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Is There Any Relationship Between Varicocele and Reproductive Hormone Status in Non-obstructive Azoospermia?

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Abstract

Objective: The aim of this study was to compare the reproductive hormone parameters according to the presence or absence of varicocele in patients having non-obstructive azoospermia.

Methods: A total of 111 non-obstructive azoospermic men were included in the study retrospectively. The patients were divided into 2 groups according to the presence of varicocele. Thirty of 111 patients had varicocele (group 1). Control group was formed with 81 patients (group 2). Two groups were compared in terms of serum total testosterone, follicle-stimulating hormone, and luteinizing hormone.

Results: Physical examination revealed varicocele in 10.8% (95% CI: 0.0854-0.1348) of the main cohort of non-obstructive azoospermia patients. Mean total testosterone level was higher in patients with varicocele compared to the other group (585 ± 412 ng/dL and 423 ± 167 ng/dL, respectively) (P = .002). The mean follicle-stimulating hormone level was lower in patients with varicocele (group 1) than patients without varicocele (group 1: 17.72 ± 13.2 mIU/mL, group 2: 21.69 ± 16.6 mIU/mL). However, this difference was not statistically significant (P = .38).

Conclusions: Serum testosterone levels of non-obstructive azoospermic men with varicocele are higher than men with idiopathic non-obstructive azoospermia. Looking from azoospermia as an endpoint of the spermatogenic failure, varicocele appears to affect testicular hormone production less than idiopathic etiology which can be attributed to genetic causes.

Keywords: Non-obstructive azoospermia, testosterone, varicocele

Varicocele is one of the well-known causes of male infertility and is seen in 40% of infertile men.[1] The relationship between varicocele and spermatogenic failure was well demonstrated in the recent literature.[2] Azoospermia is one of the unfavorable endpoints of the varicocele's effect on testes. It also affects testicular hormone production. There are several studies showing the effect of varicocele on the Leydig cell functions in the literature.[3] Patients with varicocele have lower serum testosterone than controls without varicocele. Varicocelectomy can improve spermatogenesis as well as testicular testosterone production.[4-6] But the relationship between varicocele and testicular testosterone production needs different aspects for better understanding. Investigation of this relationship in non-obstructive azoospermia (NOA) cohorts could help to meet the need. Studies identifying varicocele-caused NOA subgroup with clinical parameters such as serum reproductive hormone values are insufficient in the literature. The aim of this study was to compare the reproductive hormone parameters of men having NOA, according to the presence or absence of varicocele.

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Methods

The data of 613 patients who were admitted to our clinic between 2003 and 2018 and were diagnosed with NOA were examined. Azoospermia was diagnosed with 2 consecutive spermiograms. Patients having known etiology of obstructive azoospermia (e.g., congenital vas agenesis, ejaculatory duct obstruction) and varicocelectomy history and the patients with only ultrasound-detected varicocele and not having any physical examination findings were excluded from the study. A total of 582 patients have undergone microdissection testicular sperm extraction (microTESE). Procedures were performed as previously described by Schlegel.[7] Patients who had a known history of epididymitis and/or orchitis, cryptorchidism, the treatment with chemotherapy and/or radiotherapy, tobacco smoking, substance abuse, and hormone therapy for infertility were excluded from the study. Also, patients having hypogonadotropic hypogonadism, Y chromosome microdeletion, Klinefelter syndrome, or other structural chromosomal anomaly were excluded. Finally, 111 patients who met the inclusion criteria and have appropriate data were included in the study, retrospectively.

The patients were divided into 2 groups according to varicocele diagnosis by physical examination. The visible, palpable, and palpable after valsalva maneuver were classified as grades 3, 2, and 1 varicocele, respectively.[8] In the case of bilaterality, the higher grade was taken into account. Accordingly, patients with varicocele were included in group 1, and patients without varicocele were included in group 2.

