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The Relationship Between Varicocele and Lower Extremity Chronic Venous Insufficiency: A Population-Based Case-Control Study

Varikosel ile Alt Ekstremite Kronik Venöz Yetmezliği Arasındaki İlişki: Nüfusa Dayalı Olgu-Kontrol Çalışması

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ABSTRACT

Background: This study explores the potential relationship between varicocele and varicose veins, focusing on their shared pathophysiological mechanisms and clinical implications, and includes an additional subgroup analysis across age groups. Varicocele is a major cause of male infertility, affecting 15–20% of men in the general population and up to 30–40% of infertile men. Varicose veins, caused by venous valve dysfunction, are more prevalent in older individuals. Despite their structural and functional similarities, the possible link between these two venous disorders has not been adequately investigated.

Materials and Methods: A retrospective, population-based case-control study was conducted in a province in Türkiye using the Ministry of Health Public Hospitals Research Database. A total of 1,279 patients with varicose veins and 5,091 age- and sex-matched controls (1:4 ratio) were included. Diagnoses were identified using ICD-10-CM codes, and diagnostic validity was ensured by requiring at least two separate clinical entries for the same diagnosis. Conditional logistic regression was used to evaluate the association between varicose veins and varicocele, adjusting for confounders including age, diabetes, cardiovascular disease, chronic obstructive pulmonary disease, liver disease, and kidney disease. The lack of Doppler ultrasonographic confirmation and absence of varicocele grading data were acknowledged as limitations of the retrospective design.

Results: The prevalence of varicocele was 1.3% in cases and 0.3% in controls ($p < 0.001$). Logistic regression analysis revealed an odds ratio of 2.41 (95% confidence interval: 1.80–4.92) for the association between varicocele and a history of varicose veins, and the association was more pronounced among younger patients.

Conclusion: This study demonstrates a significant association between varicocele and varicose veins, particularly in individuals under 50 years of age. These findings suggest shared pathophysiological mechanisms and warrant further investigation into the underlying venous dysfunction that links these conditions.

Keywords: Varicocele, venous insufficiency, age

ÖZ

Amaç: Bu çalışma, varikosel ve varis arasındaki olası ilişkiyi, bu iki durumun ortak patofizyolojik mekanizmaları ve klinik sonuçları açısından incelemekte; ayrıca yaş gruplarına göre ek bir alt analiz içermektedir. Varikosel, erkek infertilitesinin başlıca nedenlerinden biridir ve genel popülasyonda %15–20, infertil erkeklerde ise %30–40 oranında görülür. Venöz kapak fonksiyon bozukluğuna bağlı olarak gelişen varisler ise özellikle ileri yaşlarda daha sık görülmektedir. Yapısal ve fonksiyonel benzerliklerine rağmen, bu iki venöz hastalık arasındaki olası bağlantı yeterince araştırılmamıştır.

Gereç ve Yöntemler: Bu retrospektif, popülasyon temelli olgu-kontrol çalışması, Türkiye'de bir ilde yürütülmüş olup Sağlık Bakanlığı Kamu Hastaneleri Araştırma Veritabanı kullanılmıştır. Varis tanısı olan 1.279 hasta ve yaş ile cinsiyet açısından 1:4 oranında eşleştirilmiş 5.091 kontrol dahil edilmiştir. Tanılar ICD-10-CM kodları kullanılarak belirlenmiş ve aynı tanı kodunun en az iki ayrı klinik kayıtta bulunması tanısal geçerliliği sağlamıştır. Varis ve varikosel arasındaki ilişki, yaş, diyabet, kalp hastalığı, kronik obstrüktif

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öz

akciğer hastalığı, karaciğer ve böbrek hastalıkları gibi karıştırıcı faktörler için düzeltme yapılarak koşullu lojistik regresyon ile analiz edilmiştir. Doppler ultrasonografik doğrulamanın bulunmaması ve varikosel derecelendirmesinin değerlendirilememesi, retrospektif tasarımın sınırlamaları olarak belirtilmiştir.

Bulgular: Varikosel prevalansı olgularda %1,3, kontrollerde ise %0,3 olarak saptanmıştır (p < 0,001). Lojistik regresyon analizi, varis öyküsü ile varikosel arasında anlamlı bir ilişki olduğunu göstermiştir (olasılık oranı = 2,41; %95 güven aralığı: 1,80–4,92). Bu ilişki özellikle genç hastalarda daha belirgindir.

