

## ORIGINAL RESEARCH

# The association between varicocele and epicardial fat thickness: a cross-sectional study

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**Abstract**

**Background:** Varicocele is a vascular disorder defined by anomalous dilatation of the pampiniform plexus and the presence of tortuous veins. Despite numerous hypotheses advanced to clarify its pathophysiology, the foundational processes involved remain incompletely understood. Epicardial adipose tissue, located between the myocardium and visceral epicardium, functions as a metabolically active endocrine organ and has been linked to systemic inflammation, endothelial dysfunction, oxidative stress, and atherosclerosis. We aimed to investigate the relationship between echocardiographically measured epicardial fat thickness (EFT) and the presence and severity of varicocele. **Methods:** In this cross-sectional study, 50 patients with high-grade varicocele, 50 patients with low-grade varicocele, and 100 group-matched healthy controls based on age and body mass index were enrolled. All participants underwent comprehensive urological evaluation, followed by referral to the cardiology department for cardiac assessment and echocardiographic measurement of EFT. **Results:** EFT was significantly higher in the varicocele group in comparison to controls ( $p = 0.048$ ), whereas other study variables did not exhibit significant difference across the groups ( $p \geq 0.05$ ). In the three-group comparison (controls, low-grade varicocele, and high-grade varicocele), EFT differed significantly only between controls and the high-grade varicocele group ( $p = 0.037$ ). Multivariable logistic regression analysis identified EFT as an independent predictor of high-grade varicocele (odds ratio: 1.853; 95% confidence interval: 1.155–2.973;  $p = 0.011$ ). **Conclusions:** These results suggest that EFT may be associated with progression rather than initiation of varicocele. A multidisciplinary approach integrating cardiovascular and urological perspectives may be beneficial for identifying factors that contribute to varicocele progression.

**Keywords**

Varicocele; Epicardial fat thickness; Oxidative stress

## La asociación entre el varicocele y el espesor de la grasa epicárdica: un estudio transversal

### Resumen

**Antecedentes:** El varicocele es un trastorno vascular caracterizado por la dilatación anormal del plexo pampiniforme y la presencia de venas tortuosas. Aunque se han propuesto varias teorías para explicar su fisiopatología, los mecanismos subyacentes siguen sin comprenderse completamente. El tejido adiposo epicárdico, situado entre el miocardio y el epicardio visceral, funciona como un órgano endocrino metabólicamente activo y se ha relacionado con la inflamación sistémica, la disfunción endotelial, el estrés oxidativo y la aterosclerosis. Nuestro objetivo fue investigar la relación entre el espesor de la grasa epicárdica (EGE), medido ecocardiográficamente, y la presencia y gravedad del varicocele. **Métodos:** En este estudio transversal, se reclutaron 50 pacientes con varicocele de grado alto, 50 pacientes con varicocele de grado bajo, y 100 controles sanos emparejados por grupo en función de la edad y el índice de masa corporal. Todos los participantes se sometieron a una evaluación urológica exhaustiva, seguida de una derivación al departamento de cardiología para la evaluación cardíaca y la medición ecocardiográfica del EGE. **Resultados:** El EGE fue significativamente mayor en el grupo de varicocele en comparación con los controles ( $p = 0.048$ ), mientras que otras variables del estudio no mostraron diferencias significativas entre los grupos ( $p \geq 0.05$ ). En la comparación de tres grupos (controles, varicocele de grado bajo y varicocele de grado alto), el EGE difirió significativamente solo entre los controles y el grupo de varicocele de grado alto ( $p = 0.037$ ). El análisis de regresión logística multivariable identificó el EGE como un predictor independiente de varicocele de grado alto (razón de probabilidades: 1.853; intervalo de confianza del 95%: 1.155–2.973;  $p = 0.011$ ). **Conclusiones:** Estos resultados sugieren que el EGE podría estar asociado con la progresión más que con la iniciación del varicocele. Un enfoque multidisciplinario que integre las perspectivas cardiovascular y urológica podría ser beneficioso para identificar los factores que contribuyen a la progresión del varicocele.

