

SPERM DNA DAMAGE RATE AMONG INFERTILE PATIENTS WITH VARICOCELE

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ABSTRACT

Background: Varicocele has a common association with male hypofertility. The prevalence of clinical varicocele is about 15% among adults and adolescents. varicocele patients are at risk of infertility. Sperm deoxyribonucleic acid (DNA) fragmentation rate (SDFR) is considered a major factor in decreased fertilization ability in males with varicocele. Varicocele increases SDFR through heat stress, increased reactive oxygen species, and reduction in the level of total antioxidants.

Objectives: To study the rate of sperm DNA fragmentation in patients with different grades of varicocele.

Patients and methods: A prospective, case-control study was conducted at Azadi Teaching hospital in Duhok city / Iraq from March 2020 to December 2021. The study included 34 infertile patients with varicocele of different grades and 30 infertile patients without varicocele. Seminal fluid analysis was performed followed by sperm DNA analysis by Alkaline Comet Assay. The obtained data were analyzed using a Prism-GraphPad to compare the mean of parameters in patients and control subjects.

Results: Sixty-four infertile patients were included. The mean of sperm immobility and abnormal morphology rates were statistically higher in infertile patients with varicocele compared with those without varicocele (39.56 ± 12.63 Vs 28.07 ± 4.541) and (51.59 ± 23.00 Vs 34.79 ± 15.72) respectively, ($P < 0.0001$). The fluorescence microscopic images of sperm DNA of infertile patients with varicocele showed a clear migration to DNA tail (DNA damage) compared with sperm DNA of those without varicocele (8.195 ± 0.3799 Vs 4.794 ± 0.2186) respectively ($P < 0.0001$). The degree of sperm DNA damage was directly related to the degree of varicocele and was significant ($P < 0.0001$).

Conclusion: Sperm DNA damage rate was higher in infertile male patients with varicocele in comparison to those without varicocele and directly related to the grade of varicocele.

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Keywords: Infertility, SDI, Sperm DNA, Varicocele

Infertility is regarded as a global public health issue as it affects around 15% of young age-group¹. Up to 50% of infertile couples are related to male factor². Unexplained infertility is commonly observed in males and is characterized by normal spermiograms and no identifiable cause³. Varicocele is one of the

associations with infertility in males. Reports about testicular varicocele go back to the Greek age². The effect of testis varicocele was first noticed at the beginning of the 20th century after improvement in the sperm quality following varicocelectomy⁴. Varicocele is categorized clinically as *grade 1*: the

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venous plexus of the spermatic cord is only palpable during the Valsalva maneuver, *grade 2*: the veins are palpable at the upright position, and *grade 3*: the veins are visible. Sub-clinical varicocele is diagnosed by ultrasound or angiography only^{5,6}.

Fertile sperms should have stable DNA which is a crucial factor for successful fertilization and embryo development and growth in natural and assisted reproductive techniques. The integrity of our DNA is continuously challenged by many known and unknown endogenous and exogenous factors (some are preventable or correctable while others are not)⁷.

The DNA damage types include 1-single-strand breaks (SSBs), 2-double-strand breaks DSBs 3- nitrogen base mismatch, 3-loss of DNA base (abasic site), 4-(DNA) base modification, and 5- cross-link and pyrimidine dimer⁸.

The type and degree of DNA damage or fragmentation depend on cell type and cell cycle stage. The cell has several ways to repair the already damaged (DNA), and inaccurate repair may have different consequences. While our somatic cells inevitably die by age or disease, the germ cell lines can maintain sufficient DNA integrity to pass on our genome to the next generations.

Damage to the DNA is caused by many endogenous and exogenous factors, intratesticular through defective apoptosis or epididymal through excessive reactive oxygen species (ROS) production⁹⁻¹¹. Varicocele, high scrotal temperature, drugs, xenobiotics, smoking, pollution, and aging have been associated with increased sperm DNA damage rates^{12,13}.

Venous stasis due to varicocele in testis leads to hypoxia, heat stress, and accumulation of metabolic waste; all of

these will lead to an increase in ROS production in seminal fluid¹⁴. In addition, venous stasis prevents blood renewal which in turn reduces the delivery of antioxidants to the affected part of the testis. An imbalance between antioxidants and ROS production leads to oxidative stress that can damage the sperm DNA¹⁵. Poor assisted reproductive outcomes such as reduction in fertilization rate and high rates of spontaneous miscarriage are related to sperm DNA integrity. Most studies depend on routine seminal fluid analysis for the evaluation of varicocele-related infertility^{10,16}.

