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Factors Associated with Improved Semen Characteristics Following Microsurgical Sub-inguinal Varicocelectomy among Infertile Men in Tamale, Ghana

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Authors' contributions

This work was carried out in collaboration among all authors. Authors YA, AAA, and NA designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors YA, SBB, VA, and PPMD carried out the sample collection and immunoassays. Authors YA, LQ, SBB, and PPMD managed the analysis of the study, software and did the validation. Authors YA, AAA, PPMD, and VA managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To determine factors associated with improved semen characteristics post microsurgical sub-inguinal varicocelectomy.
Study Design: An interventional study design
Place and Duration of Study: Department of Surgery (Urology Unit), Tamale Teaching Hospital (TTH), Ghana, between September 2017 to August 2021
Methodology: A total of 127 oligozoospermic patients with varicoceles requiring varicocelectomy

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were recruited. Patients were categorized into two groups; ‘responders’ and ‘non-responders’. Patients who showed significant improvement in semen characteristics (sperm count, concentration, motility, and morphology) 12 months after varicocelectomy were grouped as responders, whereas those who showed no improvement 12 months after surgery were considered non-responders. The predictive factors considered were; age, body mass index, varicocele grade, testicular hemodynamic, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and semen characteristics. These factors were assessed using logistic regression analysis at an alpha value of 0.05.

Results: The men were aged between 31.0 and 67.0 years old. Among the 127 patients, sperm concentration significantly ($p < 0.0001$) improved from 7.86 ± 3.876 to 32.87 ± 15.57 x 10^6/mL and sperm motility increased from 34.40 ± 5.134 to 62.41 ± 12.93 x 10^6/mL in 69 patients (54.3%). In the logistic regression analysis, pre-operative serum FSH (aOR = 0.494; 95% CI: 0.267-0.913; p = 0.02), total testosterone (aOR = 3.618; 95% CI: 1.325 - 9.879; p = 0.01) and resistive index (L_RI cap) on the left capsular arteries (aOR = 0.452; 95% CI: 0.211 – 0.969; p = 0.045) were predictors of improved sperm concentration.

Conclusion: Microsurgical sub-inguinal varicocelectomy improved sperm characteristics. The predicting factors associated with improved semen characteristics post varicocelectomy are high testosterone, low serum FSH, and low left capsular resistive index (L_RI cap).

Keywords: Varicocele; varicocele repair; infertility; hypogonadism; testicular hemodynamic.

1. INTRODUCTION

Varicocele is a disorder of venous return caused by abnormal dilatation of pampiniform plexus draining the testicles [1,2]. This condition is commonly found in men with both primary and secondary male factor fertility [3,4] with an incidence of 21% to 45% in men with primary infertility, and 75% to 81% with secondary infertility [5-7]. Due to anatomical position, the majority (> 90%) of varicoceles are left-sided with about 1.1% being bilateral, and 0.2% isolated right varicoceles [8].

Varicocele affects fertility but the etiology remains debatable. A few studies have reported no effect [9-11] but recent studies have shown that varicocele causes decrease testicular function, leading to altered spermatogenesis and diminished testosterone levels [12,13]. Sertoli and Leydig cells are responsible for spermatogenesis and testosterone production respectively and both are located nearby in the testis. These cells may be affected by changes within the testicular environment such as; hypoxia in the testes as a result of venous stasis [14], sperm DNA damage caused by increased production of reactive oxygen species [15], increased scrotal temperature [16], and reflux from the adrenal vein into the spermatic vein [17].

Long-standing varicocele is associated with Leydig cell dysfunction and hypogonadism [18]. Among patients who are affected, there is evidence of raised serum FSH and LH levels and reduced serum total testosterone concentrations [19,20]. This suggest that varicocele might lead to hormonal dysfunction through the hypothalamic-pituitary-gonadal axis [21].

