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Is There a Link Between Saphenofemoral Insufficiency and Varicocele: Imaging Study of Sub-Fertile Men

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Abstract

Background: Varicocele is an important cause of infertility in men. Some studies have suggested that because of the similar pathologic processes involved in chronic venous diseases and varicocele, saphenofemoral insufficiency is an example of chronic venous disease, which causes varicose veins in the lower extremity. It is thought that there may be a relation between saphenofemoral abnormality and the emergence of varicocele, but this relation is not backed by sufficient evidence.
Methods: In this prospective diagnostic study, a total of 50 patients suffering from varicocele and 50 control patients were included. Ultrasonography was performed to determine the emergence of saphenofemoral insufficiency (SFI).
Results: Mean age of patients in the varicocele group and the control group was 32.4 $\pm$ 8.44, and 34.9 $\pm$ 6.39, respectively. Out of 50 patients being included in the study with varicocele, 8 had left sided SFI and 9 had right sided SFI, while in the control group, 4 patients were diagnosed with SFI, 2 on each side. The difference between the two groups was statistically significant. There was no relation between the time from diagnosis of varicocele, side of varicocele and the existence of saphenofemoral insufficiency.
Conclusions: Saphenofemoral insufficiency was shown to be significantly related to varicocele, and can be a sign of probability of emergence or re-emergence of varicocele, and further can be used in clinical examination to guide clinicians in diagnosing varicocele.

Keywords: Infertility, Sonography, Varicocele

1. Background

Chronic venous disease (CVD) is amongst the relatively common chronic diseases which influences the quality of life of up to 77% of the elderly population and up to 10% of the individuals younger than 30 years (1-5). Two leading mechanisms which result in CVD are reflux and obstruction. There is a wide spectrum of clinical presentations in patients with CVD, ranging from a functional CVD with no significant signs and symptoms to varicose veins and ultimately venous ulceration at the most advanced levels (6, 7). The environmental and the physical predisposing factors of CVD are well-known, such as obesity, prolonged standing and pregnancy, which have been shown to cause dilation of veins, even in studies concerning in vivo samples (8, 9). Besides the environmental factors, some genetic factors, including mutations at Thrombomodulin, FOXC2, CADASIL and Notch3 genes have been known as possible predisposing factors for CVD (7, 9).

Varicose veins are a common symptomatic feature of CVD and it is demonstrated by various studies that the early diagnosis and treatment of this condition could elevate the quality of patient life and prevent the complications of advanced venous disease (5, 10). Although varicose veins could be found at any part of the body, patients mostly present with varicose veins at their lower extremity in which saphenofemoral insufficiency (SFI) is one of the common findings (8).

Varicocele is the state of abnormal dilatation and tortuosity of the pampiniform plexus in the scrotum. The prevalence of varicocele has been estimated to be approximately 15% amongst the male population (11-13). Even though varicocele is the most common etiology of the male population subfertility, approximately 20% of the patients with varicocele present with fertility problems (14,

15). The valvular incompetence of the veins draining blood from the pampiniform plexus gives rise to the reflux of the blood to the plexus and increased hydrostatic pressure around the testis (12, 16). A variety of mechanisms, including elevated temperature of the testis, reflux of the toxic renal metabolites, oxidative stress and inflammation, increased thickness of the testicular lamina propria, elevated levels of nitric oxide in venous blood and hypoxia of the testis have been suggested to explain the negative effect of varicocele on fertility (17-21). Like other vascular disease, color Doppler sonography could be helpful in the diagnosis of varicocele, but clinical examination is the gold standard (22).

Although varicocele is not categorized as a CVD, the pathophysiology of varicocele has common compartments with the pathophysiology of CVDs. Regarding the similarity in the pathophysiology, there may be a relationship between the occurrence of varicocele and varicose veins (23). Even though there are previous studies on the relationship between varicocele and varicose veins, no agreement exists in this regard. In this article, besides analyzing the association between varicocele and SFI, we will study the effect of age, varicocele recurrence, duration of varicocele and the anatomy of varicocele (bilateral, left-sided, and right-sided) on the existence of SFI.