Many different techniques are available to measure the rate of sperm DNA damage levels with different sensitivity and specificity. These techniques include sperm chromatin structure assay (SCSA), sperm chromatin dispersion test (SCD), terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeling (TUNEL) assay, and single-cell gel electrophoresis (Alkaline comet Assay) assay^{17,19}. The TUNEL assay and the ACA are assessing DNA damage directly and their accuracy for detection of even minimum level of sperm DNA damage is high, whereas other techniques are prone to artifacts due to the effect of acid solution²⁰.

Although the technique of ACA needs more care for its standardization and optimization for the measurement of sperm DNA damage, it is characterized by its high sensitivity and reliability for the detection of even low levels of DNA damage in sperms²¹.

STUDY DESIGN & METHODS

This study included 64 participants. Thirty-four infertile patients with different severity of varicocele and 30 infertile patients without varicocele as a control

group. Classifications of varicocele grades according to vein diameter were categorized into three grades by color Doppler ultrasound. Any patient with a history of radiation, chemotherapy, or local surgery was excluded from the study. After filling out the questionnaire form, spermograms were performed and analyzed according to World Health Organisation (WHO) after three days of abstinence. The sample was then labelled and kept in the freeze (-20 c) for later sperm DNA damage measurement by Alkaline Comet Assay.

Statistical analysis

The data and participant information were analyzed using Prism-GraphPad version 5. P value ≤ 0.05 are statistically significant. Continuous variables are expressed by mean \pm standard deviation. Categorical data were summarized as percentages.

RESULTS

From the total study group of 64 infertile patients, the age of the patients ranges between 20 and 45 years, and the duration of infertility was between 1 to 5 years, BMI was between 18 to 30. Results of age, BMI, and seminal fluid parameters including sperm morphology, motility, and

others parameter were analyzed and shown in Table 1. The mean of age between patients with varicocele and those without varicocele was not significant statistically; (31.71 ± 0.7711 vs. 34.43 ± 1.413) (p 0.2418) respectively. No statistically significant difference was found between the mean BMI in patients with varicocele and those without varicocele; (25.76 ± 1.038 vs. 26.04 ± 1.212) (P 0.1369) respectively. There was no difference statistically in the family history of infertility between patients with or without varicocele; (3.147 ± 0.239 vs. 3.759 ± 0.485) (P 0.2413) respectively. The mean of low motility and abnormal morphology rates were significantly higher in patients with varicocele compared with those without varicocele. The mean abnormal morphology rate in patients with varicocele was (39.56 ± 12.63) while in those without varicocele was (28.07 ± 4.541) (p 0.0001). Similarly, the mean rate of immotile sperms in patients with varicocele was significantly higher than in those without varicocele; (51.59 ± 23.00 Vs. 34.79 ± 15.72) respectively (P 0.0001). Table-1

Table-1 Age, BMI, and seminal analysis parameters between infertile patients with and without varicocele

| Parameter | With Varicocele (n 34) Mean \pm SD | Without Varicocele (n 30) Mean \pm SD | P value |
|--------------------------------|--|---|---------|
| Age (years) | 31.71 ± 0.7711 | 34.43 ± 1.413 | 0.2418 |
| BMI | 25.76 ± 1.038 | 26.04 ± 1.212 | 0.1369 |
| History of infertility (years) | 3.147 ± 0.239 | 3.759 ± 0.485 | 0.2413 |
| Abnormal morphology (%) | 39.56 ± 12.63 | 28.07 ± 4.541 | <0.0001 |
| Motility:Immotile (%) | 51.59 ± 23.00 | 34.79 ± 15.72 | 0.0012 |

The fluorescence microscopic images of sperm (DNA) of infertile patients with varicocele showed a clear and more DNA

migration to the tail (DNA damage), compared with sperm DNA quality of those without varicocele (Figure-1).