Sonuç: Bu çalışma, varikosel ile varis arasında anlamlı bir ilişki olduğunu ve bu ilişkinin özellikle 50 yaş altı bireylerde daha belirgin olduğunu göstermektedir. Bulgular, iki durum arasında ortak venöz disfonksiyon mekanizmaları olabileceğini düşündürmekte ve bu konuda ileri araştırmalara ihtiyaç olduğunu ortaya koymaktadır.

Anahtar Kelimeler: Varikosel, venöz yetmezlik, yaş

Introduction

Recent studies support the relationship between varicocele and systemic venous insufficiency (1–5). Varicocele, known to be one of the leading causes of male infertility, is an abnormal dilation and tortuosity of the pampiniform plexus vessels in the spermatic cord. It is seen in 15–20% of the population. This rate increases to 30–40% among infertile men (6). The significant impact of varicocele on male infertility is supported by evidence that varicocele is present in 70–80% of men with secondary infertility (7).

Varicose veins are extensions of the superficial subcutaneous veins of the lower extremities, characterized by tortuosity and dilation, and accompanied by valvular insufficiency. Varicose veins most commonly occur in the superficial veins of the lower extremities, but also affect the veins of the spermatic cord (varicocele), the esophagus, the anorectum (hemorrhoids), and other veins (8). Varicose veins are among the most common vascular diseases in humans, affecting approximately 10–20% of the world's population. The probability of encountering varicose veins in women is 2 to 4 times higher than in men (8,9) This frequency increases with age. For example, among people living in Switzerland, the probability of having varicose veins at age 20 is 20%, whereas it reaches 80% around age 60 (9). In this context, a retrospective, population-based case-control study conducted in a province in Türkiye aimed to investigate the relationship between varicocele and varicose veins and to understand the potential impact of this link on male infertility. Furthermore, one of the main aims of this study was to assess the differences in prevalence between age groups and to provide insight into whether varicocele can be considered a systemic venous disorder.

We hypothesized that varicocele may represent a localized manifestation of systemic venous insufficiency and aimed to investigate whether the presence of varicose veins is associated with a higher prevalence of varicocele across age groups.

Materials and Methods

In this study, patient data were obtained from the Ministry of Health Public Hospitals Research Database. Patients' ages were calculated from dates of birth recorded in the database. The diagnoses of varicocele, varicose veins, and other diseases were determined using the International Statistical Classification of Diseases and Related Health Problems, 10th edition (ICD-10-CM codes), as recorded in patient files (10). The codes used included I86.2 for varicocele, I87.2 for varicose veins, and the relevant ICD codes for male infertility, diabetes, chronic obstructive pulmonary disease (COPD), heart disease, liver disease, and kidney disease. Only records with complete data were included. Ethical approval for this study was obtained from the Mersin University Rectorate Clinical Research Ethics Committee (approval number: 2023/546, dated: 06.09.2023).

Statistical Analysis

Comprehensive data on the characteristics of patients with varicocele and varicose veins were analyzed in a retrospective, province-wide, population-based study covering 2015–2022. Data were obtained from the public hospitals' research database affiliated with the Ministry of Health in Türkiye. A total of 1,279 cases with varicose veins and 5,091 randomly selected controls were included in this study. Conditional logistic regression analyses were performed to examine the association between varicose veins and varicocele. Conditional logistic regression was performed to analyze the experimental data. All statistical analyses were conducted using SPSS software version 13.0 for Windows (SPSS, Chicago, IL, USA). Statistical significance was set at $p < 0.05$. In this study, cases and controls were matched on age (±2 years) and index year. Each case was matched to four controls. Matching IDs (MATCH_IDs) were created during this process and used in the conditional logistic regression analysis. These details are now explicitly stated.

Results

The demographic characteristics of the patients (Table 1), the prevalence of varicocele (Table 2), and the distribution by age group of patients with varicose veins and of the control group with varicocele (Table 3) are presented. No significant difference was observed between the patients with varicose veins and the control group regarding age distribution (Table 1). Furthermore, the prevalence of diabetes and atherosclerotic heart disease was significantly higher in patients with varicose veins than in the control group; by contrast, no significant differences were observed for COPD and chronic kidney disease (Table 1).