2. Methods

2.1. Patients

The present study was registered in the regional ethics board of Tabriz University of Medical Sciences (Ethics code: 5/D/639993- date: 96.11.1). This prospective, cross-sectional study was performed in a tertiary medical educational center which was the referral center of north-western Iran. In this study, all patients who were referred to the radiology department between January 2018 and September 2018 for Doppler imaging with the chief complaint of subfertility with a diagnosis of varicocele were included. Inclusion criteria consisted of being 15 - 45 years old and a previous clinical diagnosis of varicocele, while exclusion criteria consisted of age less than 15 years or more than 45 years, or a secondary etiology for varicocele, an equal number of patients with no clinical signs or symptoms of varicocele or any radiological findings were included as a control group and were matched for age. All of these patients underwent Doppler imaging of the saphenofemoral junction. All patients filled questionnaires containing questions regarding demographic information, past varicocele history or history of recurrence of varicocele and history of previous treatments.

2.2. Ultra-sonography

Varicocele was defined as the existence of at least three veins within the pampiniform plexus with a diameter of over 3 mm and co-existing reflux in the Valsalva maneuver. Insufficiency of the saphenofemoral junction was defined as the existence of reflux for over 1 second in the great saphenous vein during the Valsalva maneuver.

2.3. Statistical Analysis

Statistical analysis was performed by Statistical Package for the Social Sciences (SPSS) (SPSS Inc., Chicago, IL). Results were reported as mean $\pm$ Standard deviation. Chi-squared was utilized to analyze the data.

2.4. Ethical Considerations

This study was in concordance with the Helsinki Declaration. All patients had signed written informed consent forms prior to inclusion in the study.

3. Results

3.1. Clinical and Demographic Findings

The mean age of patients with varicocele was 32.4 $\pm$ 8.44, and the mean age of the control group was 34.9 $\pm$ 6.39. There was no significant difference between the two groups (P = 0.098). Of the 50 patients with varicocele, 46 patients had left sided varicocele, while 4 had varicocele in both hemi-scrotums. Twenty-two patients had a history of varicocele surgery, while 28 did not. Mean duration of being diagnosed with varicocele was 6.84 $\pm$ 2.64 years.

3.2. Saphenofemoral Insufficiency

Out of 50 patients with varicocele, 9 patients had right sided SFI, while in the control group, only 2 patients had SFI. The difference between the two groups was significant (P = 0.025). Eight patients had left sided SFI in the case group and 2 had left sided SFI in the control group. The difference between the group was also significant (P = 0.046).

Further investigation in characteristics of the patients and their clinical history revealed that there were no significant relations between the age of patients, having one sided or two-sided varicocele, recurrence of varicocele and time from diagnosis of varicocele with the presence of SFI. Results are summarized in Table 1.

Table 1. Relation Between Sides of SFI and Characteristics of Varicoceles

	Mean Age, Mean ± SD	Recurrence		Side of Varicocele		Time since Varicocele Diagnosis		
		Yes	No	Both Sides	Single Side	Less than 5 Years	6 - 10 Years	More than 10 Years
Left SFI								
With	30.42 ± 12.13	1	0	2	6	3	3	2
Without	32.72 ± 7.83	14	7	2	40	14	25	3
P value	0.511	0.484		0.053		0.252		
Right SFI								
With	28.33 ± 10.75	2	1	1	8	5	4	0
Without	33.29 ± 7.72	13	6	3	38	12	24	5
P value	0.112	0.952		0.704		0.239		

4. Discussion

Infertility is a major health issue, which is attributed to both male and female factors. Based on guidelines for diagnosis of infertility, the male partner is the first in line to undergo diagnostic evaluation (24). Varicocele is one of the main causes associated with male infertility. Systemic reviews have shown that varicocele is associated with reduced sperm count, reduced sperm motility and abnormal morphology of sperms (25). Many conditions are thought to be related with varicocele, including chronic venous insufficiency. Studies have shown that individuals with varicocele have an increased formation of varicose veins, and vice versa (26). Qiu et al. studied 100 patients with lower extremity varicose veins and compared the incidence of varicocele with individuals with no varicose veins. They found that patients with varicose veins had a significant increase in the rate of appearance of varicocele. Interestingly, they found that there was also a relation between the maximum diameter of the spermatic vein and lower extremity varicose veins (23). Varicose veins are the result of chronic venous insufficiency, of which SFI is a main cause (27).