Groups 1 and 2 were compared in terms of age, duration of infertility, and hormone parameters. In addition, the differences between the two groups in terms of postoperative findings (sperm retrieval rate, Johnsen score, testicular pathology) were investigated. The patients were divided into 3 categories according to testicular volume; normal, decreased, and atrophic. Testis volumes were measured using ultrasound imaging by experienced radiologists. Three dimensions of testis were used to calculate testicular volume with the Lambert formula (length × height × width × 0.71).[9] The average testis volume of <2 mL, 2-10 mL, and >10 mL was considered as atrophic, reduced, and normal, respectively.[10] Blood samples for testosterone measurements were obtained early in the morning. All samples were collected in our biochemistry laboratory. Reproductive hormone levels were measured with liquid chromatography-tandem mass spectrometry. Testicular tubule samples were evaluated by a biologist during the microTESE, and the presence of spermatozoa was reported. Then, Johnsen scores were determined by pathologists experienced in the field according to the method previously described in the literature.[10] Testicular pathologic diagnoses were classified into 3 categories: Sertoli cell-only (SCO), maturation arrest, and hypospermatogenesis. These pathological findings were compared in terms of follicle-stimulating hormone (FSH), and luteinizing hormone (LH) values.

Statistical analysis

Chi-square was used to calculate the difference between categorical variables. Kolmogorov–Smirnov test was used to check the normality of the sample for each variable. Then, nonparametric tests were used for nonnormally distributed series. Accordingly, Mann–Whitney U-test was used to calculate the difference between means. Kruskal–Wallis test was used to compare the means of 3 or more independent samples simultaneously. In the case of a normal distribution, Student's *t*-test was used. The data were analyzed using the Statistical Package for the Social Sciences v. 22 (IBM SPSS Corp., Armonk, NY, USA). Statistical significance was taken as $P < .05$.

This study was approved by our institution's clinical research İstanbul University-Cerrahpaşa Ethics Committee (Number: E-83045809-604.01.02-57384, date: 16.03.2021).

Results

In 613 NOA men, physical examination revealed varicocele in 66 (10.8%, 95% CI: 0.0854-0.1348) patients. A total of 111 patients with adequate clinical data were included in the study. Among them, 30 patients had varicocele (group 1); 17 (57%) patients had grade 1, 9 (30%) patients had grade 2, and 4 (13%) patients had grade 3 varicocele. Bilateral varicocele was detected in 13 (43%) patients. Control group was formed with 81 patients (group 2).

The mean age of the patients was 33.46 ± 5.9 years in group 1 and 33.46 ± 6.1 years in group 2 ($P = .86$). Median age was 34 (24-47) years in group 1 and 32 (20-58) years in group 2. There was no statistically significant difference between the groups in terms of mean infertility durations (6.34 ± 5.2 and 6.42 ± 4.9 years, respectively, $P = .81$).

The distribution of the patients according to testicular volume and the difference between the 2 groups were shown in Table 1. Accordingly, 2 groups did not show any difference in terms of testicular atrophy or loss of testicular volume ($P = .66$).

In patients with varicocele (group 1), the mean FSH level was lower than the control group (group 1: 17.72 ± 13.2 mIU/mL and group 2: 21.69 ± 16.6 mIU/mL). However, this difference was not statistically significant ($P = .38$). The mean LH was 7.65 ± 6.3 mIU/mL in group 1 and 10.17 ± 8.1 mIU/mL in group 2 ($P = .13$). Mean total testosterone level was higher in patients with varicocele compared to the control group (585 ± 412 ng/dL and 423 ± 167 ng/mL, respectively). The difference between the total testosterone levels was statistically significant ($P = .002$) (Table 1).

