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Shear Wave Elastography of the Contralateral Apparently Normal Testis in Patients with Unilateral Varicocele and Abnormal Semen Parameters

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ABSTRACT

Background: Shear wave elastography (SWE) is extensively used in testicular pathology evaluation. Varicocele subfertility complex associated with testicular fibrosis. Unilateral varicocele is not uncommon association in male infertility. The aim of the present study is answering the question, why unilateral varicocele are fertile while others are not, despite contralateral apparently normal testis?

Patients and methods: A case control study was carried out on 48 patients diagnosed with unilateral varicocele and abnormal spermogram. Patients were collected from our urology outpatient clinics of Zagazig University Hospitals, in the period between March and December 2019. A total 10 volunteers with unilateral varicocele and normal semen parameters participate to know baseline SWE figures.

Results: In the case group, the mean age was 33.83 (SD 5) years. Mean sperm count, motility and normal forms among the studied patients was 6.76 (SD 2.4 million/ml), 17.656 (SD 3.35) and 7.01 (SD 1.76) %, respectively with a negative correlation with contralateral testicular stiffness. Mean value of the apparently normal contralateral testicular stiffness was significantly higher than in control group as their mean results were 3.63 (SD 0.79) and 1.43 (SD 0.25) kpasc, respectively. During our cases SWE mapping, ipsilateral testis stiffness SWE mean value was 4.81 (SD 1.03) kpasc and insignificantly higher than control.

Conclusion: SWE data of normally apparent contralateral testis of unilateral varicocele patients with abnormal semen parameters could reveal stiffer parenchyma that may reflect the presence of a harmful insult to the testis. Thus, it could add a warning sign for surgeon to interfere in these unilateral cases, even with euspermic pattern and varicosities.

Keywords: Shear wave elastography, Varicocele, Abnormal semen, Ultrasound, case control study.

INTRODUCTION

Varicocele is a dilated and tortuous veins of the scrotal pampiniform plexus. It presents in approximately 15% of the whole male population. It reaches up to 39% and 81% of infertile men presenting with primary and secondary infertility respectively [(1)].

Bilateral Varicocele is diagnosed commonly in men seeking fertility with decline in semen quality. However varicocele can present unilaterally in those patients [(2)]. Unilateral varicocele subfertility complex occurs in the left side (17.6%), or right side (1.5%) [(3)].

Varicocele has notorious pathophysiologic effect on testicular parenchyma with its seminiferous tubules. This could be related to hemodynamic insults and their effect on increased intra-testicular pressure or hypo-perfusion and hypoxia**.** There are other factors palmed in varicocele pathologic and hypo-trophic changes like disturbed countercurrent multiplier thermal regulator, gonad toxic metabolite reflux, anti-sperm antibody formation and or oxidative stress [(4,5)]. Previous noxious changes are associated with histopathological interstitial tissue edema and fibrosis. Collagen fibril depositions are noted in both sides of extracellular space of seminiferous tubules basement membrane extracellular space of varicocele patients [(6-8)].

Shear wave elastography (SWE) ultrasound is used to estimate tissue stiffness through delivery of a high frequency pulse into the tissue. That will create energy inside the tissue. Then it followed by a usual B mode pulse that measure the velocity of the ultrasound waves spread across the stimulated tissue within the region of interest. A more stiff tissue will resist the high frequency ultrasound wave (shear wave) and consequently show less resistance and adsorption to the spread of next ultrasound waves across and shows higher values of stiffness index, and vice versa regarding softer tissues [(9)].

SWE ultrasound applications have enabled the assessment of new aspects in the structural and functional analysis of testicular tissue by detecting tissue elasticity [(9,10)]. SWE has been applied to differentiate testicular lesions nature [(11)].

Although spermogram is the initial gold slandered method in evaluation of spermatogenic function in varicocele-infertility complex, SWE can be used to assess testicular tissue stiffness both qualitatively and quantitatively. This supports the usefulness of the technique for evaluating that aspect various aspect [(12)].