Varicocelectomy is widely used for the treatment of patients with male fertility factors reporting varicocele. The ultimate aim of this surgical procedure is to improve couples’ chances of achieving a pregnancy and live birth. Several ligation methods are used but commonest and effective treatment is microsurgical sub-inguinal (lymphatic- and artery sparing) varicocelectomy [22]. Based on a long-term study, Cayan et al. [23] proposed that this method improves semen quality and is associated with low post-surgery recurrence and complication rates.

In most men presenting with varicocele, varicocelectomy results in improved semen parameters [24,25] but not all published data agrees to this [26,27]. Based on current evidence, the guidelines and the protocol by the American Urological Association (AUA), the American Society for Reproductive Medicine (ASRM), and the European Association of Urology (EAU) recommend varicocele repair for patients with palpable varicocele with one or more semen parameter abnormalities’ whether or not they are attempting to conceive a child [12,28]. However, factors to predict which of the varicocele patients are likely to benefit from the varicocele repair in terms of improved semen quality and characteristics have proven to be very difficult. Hence, the study aims to determine the predictive factors of improving semen quality post microsurgical sub-inguinal varicocelectomy.

2. MATERIALS AND METHODS

2.1 Study Duration

The study included 127 oligozoospermic patients with varicoceles referred to Tamale Teaching Hospital for assessment of fertility problems. The study was conducted between September 2017 to August 2021.

2.2 Study Participants

Participants eligible for the study were sexually active men who had maintained a stable heterosexual relationship for at least 2 years and reported male factor fertility. Male factor fertility was defined as the inability of a couple to conceive a child after one year of unprotected sexual intercourse with a normal female partner or spouse (i.e., normal reproductive history, normal ovulation, and tubal patency) [3]. However, participants with a history of mumps orchitis, orchidectomy, undescended testis, uncontrolled hypertension (blood pressure of ≥ 140/90 mmHg), and uncontrolled diabetes (glycated hemoglobin of > 7%) were excluded from the study.

2.3 Data Collection

The men were aged between 31.0 and 67.0 years old. Pre-operative evaluation included; a complete demographic history using a semi-structured questionnaire, physical examination and confirmation of varicocele by ultrasound scan examination, semen analysis, and measurement of serum hormones. Dubin and Amelar [29] approach was used to detect, confirm, and clinically-grade varicocele. Varicocele was graded as grade I (palpable only during the Valsalva maneuver), grade II (palpable without the Valsalva maneuver), or grade III (visible without palpation) [30]. A duplex Doppler ultrasound of the testes (Samsung Medison Accuvix V20 scan, Samsung Electronics, South Korea) with measurement of PSV (peak systolic velocity), EDV (end-diastolic velocity), and RI (resistive index) for capsular and centripetal arteries was done to evaluate testicular malposition, blood reflux along the pampiniform plexus, or the extent of any fluid collections.

Semen analysis was performed using two different semen specimens (mean values adopted), each obtained by masturbation after 3 to 5 days of sexual abstinence. The pre-operative semen specimens were collected at least 2 weeks before the surgery while the post-surgery specimens were collected at 9 months and 12 months intervals respectively. The semen samples were analyzed according to WHO criteria [31]. From the sperm concentration, participants were categorized into two groups; responders and non-responders. Responders were participants who showed significant improvement (more than 50% rise was recognized at least two times post-operatively in comparison with such counts before operation) in semen characteristics (sperm count, sperm concentration, motility, and morphology) 12 months post varicocelectomy, whereas those who showed no improvement 12 months after surgery were considered non-responders [32].

Blood samples were collected before and after surgery for the fertility hormones assay. Serum FSH (follicle-stimulating hormone) and LH (luteinizing hormone) were measured by electrochemiluminescence with a Hitachi-Roche analyzer (Cobas 6000, Roche Diagnostics, IN, USA). Serum total testosterone was analyzed by radioimmunoassay.

