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Impact of Varicocele and Varicocele Surgery on Semen Quality, Erectile Function, and Serum Hormone Levels

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Abstract

Introduction: The aim of our study was to analyze the impact of varicocele and varicocele surgery on testosterone level, semen quality, and erectile function.

Methods: Our study included 265 infertile males with varicocele. Patients were divided into three groups: Group 1 (193) patients who did not receive surgery, Group 2 (72 patients) who were operated on according to the Palomo procedure and Group 3 (28 patients), who acted as a control group without a varicocele. All patients completed the International Index of Erectile Function IIEF-5 (German version) and underwent semen analysis. Serum testosterone, Follicle Stimulating Hormone (FSH), and Luteinizing Hormone (LH) were measured at inclusion into the study and after surgery.

Results: The IIEF-5 scores in groups 1 and 2 were 21.01 ± 2.2; and 21.74 ± 1 respectively, and the resulting t-test for equality of variance was significant ($p<0.0001$). Total testosterone level in groups 1 and 2 were 3.16 ± 0.37, and 3 ± 0.01 respectively, and the resulting t-test for equality of variance was significant ($p<0.0001$). The results of the semen analysis were better in group 2 (after surgery) (37.5%, $p<0.001$) in comparison to Group 1. Interestingly, pre-operative serum testosterone levels were lower in patients with later improvement of semen analysis ($p=0.05$). Body mass index ($p=0.8$), pre-operative serum FSH ($p=0.9$), LH ($p=0.2$), were similar in both groups.

Conclusion: Semen quality improved in 37.5% of our patients after varicocele surgery. Erectile dysfunction improved partly after varicocele surgery. Moreover, these improvements are not necessarily correlated. Our study reported that a lower pre-operative serum testosterone level might be a possible indicator for successful surgical outcome.

Keywords: Erectile Dysfunction; International Index of Erectile Function; Follicle stimulating hormone; Luteinizing hormone; Oligo-astheno-teratospermia-syndrome

Abbreviations

ED: Erectile Dysfunction; IIEF-5: International Index of Erectile Function; FSH: Follicle Stimulating Hormone; LH: Luteinizing Hormone; OAT: Oligo-Astheno-Teratospermia-Syndrome

Introduction

A varicocele is an abnormal enlargement of the internal spermatic vein and pampiniform plexus of the testis. The prevalence of varicocele in the male population is between 10% and 15%, and 40% among infertile males [1]. Varicoceles are identified as the most common reversible cause of male infertility. Moreover, varicoceles are associated with testicular discomfort, testicular atrophy, and azoospermia in some men [2,3]. Possible explanations of the harmful effects of varicoceles on fertility and testosterone production are: Testicular hyperthermia, hormonal dysfunction, increased or decreased testicular blood flow, reflux of toxic metabolites, or seminiferous tubular hypoxia [1].

Zheng et al. [4] demonstrated in rats that surgical creation of varicoceles causes lower testosterone levels, and surgical correction results in higher levels of testosterone. The effect of varicocelectomy on serum testosterone level is not yet fully established. While some studies have found no significant effect, others report a normalization of the testosterone level following surgical repair of the varicocele [5,6]. A review of the literature demonstrated that microsurgical varicocelectomy improved testosterone levels in men with varicocele [7].

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The aim of this retrospective study was to analyze the impact of varicocele and varicocelectomy on testosterone levels and erectile function.

Material and Methods

All patients underwent thorough history taking, general and genital examination, semen analysis, hormonal assessment (serum FSH, LH, testosterone and prolactin), and scrotal color Doppler ultrasound. International Index of Erectile Function (IIEF-5) [8] questionnaires were assessed for each participant. Varicoceles were diagnosed and graded (grade 1, 2, or 3) based on physical examination and color Doppler ultrasound.

All patients were ≥ 18 years old, married and in a stable sexual relationship with a female partner for at least 6 months before enrolment. We excluded patients with physical or psychiatric disorders, congenital urogenital abnormalities, urogenital infection, hypogonadotrophic hypogonadism, hyperprolactinemia, and those who had taken psychotropic or antidepressant medications or medications for ED in the previous three months. Patients were divided into three groups according to surgical intervention: Group I; included all patients, Group II; included patients, who underwent varicocelectomy, and Group III; included a control group, and patients without varicocele.

All participants were instructed not to take any medication for ED during the follow up period. Patients were followed up on after six months. In addition to medical history and physical examination, serum testosterone, and scrotal ultrasonography, IIEF-5 scores were assessed for each participant and compared with baseline values. All serum Total Testosterone (TT) measurements were obtained between 8:00 AM and 11:00 AM. Semen analyses and serum levels of Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH) were evaluated. Normal values are as follows: Testosterone (3 ng/ml to 12 ng/ml), LH (1.5 IU/ml to 9.2 IU/ml), and FSH (1 IU/ml to 14 IU/ml).