### Palabras Clave

Varicocele; Espesor de la grasa epicárdica; Estrés oxidativo

## 1. Introduction

Varicocele is a vascular disorder defined by anomalous dilatation of the pampiniform plexus and the presence of tortuous veins [1]. Clinically, its prevalence ranges from 5% to 20%, with 78–93% of cases occurring unilaterally on the left side [2, 3]. It may cause male infertility by impairing sperm quality and yet remains the most prevalent correctable cause of infertility [4]. Although several hypotheses have been proposed regarding its pathophysiology, the precise mechanism has not been fully elucidated, with mounting data suggesting that inflammatory responses contribute to the pathogenesis of varicocele, prompting investigations into shared mechanisms that might link it with systemic inflammatory conditions [3, 5, 6]. Although numerous investigations have successfully documented a significant correlation between varicocele and inflammatory markers [6, 7], evidence exploring its relationship with systemic diseases characterized by chronic inflammation remains limited. Among these, the association between varicocele and cardiovascular diseases, conditions in which inflammation contributes to both initiation and progression, has become a topic of growing scientific interest.

Epicardial adipose tissue, a component of the visceral fat, lies between myocardial and visceral epicardium, surrounds the heart and functions as an endocrine organ with high metabolic activity. It secretes numerous cytokines, chemokines, and proinflammatory mediators that influence metabolic regulation [8, 9]. The secretion of these bioactive molecules has been linked to systemic inflammation, endothelial dysfunction, oxidative stress, and atherosclerosis [10–12]. Furthermore, epicardial adipose tissue has been linked to adverse cardiovascular outcomes independent of

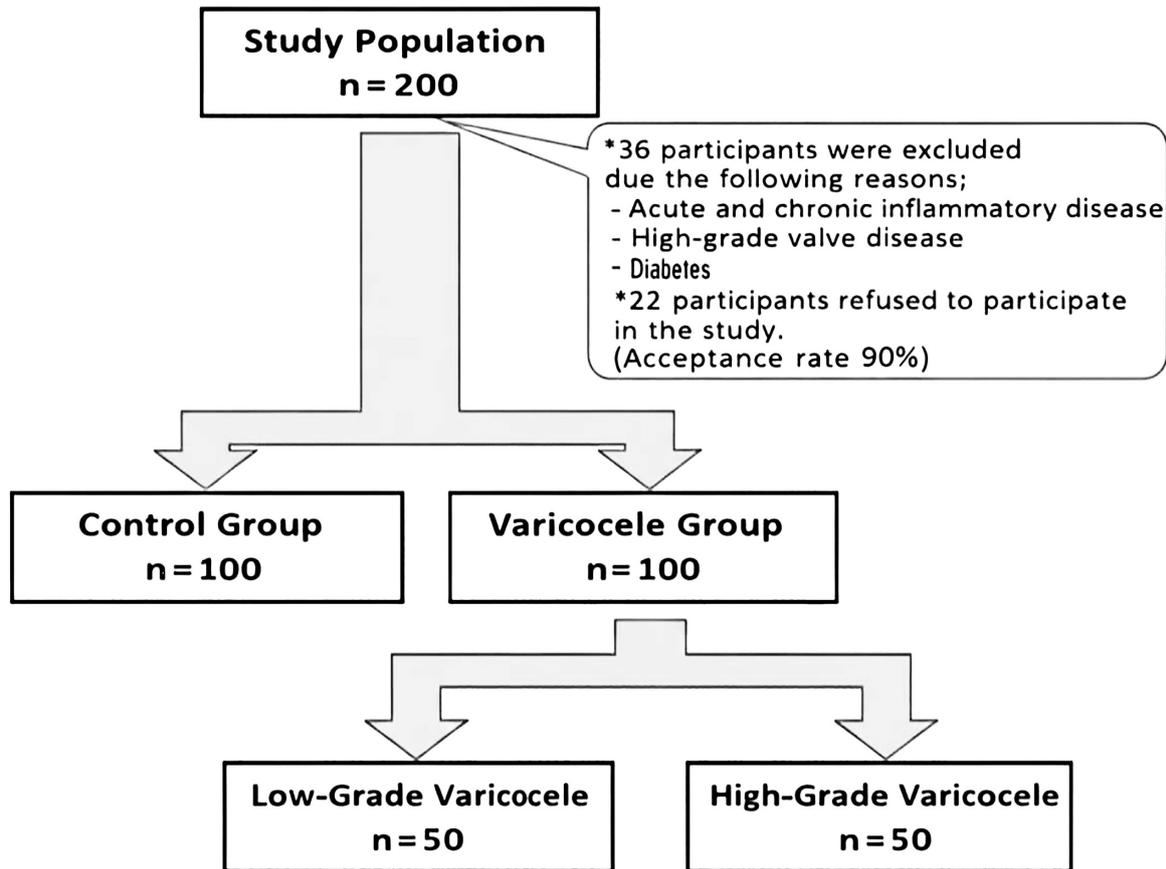
obesity [13]. The quantity of this tissue can be measured non-invasively by echocardiography, and echocardiographic measurement of epicardial fat thickness (EFT) is considered a simple, efficient, and reproducible method for assessing cardiovascular disease (CVD) risk [14, 15].