2.4 Statistical Analysis

Data were entered into Microsoft Excel version 10 (www.microsoft.com) and exported to SPSS version 23 (SPSS Inc., Chicago, IL, USA) for analysis. Categorical variables were presented as frequency (percent) and continuous variables are presented as mean ± SD. Statistical analyses were performed using the Mann-Whitney test and Chi-square test. Predictors of improved semen characteristics were assessed using univariate and multivariate logistic regression analysis. A two-tailed p-value less than 0.05 was considered statistically significant.

3. RESULTS AND DISCUSSION

3.1 Background of Oligozoospermic Patients

Among 127 patients, improved sperm concentration was observed in 69 participants (responders, 54.3%). After microsurgical sub-inguinal varicocelectomy, sperm concentration significantly increased from 7.86 ± 3.876 to 32.87 ± 15.57 million per millilitre ($p < 0.0001$) (Table 1). Significant differences were seen in post-operative L_EDVcap ($p = 0.04$), L_RIcap ($p =$

0.02), serum FSH (p = 0.01), LH (p = 0.041), total testosterone (p = 0.03), sperm concentration (p <0.0001), sperm count (p <0.0001), sperm motility (p <0.0001), and normal sperm morphology (p <0.0001) between responders and non-responders.

In the responders' group, sperm count significantly improved from 29.40 ± 8.154 to 136.0 ± 64.50 (p < 0.0001) after microsurgical varicocelectomy. Also, sperm motility and normal sperm morphology values significantly (p < 0.0001) increased post-surgery (Table 1).

Table 1. Background of oligozoospermic patients

Variable	**Oligozoospermic patients (n = 127)**		**p-value**
	Responders (n = 69)	**Non-responders (n = 58)**	
Age (years)	49.50 ± 2.677	51.00 ± 2.554	0.10
Anthropometry measurements			
BMI (kg/m^2)	25.34 ± 1.452	23.90 ± 2.944	0.14
Body fat (%)	16.25 ± 3.545	18.94 ± 8.066	0.31
Muscle mass (%)	34.10 ± 4.630	35.76 ± 4.357	0.82
Visceral fat (%)	7.500 ± 2.014	7.860 ± 3.583	0.76
Blood pressures			
SBP (mmHg)	130.5 ± 6.932	129.5 ± 6.152	0.87
DBP (mmHg)	83.70 ± 5.417	82.21 ± 5.506	0.72
Varicocele grade			
Grade II	40 (58.0%)	37 (63.8%)	0.64
Grade III	19 (42.0%)	21 (36.2%)	
Hemodynamics			
Pre-operative L_PSVcap	11.05 ± 0.3629	11.11 ± 1.624	0.90
Post-operative L_PSVcap	10.37 ± 0.2983	10.57 ± 1.347	0.63
Pre-operative L_EDVcap	4.220 ± 0.2573	4.695 ± 0.8454	0.08
Post-operative L_EDVcap	4.180 ± 0.1476	4.707 ± 0.8178	0.04
Pre-operative L_RIcap	0.6190 ± 0.01197	0.6465 ± 0.04660	0.09
Post-operative L_RIcap	0.5558 ± 0.03692	0.5840 ± 0.02171	0.02
Hormones			
Pre-operative FSH (IU/L)	24.15 ± 2.398	23.70 ± 2.905	0.68
Post-operative FSH (IU/L)	15.58 ± 2.744	18.81 ± 3.806	0.01
Pre-operative LH (IU/L)	10.350 ± 3.261	11.92 ± 3.827	0.36
Post-operative LH (IU/L)	7.790 ± 1.264	9.558 ± 2.482	0.04
Pre-operative Total Testosterone (nmol/L)	2.100 ± 0.4110	2.121 ± 0.7906	0.93
Post-operative Total Testosterone (nmol/L)	5.400 ± 1.299	4.579 ± 1.219	0.03
Semen parameters			
Pre-operative sperm concentration (x 10^6 mL^{-1})	7.86 ± 3.876	7.898 ± 3.704	0.36
Post-operative sperm concentration (x 10^6 mL^{-1})	32.87 ± 15.57	8.550 ± 4.039	< 0.0001
Pre-operative sperm count (x 10^6 mL^{-1})	29.40 ± 8.154	28.47 ± 12.45	0.47
Post-operative sperm count (x 10^6 mL^{-1})	136.0 ± 64.50	29.76 ± 9.462	< 0.0001
Pre-operative sperm motility (%)	34.40 ± 5.134	33.40 ± 7.634	0.76
Post-operative sperm motility (%)	62.41 ± 12.93	42.40 ± 14.37	< 0.0001
Pre-operative normal sperm morphology (%)	4.60 ± 2.459	3.19 ± 1.692	0.90
Post-operative normal sperm morphology (%)	7.07 ± 1.184	4.20 ± 1.269	< 0.0001