This study was approved by the institutional review board of our hospital. The study was conducted between January 2015 and December 2016. The varicocele surgery in our patients was performed according to the Palomo procedure, which is open retroperitoneal high ligation [9].

Statistical analysis

The SPSS 17.0 package for Windows (SPSS, Chicago, IL) was used for statistical analysis and all the values were expressed in terms of means ± SD.

Comparisons of data within groups were performed using paired *t*-test, and comparisons between groups using independent *t*-tests, when appropriate for continuous variables. A *P*-value of ≤ 0.05 was considered statistically significant. Independent variables were: binary variables (smoking status), continuous variables (age, body mass index, BMI), and categorical variable (grade of varicocele). Comparison of data within groups was performed using paired t-test, and comparison between groups using independent t-test.

Results

The study included 265 infertile patients at the andrology department diagnosed with varicocele (group 1), out of which 72 patients were operated on (group 2), and 28 healthy men; served as the control group.

Table 1: 72 patients after varicocele surgery.

Semen analysis	IIEF-5	Testosterone	FSH
Normospermia, n=27	Mean 21.74 ± 1	Mean 3 ± 0.01	Mean 2.2 ± 2
Asthenospermia, n=12	IIEF-5 <22, n=22 (30.5%)	Median 3.1	Median 1.2
Oligospermia, n=6	IIEF-5 ≥ 22, n=50 (69.5%)		
Teratospermia, n=3			
OAT-Syndrome, n=12			
Astheno-Teratospermia, n=6			
Oligo-Asthenospermia, n=3			
Oligo-Teratospermia, n=3			

Descriptive and clinical characteristics of group 2 are shown in Table 1. Of 265 patients, only 72 patients agreed to surgery. Average follow-up was 22 months. There was no varicocele recurrences noted during this period.

In the study group, the mean age was 33.6 ± 6.9 years, sixty patients had varicocele grade I on the left side, 101 patients had varicocele grade II on the left side, 93 patients had varicocele grade III on the left side, 3 patients had a bilateral varicocele, and 8 patients had a varicocele on the right side. The mean BMI was 24 ± 3.2, and 176 patients were non-smokers. Sixty-nine patients had normospermia in semen analysis, 47 patients had asthenospermia, and 44 had OAT-Syndrome (Oligo-Astheno-Teratospermia-Syndrome). The majority of patients (184, 69.4%) had normal IIEF-5 scores, 81, patients (30.6%) had IIEF-5 scores under 22 and 4 (1.5%) patients had lower total testosterone values under 3.

The indication for surgery was only pathologic semen analysis. In group 2 (operation group), 27 patients had normospermia, 12 patients had OAT-syndrome in semen analysis, 22 patients had erectile dysfunction despite operation, and all patients had normal total testosterone values.

The relative risk to have erectile dysfunction in patients with a varicocele in our study was 8.55, 95% CI: 1.23-59.15 (p=0.02), odds ratio was 11.8, 95% CI: 1.58-88.97 (p=0.01), z-statistic was 2.3, chi-square test for association was 6.83, (p-value: 0.004) , absolute risk increase was 0.2 (95% CI: 0.39-0.14), relative risk increase was 7.5 (95% CI: 59.4-0.21), number needed to harm was 3.7 (95% CI: 2.5-6.98), and patient expected event rate was 0.035. The relative risk to have a pathologic total testosterone level in patients with a varicocele in our study was 0.42 (95% CI: 0.049-3.65), odds ratio was 0.41 (95% CI: 0.04-3.8), z-statistic was 0.7, chi-square test for association was 0.001, (p-value: 0.4), absolute risk reduction was 0.02 (95% CI: -0.04 to 0.09), relative risk reduction was 0.5 (95% CI: -2.6 to 0.9), and number needed to treat was 48.49 (95% CI: 11 to -20,1).