Although obesity is a well-recognized risk factor for numerous cardiovascular conditions, anthropometric parameters such as weight and body mass index (BMI) alone may be insufficient to accurately estimate cardiovascular risk [16, 17]. The visceral adiposity index (VAI) has yielded significant results in certain urological populations where conventional measures such as height, weight, and BMI have shown inconsistent associations [18].

Based on these considerations, the present study designed to examine the link between echocardiographic EFT, VAI, and varicocele.

## 2. Methods

This study employed a cross-sectional design. An a priori power analysis indicated that we needed a minimum sample size of 45 subjects in each group to ensure a statistical power of 90% with an alpha level of 0.05. Accordingly, 50 participants with low-grade varicocele, 50 participants with high-grade varicocele, and 100 healthy controls were enrolled between September 2020 and March 2021. An individual matching design was adopted, and for each patient with varicocele included in the study, one control matched by age and BMI was contemporaneously selected from healthy community volunteers without evidence of varicocele (Fig. 1). All participants were between 18 and 50 years of age. The study was conducted in



**FIGURE 1. Enrollment diagram for the study population.**

accordance with the principles of the Declaration of Helsinki and was approved by the Yozgat Bozok University Clinical Research Ethics Committee (2017-KAEK-189\_2019.07.24\_05). Written consents were taken from all subjects before they were included in the study. Exclusion criteria included defined CVD, diabetes mellitus, cardiac failure, high-grade valvular disease, hormonal disturbances, hypogonadism (testosterone  $\leq 350$  ng/dL), or any acute or chronic inflammatory condition.

All participants underwent a physical examination in a standing position while performing the Valsalva maneuver. Varicocele was graded according to the Dubin and Amelar classification as follows: grade 1, varicocele palpable only during the Valsalva maneuver; grade 2, varicocele palpable at rest but not visible; and grade 3, varicocele visible at rest [19]. Patients with grade 1 or 2 varicocele were assigned to the low-grade varicocele group, whereas those with grade 3 varicocele were assigned to the high-grade varicocele group. Color Doppler ultrasonography (USG) was performed in all participants to confirm the diagnosis. The controls were composed of subjects without evidence of varicocele on physical inspection, during the Valsalva maneuver, or on Doppler USG. The inter-observer reliability for varicocele evaluation showed a correlation coefficient of 0.90, indicating excellent agreement. All participants underwent measurement of 12-hour fasting serum glucose levels and a complete lipid panel. Comprehensive cardiac assessment was performed for every individual by the same cardiologist, who was unaware of the clinical and urological data.

## 2.1 Cardiac evaluation

All participants underwent cardiac evaluation in the cardiology outpatient clinic. Following a comprehensive physical examination, transthoracic echocardiograms were obtained with an Affiniti 50G ultrasound system (Philips, Amsterdam, The Netherlands) in accordance with the guidelines of the American Society of Echocardiography [20]. Imaging was conducted with a broadband transducer and simultaneous electrocardiographic monitoring while the participants were positioned in the left lateral decubitus position. Epicardial fat was defined as the echo-free space between the outer myocardial wall and the visceral pericardium. EFT was measured perpendicularly on the free wall of the right ventricle at end-diastole and end-systole across three consecutive cardiac cycles in both parasternal long-axis and short-axis views. The mean of all measurements obtained from the three cardiac cycles was used for statistical analysis [8]. All echocardiographic evaluations were performed by the same cardiologist, who was blinded to the participants' clinical and demographic information. The intraobserver reliability for echocardiographic measurements was excellent, with a correlation coefficient of 0.96.