Quantitative variables were compared using the Mann-Whitney test and varicocele grading were compared using Chi-square test. BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; L_PSVcap – Left peak systolic velocity for capsular and centripetal arteries; L_EDVcap – Left_end diastolic velocity for capsular and centripetal arteries, L_RIcap – Left resistive index for capsular and centripetal arteries, FSH – a follicle-stimulating hormone, LH – luteinizing hormone

Table 2. Predictors of sperm concentration improvement

Variable	Univariate		Multivariate	
	Odds ratio (95% CI)	**p-value**	**Odds ratio (95% CI)**	**p-value**
Age (years)	0.467 (0.284 - 1.766)	0.68	0.452 (0.183 - 1.115)	0.08
BMI (kg/m^2)	1.197 (0.939 - 1.527)	0.14	1.654 (0.901 - 2.708)	0.06
Varicocel grade	0.966 (0.778 - 1.200)	0.75	0.942 (0.840 - 1.056)	0.30
Blood pressures				
SBP (mmHg)	1.003 (0.963 - 1.045)	0.86	1.023 (0.939 - 1.114)	0.60
DBP (mmHg)	1.099 (0.710-1.196)	0.51	1.207 (0.825 - 1.421)	0.31
Pre-operation Hemodynamic				
L_PSVcap	0.864 (0.475 - 1.570)	0.63	0.737 (0.338 - 1.609)	0.44
L_EDVcap	0.308 (0.077 - 1.234)	0.09	0.305 (0.071 - 1.314)	0.11
L_RIcap	0.528 (0.148 - 0.989)	0.04	0.452 (0.211 – 0.969)	0.04
Hormones				
FSH (IU/L)	0.645 (0.445 - 0.937)	0.02	0.494 (0.267-0.913)	0.02
LH (IU/L)	0.811 (0.648 - 1.016)	0.06	0.803 (0.467 - 1.380)	0.42
Total Testosterone (nmol/L)	2.301 (1.274 - 4.156)	0.01	3.618 (1.325 - 9.879)	0.01
Semen parameters				
Pre-operative sperm concentration (x 10^6 mL^{-1})	1.798 (1.234-2.619)	0.002	2.176 (1.108 - 4.273)	0.02
Pre-operative sperm count (x 10^6 mL^{-1})	1.082 (1.012 - 1.157)	0.02	1.059 (0.975 - 1.149)	0.17
Pre-operative sperm motility (%)	1.052 (0.981 - 1.127)	0.15	1.058 (0.951 - 1.178)	0.29
Pre-operative morphology (%)	0.997 (0.947 - 1.049)	0.90	0.980 (0.913 - 1.052)	0.57

Predictors of improved semen characteristics were assessed using univariate and multivariate logistic regression analysis; BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; L_PSVcap – Left peak systolic velocity for capsular and centripetal arteries; L_EDVcap – Left_end diastolic velocity for capsular and centripetal arteries; L_RIcap – Left resistive index for capsular and centripetal arteries; FSH – a follicle-stimulating hormone, LH – luteinizing hormone