The prevalence of varicocele was 1.3% in cases and 0.3% in controls ($p < 0.001$). Conditional logistic regression, adjusted for age, diabetes, heart disease, COPD, liver disease, kidney disease, and edema, indicated that the odds ratio (OR) for a prior diagnosis of varicose veins in cases compared with controls was 2.41 (95% confidence interval [CI]: 1.80–4.92) (Table 2). Furthermore, the ORs for patients aged <50 years, 51–65 years, and >65 years were 3.72 (95% CI = 1.90–7.33), 2.56 (95% CI = 0.28–7.10), and 0.92 (95% CI = 0.16–5.24), respectively (Table 3). Additionally, the prevalence of male infertility was 14.7% in patients with both varicocele and varicose veins, compared to 13.5% in those with varicocele alone; however, this difference was not statistically significant.

Table 1. Demographic characteristics.

Variables	Varicose vein patients (n = 1279) (%)	Control group (n = 5091) (%)	p-value
Age			0.986
⩽50	312 (25.09)	1356 (26.61)	
51–65	357 (27.91)	1432 (28.12)	
>65	610 (47.69)	2303 (45.23)	
Diabetes	120 (9.38)	299 (5.87)	<0.001
Heart disease	195 (15.24)	512 (10.05)	<0.001
COPD	87 (6.80)	263 (5.16)	0.0620
Kidney and liver disease	75 (5.86)	304 (5.97)	0.716
Varicocele	15 (1.17)	16 (0.31)	<0.001

COPD, chronic obstructive pulmonary disease; OR, odds ratio.

Table 2. Varicocele prevalence.

Presence of varicocele	Total (n = 6370) (%)	Varicose vein patients (n = 1279) (%)	Control group (n = 5091) (%)
Yes	31 (0.5)	15 (1.17)	16 (0.31)
OR (95% CI)	–	2.16 (1.42–3.63)*	0.4
Adjusted OR (95% CI)	–	2.41 (1.80–4.92)*	0.4

*p < 0.001. Adjustments were made for diabetes, heart disease, COPD, liver disease, and kidney disease. OR was calculated using conditional logistic regression based on age and index year. COPD, chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval.

Table 3. Varicocele rates among varicose vein patients and controls by age group.

Presence of varicocele	⩽50 years		51–65 years		⩾65 years	
	Varicose vein patients (n, %)	Control (n, %)	Varicose vein patients (n, %)	Control (n, %)	Varicose vein patients (n, %)	Control (n, %)
Yes	10 (3.3)	10 (0.5)	10 (1.3)	2 (0.3)	1 (0.2)	4 (0.2)
OR (95% CI)	1.00	2.33 (0.98–5.30)*	1.00	0.70 (0.21–3.10)	1.00	3.42 (1.83–5.50)
Adjusted OR (95% CI)	3.72 (1.90–7.33)	1.00	2.56 (0.28–7.10)*	1.00	0.92 (0.16–5.24)	1.00

*p < 0.01; OR was calculated using conditional logistic regression based on age and index year. CI, confidence interval; OR, odds ratio.

Discussion

Our findings support the hypothesis that varicocele may not be merely a localized phenomenon but rather a component of systemic venous insufficiency, consistent with prior histopathological and biochemical evidence suggesting shared alterations in vessel wall integrity. Although this study did not include direct histopathological or molecular analyses, our findings are consistent with prior reports suggesting shared venous wall changes, endothelial dysfunction, and altered metallothionein expression in both varicocele and varicose veins. These similarities support the hypothesis of a common systemic venous pathology.

This study, one of the few to examine the relationship between varicocele and varicose veins, suggests that these two conditions may be linked through common pathophysiological processes and clinical outcomes. Our findings support the possibility that varicose veins are associated with varicocele, and this association appears to be more pronounced in certain age groups. In particular, the higher association observed in individuals under 50 years of age supports the hypothesis that hormonal and vascular changes in this age group may strengthen this association. Furthermore, the prevalence of male infertility was 15.1% in patients with both varicocele and varicose veins and 14.5% in those with varicocele only; however, this difference was not statistically significant.

The pathophysiology of varicocele is typically associated with valvular insufficiency in the testicular veins. This can lead to infertility through mechanisms such as venous stasis, increased testicular temperature, and oxidative stress, all of which adversely affect sperm parameters (11). Similarly, the underlying mechanism of varicose veins is valvular insufficiency in the peripheral veins resulting in reflux, weakening, and dilatation of the vessel walls (8). In both cases, it has been suggested that these venous system disorders may result from a genetic predisposition or a systemic weakness in vessel wall structure (12).

