

Original Research

Sperm DNA Fragmentation in Infertile Men With Varicocele: Clinical Epidemiology and Comparative Assessment of Microsurgical Varicocelectomy and Antioxidant Therapy

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Abstract

Background: Varicocele, a common condition affecting male fertility, has been linked to impaired semen quality and elevated sperm DNA fragmentation (SDF). This study aimed to evaluate the epidemiological prevalence of varicocele and SDF in infertile men and compare the effectiveness of microsurgical varicocelectomy and antioxidant therapy in improving semen parameters and reducing SDF. **Methods:** This multi-center study included 3632 subfertile and 276 fertile men in the epidemiological phase (retrospective) and 182 infertile men in the comparative analysis phase (prospective). Patients were stratified into three groups: Group 1 (microsurgical varicocelectomy, $n = 86$), Group 2 (antioxidant therapy, $n = 63$), and Group 3 (control, $n = 33$). Varicocele prevalence, semen parameters, and SDF levels were assessed, with follow-up evaluations conducted three months post-intervention. Semen parameters were evaluated using the World Health Organization (WHO) Fifth Edition guidelines, and SDF was measured using the sperm chromatin dispersion test. **Results:** Varicocele was observed in 29.5% of subfertile men and 27.2% of fertile men, with no statistically significant difference noted ($p = 0.18$). However, subfertile men with varicocele exhibited significantly higher median SDF levels (20.8%, interquartile range (IQR): 14.1–27.9) compared to fertile men (12.3%, IQR: 9.1–16.5; $p < 0.001$). Microsurgical varicocelectomy significantly improved semen parameters, with the median sperm concentration increasing by +25.0 million/mL (IQR: 18.4–31.5; $p < 0.001$) and progressive motility by +67.0% (IQR: 50.0–83.5; $p < 0.001$). Antioxidant therapy yielded moderate improvements in sperm concentration (+11.0 million/mL, IQR: 8.0–14.5; $p < 0.001$) and motility (+6.0%, IQR: 4.0–8.5; $p = 0.01$). The control group showed no significant changes. **Conclusion:** This study reveals comparable varicocele prevalence between subfertile (29.5%) and fertile men (27.2%), with impaired semen quality and elevated SDF levels in subfertile cases. Microsurgical varicocelectomy proved most effective, while antioxidant therapy offered a viable alternative or adjunct for non-surgical candidates, underscoring the need for tailored varicocele infertility treatments.

Keywords: varicocele; sperm DNA fragmentation; semen parameters; antioxidant therapy; varicocelectomy

1. Introduction

Varicocele, a condition marked by abnormal dilation of the pampiniform plexus veins, affects approximately 15–20% of men in the general population and up to 40% of men with primary infertility, making it a significant contributor to male infertility [1,2]. The detrimental effects of varicocele are primarily attributed to increased scrotal temperature, oxidative stress, and hypoxia in the testicular environment, all of which promote reduced routine semen parameters and increased sperm DNA fragmentation (SDF) [3,4].

SDF has emerged as a critical biomarker for male fertility, correlating with poor embryo quality, lower fertilization rates, and increased miscarriage risk [5–7]. The relationship between varicocele and elevated SDF has been well-documented, highlighting the roles in reducing sperm chromatin integrity and impairing fertility outcomes [2,8]. High levels of reactive oxygen species (ROS) in varicocele

patients are also implicated as the primary cause of oxidative DNA damage, further exacerbating the negative effects on reproductive potential [6,9].

Microsurgical varicocelectomy has become an effective intervention for restoring fertility in varicocele patients, with meta-analytic evidence supporting its role in improving semen parameters and reducing SDF [10–12]. In parallel, antioxidant therapy, utilizing agents such as coenzyme Q10, selenium, and vitamins C and E, offers a less invasive approach by mitigating oxidative stress and protecting DNA integrity [11,13–15]. However, comparative studies on the efficacy of these interventions remain limited.

This study aimed to provide a comprehensive analysis of the epidemiology of varicocele, its impact on SDF, and a comparative evaluation of microsurgical varicocelectomy and antioxidant therapy in reducing SDF and improving semen quality.



2. Materials and Methods

2.1 Study Design and Patient Selection

This multi-center study was conducted in two primary phases: an epidemiological analysis (Phase 1: case-control retrospective study) and a comparative treatment analysis (Phase 2: retrospective study). Uniform inclusion and exclusion criteria were consistently applied to ensure standardization in this multi-center study, and data were meticulously reviewed to ensure accuracy and comparability across centers.