## 2.2 Visceral adiposity index

BMI was calculated using the formula:  $\text{weight (kg)}/\text{height}^2$  ( $\text{m}^2$ ). Waist circumference, triglyceride, and high-density lipoprotein cholesterol (HDL-C) levels were recorded for all participants. VAI was calculated using the formula established for men [18] (Eqn. 1):

$$\text{VAI (men)} = \left[ \frac{\text{Waist circumference (cm)}}{39.68 + (1.88 \times \text{BMI})} \right] \times \left[ \frac{\text{Triglycerides}}{1.03} \right] \times \left[ \frac{1.31}{\text{HDL-C}} \right] \quad (1)$$

### 2.3 Statistical analyses

Statistical analyses were performed using SPSS Statistics version 18.0 (SPSS Inc., Chicago, IL, USA). The distribution of continuous variables was evaluated using the Kolmogorov-Smirnov test. The chi-square test was performed for comparison of categorical data across the groups. We utilized the independent samples *t*-test for comparing continuous data that adhered to a normal distribution. Conversely, data without a normal distribution were analyzed using the Mann-Whitney *U* test. For comparisons among the three groups, one-way analysis of variance (ANOVA) was applied, followed by Bonferroni post hoc analysis. Multivariable logistic regression was used to analyze independent variables which may be associated with varicocele. Statistical significance was set at a value of  $p < 0.05$ .

## 3. Results

Data from 100 patients with varicocele (mean age:  $29.9 \pm 5.6$  years; mean BMI:  $26.1 \pm 3.9$  kg/m<sup>2</sup>) and 100 age- and BMI-matched healthy controls (mean age:  $29.9 \pm 5.8$  years; mean BMI:  $26.5 \pm 4.1$  kg/m<sup>2</sup>) were analyzed. The two groups were statistically comparable with respect to age, BMI, VAI, smoking status, blood pressure, fasting serum glucose, serum creatinine, lipid profile, and left ventricular ejection fraction ( $p > 0.05$ ) (Table 1). EFT was significantly higher in patients with varicocele compared with the control group ( $5.19 \pm 0.85$  mm vs.  $4.95 \pm 0.78$  mm,  $p = 0.048$ ) (Fig. 2).

In the three-group comparison using one-way ANOVA with post hoc multiple comparisons, age, BMI, VAI, smoking status, blood pressure, fasting serum glucose, serum creatinine, lipid profile, and left ventricular ejection fraction values did not significantly differ among the groups ( $p > 0.05$ ). In the three-group analysis only EFT values differed significantly among groups, and the difference was significant between controls and the high-grade varicocele group ( $4.95 \pm 0.78$  mm vs.  $5.31 \pm 0.84$  mm,  $p = 0.037$ ) (Fig. 3). Multivariable logistic regression analysis identified EFT as a significant predictor of high-grade varicocele, with an odds ratio (OR) of 1.853 (95% confidence interval (CI): 1.155–2.973;  $p = 0.011$ ) (Table 2).

## 4. Discussion

The main finding of our study was the significantly higher EFT measurements in varicocele patients compared with the controls, whereas the groups were comparable concerning BMI and VAI. The subgroup analysis showed that this statistical difference was mainly due to the difference between the high-grade varicocele group and controls.

Varicocele is the most prevalent disease in men investigated due to male infertility [21]. The mechanisms involved in the formation of this pathology, which is quite common and related to the vascular wall structure, have not been fully clarified.

The relation between varicocele and inflammation, endothelial dysfunction, and oxidative stress, especially within infertile subjects, is a current topic of research. Different inflammatory pathways have been implicated in the initiation and/or progression of vascular diseases [22, 23]. The findings obtained from extensive studies on atherosclerosis have opened new perspectives in the development of treatment strategies [22]. Although not as thoroughly investigated as atherosclerosis, the association between varicocele and inflammation has also gained attention. Demirer *et al.* [24] demonstrated a significant association between varicocele and mean platelet volume, an established indicator of inflammation. Similarly, Nazari *et al.* [25] reported a relationship between varicocele and inflammatory mediators such as epithelial neutrophil-activating peptide-78 and interleukin-1 $\beta$ .