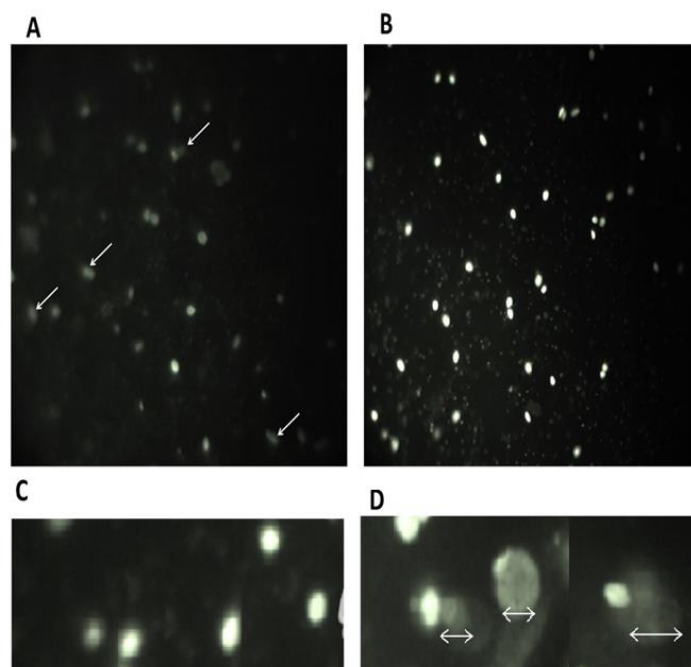


Figure-1 A fluorescence microscopic image of sperm DNA of the infertile patient with varicocele (A) and without varicocele (B). Magnified picture of intact sperm DNA (C). Magnified picture of damaged sperm DNA (D).

Further analysis of data using CASP Lab software revealed that both groups of infertile patients have SDF, however, the damage rate in patients with varicocele

was significantly higher in varicocele patients compared with those without varicocele, 8.195 ± 0.3799 Vs. 4.794 ± 0.2186 , respectively ($P < 0.0001$) table-2.

Table-2 SDF level in infertile patients with and without varicocele.

| Patients | With varicocele | Without Varicocele | P value |
|----------|--------------------|--------------------|------------|
| SDFR (%) | 8.195 ± 0.3799 | 4.794 ± 0.2186 | < 0.0001 |

The statistical analysis showed a higher rate of SDF in patients with varicocele with more sperm morphological

abnormalities and low sperm motilities in contrast with that in patients without varicocele (Figure-2A & B).

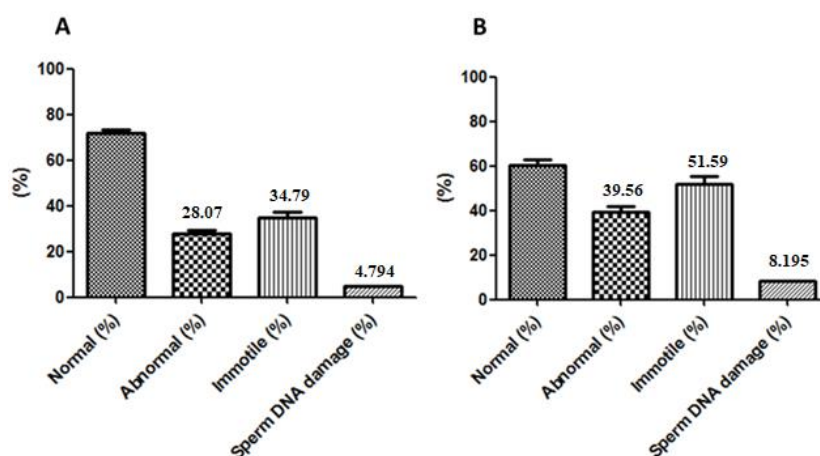


Figure-2 Comparisons between morphological parameters of seminal fluid and the SDF rate in infertile patients without varicocele (A) and with varicocele (B).

The SDF rate with the grades of the varicocele, data showed that patients with grade-1 varicocele have the lowest level of SDF rates compared with those with grade 2 and grade-3 varicocele. The SDF rate in grade-3 patients was 1.3-fold higher than those of grade-2 and 2-fold than those of grade-1 varicocele. Table 3.

Table-3 The rate of SDF with grades of varicocele

| | Grade 1 varicocele | Grade 2 varicocele | Grade 3 varicocele |
|----------------------|-----------------------|-----------------------|-----------------------|
| Sperm DNA damage (%) | 4.703 ± 0.9211 | 7.956 ± 0.8365 | 10.46 ± 1.001 |

DISCUSSION

Varicocele is considered an andrological disease with a high incidence (15%) in the general population and is positively associated with reduced male fertility rates^{11,22,23}. The effect of clinical varicocele on the conventional semen quality and male fertility potential is controversial, and whether surgical ablation (varicolectomy) could improve seminal fluid quality still needs further evaluation and studies to explore. Sperm genomic integrity is important for sperm cell function both in vivo and in vitro fertilization¹². Over the past decades, many clinical studies were conducted to demonstrate 1.6% higher SDF rates in infertile patients than in fertile men (95% CI: 1.2-2.1; $P < 0.001$)²⁴.

