

Varicocele: tissue stress in the etiology

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Background/aim: It is accepted that red blood cell distribution width (RDW) is a novel prognostic marker that reflects oxidative stress and chronic inflammation. In this study, we aimed to investigate the correlation between RDW and varicocele, the etiology of which has not fully elucidated yet. This study also aimed to study the mean platelet volume (MPV) values of the patient and control group.

Materials and methods: RDW and MPV levels were measured in 50 varicocele subjects (group 1) and 48 healthy controls (group 2) from January 2012 to January 2014, retrospectively.

Results: MPV levels were significantly higher in group 1 than in group 2 ($P < 0.001$). Although the relationship was weak, the patients with varicocele had significantly lower RDW values than did the controls ($r: 0.24$ $P = 0.026$). Positive correlations were not found between varicocele grade and MPV and RDW values ($P < 0.05$)

Conclusion: Higher MPV values are associated with increased odds of developing varicocele.

Key words: RDW, MPV, varicocele, infertility, BMI

1. Introduction

The most common type of male infertility is idiopathic infertility, with no identifiable cause, and the most common cause of male infertility is varicocele, whose etiology is unknown (1). According to a strong theory, varicocele is the result of structural factors of the testicular vein anatomy (1).

The coexistence of arterial and venous system pathologies has been exhibited in previous studies including varicosities of the coronary venous tree, leg veins, and pampiniform venous plexus (2–5). It may be suggested as a possible common etiology for vascular diseases. In recent years, there has been growing interest in the clinical implications of oxidants. Moreover, it has become increasingly clear that oxidative stress is involved in cardiovascular diseases (6). Reactive oxygen species are common byproducts of many oxidative biochemical and physiological processes. Although there is still no biochemical marker that allows simple direct measurement of oxidative stress in the blood, red blood cell distribution width (RDW) is an indirect marker that reflects oxidative stress (7).

Two occurrences are well explained in the medical literature: Higher RDW values are associated with the

incidence of both micro- and macrovascular complications in cardiovascular disease and used to predict mortality and morbidity (8,9). Higher mean platelet volume (MPV) values are dependent on the varicocele (10,11). The potential relationship between varicocele and other vascular system disorders led us to perform a study in which the relationship between varicocele and RDW and MPV as a chronic vascular risk indicator could be investigated. We conducted a case-control study to compare RDW and MPV values in varicocele patients.

2. Materials and methods

2.1. Study population and design

Ankara GATA Ethics Committee approved our retrospective study in its judgment of May 2014. Ninety-eight male patients were evaluated retrospectively. These patients were admitted to the radiology unit for scrotal color Doppler ultrasound (CDUS) with a varicocele prediagnosis between January 2012 and January 2014. Histories of inguinoscrotal surgery, systemic diseases, nutritional deficiencies (iron, folate, or vitamin B12), or medical therapy were determined as exclusion criteria. Demographic data (including age, lipid profiles, fasting

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blood glucose) were recorded. It was ensured that the patients had the same ethnic origin.

Patients with the clinical diagnosis of varicocele were referred from the urology outpatient clinic. A single urologist examined and determined the varicocele in all patients, and a single radiologist blinded to the patients' clinical grades of varicocele performed all CDUS examinations. All patients provided informed consent for the examination.

2.2. Color Doppler ultrasound examination

All patients underwent a CDUS examination performed using a 10 MHz transducer (G40, Siemens Healthcare, Mountain View, CA, USA).

First, CDUS was performed while patients were in the upright position. Then patients were re-examined in the supine position. All ultrasonographic studies were performed at rest and also during the Valsalva maneuver. Diameter of the testicular vein was measured at four sites including the inguinal canal and at the head, body, and tail of the epididymis.

2.3. Statistical analysis

Statistical analyses were performed using SPSS version 17 (SPSS Inc., Chicago, IL, USA). The variables were investigated using visuals (histograms, probability plots) and analytical methods (Kolmogorov–Smirnov/ Shapiro–Wilk test) to determine whether they were normally distributed or not. Descriptive analyses were presented using means and standard deviations for normally distributed variables. Medians and interquartile range (IQR) were used for nonnormally distributed

parameters. Student's t-test was used to compare normally distributed parameters. The Mann–Whitney U test was used to compare nonnormally distributed parameters. While investigating the relations between nonnormally distributed and/or ordinal variables, the correlation coefficients and their significance were calculated using the Spearman test. A 5% type-I error level was used to infer statistical significance.