Varicocele is a condition primarily associated with vascular pathology, and endothelial dysfunction is considered one of the key mechanisms implicated in its etiopathogenesis [26]. Yildiz *et al.* [27] documented that individuals with varicocele exhibited elevated vasoconstrictor reactivity and reduced endothelial function. Moreover, they found that endothelial dysfunction was more pronounced in individuals with high-grade varicocele [27]. In a cross-sectional investigation including 128 participants, flow-mediated dilatation, an important indicator of endothelial function, was reported to be significantly lower in participants with varicocele, further supporting the relation between varicocele and endothelial dysfunction [28].

The presence of elevated levels of inflammatory cytokines in men with varicocele suggests that these mediators may contribute both to the etiopathogenesis of varicocele and to the development of varicocele-induced infertility [29, 30]. Cytokines play a central role in intracellular signaling and exhibit diverse biological activities. During cytokine-mediated inflammatory processes, oxidant and antioxidant mechanisms may fluctuate considerably. Although the immune response to inflammation aims to regulate these processes and prevent tissue injury, it can paradoxically cause additional cellular damage if dysregulated [31]. The association between oxidative stress resulting from these mechanisms and the occurrence of varicocele, as well as varicocele-induced infertility, has been extensively investigated. Studies have demonstrated increased levels of cytokines and reactive oxygen species, with a concomitant decrease in total antioxidant capacity, in infertile men with varicocele [32]. Furthermore, oxidative stress is reported to be correlated with the severity of varicocele, supporting discussions on the potential therapeutic role of antioxidant treatment in managing this condition [33–35].

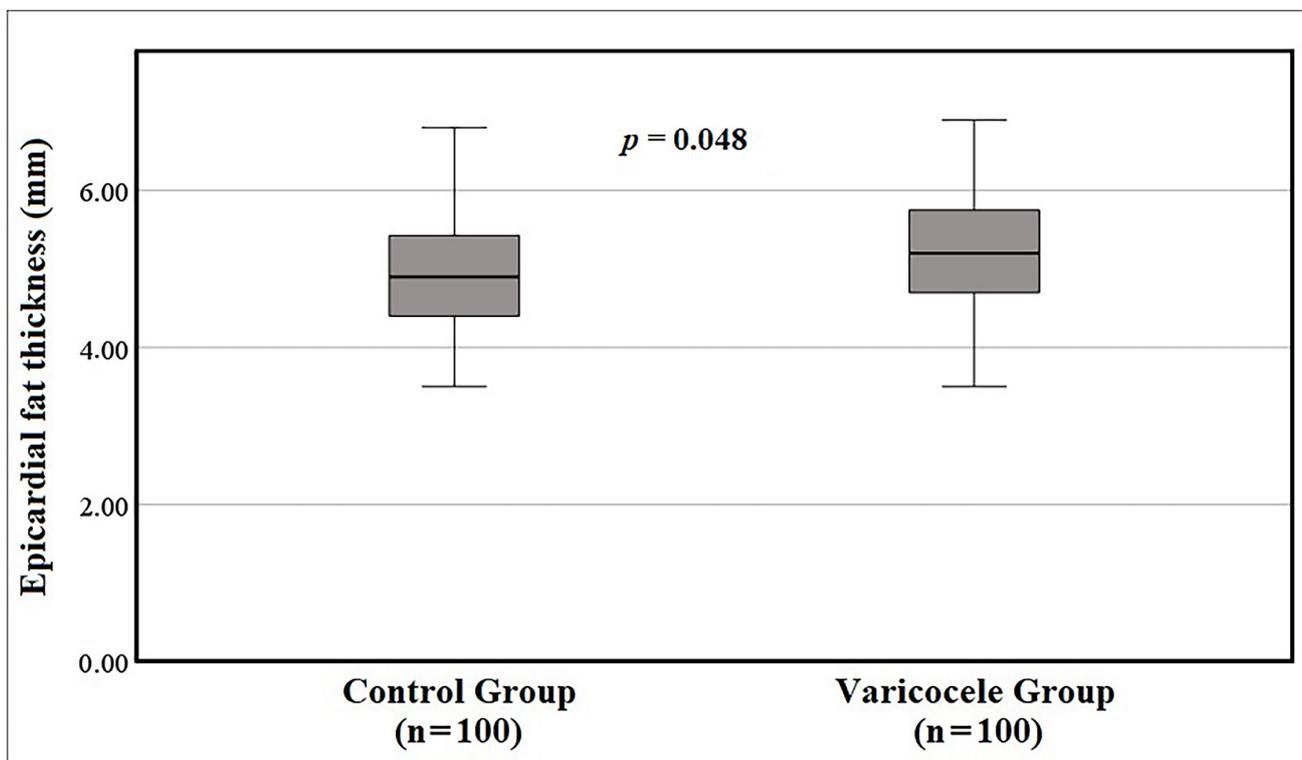
Given the various vascular alterations identified in patients with varicocele, an additional area of interest is the potential association between varicocele and other systemic or vascular diseases [36]. Studies addressing this topic have reported relationships between varicocele and several vascular system disorders [36, 37]; however, data regarding its association with cardiovascular diseases remain limited.