The paired t-test showed significant p values (p<0.001) in the following paired parameters: Age and IIEF-5 scores, BMI and varicocele grade, semen analysis and varicocele grade, varicocele grade and testosterone values, smoking status and IIEF-5 scores, testosterone values and BMI and testosterone and IIEF-5 scores. ANOVA analysis showed significant p values (p=0.002) between varicocele grades on both BMI and IIEF-5 scores. On multiple regressions there was a significant relationship between the different grades of varicocele and BMI and IIEF-5 scores. Independent t-test (Levene's test for equality of variances) showed a significant

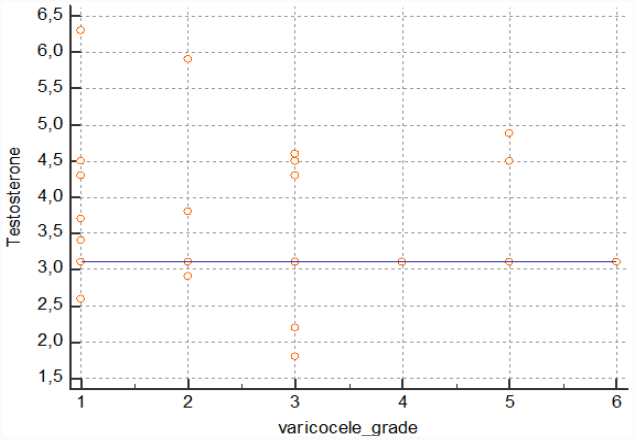

Figure 1: Shows distribution of testosterone values in different grades of uni or bilateral varicoceles.

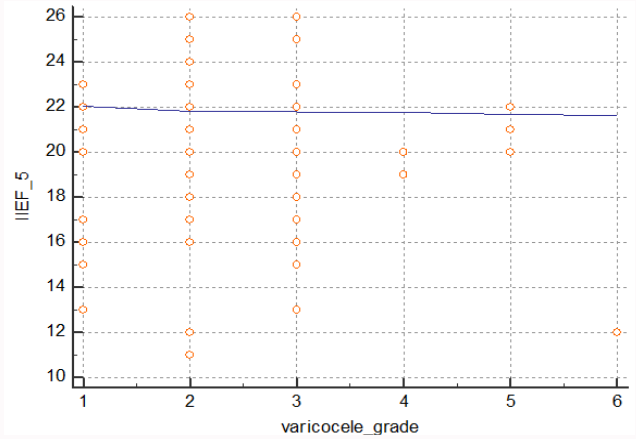

Figure 2: Shows distribution of IIEF-5 score in patients with different grades of varicocele.

correlation between grade of varicocele and IIEF-5 scores (p=0.02), BMI and total testosterone (p=0.01). Figure 1: Shows distribution of the total testosterone in patients with different grades of varicoceles.

In linear regression there was a significant relationship between grade of varicocele and IIEF-5 scores (p=0.006), grade of varicocele and total testosterone (p=0.003), grade of varicocele and semen analysis (p=0.004), and grade of varicocele and BMI (p=0.03). Figure 2: Shows the distribution of IIEF-5 score in patients with different varicoceles. The IIEF-5 scores in groups 1 and 2 were 21.01 ± 2.2, and 21.74 ± 1 respectively, t-test for equality of variance was significant (p<0.0001). Total testosterone level in group 1 and 2 were 3.16 ± 0.37, and 3 ± 0.01 respectively, and t-test for equality of variance was significant (p<0.0001). The results in semen analysis were better in group 2 (after surgery) (28.6%, p<0.001) in comparison to group 1. Interestingly, pre-operative serum testosterone levels were lower in patients with later improvement of semen analysis (p=0.05). Body mass index (p=0.8), pre-operative serum FSH (p=0.9), LH (p=0.2), and nicotine consumption (p=0.6) were similar in both the groups that saw improvement and the group with no change in semen quality.

Discussion

Varicocele surgery improved partly erectile function, as well as serum testosterone. Furthermore, these improvements are not necessarily correlated.

Indication for surgery in our study was male infertility, as this is the most common indication accepted amongst experts [10]. Semen parameters improved by 37.5%, which may potentially have an impact on overall fertility and pregnancy rates. However, some studies do not show that varicocele surgery could improve pregnancy rates [11].

There are two main surgical approaches to varicocele correction: High spermatic vein ligation (open or laparoscopic) and (sub) inguinal (macroscopic or microscopic) spermatic vein ligation. Current studies cannot provide clear evidence as to which technique provides the best outcomes, yet indicate that microsurgery should be a first choice [15,16]. The only disadvantage of this technique is the duration of the surgery and there is a higher likelihood of spermatic artery injury resulting in testicle atrophy. In our study there were no complications documented, and no testicle atrophy.

Given the progressive nature of the effects of varicoceles on spermatogenesis and testosterone production [12], early repair can be advocated for, as it is easier to prevent future infertility and androgen deficiency rather than treating it after it has occurred. Current challenges in the management of varicoceles lie in determining which patients stand to benefit the most from surgical correction in when facing low testosterone levels [13]. In our study, total testosterone levels after surgery were normal in all patients, potentially due to the fact that only four patients had pathologic testosterone levels before surgery.

