

The pathophysiological role of inflammatory parameters in patients with varicocele

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Abstract. – OBJECTIVE: Varicocele is the abnormal enlargement of the pampiniform plexus in the scrotum and is one of the diseases that have negative consequences on reproduction in men today. The aim of this study is to investigate the pathophysiological role of inflammatory parameters in patients diagnosed with varicocele.

PATIENTS AND METHODS: Patients who applied to Viransehir state hospital urology outpatient clinic between January 2016 and January 2022 were evaluated retrospectively. Among the patients whose varicocele diagnosis was evaluated by physical examination, 112 patients diagnosed with Grade III varicocele were included in the study. Obtained hemogram results [red blood cell, red cell distribution width (RDW), mean red cell volume, white blood cell, hematocrit, hemoglobin, mean hemoglobin amount, platelet, platelet distribution width (PDW), neutrophil, lymphocyte, monocytes, and mean platelet volume (MPV)] were compared with the control group values.

RESULTS: There was no statistical difference between the two groups in terms of mean age ($p=0.270$). Statistically significant parameters between both groups were erythrocyte ($p=0.011$), MCV ($p=0.028$), RDW ($p=0.018$), and PDW ($p=0.004$), respectively. However, Neutrophil/Lymphocyte ratio (NLR), PLT/Lymphocyte ratio (PLR) and MPV/PLT ratio (MPVPR) values were found to be statistically significantly higher in the varicocele group ($p=0.034$, $p=0.043$ and $p=0.045$, respectively).

CONCLUSIONS: According to our results, it is possible to recommend using the inflammatory parameters as markers to screen for the pathophysiological basis of varicocele.

Key Words:

Varicocele, MPV, PDW, Erythrocytes, RDW, NLR, PLR, MPVPR.

Introduction

Varicocele is the abnormal enlargement of the pampiniform plexus in the scrotum and is one of

the most common diseases that cause adverse reproductive outcomes in men today¹.

There are 2 types of varicocele as primary (idiopathic, unknown cause) and secondary. Primary varicocele develops as a result of insufficient valves in the internal spermatic veins. The blood refluxes retrogradely to the pampiniform plexus. Secondary varicocele is encountered with the co-existence of intra-abdominal and retroperitoneal pathologies that cause increased pressure on the spermatic veins^{2,3}. While varicocele affects approximately 15% of men, this rate rises to 40% in men who apply to the infertility outpatient clinic^{2,3}. The most common correctable cause of male infertility is varicocele⁴. Ultrasonography in infertile men aids in the diagnosis of clinically palpable and sub-clinical varicoceles⁵. It is also useful in the evaluation of testicular size before and after treatment, as varicocele may cause a decrease in testicular volume. There is a weak correlation between the size of the varicocele and the degree of testicular destruction leading to infertility³.

Although varicocele has been known for many years, its pathophysiology has not been fully elucidated. Although there is limited information on the pathophysiology of varicocele, these include reflux of renal or adrenal toxic metabolites, impaired hormone balance, stasis secondary to testicular hypoxia, abnormal temperature regulation, increased apoptosis, and increased oxidative stress. Venous stasis due to varicocele causes hypospermatogenesis by causing intratesticular hypoxia, decrease in pH and increase in pCO_2 ^{6,7}.

Reactive oxygen species are by-products of many oxidative biochemical and physiological processes. Although there are no biochemical markers that directly measure oxidative stress in the blood, Neutrophil/Lymphocyte ratio (NLR), PLT/Lymphocyte ratio (PLR) and MPV/PLT ratio (MPVPR) and erythrocyte distribution width (RDW) are indirect markers reflecting oxidative

stress⁸⁻¹¹. High NLR, PLR, MPVPR and RDW values are associated with the incidence of both micro and macrovascular complications in cardiovascular disease and are used to predict mortality and morbidity^{8-10,12}. Higher mean platelet volume (MPV) values are associated with varicocele^{13,14}. PDW are blood values that are used to measure the distribution of platelets in the blood and to determine whether the platelets are working or not. A high PDW shows that platelets are more variable in volume than normal¹⁵. Previous studies¹⁶ have shown that large platelets are more metabolically and enzymatically active than small platelets.

The possible relationship between varicocele and other vascular system diseases enabled us to conduct a study examining the relationship between varicocele, a chronic vascular risk indicator, and inflammatory markers, PDW, RDW, and MPV.

Our study aimed at contributing to the literature on the pathophysiology of varicocele through its effects on blood biochemical parameters by comparing the blood samples taken from the varicose veins and the median cubital vein in the pampiniform plexus simultaneously with the levels of biochemical parameters in normal individuals who were not diagnosed with varicocele.

