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A radiological and clinical overview of the effects of COVID-19 on the male reproductive system: micro V Doppler, spermiogram and international erectile function form survey results

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ABSTRACT

Introduction: Micro V Doppler is a different technique from the conventional Doppler US method, which reveals the small vessel structure developed in recent years. We planned to reveal whether there are significant difference between spermiogram test, scrotal US, Micro V Doppler and international erectile function form questionnaire results between patients who had recently COVID-19 and the control group.

Material and Method: Our study included 45 patients who had recently had COVID-19 infection, and 45 control patients. Spermiogram test, scrotal US, Micro V Doppler and erectile dysfunction score, orgasmic function score, sexual desire score, sexual satisfaction score, and general satisfaction scores were evaluated for our patients and control groups included in our study.

Results: On scrotal US, there was no sequelae in the parenchyma in all patients (n=45, 100%) who had experienced COVID-19. When the spermiogram tests of the control group and our patients with COVID-19 infection were compared, the presence of oligozoospermia, leukocytospermia and other abnormal positive findings was similar between the two groups ($p>0.005$). Micro V Doppler findings of the control group and our patients who did not have COVID-19 infection were similar. Sexual Desire and sexual satisfaction scores of patients with COVID-19 were significantly lower than the control group without COVID-19 infection ($p<0.05$), however, there was no significant difference between the groups in terms of erectile dysfunction, orgasmic function and overall satisfaction.

Conclusion: COVID-19 does not cause a permanent significant difference in the morphological structure of testicles on Micro V Doppler examination and spermiogram tests. Sexual desire and sexual satisfaction scores are decreased in patients who had recently COVID-19.

Keywords: Doppler, micro V Doppler, COVID-19, testis

INTRODUCTION

The COVID-19 virus (SARS-CoV-2) is known to have important effects on vital organs such as the heart, lungs, kidneys, and brain, but its physical and psychological effects on general reproductive system in men are not well known (1). The brain and testicles are two important structures that are in close relationship with each other via gonadotropins and sex steroid hormones (2). There are studies discussing that COVID-19 may affect the hypothalamus and decrease gonadotropins and testosterone, and there may be variability in sexual desire and satisfaction of patients. In addition, it has been reported in these studies that hyperthermia caused by systemic infection causes an increase in leukocytes and an inflammatory response in the testicular tissue (2,3).

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Micro V examination is a newly developed technology which evaluate the slow flow of microvascular structures and discriminated from tissue motion artefact. Micro V benefit from the rapid frame rates, thus clutter signals are suppressed and slow flow of microvessel can be exracted (4).

We planned to reveal whether there are significant difference between spermiogram test, scrotal US, Micro V Doppler and international erectile function form (IIEF) questionnaire results between patients who had recently COVID-19 and the control group. We contribute to the literature as one of the pioneering studies that perform Micro V Doppler, and IIEF evaluation in patient groups with COVID-19.

MATERIAL AND METHOD

The study was conducted with the permission of Başakşehir Çam and Sakura Research Hospital Non-invasive Clinical Researches Ethics Committee (Date: 07.02.2021, Decision No: 2021.05.100). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

General Data

Our study included 45 patients between the ages of 18-55 who applied to the outpatient clinic and had COVID-19 infection in the last 3 months, and 45 patients who did not have COVID-19 infection and applied to the polyclinic. Patients with varicocele, previous inguinal hernia operation, systemic disease such as malignancy, diabetes mellitus, hypertension, those with a history of testicular tissue damage due to other reasons in previous scrotal US controls, and those with a history of torsion were excluded from the study. Our patients included in our study were evaluated for spermiogram test, scrotal US, Micro V Doppler and IIEF erectile dysfunction score, orgasmic function score, sexual desire score, sexual satisfaction score, and general satisfaction scores. The spermiogram tests of all our patients were examined and the presence of oligozoospermia, leukocytospermia and other abnormal positive findings (motility, morphology) were noted. When the spermiogram tests of our patients in the control group who did not have COVID-19 were compared with those in the patients who had COVID-19 infection, it was evaluated whether there was a significant difference between the two groups in terms of these parameters.