Epicardial adipose tissue, a fat deposit surrounding the heart with notable endocrine properties, is known to secrete metabolically active molecules and has been primarily associated with cardiovascular risk independent of obesity [38]. This tissue releases cytokines—also referred to as adipokines—such as

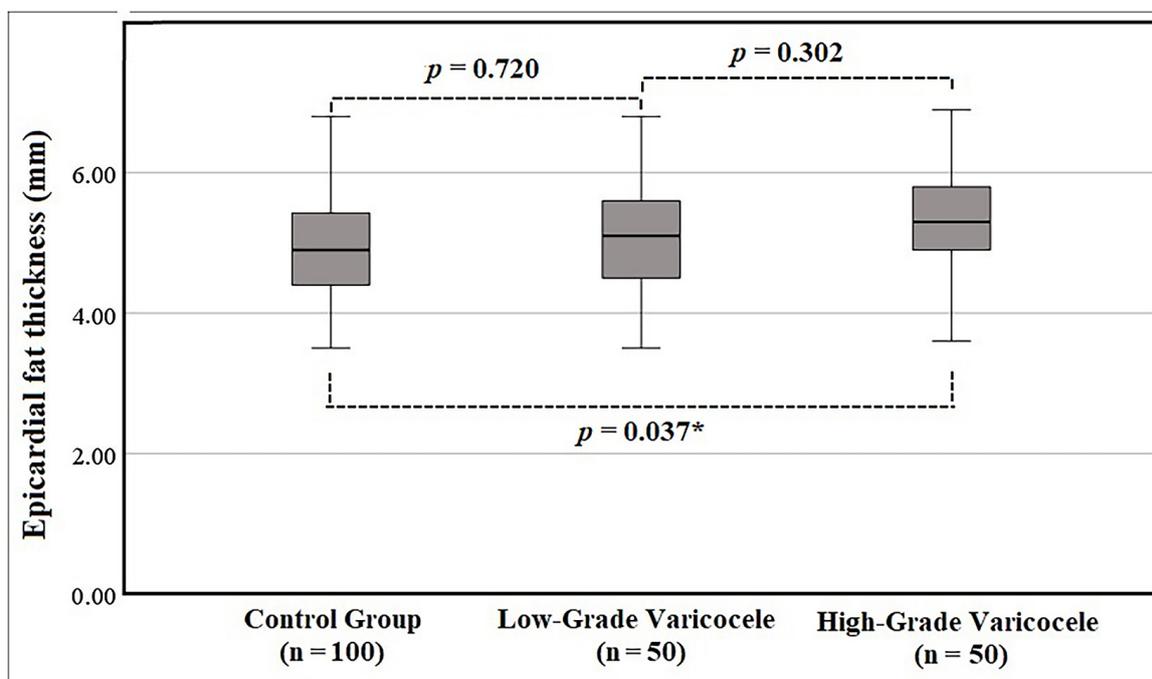
**TABLE 1. Demographic, clinical and laboratory features of the participants.**