3. Results

The study was conducted in a total of 98 males (mean age 21.69 years, SD ±1.8). Group 1 was composed of 50 varicocele subjects and group 2 contained 48 healthy control subjects whose CDUS examination results were within the normal range. Group 1's mean age was 21.8 years (range 20–28 years, SD ±1.95), whereas group 2's mean age was 21.5 years (range 19–27, SD ±1.69). There was no statistically significant difference between mean BMI values of the two groups (P = 0.843). The MPV values were significantly higher in group 1 than in group 2 (P = 0.010). The patients in group 1 with varicocele had significantly lower RDW values than the patients in group 2 (P = 0.027) (Table 1). There was no statistically significant correlation between the grade of varicoceles and MPV and RDW values (Table 2).

4. Discussion

The main finding of this study is that high MPV values are highly associated with varicocele and this finding supports the hypothesis that MPV can be predictive of

Table 1. The differences between baseline characteristics of the patient and control groups.

	Varicocele	Control	P =
Age (year)	21.8 ± 1.95 mean ± SD	21.5 ± 1.69	0.286**
BMI	23(4) median (IQR)	23 (4)	0.843*
MCV (fL)	84.9 ± 6.2 mean ± SD	84.8 ± 5.8	0.573*
RDW(%)	12.24 (1.5) median (IQR)	12.8 (0.8)	0.027*
MPV (fL)	8.6 ± 1.1 mean ± SD	8.0 ± 0.9	0.01**
PDW (fL)	11.5 ± 2.2 mean ± SD	11.6 ± 2.4	0.816**

*Mann–Whitney U test

**Student's t-test

BMI: body mass index

MCV: mean corpuscular volume

RDW: red cell distribution width

MPV: mean platelet volume

PDW: platelet distribution width

fL: fluid ounce

SD: standard deviation

IQR: interquartile range

Table 2. Spearman correlation between left and right testicular varicocele grades and RDW, MPV values.

	RDW (%)	MPV (fL)
Left testicle varicocele grade	r: -0.048 (P: 0.742)	r: 0.216 (P: 0.131)
Right testicle varicocele grade	r: 0.005 (P: 0.974)	r: 0.186 (P: 0.197)

fL: fluid ounce

RDW: red cell distribution width

MPV: mean platelet volume

the varicocele. This result is similar to previous studies (10,11). In the literature, a positive correlation is reported between MPV and varicocele grade (10). However, unlike the literature, we did not find any relationship between the grades of varicocele and MPV and RDW values. The inconsistency between the literature and our findings may be caused by the differences in the grading method of varicocele. We used the CDUS technique, which is more sensitive than physical examination in the evaluation of varicocele grade.

In the literature, it is reported that oxidative stress induces vascular inflammation, which plays a key role in the progression of atherosclerotic disease (12,13). Oxidative stress directly and through the release of cytokines in response to inflammation damages erythrocytes and leads to shortened erythrocyte survival, resulting anemia in increased RDW (14–16). There is still no clinical biomarker that allows simple and direct measurement of oxidative stress. RDW is an indirect marker that reflects oxidative stress and inflammation (7). Previous prospective studies have described a role of RDW as a predictive marker for cardiovascular disease morbidity and mortality in several populations (17–20). However, that meta-analysis was focused on elderly participants and did not investigate the specific relationship between RDW and vascular complications. Recently, Malandrino et al. (9) evaluated RDW as a marker of macrovascular and microvascular complications in a nationally representative sample of the adult diabetes population. They reported RDW may be an important clinical marker of vascular complications in diabetes and if RDW levels are high, dyslipidemia, hypertension, and albuminuria might be closely monitored even without symptoms of cardiovascular disease. In accordance with these reports, our study represents the first research on the role of RDW

as a marker of venous disease. We found that patients with varicocele had statistically significant lower RDW values than the healthy group although the level was weak.

However, there are some differences between the literature and our study in terms of investigated vascular pathology. The studies in the literature associated with RDW were about cardiovascular and systemic disease (21,22), and the patients with high RDW values are more likely to be older, show dyslipidemia, and have glucose intolerance. The affected vasculature in these elderly patients is particularly the arterial and microvascular systems. In our study, we examined the venous pampiniform plexus surrounding the testis as a point of differentiation from other studies. This was a nonsystemic pathophysiology localized to the testicular vein. Our experiment and control groups consisted of young men and none of the groups had high BMI values. Due to the lack of obese patients in our study, the BMI values in both groups were very close to each other, in contrast to the BMI values in the literature (23,24). These circumstances in our study group were possible appropriate preventive measures against oxidative stress in the body. Nevertheless, one of the limitations of our study was that we were not able to study antioxidant enzymes in the pampiniform plexus and the soft tissue of the paratesticular region. Furthermore, C reactive protein (CRP), which is one of the best-established biomarkers of chronic inflammation, was not explored in the study group.

In conclusion, today, the etiology of varicocele is still unknown and the strongest idea about the etiology may be the hemodynamic effects within the result of anatomical differences between the right and left testicular veins. Future studies should aim to determine how MPV values act and to study tissue oxidative stress in the pampiniform plexus in patients with varicocele in particular.

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