Despite the high rates of varicocele among infertile cases, the mechanism behind its negative impact on sperm quality and sperm activities is still not very clear¹¹. Based on the studies by World Health Organization (WHO), the relationship between varicocele occurrence and testicular dysfunction is strong. It has been shown that 25% of those with varicocele have alteration in seminal fluid

parameters²⁵. Factors associated with varicocele include heat stress, androgen deprivation, exposure to toxic agents and testicular hypoxia lead to an increase in oxidative stress which in turn induces the pathways that lead to increased SDF rates. The seminal plasma normally contains antioxidant agents that protect human gametes from damaging attacks of ROS. Studies have observed that there is a high level of ROS and a reduced amount of total antioxidant in the semen of patients with varicocele^{26,27}. Experimentally, exposing human sperms to exogenous ROS has resulted in increased DNA fragmentation after the exposure¹³. Although the rate of SDF rate was low in our study, we have observed statistically significant ($P < 0.0001$) more sperm DNA damage levels in infertile patients with varicocele than in those without varicocele. A recent study done by Finelli et al. (2021) using a TUNEL assay, have found significant and more levels of SDF in patients with varicocele compared to those without varicocele (20.8% vs 10.1%), $P < 0.01$, respectively²⁸.

Zini and Dohle (2011) in their meta-analysis found that in five studies, the SDF levels were similar in infertile patients with or without having varicocele, while in other four studies higher SDF levels were found in infertile men with varicocele than those without varicocele²⁹.

Another meta-analysis study by Zhang et al. (2021) concluded that patients with clinical varicocele have a higher SDF index than healthy controls³⁰.

Moreover, we have found a direct relation between SDF level and the grades of the varicocele. Patients with grade-1 varicocele have the lowest level of SDF level compared to those with grade-2 and grade-3 varicocele. The differences in the

means of DNA damage in the sperms of patients with grade-1 and grade-2 compared with those of grade-2 and grade-3 varicocele collectively was significant ($P < 0.0001$), a similar result is seen by Jellad et al., (2020) concluded that sperm DFI was directly and significantly related with the severity of varicocele³¹.

Blumer et al, (2008) used classes of damage to measure the level of genomic damage by Comet Assay in sperm and they found a higher level of SDF patients with advanced grades (Grade 2 and Grade 3) of varicocele compared with that in patients without varicocele; (6.1 ± 4.5 Vs. 5.5 ± 4.6) respectively, $P = 0.55732$. A meta-analysis study performed by Wang et al., (2012) showed that patients with varicocele have significantly higher SDF rates than the control group ($P < 0.00001$) and varicocelectomy improved sperm DNA integrity ($P < 0.00001$)³³.

Another meta-analysis performed by Roque et al., (2018) involved 1,153 men with clinical varicocele and SDF measurements. Overall, there was a significant decrease in the rates of SDF after repair of their varicoceles (MD - 8.31%, 95% CI -10.27%, -6.36%; $P < 0.0001$)³⁴.

Varicocele has a huge impact on sperm's physical activities and morphological characteristics. Previous studies showed high rates of sperm abnormalities among those with varicocele^{32,35}. Blumer et al, (2012) showed no differences in the total motile sperms in patients without varicocele compared to those with varicocele (140.6 ± 160.1 Vs. 99.8 ± 119.0 ; $p = 0.262$, respectively)³⁶. The data of this study revealed more levels of sperm abnormalities and decreased activities in those with varicocele compared with those

without varicocele, which corroborates the findings of other recent studies^{31, 37}.

CONCLUSION

The results of this study showed that infertile men with clinical varicocele have a higher rate of SDF than those without varicocele, and the rate of SDF is directly related to the grade of varicocele.

Conflict of interest: No conflict of interest.

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پوخته

ریزا ژکارکهفتنا DNA یی سپیری نه خوشییت نه زوک کو توو شیفاریکوسیل بوین

پیشه کی و نارمانج: فاریکوسیل ئیکه ژپشکداریت گهلهک باو و مشه لگهل نه زوکیا زه لاما (نیرا). مشه یی فاریکوسیل کلینیکی دگه هیهته نزیکی 15% د ناف مزین و سنیلادا. نه خوشییت فاریکوسیل هیهتییه ههفه کو بهر منگاریقی نه خوشییت کو گونیت وی ژ کاربکهفن و بیته نه گهرا نه زوکی.

ژکارکهفتنا DNA سپیری و پرت پرت بوونا وی گرنگترین نه گهره و فاکتیره بو نه زوکی لنیرا و لنک وان زه لاما کو فاریکوسیل هیهتن. هندهک ژفاکتیریت گرنگ و هک ستریتا گهرمایتی وزیده بوونا جوریت ئوکسجینی کارلیکی و کوم بوونا ناستی دژمئوکسیدینتا ژیک.

نارمانج: فهولینا پلا پرت پرت بوونا (DNA یی سپیری لنک نه خوشییت فاریکوسیل هیهتن د قوناغیت جدا جدا دا.