Patients and Methods

Study Design and Patients

Patients who applied to the urology outpatient clinic of Viransehir State Hospital between April 2016 and January 2022 were evaluated retrospectively. Physical examination revealed 148 patients diagnosed with Grade III varicocele. Patients whose age ranged between 20-30 years and whose hemogram results could be reached in the system were included in the study. Those with known chronic diseases, those with acute infection that may have caused changes in the parameters at the time of hemogram, and those outside the defined age group were not included in the study. A total of 112 patients who met the inclusion criteria were included in the study. Varicocele was evaluated by physical examination, as defined by Dubin and Amelar¹⁷, when the patient is standing, dilated veins were clearly visible in the spermatic cord from the skin of the scrotum, and it was considered as Grade III varicocele. The hemogram results of the patients who were scheduled for varicocelectomy during the preparation for anesthesia were evaluated. As the control group, patients with non-specific symptoms, such

as scrotal pain, flank pain, etc., uncircumcised patients who applied for circumcision and a total of 70 patients who applied due to hypospadias were included. White blood cell (WBC), hemoglobin (HGB), hematocrit (HCT), erythrocyte, platelet (PLT), neutrophil, lymphocyte, monocytes, mean red blood cell volume (MCV), mean amount of hemoglobin (MCH), red cell distribution width (RDW), platelet distribution width (PDW), mean platelet volume (MPV) values were compared. Neutrophil/lymphocyte, monocyte/lymphocyte, PLT/lymphocyte and MPV/PLT ratios were compared among the parameters obtained as a result of complete blood count.

Statistical Analysis

The data obtained from the samples were transferred to the computer environment *via* the Statistical Package Program (SPSS 21.0, IBM Corp., Armonk, NY, USA) and related analyzes were made for each variable. Student's *t*-test and Mann-Whitney U test were applied according to the distribution analysis of the obtained data, and the data were sorted and compared. In our study, the results of the groups were given as mean±standard deviation (Mean±SD). Comparisons were questioned, with a significance level of $p<0.05$.

Results

Comparison of biochemical parameters of varicocele and control group is shown in Table I. There was no statistical difference between the two groups in terms of mean age ($p=0.270$). There were statistically significant differences between both groups in terms of erythrocyte ($p=0.011$), MCV ($p=0.028$), RDW ($p=0.018$), and PDW ($p=0.004$), respectively. However, neutrophil/lymphocyte ratio (NLR), PLT/lymphocyte ratio (PLR) and MPV/PLT ratio (MPVPR) values were found to be statistically significantly higher in the varicocele group ($p=0.034$, $p=0.043$ and $p=0.045$, respectively). No statistically significant difference was found between other parameters and rates.

Discussion

As a result of our study, erythrocyte, PDW and RDW values were found to be considerably higher in patients with varicocele compared to the control group. The MCV value was found to

be low in patients with varicocele. Although the MPV value was higher in patients with varicocele, the results were not statistically significant. However, neutrophil/lymphocyte ratio (NLR), PLT/lymphocyte ratio (PLR) and MPV/PLT ratio (MPVPR) values were found to be statistically significantly higher in the varicocele group.

The effect of increased platelet activity was primarily investigated in vascular diseases^{18,19}. In addition, other studies^{20,21} have shown that high MPV is associated with familial Mediterranean fever, Behçet's disease and Alzheimer's Disease. In the study of Cüce et al²², MPV values were found to be significantly higher in patients with varicocele. Bozkurt et al¹⁴ reported that MPV values in the varicocele group were significantly higher than the control group¹⁴. Pyo and Cho²³ reported that MPV values of varicocele patients were significantly higher than healthy individuals. However, there was no significant difference in terms of PDW values²³. In the study of Polat et al²⁴, no difference was found between the control group and the varicocele group in terms of MPV and PDW values. But Coban et al¹³ reported that MPV decreased significantly after surgery. In the study of Aslan et al²⁵, it was found that the PDW value was higher in varicocele patients compared to the healthy group. In our study, however, PDW values were found to be significantly higher in the varicocele group, and although MPV values were numerically higher in the varicocele group, this

elevation was not statistically significant. On the other hand, we found that patients with varicocele had statistically significantly higher MPVPR values compared to the healthy group.

It has been reported^{26,27} in the literature that oxidative stress triggers vascular inflammation, which plays a key role in the atherosclerotic disease progression. Oxidative stress, which occurs directly and due to the cytokines releasing due to inflammation, detriments erythrocytes and leads to a decrease in erythrocyte survival, resulting in anemia which results itself in an increase in RDW^{28,29}. It has been shown³⁰ that RDW may be an indicator of mortality in cardiac diseases, cerebrovascular events, infections and peripheral arterial diseases. The proinflammatory cytokines of sepsis affect circulating erythrocyte survival, damage membranes, suppress maturation, and cause larger and newer reticulocytes to enter the circulation and increase RDW. In addition, high oxidative stress can reduce erythrocyte lifespan and increase the early release of large immature erythrocytes into the circulation. Another important aspect of RDW is its strong correlation with inflammatory parameters^{26,27}. It is positively correlated with disease severity in chronic inflammatory diseases such as systemic sclerosis, Systemic Lupus Erythomatosus and Sjögren. The reason for the change in these diseases is that cytokines that occur in inflammation disrupt erythrocyte maturation and affect RDW values^{8-10,31}. Malandrino

Table I. Comparison of age and blood parameters between groups.