	Control Group (n = 100)	Varicocele Group (n = 100)	<i>p</i>
Age (yr)	29.9 ± 5.8	29.9 ± 5.6	0.971
Height (cm)	175.4 ± 5.9	176.0 ± 6.1	0.516
Weight (kg)	81.6 ± 11.7	81.0 ± 12.9	0.724
Body Mass Index (kg/m <sup>2</sup> )	26.5 ± 4.1	26.1 ± 3.9	0.458
Waist (cm)	87.6 ± 9.6	86.8 ± 7.8	0.448
Smoking, n (%) <sup>¶</sup>	31 (31%)	37 (37%)	0.370
Systolic BP (mmHg) <sup>†</sup>	120 (120–140)	120 (100–145)	0.527
Diastolic BP (mmHg)	75.9 ± 7.4	76.5 ± 7.5	0.718
Serum Glucose (mg/dL)	92.3 ± 9.8	91.4 ± 10.1	0.391
Serum Creatinine (mg/dL)	0.86 ± 0.12	0.88 ± 0.24	0.971
Total Cholesterol (mg/dL)	172.1 ± 21.5	174.4 ± 29.9	0.521
Triglycerides (mg/dL) <sup>†</sup>	152 (52–238)	149 (59–227)	0.872
HDL-C (mg/dL)	42.8 ± 6.9	42.6 ± 9.8	0.890
LDL-C (mg/dL)	98.6 ± 20.1	98.3 ± 27.5	0.252
Ejection Fraction (%) <sup>†</sup>	65 (60–68)	65 (60–68)	0.968
VAI <sup>†</sup>	1.81 (0.47–14.98)	1.84 (0.38–8.79)	0.816
EFT (mm)	4.95 ± 0.78	5.19 ± 0.85	0.048*

Data are presented as mean ± SD and compared by independent samples *t*-test. <sup>†</sup>Data are presented as median (interquartile range) and compared by Mann-Whitney *U* test. <sup>¶</sup>Data are presented as absolute and relative frequencies and compared by Chi-square test. Statistical significance was set at a value of *p* < 0.05. \*indicates statistical significance. BP: blood pressure; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; VAI: visceral adiposity index; EFT: epicardial fat thickness.



**FIGURE 2. Comparison of epicardial fat thickness between the control (n = 100) and varicocele (n = 100) groups (*p* = 0.048).** Values are mean ± SD and compared by independent samples *t*-test. Statistical significance was set at a value of *p* < 0.05.



**FIGURE 3.** Comparison of epicardial fat thickness among the control ( $n = 100$ ), low-grade varicocele ( $n = 50$ ) and high-grade varicocele ( $n = 50$ ) groups. Values are mean  $\pm$  SD and the differences between the groups were tested using the ANOVA. *Post-hoc* analysis was performed with Bonferroni test. Statistical significance was set at a value of  $p < 0.05$ . \*indicates statistical significance.

**TABLE 2.** Multivariable logistic regression analysis to determine predictors of high-grade varicocele.

	Beta	Standard error	<i>p</i> -value	Odds ratio	95% CI for Odds ratio	
					Lower	Upper
EFT	0.617	0.241	0.011*	1.853	1.155	2.973
Age	-0.027	0.031	0.386	0.973	0.916	1.035
Body Mass Index	-0.067	0.050	0.179	0.935	0.849	1.031
Systolic BP	-0.008	0.017	0.636	0.992	0.960	1.026
Smoking	-0.304	0.383	0.427	0.738	0.348	1.562
Glucose	-0.004	0.017	0.809	0.996	0.962	1.031
LDL-C	0.001	0.008	0.850	1.001	0.986	1.017

EFT: epicardial fat thickness; BP: blood pressure; LDL-C: low-density lipoprotein cholesterol; CI: Confidence interval. \*indicates statistical significance.

tumor necrosis factor- $\alpha$ , leptin, visfatin, resistin, chemerin, interleukin-6, and interleukin-16, and was reported to be independently associated with CVD risk [39]. Through the secretion of these bioactive molecules, epicardial adipose tissue activates multiple biological pathways involved in the initiation and progression of vascular diseases, including oxidative stress, inflammation, and endothelial dysfunction, ultimately contributing to vascular remodeling [11]. Based on this evidence, echocardiographic EFT measurement may serve as an indirect parameter for evaluating the potential relationship between varicocele and non-obesity-related cardiovascular risk.