Table 1. Patient Baseline Characteristics

Characteristic	NOA + Varicocele (Group 1)	NOA (Group 2)	*P*
Number	30	81	
Age (year, mean)	33.46 ± 5.9	33.46 ± 6.1	.86*
(median, range)	34 (24-47)	32 (20-58)	
Infertility duration (year)	6.34 ± 5.2	6.42 ± 4.9	.81*
Testis volume (%)			
Normal	17 (56.6)	47 (58)	
Reduced	5 (16.6)	18 (22)	.66α
Atrophic	8 (26.8)	16 (20)	
FSH (mIU/mL, mean)	17.72 ± 13.2	21.69 ± 16.6	.38*
LH (mIU/mL, mean)	7.65 ± 6.3	10.17 ± 8.1	.13*
T. Testosterone (ng/dL, mean)	585 ± 412	423 ± 167	.002β

*Mann–Whitney *U*-test; αChi-square test; βStudent's *t*-test.
NOA, non-obstructive azoospermia; FSH, follicle-stimulating hormone; LH, leutinizing hormone.

Table 2 shows the rates of surgical sperm retrieval and the pathological findings. The rate of surgical sperm retrieval in patients with varicocele was 46.7%. This rate was slightly higher in the control group (50.6%) ($P = .71$). Although the groups did not show statistical differences according to histopathological examination, it was found that SCO was less common in patients with varicocele ($P = .46$). Finally, the groups were compared in terms of Johnsen scores. There was no statistically significant difference in the mean Johnsen scores between the groups ($P = .24$).

Patients without varicocele were divided into 3 subgroups according to their pathological findings. There was a statistically significant difference between the groups in terms of serum FSH and LH values ($P < .00001$ and $P < .00001$, respectively). Patients with varicocele were subgrouped similarly. There was a statistically significant difference between the serum FSH values of the patients but not between the LH values ($P = .012$ and $P = .16$, respectively). Patients with hypospermatogenesis in both groups (group 1 and group 2) had the lowest FSH and LH values. The highest serum FSH and LH values were found in the SCO subgroups (Table 3).

Discussion

In this study, the mean serum total testosterone level of the varicocele group was higher than the control group ($P = .002$). According to this finding, it can be said that the varicocele causes

Table 2. MicroTESE and Patology Outcomes

Characteristic	NOA + Varicocele (Group 1)	NOA (Group 2)	*P*
Number	30	81	
Surgical sperm retrieval (%)	14/30 (46.7)	41/81 (50.6)	.71[α]
Histology (%)			
Sertoli cell-only	11 (36.7)	40 (49.4)	.46[α]
Maturation arrest	11 (36.7)	22 (27.2)	
Hypospermatogenesis	8 (26.6)	19 (23.4)	
Johnsen score (mean)	4.22 ± 2.4	3.91 ± 2.9	.24[*]

*Mann–Whitney *U*-test; [α]Chi-square test.
NOA, non-obstructive azoospermia.

a testicular failure pattern in which the hormone production is affected relatively less or slowly compared to idiopathic NOA.

The incidence of varicocele in men with NOA was 10.8% in our study. Similar incidences have been reported by many studies in the literature.[8,11,12] Varicocele in infertile men is seen in about 40%.[2] Although varicocele is common in infertile patients, the incidence is much lower in azoospermic men. When azoospermia is considered as an endpoint, it seems that varicocele is an etiological factor from the aspect of testicular hormone production, with a relatively good prognosis compared to idiopathic causes.

The fact that varicocele can be seen coincidentally makes it difficult to address the results mentioned above on solid evidence. A recent study indicated that there might be another possibility.[13] In the study, varicocele was detected in 23% of patients who received gonadotropin treatment for hypogonadotropic hypogonadism. None of the patients had varicocele before treatment. After the treatment, subcapsular arterial flow, testicular size, and epididymal diameter increased and varicocele developed. In the light of these findings, the relationship between azoospermia and varicocele can also be explained by an unknown cause of testicular insufficiency which is underlying and exposing the testis to high gonadotropin. Most of the azoospermic men (approximately 90%) do not have varicocele. Moreover, the testes of these patients are stimulated with high serum FSH values. The cause-effect relationship between varicocele and testicular failure is not known well yet. But in both cases, the testes of men with NOA and varicocele may be responding better to the FSH stimulation than the idiopathic NOA group. An important portion of the idiopathic NOA cases may be attributed to genetic causes.[14] Probably, genetic etiologies affect testicular functions in a different way than the longitudinal effect of varicocele.