2.1.1 Phase 1: Epidemiological Analysis

A total of 3632 patients were recruited to assess the prevalence of varicocele and its impact on semen parameters. These patients were stratified into subfertile men and fertile controls based on their reproductive status.

2.1.2 Phase 2: Comparative Treatment Analysis

A total of 182 patients with clinically diagnosed varicocele and abnormal semen parameters participated in this phase to evaluate the efficacy of microsurgical varicocelectomy and antioxidant therapy.

2.2 Inclusion Criteria

- Men aged 18 to 50 years.
- Clinically diagnosed left-sided or bilateral varicocele.
- Abnormal semen parameters (according to the World Health Organization (WHO) manual Fifth Edition guidelines).
- Seeking infertility treatment, defined as over one year of failed conception attempts.

2.3 Exclusion Criteria

- Azoospermia.
- Severe oligozoospermia (sperm concentration <1 million/mL).
- Normozoospermia (according to the WHO manual Fifth Edition guidelines).
- Active reproductive tract infections.
- Infertility causes other than varicocele, including the female factor of infertility.

Patients in Phase 2 were allocated into three groups:

- Control group (n = 33): Patients receiving no specific treatment beyond observation.
- Antioxidant therapy group (n = 63): Patients undergoing a three-month course of antioxidants.
- Microsurgical varicocelectomy group (n = 86): Patients who underwent microsurgical varicocelectomy.

The control and antioxidant therapy groups included patients who either declined surgery for personal reasons or were unsuitable for surgical intervention due to medical contraindications.

2.4 Interventions

2.4.1 Microsurgical Varicocelectomy

Microsurgical varicocelectomy was performed using a subinguinal approach, which minimizes postoperative pain and vascular injury while enhancing success rates for reducing varicocele and improving semen quality. The procedure was conducted under magnification, which aids in the precise identification and preservation of the testicular artery and lymphatic vessels, reducing the risk of recurrence and postoperative complications. Patients received standard postoperative care, including monitoring for recurrence or adverse events.

2.4.2 Antioxidant Therapy

The antioxidant therapy in this study utilized commercially available nutraceutical formulations frequently prescribed for male infertility. These supplements were tailored to reduce oxidative stress and improve sperm parameters in varicocele patients. The formulations contained the following average components and dosages:

- L-carnitine (1000–2000 mg/day): supports mitochondrial function, enhancing energy production and sperm motility.
- L-arginine (500–1000 mg/day): improves blood flow and supports nitric oxide production, benefiting sperm quality.
- Vitamin C (90–1000 mg/day): a potent antioxidant that neutralizes ROS and protects sperm DNA integrity.
- Vitamin E (200–400 IU/day): stabilizes cellular membranes and prevents lipid peroxidation, enhancing sperm motility and viability.
- Zinc (10–30 mg/day): critical for DNA synthesis, spermatogenesis, and maintaining sperm morphology.
- Folic acid (400–800 µg/day): supports DNA synthesis and repair, contributing to improved sperm quality.
- Selenium (50–100 µg/day): acts as an antioxidant, protecting sperm from oxidative damage and aiding motility.
- Coenzyme Q10 (30–200 mg/day): boosts mitochondrial activity, providing energy for sperm motility and reducing ROS.
- Glutathione (200–300 mg/day): enhances antioxidant defenses, supporting sperm membrane integrity.
- Omega-3 fatty acids (500–1000 mg/day): improves sperm membrane fluidity and may positively affect motility.

These supplements and dosages were selected based on prior studies, which evaluated their effectiveness in mitigating oxidative stress and improving sperm parameters. While uniform doses were applied across all patients, future research should consider weight-based dosing to optimize treatment outcomes [16–18].

Each supplemental combination of these components was tailored for optimal support of sperm quality, with the

course lasting three months. Follow-up semen analysis after the intervention assessed improvements in sperm concentration, motility, morphology, and overall fertility potential.

2.5 Semen Analysis and DNA Fragmentation Testing

Semen samples were collected after a 3–7-day period of sexual abstinence and analyzed according to the WHO Fifth Edition Laboratory Manual for the Examination and Processing of Human Semen. Parameters, including sperm concentration, motility, morphology, and total sperm count, were recorded. SDF was assessed using the sperm chromatin dispersion (SCD) test in agarose gel, providing a robust indicator of oxidative stress and DNA integrity.

The threshold for “clinically significant improvement” (CSI) was calculated based on a reference semen volume of 1.5 mL, sperm concentration of 15 million/mL, and progressive motility of 32%; multiplying these values yields a benchmark of approximately 7.2 million progressively motile sperm.