This is of great importance as chronic venous insufficiency could be diagnosed before varicocele has even been diagnosed clinically, and it could lead clinicians to diagnose varicocele in early stages (28).

Ultra-sonography is a routine method to stablish the diagnosis of varicocele, and is done beside clinical examination in chronic venous insufficiency. Some studies have suggested that there could be a relation between the formation of varicocele and SFI, but there is no agreement regarding this matter. Yazici et al. included 100 patients with varicocele in a cross-sectional study and matched them with 50 individuals with no history of varicocele. They found that in the group of patients with varicocele, 36 patients had evidence of SFI, while in the control group, 13 had evidence of SFI. There was no significant relation between the existence of SFI and varicocele (P = 0.32). The authors suggested that the attained evidence showed that varicocele may not be related to a systemic vascular disorder, and it could rather be an isolated finding (29).

Some scholars have suggested otherwise. Sallam et al. performed a case-control study in which 50 varicocele patients and 40 matched individuals were included. They found that out of all the patients in the case group, 25 had evidence of SFI, while only 11 patients had evidence of SFI in the control group. The difference between the two groups was of statistical significance (P = 0.02). More so, they suggested that there was an even greater relation between recurrent varicocele and SFI, as of 10 patients with recurrent varicocele, all had SFI (30). This is of clinical importance, as recurrent varicocele may be underdiagnosed in couples suffering from infertility, and accurate diagnosis of any kind of systemic vascular insufficiency should lead clinicians to consider recurrent varicocele as a possible cause of continued infertility (31).

Ciaccio et al. studied the existence of SFI in 42 patients suffering from varicocele. They found that of all the patients, 36 (85.7%) had evidence of bilateral or unilateral SFI, and 6 (14.3%) did not have evidence of insufficiency. The authors did suggest that a relation existed between CVI and varicocele, but they did suggest that it the temporal relation between venous insufficiency and the development of varicocele should be studied more rigorously (32).

Interestingly, chronic venous insufficiency could also be associated with fertility problems in women. Early observational studies have found that the venous conditions of the ovaries could be associated with premature ovarian failure, and reduced fertility in young ages (33). Interestingly, the venous insufficiency of the ovaries is related to lower limb venous insufficiency (34). It seems that more attention should be given to venous conditions in infertile couples, and clinical examination of the veins could be in-

corporated into guidelines of infertility workup.

Our study showed that there may be a significant link between SFI and varicocele, but more studies, especially large scale, multi-center ones are needed to make more general considerations. Importantly, technical limitations of ultra-sound imaging may limit the extent to which the results could be generalized (35).

4.1. Conclusion

The results of the present study show that there is a significant relation between the emergence of SFI and varicocele. No significant relation was found between duration of suffering from varicocele, anatomic location and mean age of patients with SFI.

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Footnotes

Authors' Contribution: Sina Farhadi: study conception, data acquisition, statistical analysis; Javad Jalili: study conception, patient selection, systemic review of literature; Abolhassan Shakeri Bavil Olyaei: study conception, overall supervision, data acquisition; Mohammad Mirza-Aghazadeh-Attari: manuscript preparation, final edit, systemic search of literature, the final revision; Amin Arasteh: manuscript preparation, final edit, systemic search of literature; Armin Zarrintan: study conception, interpretation of imaging findings, final edit and final revision.

Conflict of Interests: The authors declare no conflict of interest.

Ethical Approval: This study was approved by the Local Ethics Board of Tabriz University of Medical Sciences. The study was in compliance to the Helsinki Declaration.

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Informed Consent: All of the patients being included have signed written informed consent notes.

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