Micro V Doppler Examination

In the scrotal US (Esaote MayLab 9 Xp device using a 5-14 MHz linear transducer probe) examination, both testicular parenchyma, volumes and color Doppler vascularity were examined, and patients with abnormal conditions were noted. Then, Micro V Doppler examination, which shows the microvascular bed and has its own special software at high frame rate, was started. Testicular parenchyma was examined with Micro V examination, focal damage area in blood supply in micro vascular structures and decrease in general blood supply were evaluated. We used the grading system created by Arslan et al. (5) which is a grading for imaging systems using high fram rate and used for imaging the microvascular bed. According to this visual system, Grade 1 was classified as several punctate blood supplies and minimal vascularity, on Micro V Doppler. The vascularity without anarchic vascular structures and no more than two linear microvascular signals are accepted as grade 2. In grade 3 vascularity, more than two vascular structures are seen. Multiple irregularly shaped and curved microvascular structures in the center and periphery of the parenchyma is defined as grade 4 (5, 6).

The use of simplified International Index of Erectile Function (IIEF-5)

The IIEF-5 questionnaire was used to evaluate the sexual quality of life of the patients. Accordingly, our patients were asked to answer a 15-question questionnaire on the form so that we could evaluate erectile and orgasmic functions (max points 30 and 10), sexual desire (max points 10), satisfaction with intercourse(max points 15) and overall sexual satisfaction(max points 10) (7,8). In one of our patients who could get 30 points in total, if the score was 25 or less, the diagnosis of erectile dysfunction was established.

Statistical Analysis

All statistical analysis was performed using R 3.6.0 (https://www.r-project.org). Shapiro-Wilk's normality test and Q-Q plots were used to check the normality of the data, and also Levene's test was used to check the homogeneity of groups' variances. Categorical data were described as numbers (n) and percentages, numerical data were expressed as mean±standard deviation. The McNemar test was used to determine if there were difference in proportions between pre and post-disease of the patients with COVID-19 in terms of oligozoospermia, leucocytospermia and anormal positive findings. Chi-square test was used to examine the association between study groups and Micro V Doppler findings. In addition to, independent samples t-tests were used to compare the differences between COVID-19 patients and healthy controls with regard to IIEF score, orgasmic function score, sexual desire score, intercourse satisfaction score and overall satisfaction score. A value of p less than 0.05 was considered as statistically significant.

RESULTS

The mean age of 45 patients was 30.60±7.32 (range: 17-49 years), right testis volume mean 13.12±0.82 cc (range: 11-15 cc), left testis volume mean 12.74±0.95 cc (range:

11-16 cc). No sequelae change was observed within the parenchyma in all patients who had COVID-19. When the spermiogram tests of the patients who had COVID-19 and the healthy control group were compared; oligozoospermia, leucocytospermia and abnormal positive findings are given in **Table 1**. The presence of oligozoospermia, leucocytospermia and abnormal positive findings in the past and post-infection of the patients were similar (p>0.05). The differences between the Micro V Doppler findings, IIEF score and subheadings of patients with COVID-19 and healthy controls were examined. Micro V Doppler findings of the patients with COVID-19 and the control group were similar (p=0.158) (**Figure 1**). The IIEF Sexual Desire (5.16±1.19 vs. 8.62±1.27, Mean diff.= 3.47, [95% CI, 2.95-3.98], t(88)= 13.40, p<.001, Cohen's d=2.83) and Sexual Satisfaction (10.60±1.50 vs. 11.82±1.30, Mean diff.= 1.22, [95% CI, 0.63-1.81], t(88)= 4.13, p<.001, Cohen's d=0.87) scores of patients with COVID-19 were significantly lower in the group of patients with COVID-19 infection. However, there was no significant difference between the groups in terms of erectile dysfunction, orgasmic function, and general satisfaction (all p-value>.05) (**Graphic 1**).

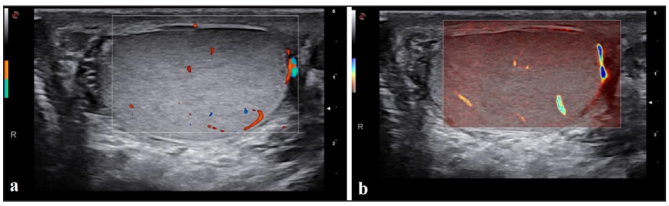


Figure 1. 25 year-old patient who had formerly known COVID-19, (a) on color Doppler image (b) on Micro V Doppler imaging grade 2 parenchymal vascularity is seen.