2.6 Statistical Analysis

Data were analyzed using IBM SPSS software (Version 21.0, IBM Corp., Armonk, NY, USA) and Microsoft Office Excel 2016 (Version 16.0, Microsoft Corp., Redmond, WA, USA). The normality of the data distribution was evaluated using the Kolmogorov–Smirnov test. The mean and standard deviation are presented for normally distributed variables, and parametric tests such as the Student’s *t*-test were applied. The median and interquartile range (IQR) were used for non-normally distributed data, with comparisons made using the Mann–Whitney U test or the Kruskal–Wallis test for more than two groups. Categorical variables were analyzed using the chi-square test, and a *p*-value of <0.05 was considered statistically significant.

Data are expressed as the mean $\pm$ SD for parametric data, while medians with ranges are presented for non-parametric variables. The primary outcomes assessed were improvements in SDF, sperm concentration, motility, and morphology across the different treatment groups and the clinical impact of microsurgical varicocelelectomy and antioxidant therapy on reducing SDF.

A formal power analysis was not conducted due to the retrospective nature of the study. However, the sample size was based on prior researches to ensure adequate statistical power for detecting group differences. Missing data were excluded from the analysis, and no imputation methods were employed.

3. Results

3.1 Epidemiological Findings

In this phase, 3632 subfertile men (Group 1) and 276 fertile men (Group 2) were analyzed for the prevalence of varicocele and its association with semen quality and SDF. Varicocele was observed in 29.5% of subfertile men

and 27.2% of fertile men. Subfertile men exhibited higher rates of Grade III varicocele (1.1%) compared to fertile men (0.7%; *p* = 0.04).

Median SDF levels were significantly elevated in subfertile men (20.8%, IQR: 14.1–27.9) compared to fertile men (12.3%, IQR: 9.1–16.5; *p* < 0.001). Grade III varicocele was associated with the highest SDF levels, emphasizing its negative impact on sperm DNA integrity.

Subfertile men had significantly lower ejaculate volume (median 2.8 mL, IQR: 2.0–3.5), reduced sperm concentration (16.3 million/mL, IQR: 12.0–20.5), and impaired progressive motility (28.7%, IQR: 20.4–36.9) compared to fertile men (median values: 3.1 mL, 34.1 million/mL, and 46.5%, respectively; *p* < 0.001 for all comparisons). Morphologically normal sperm forms were also markedly lower in subfertile men (3.2%, IQR: 2.5–4.1) compared to fertile men (6.7%, IQR: 5.8–7.5; *p* < 0.001). All the above parameters are demonstrated in Table 1.

3.2 Comparative Analysis of Treatment Approaches

This phase included 182 infertile men with varicocele, divided into three groups: Group 1 (microsurgical varicocelelectomy, *n* = 86), Group 2 (antioxidant therapy, *n* = 63), and Group 3 (control, *n* = 33). The outcomes were assessed after three months. The baseline characteristics of the groups are shown in Table 2.

The studied semen parameters changed after the treatment (in 3 months) in Groups 1, 2, and 3 (microsurgery, antioxidant therapy only, and no treatment, respectively), as follows:

3.2.1 Sperm Concentration

Group 1 experienced a significant median increase of +25.0 million/mL (IQR: 18.4–31.5; *p* < 0.001), compared to moderate improvement in Group 2 (+11.0 million/mL, IQR: 8.0–14.5; *p* < 0.01). Group 3 exhibited minimal change (+0.4 million/mL, IQR: –0.5–1.3).

3.2.2 Progressive Motility

Group 1 showed a substantial improvement of +67.0% (IQR: 50.0–83.5; *p* < 0.001), significantly greater than Group 2 (+6.0%, IQR: 4.0–8.5) or Group 3 (no significant change).

3.3.3 SDF Reduction

Groups 1 and 2 demonstrated a median SDF reduction of –5.5% (IQR: –3.5 to –7.5 and –3.2 to –6.8, respectively; *p* = 0.03). No significant improvement was observed in Group 3 (+0.5%, IQR: –0.3 to 1.2).

3.3.4 Morphology and Clinical Improvement

Group 1 exhibited the most pronounced reduction in abnormal sperm morphology (–4.4%, IQR: 3.3–5.0; *p* = 0.05), while Group 2 showed a smaller effect (–2.3%, IQR: 2.1–2.6). Clinically significant improvement, defined as

Table 1. Baseline characteristics of groups (epidemiological study).