Despite the presence of contralateral apparently normal testis in unilateral varicocele patients, but their spermogram profile is not uniform and a considerable percent of these cases need intervention for subfertility [(13,14)]. Our primary end point is to investigate SWE (fibrosis) of contralateral testis in unilateral varicocele with semen parameter abnormalities. Our secondary end point was mapping of both testis using SWE. We aimed to early detect testicular insult of contralateral apparently normal testis that could be considered as

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added information pushing urologist to interfere even with euspermogram pattern.

PATIENTS AND METHODS

A case control study was carried out on 48 patients diagnosed with unilateral varicocele and abnormal spermogram. Patients were collected from our urology outpatient clinics of Zagazig University Hospitals, in the period between March and December 2019. A total 10 volunteers with unilateral varicocele and normal semen parameters participate to know baseline SWE figures.

All patients and volunteers were informed and consented about their medical condition and the study details. Patients who refused to participate were excluded from our study.

Included cases were those adult patients (above 18 years old) with clinical and radiological unilateral varicocele with abnormal semen analysis according to WHO 2010 criteria.

We excluded cases with previous scrotal or testicular surgeries, chemotherapy or radiotherapy, undescended testis, chromosomal abnormalities as Klinefelter's, syndrome, hormonal abnormalities, evidence of seminal vesicle obstruction and history of chronic drug users or abusers e.g. cocaine and opioids or any abnormal or radiological data.

History and clinical examinations include especially epididymis, vas deference, testes (size, firmness, or hydrocele) and varicocele degree.

Semen parameters were assessed before SWE was done. Hormonal profile was requested when indicated.

Scrotal ultrasound with power Doppler ultrasound was done for all patients to diagnose unilateral varicocele stratifying its grade, estimate testicular size and detect any associated scrotal abnormalities.

Testicular elastography was performed by the same radiologist using a linear probe type 5-12 MHZ (Philips IU 22, Serial number BZE802). The process of SWE calculation was done at 3 different areas (upper, middle and lower) of ipsilateral and contralateral normally apparent testis and the mean value of each side was estimated.

Ethical consent:

An approval of the study was obtained from Zagazig University Academic and Ethical Committee (ZU-IRB.#5054-16/12/2018). Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The collected data groups of normally distributed variables (parametric data). P value $\leq$0.05 was considered significant.

RESULTS

Our study included 48 cases and 10 control volunteers with a mean age 33.83 (SD 5) years and 35.3 (SD 4.52) years, respectively. Age was of statistically non-significant difference between the case and control cases.

The case group patients had unilateral varicocele mainly on left side (79.2%) with grade II (47.9%) and grade III (52.1%). There was statistically significant difference between cases and volunteers regarding sperm count and motility, as mean sperm count among the patients was 6.76 (SD 1.403) million/ml and 23.3 (SD 2.87) million /ml in volunteers while mean sperm motility among the patients was 17.66 (SD 3.35) and 46.3 (SD 3.56) % in volunteers. Mean normal sperm forms among the studied patients were lower than volunteers but statistically non-significant (**Table 1**).

Table (1): Comparison between the studied groups regarding demographic data and sperm analysis.

Parameters	Groups		Test	
	Case group N (48)	Control group N (10)	T	P-value
Age: Mean ± SD Range IQR	 33.833 ± 5.00 22 – 40 6.75	 35.3 ± 4.523 25 – 40 6.25	-0.865	0.396
Sperm count: Mean ± SD Range IQR	 6.763 ± 1.403 3.9 – 12.2 4.56	 19.3 ± 2.869 15 – 24 9	-14.25	<0.001**
Sperm motility (%): Mean ± SD Range IQR	 17.656 ± 3.354 12.1 – 24 5.32	 46.3 ± 3.561 40 – 52 6	-24.23	<0.001**
Normal form: Mean ± SD Range IQR	 7.01 ± 1.61 4 – 9.8 3.15	 10.97 ± 0.96 11.49-6.79 3.5	-9.894	<0.001**

There was non-significant difference in the Ipsilateral testes elastography between cases and controls, however there was statistically significant difference regarding testicular elastography of the contralateral normally apparent testes in cases and controls, as the mean testicular elastography valus were 3.63 (SD 0.79) Kpasc and1.43 (SD 0.25) kpasc, respectively (**Table 2**).

