be attributed to this hormonal effect.

Our study is significant in terms of being the first study to measure the activity of Paraoxonase and Arylesterase enzymes in different phases of the menstrual cycle in patients with primary dysmenorrhea. We examined the balance of oxidative stress and antioxidant systems in the etiopathogenesis of primary dysmenorrhea, specifically focusing on the secretory and luteal phases. However, we did not find any significant results when evaluating these parameters between the patient and control groups and across different phases of the menstrual cycle. Further investigation into the oxidative/antioxidant balance, which is believed to play a role in the etiopathogenesis of primary dysmenorrhea, is necessary to contribute to our understanding of dysmenorrhea etiology. Comprehensive studies that explore other components of the system may be planned to demonstrate the clear relationship between dysmenorrhea and oxidative stress.

Conflict of Interest

We declare that we have no conflict of interest

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