Parameter	Group 1 (Subfertile men)	Group 2 (Fertile men)	<i>p</i> -value
Total number of patients	3632	276	-
Male age (years), M ± SD	33.1 ± 5.7	32.1 ± 5.5	0.12
Primary infertility (%)	62.9	-	
Secondary infertility (%)	37.1	-	
SDF level (%), median: IQR	20.8 (14.1–27.9)	12.3 (9.1–16.5)	<0.001
Semen volume (mL), median: IQR	2.8 (2.0–3.5)	3.1 (2.4–3.8)	0.02
Sperm concentration (million/mL), median: IQR	16.3 (12.0–20.5)	34.1 (29.8–41.2)	<0.001
Progressive motility (%), median: IQR	28.7 (20.4–36.9)	46.5 (40.1–53.3)	<0.001
Morphologically normal forms (%), median: IQR	3.2 (2.5–4.1)	6.7 (5.8–7.5)	<0.001
Presence of varicocele (%)	29.5	27.2	0.18
Distribution by varicocele grade:			
Grade I	21.6%	18.8%	0.15
Grade II	6.9%	7.6%	0.23
Grade III	1.1%	0.7%	0.04

SDF, sperm DNA fragmentation; IQR, interquartile range.

Table 2. Baseline characteristics and interventions in comparative analysis.

Parameter	Group 1 (microsurgery)	Group 2 (antioxidant therapy)	Group 3 (control group)	<i>p</i> -value
Type of intervention	Microsurgery	Antioxidants	Observation only	-
Number of patients	86	63	33	-
Mean age (years)	32.1 ± 4.9	33.7 ± 5.2	34.0 ± 5.8	0.09
Varicocele side				
Left, n (%)	70 (81)	46 (73)	25 (76)	0.39
Bilateral, n (%)	16 (19)	17 (27)	6 (24)	0.10
Baseline sperm concentration, median: IQR	15.8 (12.3–18.9)	16.7 (12.5–19.3)	15.1 (12.1–17.8)	0.21
Baseline progressive motility (%), median: IQR	37.6 (25.3–45.8)	32.8 (24.2–42.1)	31.4 (20.4–38.3)	0.15
SDF levels (%), median: IQR	23.4 (15.1–30.7)	20.9 (14.6–28.8)	22.7 (16.5–28.4)	0.12

an increase in progressively motile sperm of more than 7.2 million (WHO 2010 reference values: 1.5 mL (V) × 15 million/mL (C) × 0.32 (PM)), was the highest in Group 1 (65%), followed by Group 2 (42%) and Group 3 (38%; *p* = 0.01). All the above changes are demonstrated in Table 3.

4. Discussion

Varicocele is the most common correctable cause of male infertility, affecting approximately 15–20% of the general population and up to 40% of men with primary infertility [19,20]. The role of varicocele in impairing spermatogenesis through mechanisms such as oxidative stress, elevated scrotal temperature, and hypoxia is well-documented. This study adds to the growing body of literature by exploring the clinical and molecular impact of varicocele on SDF and assessing the effectiveness of microsurgical varicocelectomy and antioxidant therapy in mitigating these effects.

This epidemiological analysis revealed that 29.5% of subfertile men in our cohort presented with varicocele, consistent with global prevalence rates [21,22]. A significant correlation was observed between the severity of varicocele

and increased SDF levels, with Grade III varicocele showing the highest median SDF rate. These findings highlight the role of varicocele-induced oxidative stress in exacerbating DNA damage, reinforcing previous evidence on the association between varicocele severity and impaired semen quality [23–25].

Our results demonstrate that microsurgical varicocelectomy has emerged as the most effective intervention, improving semen parameters, including sperm concentration and motility, and reducing SDF. The superior outcomes of this procedure can be attributed to the precise subinguinal approach, which ensures optimal preservation of testicular arteries and lymphatic vessels while minimizing vascular injury. Similar studies have corroborated these findings, emphasizing the role of microsurgery in restoring normal venous drainage and reducing scrotal temperature, which collectively alleviates testicular hypoxia and oxidative stress, consequently reducing SDF [11,26,27]. These physiological changes contribute to stabilizing sperm chromatin structure and improved DNA integrity, ultimately enhancing fertility potential.

Table 3. Changes in semen parameters three months post-intervention.