Table (2): Contralateral testicular elastography.

Parameters	Group		Test	
	Case group N=48	Control group N=10	T	P-value
Elastography: Mean ± SD Range	3.631 ± 0.79 (2.6 – 5.21)	1.43 ± 0.25 (1.1 – 1.9)	18.199	<0.001**

Shear wave elastography mapping, ipsilateral testis stiffness shear wave elastography mean value was 4.81 (SD 1.03) kpasc and insignificantly higher than control (**Table 3**).

Table (3): Ipsilateral (varicocele side) testicular elastography.

Elastography (Ipsilateral)	Case group N=48	Control group N=10	T	P-value
Mean ± SD	4.81 ± 1.03	4.52 ± 1.11	0.743	0.461
Range	4.01 – 6.6	3.89 – 6.2		

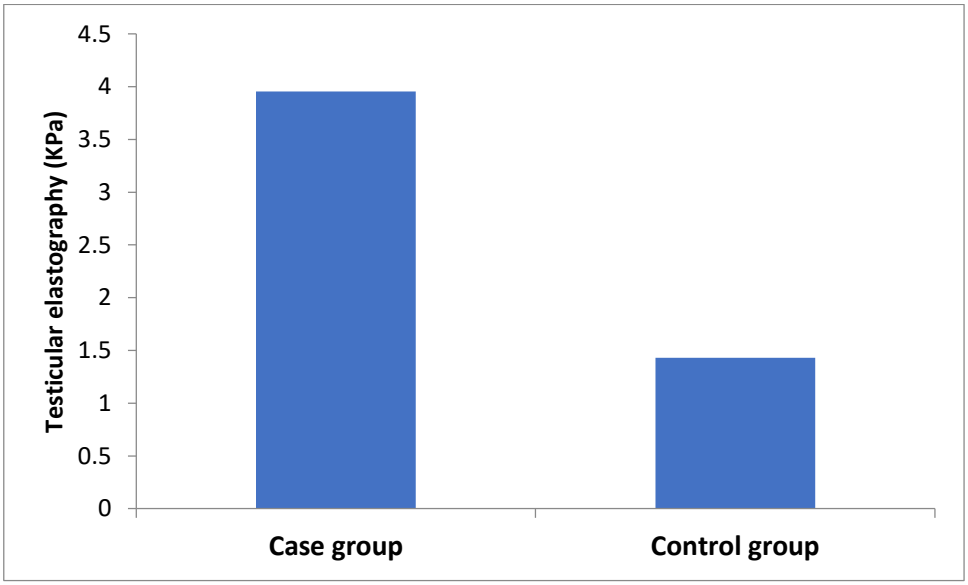

Figure (1): Simple bar chart showing comparison between the studied groups regarding contralateral testicular elastography.

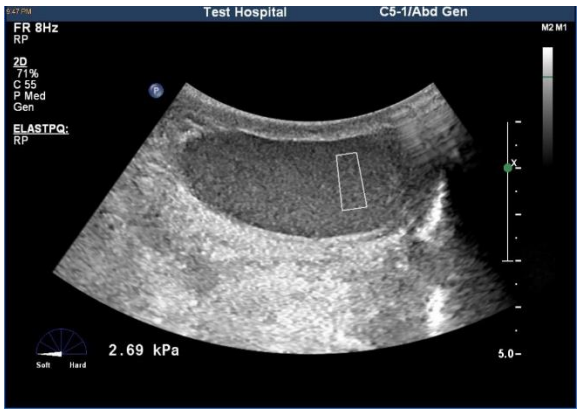

Figure (2): Shear wave elastography of a testis with estimated stiffness of 2.69 kPa.