3.2 Factors Associated with Improvement of Sperm Concentration

In the univariate binary logistic regression analysis, resistive index (L_RIcap) [odds ratio (OR) = 0.528; 95% confidence interval (95% CI): 0.148 - 0.989; p = 0.04], serum FSH (OR = 0.645; 95% CI: 0.445 - 0.937; p = 0.02), total testosterone (OR = 2.301; 95% CI: 1.274 - 4.156; p = 0.01), and sperm count (OR = 1.082; 95% CI: 1.012 - 1.157; p = 0.02) were the factors associated with improvement of sperm concentration. In the multivariate analysis, after adjusting for resistive index, serum FSH, serum total testosterone, and sperm count; a positive correlation with serum total testosterone (aOR = 3.618; 95% CI: 1.325 - 9.879; p = 0.01) and negative correlations with both serum FSH (aOR = 0.494; 95% CI: 0.267-0.913; p = 0.02) and L_RIcap (aOR = 0.452; 95% CI: 0.211 – 0.969; p = 0.04) were observed. In summary, pre-operative high testosterone, low serum FSH, and low resistive index were factors associated with improved sperm concentration (Table 2).

4. DISCUSSIONS

Varicocele affects spermatogenesis [33] and many studies have reported alterations in semen characteristics in patients with varicocele [13,16,34,35]. These had led to the conclusions that varicocele is responsible for 45 – 80% of infertility in men [36-38].

Though several studies concluded that varicocele repair results in improvement of semen characteristics [24, 25], not all findings support this claim [26,27]. We initially reported significant improvement of semen characteristics following microsurgical sub-inguinal varicocelectomy [35]. In this study, however, the aim is to retrospectively analyze the factors potentially related to the surgery outcome. Among the 127 participants studied, 54.3% had improved sperm concentrations post varicocelectomy. This is in line with the findings by Kondo et al. [32] in which 57% of patients were reported to have improved sperm parameters following a varicocele repair. Again, Chen and Chen [39] reported a much higher (71.4%) improvement of semen characteristics in infertile patients 6-months after the varicocele repair.

Dubin and Amelar [40] performed surgical correction of varicocele on 986 cases over twelve years and found that 70 percent of patients had improved semen quality, and 53 percent of wives became pregnant. The study concluded that the results were better for patients who had pre-operative sperm counts greater than 10^6 mL^{-1} than for patients who had pre-operative sperm counts of less than 10^6 mL^{-1} [40]. Segenreich et al. [41] later reported a better pregnancy outcome despite counts below these values (< 10^6 mL^{-1}). In this study, patients with sperm count greater than 10 million per milliliters before varicocele repair had improved semen characteristics (OR = 1.082; p = 0.021) compared with those with a sperm count of lesser values. However, sperm count was not a better predictor when adjusted for by confounders. This result contradict the findings by Kondo et al. [32] who reported that sperm count before ligation was not a predictor of improved seminal parameters.

The absence of universally standardized criteria for improvement of semen parameters has predicted patients who are likely to benefit from varicocele repair very difficult. Fewer studies have considered factors associated with surgical outcome in varicocele. For instance, Giannakis et al. [42] found that testicular telomerase activity was the main parameter predicting the effect of varicocelectomy on spermatogenesis but Ishikawa and Fujisawa [43] and Kondo et al. [32] found that age (i.e., as one grows older, telomerase activity decreases) was not a significant predictor in both univariate and multivariate analysis.