Semen parameter	Group 1 (microsurgery)	Group 2 (antioxidant therapy)	Group 3 (control)	<i>p</i> -value
Sperm concentration (million/mL), change of median	+25.0	+11.0	+0.4	<0.001
Progressive motility (%), change of median	+67.0	+6.0	No significant change	<0.001
SDF (%), change of median	−5.5	−5.5	+0.5	0.03
Sperm morphology, change of median	−4.4	−2.3	No significant change	0.05*
Clinically significant improvement (%)	65%	42%	38%	0.01

* statistically significant difference.

This study showed that antioxidant therapy also demonstrated a capacity to reduce SDF and improve semen parameters, albeit less pronounced than the effects of varicocelectomy. Nutraceuticals such as coenzyme Q10, selenium, and vitamins C and E have established roles in counteracting oxidative stress through an ability to neutralize ROS and stabilize sperm DNA. Previous studies have similarly reported moderate improvements in sperm quality following antioxidant therapy, particularly in cases where varicocele-induced oxidative damage was not severe [14,15,18,28]. Despite these benefits, the limited efficacy of antioxidants in cases involving advanced varicocele highlights their role as an adjunct rather than a primary intervention.

These findings suggest that varicocele-induced infertility stems not only from oxidative stress but also from disrupted testicular microvascular and hormonal dynamics, which antioxidant therapy alone may not fully address. Thus, this underscores the potential benefit of a combined treatment approach, integrating the immediate vascular benefits of surgery with the supportive antioxidant effects on sperm DNA integrity [29]. Further investigations, particularly into the molecular mechanisms underlying these interventions, are warranted to optimize treatment strategies and explore potential synergistic effects [30]. Additionally, large-scale longitudinal studies are needed to evaluate the impact of these treatment strategies and synergistic effects on live birth rates and other reproductive outcomes.

The control group, which received no active treatment, showed negligible improvements in semen parameters and SDF levels, reaffirming the need for targeted therapeutic interventions in managing varicocele-related infertility [31–33]. The comparative analysis between groups also highlights the importance of tailoring treatment based on varicocele severity and individual patient characteristics.

However, the relatively short follow-up period may underestimate the long-term benefits of both surgical and antioxidant therapies. Additionally, this retrospective study did not assess reproductive outcomes, such as natural conception or live birth rates, which could provide a more comprehensive evaluation of treatment efficacy. Moreover, this study did not evaluate the potential benefits of combining microsurgical varicocelectomy with antioxidant ther-

apy. Therefore, future studies should explore the synergistic effects of these interventions to optimize treatment outcomes for patients with varicocele. Another limitation was the use of uniform antioxidant doses. Although uniform doses were used for practical reasons, we acknowledge that weight-based dosing could provide additional insights and should be explored in future studies. In addition, while every effort was made to standardize protocols across participating centers, unmeasured variations in clinical practices may have influenced the outcomes. Despite the mentioned limitations, this study underscores the pivotal role of varicocele in male infertility and increased SDF levels and highlights the superior efficacy of microsurgical varicocelectomy in improving routine semen parameters and SDF levels. These findings support the development of personalized treatment strategies to optimize fertility outcomes in men with varicocele.

5. Conclusion

This study reveals that the prevalence of varicocele is comparable between subfertile (29.5%) and fertile men (27.2%), but varicocele in subfertile men is significantly associated with impaired semen quality and elevated SDF levels. Microsurgical varicocelectomy demonstrated superior efficacy in improving semen quality, while antioxidant therapy served as a beneficial alternative or adjunctive approach for surgically unsuitable patients. These findings emphasize the importance of tailored treatment strategies to manage varicocele-associated infertility effectively. Further large-scale studies are needed to confirm the true significance of these findings.

Abbreviations

SDF, sperm DNA fragmentation; IQR, interquartile range; ROS, reactive oxygen species; WHO, World Health Organization; SCD, sperm chromatin dispersion.

Availability of Data and Materials

All data reported in this paper will be shared by the corresponding author upon reasonable request.

Author Contributions

AS elaborated the concept and designed the research study, SA, AF performed the research. VB substantially

contributed to the data analysis and critical revision of the manuscript, LA analyzed the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was conducted following the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Medical Research and Education Center of Lomonosov Moscow State University (№ 2/21, dated 8th February 2021); Kulakov National Medical Research Center for Obstetrics, Gynecology, and Perinatology, Ministry of Health of Russia (№ 3, dated 13th March 2021); Moscow, Russia; Republican Specialized Scientific and Practical Medical Center of Urology (№ 1, 25th August 2020), Tashkent, Uzbekistan. All patients or their families/legal guardians provided written informed consent for participation, acknowledging their understanding of the study procedures, potential benefits, and associated risks.

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Conflict of Interest

The authors declare no conflict of interest

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