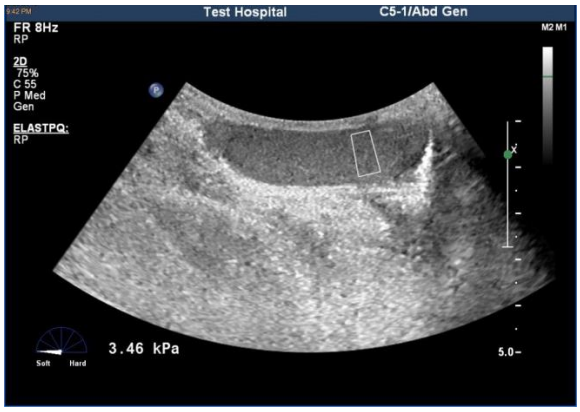

Figure (3): Shear wave elastography of a testis with estimated stiffness of 3.46 kPa.

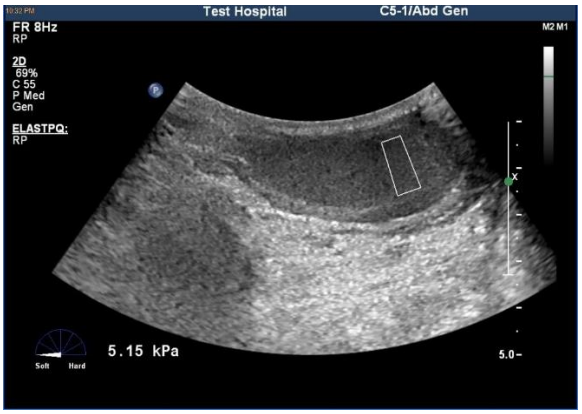

Figure (4): Shear wave elastography of a testis with estimated stiffness of 5.15 kPa.

There was negative correlation between testicular elastography and sperm count, motility or normal forms it was significant in both count and motility but insignificant with normal forms. Our patient age showed non-significant positive correlation with testicular elastography values (**Table 4**).

Table (4): Correlation between testicular elastography values and both demographic and semen analysis data among the studied patient.

Variables	Testicular elastography values	
	R	P
Age (years)	-0.004	0.978
Count (million/ml)	-0.531	0.003*
Motility	-0.513	0.004*
Normal form	-0.155	0.294

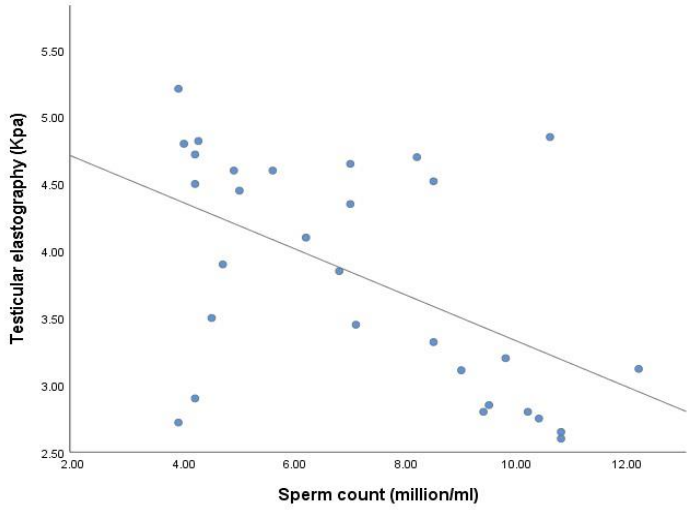

Figure (5): Scatter dot graph showing significant negative correlation between testicular.