Current study compared cardiometabolically similar varicocele and control groups to minimize potential confounding factors. The varicocele group and controls were matched based on age and BMI and showed no significant difference in demographic and anthropometric measures, blood pressure, fasting glucose, or lipid profiles (Table 1). The VAI values

were also comparable between the two groups, further confirming metabolic similarity. Despite this, EFT measurements were significantly higher in the varicocele group in comparison to controls. To further clarify the relationship between EFT and varicocele severity, the varicocele group was subdivided into low-grade and high-grade categories. While EFT values were comparable between low-grade varicocele group and the controls, a significant difference was observed between high-grade varicocele group and the controls. Although the absolute difference in mean EFT between groups was relatively small, the high measurement precision and supporting logistic regression analysis confirm that this difference is statistically significant.

Based on the aforementioned results, increased EFT appears to be associated with high-grade varicocele, whereas this association is less evident in low-grade varicocele. The most widely accepted theory regarding the etiopathogenesis

of varicocele involves hemodynamic alterations resulting from anatomical variations in the testicular veins [19]. In our study, EFT values were comparable between the low-grade varicocele and control groups; however, EFT was significantly higher in the high-grade varicocele group in comparison to controls. This finding suggests that EFT-related inflammation, endothelial dysfunction, and oxidative stress may be linked to the progression and chronicity of varicocele rather than its initiation. In asymptomatic individuals, subclinical low-grade inflammation and oxidative stress, independent of other risk factors, may contribute to vascular disease progression. A prospective study in which participants underwent repeat imaging after 3–5 years demonstrated that increment of epicardial fat volume was correlated with progression of CVD in asymptomatic individuals with intermediate cardiovascular risk [40].

EFT provides information distinct from general adiposity indices. The significant difference observed in EFT, despite the absence of significant variation in other adiposity-related parameters, may be attributed to the unique biological characteristics of epicardial adipose tissue. Unlike other fat depots, it exhibits higher cytokine concentrations, greater expression of genes concerning oxidative stress, and elevated concentration of reactive oxygen species (ROS) [41, 42]. ROS can induce chronic inflammation, and sustained oxidative stress may activate inflammatory signaling pathways that contribute to vascular disease progression. These mechanisms are increasingly being explored in the context of varicocele-related infertility. Accordingly, cardiovascular evaluation in subjects presenting with varicocele or varicocele-related infertility is of clinical importance. Such evaluation may help identify risk factors that contribute to disease progression, particularly during the early stages of varicocele. Multidisciplinary assessment may further assist in addressing these risk factors and in managing other cardiovascular conditions that coexist with varicocele. Moreover, investigating the molecular mechanisms underlying varicocele progression through coordinated clinical and experimental research may pave the way for the development of new monitoring and therapeutic strategies aimed at preventing the progression of early-stage varicocele and reducing the risk of varicocele-related infertility.

This study has several limitations. First, it was cross-sectional in design and included a relatively small sample size. Second, strict exclusion criteria were applied for conditions that might influence EFT, potentially limiting generalizability. Third, data regarding varicocele laterality, fertility-related parameters, lifestyle factors, and inflammatory markers were not evaluated. The absence of this data restricts the ability to assess the full clinical relevance of the findings. Therefore, future large-scale prospective studies with long-term follow-up are warranted to validate and expand upon these results.

## 5. Conclusions

Although no significant difference in EFT was observed between the control group and patients with low-grade varicocele, EFT was significantly higher in patients with high-grade varicocele compared with controls. These findings suggest that increased EFT may be related to the progression

rather than the initiation of varicocele. A multidisciplinary approach incorporating cardiovascular assessment may help identify concomitant risk factors in patients with varicocele and facilitate the development of targeted strategies to prevent disease progression.

## AVAILABILITY OF DATA AND MATERIALS

The data is available on request from the corresponding author.

## AUTHOR CONTRIBUTIONS

YT, ÜÖ and ET—designed the research study; wrote the manuscript. YT and ÜÖ—performed the research. RY and MY—provided help and advice on methodology and interpretation. YT—executed the statistical analysis. All authors participated in editorial revision of the manuscript. All authors reviewed and confirmed the final manuscript.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Yozgat Bozok University Clinical Research Ethics Committee (2017-KAEK-189\_2019.07.24\_05). Written consents were taken from all subjects before they were included in the study.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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