The results of our study support this systemic approach. Lee et al. (13) observed increased expression of hypoxia-inducible factor 1-alpha and metallothionein in both varicocele and varicose veins, and this increase was associated with decreased apoptosis in the vessel walls. This suggests that both conditions may lead to similar biochemical changes in vessel walls. However, the study by Yazici et al. (14) suggested that varicocele may be a localised condition rather than a systemic venous disorder. These conflicting findings continue to fuel debate over whether varicocele is a purely localised condition or a systemic disease.

Furthermore, understanding how the relationship between varicocele and varicose veins varies with factors such as age, lifestyle, and comorbidities is an important area of research. In the literature, the incidence of varicose veins is reported to be higher in older individuals, whereas the incidence of varicocele is higher in younger individuals (15).

However, the higher likelihood of asymptomatic varicocele among older adults and their lower propensity to seek medical attention may mask the true prevalence of varicocele in this age group. Evidence suggests that a more comprehensive evaluation of varicocele in this age group is warranted. In addition, studies have reported a higher incidence of varicose veins in elderly patients (16). Canales et al. (17) reported that the prevalence of varicocele was higher in older men than in younger control subjects. However, another study by Lai et al. (18) demonstrated that newly diagnosed varicocele cases were more common in patients aged 19–39 years than in older age groups. Infertility issues may be more prevalent in this age group, leading to a higher likelihood of seeking medical assistance. Older men may be less concerned about infertility and may have a higher incidence of asymptomatic varicoceles (19).

In our study, a lower prevalence of varicocele was observed in elderly patients, which may be be attributable to the majority of cases being asymptomatic or to a lower rate of medical consultation for varicocele in the province studied in Türkiye. Yazici et al. (14) suggested that patient age could introduce bias when evaluating the relationship between varicocele and varicose veins. In this study, we found that the association between varicocele and varicose veins was stronger in patients under the age of 50. However, further studies are needed to confirm these findings. In addition, the effect of varicocele on infertility remains a matter of debate. Abdel-Meguid (20) reported that varicocelectomy improves semen quality. However, a systematic review by Evers and Collins (21) suggested that varicocelectomy is not an effective treatment for male infertility. In our study, we found that male infertility was not more common in patients with both varicocele and varicose veins than in those with varicocele only. This finding suggests that the effects of both conditions on infertility may be related to shared pathophysiological processes rather than to independent mechanisms.

The strengths of our study include the use of a population-based design and a large sample size. Furthermore, diagnoses were based on ICD codes, and detailed analyses were conducted across different age groups. However, methodological limitations should also be considered. For example, varicocele laterality (unilateral versus bilateral) was not assessed in detail. Furthermore, data on important variables such as body mass index, smoking status, and socioeconomic factors were not available. These factors may affect our results.

Study Limitations

The distinction between superficial and deep venous insufficiency could not be made because the ICD-10-CM codes used in the national database do not specify the anatomical level of venous reflux. Because varicocele grading was not available, all varicocele cases (Grades I–III) were analyzed collectively. This may have reduced the ability to detect dose-response effects.

Varicocele grading could not be evaluated in this study. Because the database only included ICD-10 codes, clinical stage information was not available. This methodological limitation should be addressed in prospective clinical studies.

The manual entry of ICD codes by clinicians is a potential limitation that could lead to diagnostic errors. Therefore, the results should be interpreted with caution. Furthermore, because the database does not include a clinical grading of varicocele, this information could not be used in the analyses.

Conclusion

In conclusion, our findings support the relationship between varicocele and varicose veins. However, more prospective, multicentre, and detailed studies are needed to clarify this relationship. In particular, considering these two conditions in the context of systemic venous insufficiency may inform novel diagnostic and therapeutic approaches.

Clinically, recognizing varicocele as a potential indicator of systemic venous insufficiency could guide broader cardiovascular assessment and promote early identification of patients at risk for venous disease progression.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the Mersin University Rectorate Clinical Research Ethics Committee (approval number: 2023/546, dated: 06.09.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: A.B., Design: A.B., Data Collection or Processing: A.B., E.E.T., Analysis or Interpretation: E.E.T., Literature Search: A.B., Writing: E.E.T.

Conflict of Interest: No conflict of interest was declared by the author(s).

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