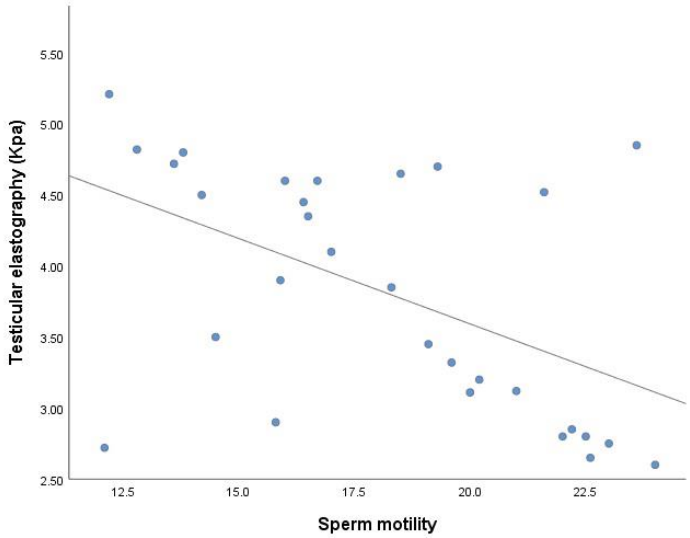

Figure (6): Scatter dot graph showing significant negative correlation between testicular elastography values and sperm motility(r=-0.513, p=0.004).

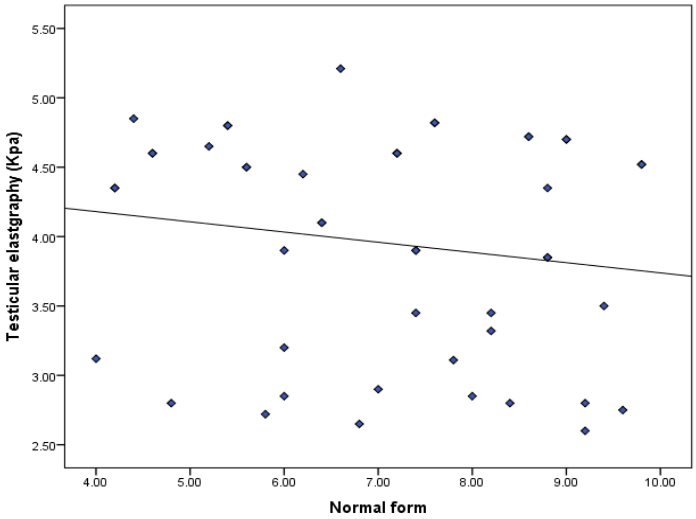

Figure (7): Scatter dot graph showing non-significant negative correlation between testicular elastography values and normal forms.

On doing linear stepwise regression of factors significantly correlated with testicular elastography values, only sperm count and motility were significantly independently associated with it (unstandardized β= -0.094 and -0.166 for sperm count and motility respectively), p<0.05 (**Table 5**).

Table (5): Linear stepwise regression analysis of variables associated with testicular elastography among the studied patients:

Variables	Unstandardized coefficient		Standardized coefficient	T	P-value
	B	SEM	B		
Sperm count	-0.094	0.032	-0.285	-2.914	0.006*
Sperm motility	-0.166	0.023	-0.703	-7.201	<0.001**

There was non-significant correlation between age of the studied patients and semen analysis data (**Table 6**).

Table (6) correlation between patient age and semen analysis values:

Variables	AGE	
	R	P
Count (million/ml)	0.061	0.679
Motility	-0.025	0.866
Normal form	-0.006	0.97

DISCUSSION

A varicocele has a clear impact of testicular growth and spermatogenesis. It is considered the most common and treatable cause of male infertility [9].

Varicocele is diagnosed in 19% to 41% of men with primary infertility and even up to 80% of men evaluated for secondary infertility [15].

In subfertile men with bilateral varicocele, abnormal spermogram is the common presentation. However it could occur in unilateral cases despite apparently normal contralateral testicle. Male sub-fertility could be associated with left varicocele in 17.6% and right varicocele in 1.5% [2].