Few studies evaluated the association between varicoceles and erectile dysfunction. In a study that performed a population-based analysis to evaluate these associations after stratifying by age, the youngest men with ED were found to have the strongest magnitudes of association with a varicocele (OR: 5.2, CI: 3.27–8.28; *P*<0.001) [14]. In our study, the odds ratio for this association was 11.8 (95% CI: 1.58-88.97; p=0.01).

The most significant improvement in sperm parameters were found three months post-operatively in both groups in 28.6% of patients. There were no complications. According to Bryniarski et al. [17] in the microsurgical group, such an improvement is not significant and may only weakly influence pregnancy rate. There is no explanation for why some parameters improve better than others. Moreover, this group did not show testicular volume increases after the operation, and hormone levels and erectile function were unaffected. This is in agreement with our findings, although we did not use the microsurgical approach, as only four patients had low testosterone levels and we did not notice testicular atrophy after surgery. It also suggests that varicoceles might be a heterogeneous condition with different levels of testicle parenchyma injury [17].

Weiss et al. [18] reported impaired testosterone synthesis in patients with varicoceles. Other studies have suggested Leydig cell dysfunction and impaired testosterone synthesis [19]. The effect of varicocelectomy on serum testosterone level is not yet fully established. While some studies have found no significant effect, others reported a normalization of the testosterone level following surgical repair of the varicocele [20]. This is in agreement with our results, as all patients had normal testosterone after surgery.

Animal models of varicoceles have demonstrated decreased intratesticular levels of testosterone and increased Leydig cell

apoptosis compared to controls [21-23].

Testicular biopsies of men with varicoceles demonstrate decreased intracellular Leydig cell testosterone with compensatory hyperplasia [24].

In a study of over 800 men, infertile men with varicoceles had lower serum testosterone compared to fertile men undergoing vasectomy (416 ng/dL *vs.* 469 ng/dL, respectively) [25]. Additionally, fertile men with varicoceles had lower testosterone compared to fertile men without varicocele (397 ng/dL *vs.* 505 ng/dL, respectively) [15]. A meta-analysis of nine human studies analyzing testosterone changes after varicocelectomy reported a mean increase of 97.48 ng/dL (95% CI, 43.73-151.22) after repair [13].

The significance of the increase in serum testosterone after varicocele surgery has not been studied extensively. Sexual dysfunction is one of the most prevalent manifestations of hypogonadism. In a study of 48 impotent men who underwent bilateral varicocelectomy, the authors reported an improvement in sexual activity of 50% to 70%. The impact of varicocele surgery on erectile function was evaluated using the 5-item version of the International Index of Erectile Function (IIEF-5) [26]. Forty-nine hypogonadal men who had a varicocelectomy improved their IIEF-5 score from a baseline of 17.1 ± 2.7 to 19.7 ± 1.8 ($P = 0.001$) six months after surgical repair [27]. No study so far has shown that increasing testosterone levels results in improvement in erectile function, especially in eugonadal men [28], this completely in agreement with our results. Consistent with the most studies, patients in this study experienced a significant increase in total testosterone and sexual function after varicocele surgery. The surgical approach used might have played a role in this response, as the Palomo procedure was used. Additionally our center is a high-volume center for varicocele surgery; all patients were infertile with a grade II or III varicocele.

In our study, 81 patients from 265 had erectile dysfunction, which was reduced to 22 patients after surgery. Of these, only 4 had abnormal testosterone. There is no solid explanation for this outcome.

Luo et al. [29] reported that impairment of the testis associated with a varicocele was gradual and the level of intratesticular testosterone declined earlier than the level of serum testosterone. This difference in declining times between the intratesticular and periphery testosterone could be one of the reasons for the contradictory outcomes reported by many investigators, and this could be one explanation for the results of this study.

In contrary to the reports of these studies, other studies showed no significant difference in testosterone production in varicocele patients after surgery [30-32]. Reşorlu et al. [33] reported that no significant change in testosterone levels was observed in three age-groups with varicoceles after surgery.

One limitation of our study is its retrospective nature and the short follow up. The findings of this study are consistent with previous reports, which show improvements in testosterone and erectile function in patients undergoing a varicocele surgery. A large prospective study to further analyze this subject is highly recommended.

Conclusion

Semen quality improved in 37.5% of our patients after varicocele surgery. Erectile dysfunction improved partly after varicocele surgery. Moreover, these improvements are not necessarily correlated. Our study reported that a lower pre-operative serum testosterone level might be a possible indicator for successful surgical outcome.

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