Table 1. Spermiogram test findings of patients who had recently COVID-19 and control

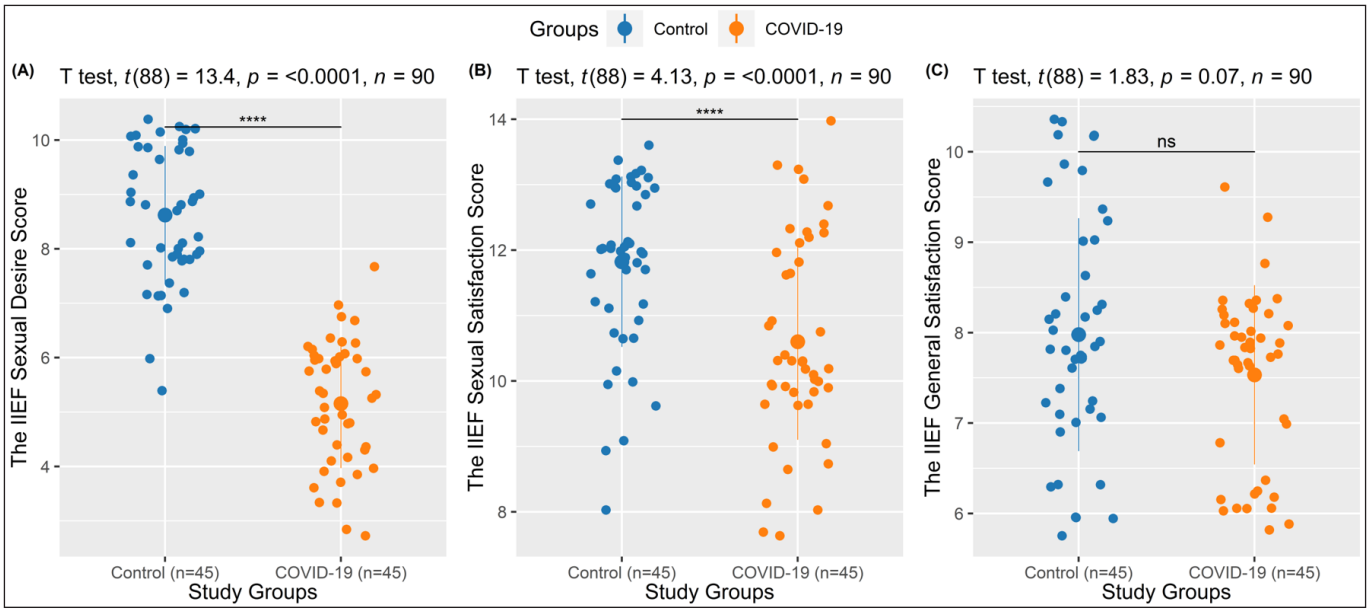
Parameters	Patients who had not COVID-19 (control)		Patients who had recently COVID-19		p value
	Positive findings	Negative findings	Positive findings	Negative findings	
Oligozoospermia	1 (2.2)	44 (97.8)	2 (4.4)	43 (95.6)	0.317
Leucocytospermia	2 (4.4)	43 (95.6)	2 (4.4)	43 (95.6)	>.999
Abnormal positive findings	1 (2.2)	44 (97.8)	2 (4.4)	43 (95.6)	0.317

Data were described as numbers of patients (n) and percentages (%). p-value calculated using McNemar chi-square test.

DISCUSSION

In this prospective study, when the spermiogram tests of the patients who had COVID-19 and the healthy control group were compared; oligozoospermia, leucocytospermia and abnormal positive findings were similar (p=.317, p>.999 and p=.317, respectively). When we compared the two groups, no difference was found in terms of Micro V Doppler. Sexual Desire and Sexual Satisfaction scores were significantly lower in the patients with post COVID-19 infection (p<0.05).

It has been reported that ACE2 receptors are found in the kidneys, Sertoli and leyding cells, and spermatogonia within the genitourinary system. SARS-CoV virus uses ACE2 receptors to enter cells (9). Honggang et al. (10) reported that severely ill-deceased COVID-19 patients in whom they performed postmortem examination showed thinning of the seminiferous epithelium thickness and a significant increase in the number of apoptotic cells at this level. They detected oligospermia in semen samples and thus reported that COVID-19 directly affects the



Graphic 1. Comparisons of International Index of Erectile Function (IIEF) Questionnaire between COVID – 19 patients and healthy controls. Data were presented as mean with standard deviations *: a significant difference between groups, ns: not significant. Error–plots, which show the (A) The IEFF Sexual Desire score, (B) The IEFF Sexual Satisfaction score in the COVID–19 patients and healthy controls. Significantly decreased these scores were noted in the COVID–19 patients when compared with the healthy controls. However, (C) A error–plot, which show the IEFF General Satisfaction score in the groups, and there was no statistically significant difference between COVID–19 patients and healthy controls.