The impact of varicocele on the testis and its function is not clearly defined. It includes a broad spectrum of seminal changes ranging from oligospermia up to testicular atrophy [16].

Screening of the nature of pathologic changes in the testes in men with varicocele may clarify its relation with male sub-fertility. Also it will help in predicting the results of varicocele treatment, which may be the most crucial step in management plan for an infertile man with abnormal sperm-gram [17,18].

In the current study, we don't depend on the grade of Ipsilateral tesitcle with varicocele in patients selection or stratification. That go with **Rocher *et al.*** [19] with their colleague who reported that there was no statistically significant relationship between the grade of the varicocele and testicular hypotrophy or mean testicular shear wave values.

In this study we estimated the mean of 3 shear wave measures for each unite. That was agreed with **Trottmann and his associates** [20] who concluded that there were no statistically-significant difference in mean shear wave was observed between testicular zones (poles). However it was disagreed with **Jedrzejewski and his associates** [21] who stated zonal differences in their shear wave results in boys.

We found that normal baseline readings in volunteers contralateral testis elastography rang was 1.1–1.9 Kpa and this goes with another study done by **Camoglio *et al.*** [22] **and Abdelwahab *et al.*** [23] with their colleagues. But it was lower than another work done by **Jedrzejewski *et al.*** [21] **and Onder *et al.*** [24] with their colleagues who try to map SWE on both testis in adolescent and adults.

In the current work, contralateral testicular SWE in cases with abnormal semen parameters mean value was 3.6 kpasc (range 5.2 to 2.6 Kpasc). It was statistically significant higher than volunteers with normal semen paramerters. This stiffness values goes with the same results of **Jedrzejewski *et al.*** [21] **and Camoglio *et al.*** [22] with their colleagues who stated that boys with varicocele bearing testis are stiffer than normal testis. Also they founded a positive correlation between SWE and the clinical grade of spermatic vein reflux, and testis with hypotrophy. Also our data in that issue was comparable to **Onder *et al.*** [24] who reported 3.81 kpasc as a mean of contralateral testis of varicocele patients.

In the Ipsilateral testes (varicocele side) in cases and controls showed high SWE values (more stiffer), but without significant difference. This can be explained by varicocele impact in both groups ipsilateral testis.

In apparently normal contralateral testes has been showed higher stiffness values than volunteer group with normal semen analysis. This can explain that unilateral varicocele can cause male infertility due to changes occurs in the contralateral unite.

In this study, the percentage of progressive motility, and sperm count were (17.6%, and 6.76, respectively), which was lower than control group and normal values conducted by the World Health Organization involving 9034 men [25].

In respect to percent of normal forms, our study showed normal values in cases and controls. Although normal form was higher in normal semen parameters controls but when it was compared with the parameters of cases there was no significant difference, the later statement was in agree with **Tawadrous *et al.*** [26] in there study on oxidative stress in infertile men with varicocele.

In this study we focused on evaluation of SWE changes occurring in the contralateral normally appearing testis of unilateral varicocele with abnormal semen analysis. We could demonstrate statistically significant negative correlation between stiffness index and both total count (million/mL) and percentage of total motility, but regarding normal form we can't gain a significant relation. These results go with what proposed by **Tawadrous *et al.*** [26] who stated a comparable results.

LIMITATIONS

Our work limitations could be small cases number. Also despite we omitted inter-observer variability as a single radiologist collaborated in our team, we did not calculate inta-robserver variability. Additionally, we did not obtain any histopathological data compatibility.

In conclusion, SWE data of normally apparent contralateral testis of unilateral varicocele patients with abnormal semen parameters could reveal stiffer parenchyma. That may reflect the presence of a harmful insult to the testis. So it could add a warning sign for surgeon to interfere in these unilateral cases even with euspermic pattern and varicosities. Moreover it could be added to other obvious indications for surgery as abnormal semen analysis, testicular size affection or softness.

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Author contribution: Authors contributed equally in the study.

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