	Control (n = 70) mean ± SS	Varicocele (n = 112) mean ± SS	p
Age	22.05±1.78	23.26±2.95	0.270
WBC (mm ³ /μL)	6.75±1.89	7.04±1.24	0.587
HGB (g/dl)	15.24±1.10	15.44±1.40	0.475
HCT (%)	44.64±2.87	45.07±3.04	0.585
PLT (mm ³ /μL)	244.22±57.16	243.92±44.43	0.876
Erythrocyte (mm ⁶ /μL)	5.07±0.36	5.24±0.23	0.011*
Neutrophil (mm ³ /μL)	4.14±1.40	4.28±1.37	0.477
Lymphocyte (mm ³ /μL)	2.27±1.70	2.07±0.72	0.064
Monocyte (mm ³ /μL)	0.49±0.65	0.40±0.21	0.462
MCV (fL)	85.14±5.64	83.24±5.2	0.028*
MCH (pg)	30.35±1.92	29.22±2.04	0.142
RDW (%)	14.01±1.10	14.97±1.20	0.018*
PDW (fL)	25.46±14.10	39.12±15.32	0.004***
MPV (fL)	9.25±1.07	10.52±9.58	0.612
Neutrophil/Lymphocyte	1.82±0.37	2.17±0.45	0.034*
Monocyte/Lymphocyte	0.19±0.36	0.16±0.15	0.201
PLT/Lymphocyte	118.25±29.39	128.97±22.32	0.043*
MPV/PLT	0.04±0.01	0.05±0.02	0.045*

WBC: White blood cell. HGB: Hemoglobin. HCT: Hematocrit. MCV: Mean erythrocyte volume. PLT: Platelet. RDW: Erythrocyte distribution width. PDW: Platelet distribution width. MPV: Mean platelet volume.

et al³¹ reported the RDW as a marker of vascular complications in the adult diabetic patients. In the study of Aslan and Çirakoğlu²⁵, it was found that the RDW value was higher in varicocele patients compared to the healthy group. According to these studies, our study shows that RDW can be considered as a marker of venous disease. In our study, we found that patients with varicocele had statistically significantly higher RDW values compared to the healthy group.

Conditions that cause inflammation in the male reproductive system include ejaculatory duct obstructions, infections, varicocele and drug treatments. The main molecules that regulate the inflammatory response are leukocytes and neutrophils. NLR and PLR have been used frequently as systemic inflammation markers in recent years³². Aykan et al³³ investigated the relationship between seminal parameters and inflammation markers in their study; they also reported that there was no significant difference in terms of these markers in men with normal and abnormal semen analysis. In the same study, no correlation was found between NLR and PLR and semen parameters, and it has been reported that these markers cannot yet be recommended for the evaluation of male infertility³³. In the study of Küçükdurmaz et al³⁴ on infertility, similar to the study of Aykan et al³³, no relationship was found between PLR, NLR values and sperm parameters, and these values did not differ significantly between the groups³⁴. On the other hand, in another study, it was revealed that NLR value is an independent predictive factor for the probability of finding sperm in patients who underwent surgery for azoospermia, while PLR values could not predict the probability of finding sperm³⁵. Ates et al³⁶, in their study to reveal the role of inflammation in the pathophysiology of varicocele-induced infertility, showed that the NLR value in the group with no increase in sperm parameters after varicocelectomy was statistically significantly higher than the group with an increase³⁶. According to these studies, our study shows that NLR, PLR, and MPVPR can be considered as a marker of venous disease. In our study, we found that patients with varicocele had statistically significantly higher NLR, PLR, and MPVPR values compared to the healthy group.

Limitations

Potential limitations of this study are that it is a retrospective study and the short follow-up period. Despite the relatively high number of patients, studies with larger patients are needed on this subject.

Conclusions

Our research shows that erythrocyte, RDW, and PDW values are higher in patients with varicocele. However, NLR, PLR and MPVPR values as inflammatory markers were found to be high in patients with varicocele. According to our results, it is possible to recommend using the inflammatory parameters as markers to screen for varicocele. We think that inflammatory markers, platelet and erythrocyte activation could be a crucial role in the pathophysiological basis of varicocele, but this study is cross-sectional and cannot confirm causality. Therefore, large and large-scale prospective studies are needed to confirm this relationship.

Conflict of Interest

The Author declares that he has no conflict of interests.

Funding

None.

Ethics Approval

Our study was approved by the Ethics Committee of Viranşehir State Hospital and was conducted in accordance with the Helsinki Declaration. Informed consent was obtained from the patients before the study.

Authors' Contribution

Concept, Design, Supervision, Data Collection and/or Processing – I.Y.

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