male reproductive system. Xu et al. (11) reported that T-lymphocytes and macrophages attack the testicular parenchyma as a mechanism, which causes viral-associated epididymorchitis. Another theory is that abnormal amounts of IgG precipitates are observed in the seminiferous tubules after macrophage and T lymphocyte attack, and therefore, secondary autoimmune response to the viral infection may develop and orchitis may develop due to autoimmune (11). Bridwell et al. (12) reported two orchitis case caused by SARS-CoV and they also suggested that it would be beneficial to follow-up fertility in these patients. Another study reported that imaging these patients and getting control with spermiogram test is important for us to understand whether the effects are reversible (10). In these studies, spermiogram tests and scrotal Doppler US were performed in very early periods. And in the acute process, significant inflammation, significant increase in vascularity in Doppler and deterioration in spermiogram were detected. We think that the reason why there were no significant radiological (Micro V) or laboratory differences between the two groups in our study, unlike the literature, is due to the fact that the examination was performed at a later time. Thus, we think that the effects are reversible. Classical color and power Doppler algorithms perceive the slow flow of micro vascular structures as clutter and cannot distinguish this slow flow from the mechanical movement of the background tissue (5). For this reason, they also delete the slow flow which considered as an artifact. Doppler methods have been developed by different companies, which use the recently developed high frame rate and can see microvascular structures with its unique algorithm rather than large-medium diameter vascular structures (Esoate: Micro V Doppler and Toshiba: Superb microvascular imaging) (5,6). There are publications reporting that microvascular imaging techniques are extremely successful in superficial organs such as testis and breast in examinations performed with a lineer probe (13). Fu et al. (13) conducted a study which evaluates the clinical applications of microvascular imaging methods. They reported that angiogenesis is very important in the mechanism of inflammation and metastasis of diseases, and therefore, microvascular imaging methods may have an important role in demonstrating the course and permanent effects of diseases. According to Visalli et al. (14) found that microvascular imaging techniques can detect vascularization in healthy testicles which have no signal on power Doppler. In a recent study evaluating active synovitis by using microvascular imaging techniques; they reported Micro V Doppler can demonsrate low-grade inflammation more succesfully compared to color Doppler (15). Moreover, the degree of visuliazed slow blood flow on microimaging methods reflected the inflammatory process. As the severity of vascularity detected on microimaging examination increase, symptoms and magnetic resonance imaging findings also increase. According to Ayaz et al. (16) conducted a large-scale study in which they examined the testicles of newborns. They found that Micro V Doppler provide additional information about the structure distribution and number of microvessels.

There are current studies reporting some changes in the hormone profile in men with COVID-19 (17,18). It has been reported that these patients have increased luteinizing hormone, follicle-stimulating hormone, prolactin and decreased estradiol, progesterone, and testosterone levels. Tian et al. (18) reported that SARS-CoV RNA was detected in acidophilic cells of the pituitary. And thus, it has been reported that COVID-19 may have some effects on the hypothalamus and pituitary gland. It may cause abnormal sex hormone levels by affecting the hyphthalamo-pituitary axis, thus leading to sexual dysfunction (18). In our study, the sexual desire and sexual satisfaction scores were significantly lower in the patient group with COVID-19 infection. We think that another important reason why the disease causes a decrease in sexual desire without physically creating an erectile dysfunction or without significant changes in the testicular parenchyma in Micro V examination may be the significant mental stress experienced during COVID-19. Kaya et al. (19) conducted a study evaluating the effect of COVID-19 on sexual dysfunction in women. And they reported that the frequency of sexual intercourse and sexual satisfaction in women decreased after COVID-19 disease. Cito et al. (20) reported that during COVID-19 disease couple has more chance to improve their sexuality thanks to quarantine. But they also found that a decrease in the number of sexual intercourse was observed in the patients included in the study, which may be due to the decrease in psychological stimuli and emotional stress. In another study, it was found that the satisfaction score decreased in patients after COVID-19 (19).

There were some limitations in our study. First, we did not examine the pre- and post-disease conditions of the patient group. We compared them with the patient who did not have recently COVID-19. And patients with COVID-19 were not divided into groups as severe and mild. In the literature, patients with oligospermia on spermiogram were generally those with severe or lethal disease. Secondly, we had relatively small sample size. Interobserver variability was not evaluated in Micro V doppler examinations.

CONCLUSION

COVID-19 does not cause a permanent significant difference in the morphological structure of testicles on Micro V Doppler examination and spermiogram tests.

Sexual desire and sexual satisfaction scores are decreased in patients who had recently COVID-19. Decreased sexual desire and sexual satisfaction scores without any impairment in functional and morphological findings, it may be an associated with anxiety created by the psychological dimension of COVID-19.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was conducted with the permission of Başakşehir Çam and Sakura Research Hospital, Non-invasive Clinical Researches Ethics Committee (Date: 07.02.2021, Decision No: 2021.05.100).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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