Huang et al. [44] in a more recent study grouped men who had varicocele into “responders” and “non-responders” base on semen analyses at 3, 6, and 12 months post-operatively. They found that patient age (OR = 0.56; p < 0.0001) and pre-operative sperm density (OR: 1.22; p = 0.0001) were significantly associated with the likelihood of successful varicocele repair [44]. Similarly, Samplaski et al. [4] also found that patient age, varicocele grade, and pre-operative semen parameters (ejaculate volume, sperm concentration, total motile sperm count, motility, and normal sperm morphology) were associated with improved semen parameters post varicocelectomy. In this study, pre-operative sperm count predicts improved sperm concentration at the univariate analysis but patient age and varicocele grade were not predictors of sperm concentrations.

The effect of varicocele on Leydig cell function and testosterone biosynthesis is still a subject of debate. Many of the existing findings have conflicting results. Studies by Pasqualotto et al. [45] and Segenreich et al. [41] found no significant effects of varicocele repair on testosterone levels. However, other studies reported a significant improvement of gonadal function following varicocelectomy [18,46,47]. According to WHO [48], a varicocele may be a factor in the progressive worsening of testicular function (both steroidogenesis and spermatogenesis) over time and this may result in high serum FSH and low testosterone levels in patients. In this study, pre-operative low serum FSH and high testosterone were predictors of improved sperm concentration. This is consistent with the findings of Kondo et al. [32] who reported similar results as good prognostic factors for varicocelectomy. Similarly, studies by Chen and Chen [39] found that among other factors, low serum FSH (<11.3 mIU/Ml) was a predictor of improved semen characteristics after varicocele repair. The possible explanation may be that patient with normal Sertoli and Leydig cell functions benefits from the microsurgical sub-inguinal varicocelectomy.

An inverse correlation between body mass index (BMI) and incidence of varicocele has been reported [49,50]. However, there is limited available published data on the correlation of BMI with the improvement of semen characteristics post-varicocelectomy. In this study, BMI was not a predictor of improved semen concentration and this agrees with findings by Chen and Chen [39] who reported similar findings among 35 men who had undergone varicocelectomy.

Varicocele is a disorder in which the pampiniform plexus draining the testicle is enlarged, with reflux of venous blood [2,51]. The consequence of this venous abnormality is often arrest of ipsilateral testicular growth, thus arterial ‘insufficiency’ and hypoperfusion of testicular tissues. Afoko et al. [1] reported a significant reduction in arterial perfusion of testicular tissues evidenced by the increase in the resistive index (RI) in an observed group compared with improved testicular perfusion evidenced of decreased RI in the surgery group among adolescents with left-sided varicocele. Resistive index (RI) is an ultrasonic parameter showing microcirculation function and testicular parenchymal perfusion [52] The S-D/S formula, where S represents peak systolic velocity (PSV) and D stand for end-diastolic velocity (EDV), is used to measure the index (RI). Increased RI in the testes is associated with disruptions in microcirculation as a result of a significant reduction in testicular blood flow [52-54]. In this study, pre-operative low resistive index (RI) on the left capsular artery was a factor associated with improved sperm concentration in logistic regression analyses. Afoko et al. [1] concluded that the main hemodynamic indicator that strongly correlates with semen quality characteristics among adolescents with varicocele was resistive index (RI) especially in centripetal arteries and this may be true for adults as well.

Given the predictive factors associated with improved semen parameters in patients with varicocele, it is worth recognizing that improvement on the semen quality post varicocele repair does not guarantee patients to father children. Further studies on a larger population of varicocele patients with pregnancy rate as the primary outcome will help to conclusively determine the effectiveness of microsurgical sub-inguinal varicocelectomy.

5. CONCLUSION

These findings suggest that the significant predictive factors associated with improved semen characteristics following microsurgical sub-inguinal varicocelectomy in infertile men are; pre-operative low serum FSH, high testosterone, and low left capsular resistive index (L_RI cap).

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

All authors declare that written informed consent was obtained from all participants before the study. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal.

ETHICAL APPROVAL

The study was approved by the Ethics and Review Board of the Department of Research and Development, Tamale Teaching Hospital (Number: TTH/R&D/SR/119). Thus, the study has been performed following the standard laid down protocol in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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