Varicocelectomy may provide a possibility to measure the response of a testis affected by varicocele to endogenous gonadotropins. There are many studies showing the effect of varicocele and varicocelectomy on hormone parameters. A meta-analysis was published in 2018 with data from 5 studies examining the effect of varicocelectomy on serum FSH and LH values.[15] According to the meta-analysis, varicocelectomy decreases serum FSH and LH levels in men with varicocele. But a recently published study found no statistically significant association between serum testosterone and varicocele.[16] In another meta-analysis conducted in 2017, varicocelectomy was found to be effective in the treatment of hypogonadism in subfertile men.[17] Bernie and colleagues[18] concluded that varicocelectomy may be an alternative to testosterone treatment in elderly men with androgen insufficiency.[18] As we have seen, stronger evidence is in favor of varicocelectomy in hypogonadism. Animal studies also show that the activity of enzymes in testosterone biosynthesis pathway decrease in experimental varicocele-induced rats.[19] It is also well known that human varicocele causes structural changes in Leydig cells and decreases testosterone positive Leydig cell count.[20] Varicocele, which is coincidental or developed secondary to testicular failure or direct cause of azoospermia, heterogenizes the NOA population. Studies in the literature are inadequate to reveal the longitudinal effect of varicocele on testes. Most studies provide cross-sectional data.

Table 3. Comparative Analysis of Subgroups According to Pathological Categories

	FSH (mIU/mL, mean)		LH (mIU/mL, mean)	
Variables	**NOA + Varicocele**	**NOA**	**NOA + Varicocele**	**NOA**
Hypospermatogenesis	9.77 ± 12.06	9.15 ± 6.63	4.76 ± 2.45	4.50 ± 2.75
Maturation arrest	14.80 ± 11.09	12.19 ± 7.76	7.14 ± 5.00	5.81 ± 2.31
Sertoli cell-only	26.45 ± 11.78	32.88 ± 15.94	10.28 ± 8.52	15.08 ± 8.80
P (Kruskal–Wallis test)	.012	<.001	.16	<.001

NOA, non-obstructive azoospermia.

There was no difference between the groups according to surgical sperm retrieval rates in our study. Although the effect of varicocele repair on the rates of surgical sperm retrieval has been well established in current literature,[21] there are limited data for the direct comparison of men with NOA according to the varicocele presence. A recent study revealed that the presence of varicocele is not an unfavorable factor affecting the sperm retrieval rates in men with NOA.[22]

Study limitations

There are some limitations to our study. The data were collected retrospectively. During the long period, patients underwent varicocele examination by different experts. Long-term data collection was continued by different persons. In addition, the procedures were performed by multiple surgeons. Only a small number of patients whose data were available from a large NOA cohort could be included in the study. Therefore, advanced statistical analysis could not be performed. Also, as an external limitation, the causative link between varicocele and NOA cannot be proved with recent diagnostic tools. Future prospective and longitudinal studies which can reveal evidence showing varicocele as a cause of NOA are warranted.

Varicocele is found in approximately 10% of NOA men. Our study showed that serum testosterone levels of NOA men with varicocele are higher than men with idiopathic NOA. Looking from azoospermia as an endpoint of the spermatogenic failure, varicocele appears to affect testicular hormone production less than idiopathic etiology which can be attributed to genetic causes.

Ethics Committee Approval: This study was approved by our institution's clinical research İstanbul University-wCerrahpaşa Ethics Committee (Number: E-83045809-604.01.02-57384, date: 16.03.2021).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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