ریک و دیزاین فیه کولینی: فهولینهکا پروسیپکتیفیکونترول کروس سیکشنل بو هاته نهجامدان لزانکویا دهوک نه خوشخانا نازادییا فیرکرنی لدهوکئ/ عیراق/ هرژ مه ها نادارا 2020 تاکومه ها بهفرانبارا 2021 ئ

لقیه کولین 34 نه خوشییت نه زوکییت کو فاریکوسیل هیه و 30 نه خوشییت نه زوک بیفاریکوسیل و هکو کوما کونترول بخوفه دگریت. شروفه و شیرکنا شلی ئافا زه لاما هاته نهجامدان و هروسا شروفه کرنا دی ئین ئی یاسپیری ژی هاته کرن بریکا Alkaline Comet Assay

ژماره و نهجامیت هاتینه و مرگرتن هاتنه شروفه کرنا بریکا prism graph – pad ژبو بهروردکرنی لگهلیت کونترولی نهجام: ژ 64 نه خوشییت نه زوک ریزا نه لافینا سپیرما بارا پتر یا بلند بو لنک نه خوشییت نه زوک کو ییت توو شیفاریکوسیل بوین بیته وانه ی وان کهسایت کو نه زوک بوون و نه خوشییت فاریکوسیل نه بیت 56 ± 39.56 بهرام بهر 4.541 ± 28.7 و هروسا موزفولوجیا نه یادرستیا سپیری 23.0 ± 51.56 بهرام بهر 15.72 ± 34.79 $P < 0.0001$

وینیت مایکروسکوپا فلورسینیا DNA یی سپیرمییت نه خوشییت نه زوک کو توو شیفاریکوسیل بوین دیارکر کو فهربوونهکا دیارو زه لال هاته دیتن لنک کوریا DNA جنی ژکارکهفتنی لگهل بهروردیا نه خوشییت بیفاریکوسیل 0.3799 ± 8.195 بهرام بهر 0.2186 ± 4.794 $P = 0.0001$ پلا ژکارکهفتنا یی سپیری راسته خو پیومندی هه بو لگهل پلا فاریکوسیل کو یا بهرچاچ بو $P < 0.0001$

دهر نهجام: پلا ژکارکهفتنا DNA یی سپیری بلند تر بوو لنک نه خوشییت نه زوکییت کو توو شیفاریکوسیل هیه لگهل بهروردی بووان نه خوشییت بیفاریکوسیل و راسته خو گریدای ب قوناغیت جدا جدا بیفاریکوسیل.

الخلاصة

معدل تلف الحمض النووي للحيوانات المنوية بين مرضى العقم المصابين بدوالي الخصية

الخلفية والأهداف: دوالي الخصية هي أحد الأسباب الرئيسية للعقم عند الذكور. تبلغ نسبة انتشار دوالي الخصية السريرية حوالي 15% بين البالغين والمراهقين. مرضى دوالي الخصية معرضون لخطر الإصابة بضعف أداء الخصية والعقم. يعتبر تلف الحمض النووي للحيوانات المنوية وتفتيتها عاملاً رئيسياً في العقم عند الذكور المصابين بدوالي الخصية. العوامل المرتبطة بدوالي الخصية التي تزيد من تلف الحمض النووي للحيوانات المنوية هي الإجهاد الحراري وزيادة أنواع الأكسجين التفاعلية وتقليل مستوى مضادات الأكسدة الكلوية.

الأهداف: دراسة العلاقة بين درجة تلف الحمض النووي للحيوانات المنوية ومعامل الحيوانات المنوية (النشاط والتشكل) في المرضى الذين يعانون من درجات مختلفة من دوالي الخصية.

طرق البحث: أجريت دراسة مقطعية مقارنة مستقبلية في جامعة دهوك ومستشفى آزادي التعليمي في مدينة دهوك ، العراق من آذار 2020 إلى كانون الأول 2021. وشملت الدراسة 34 مريضاً يعانون من العقم مع درجات مختلفة من دوالي الخصية و30 مريضاً بالعقم بدون دوالي الخصية. تم تحليل السائل المنوي ودراسة نسبة تلف الحمض النووي للحيوانات المنوية بواسطة فحص المذنب القلوي. تم تحليل البيانات التي تم الحصول عليها باستخدام لوحة الرسم المنشوري لمقارنة متوسط المعلومات في المرضى والعينة الضابطة.

النتائج: تم تضمين أربعة وستين مريضاً يعانون من العقم. كان متوسط عدم حركة الحيوانات المنوية ومعدلات التشكل غير الطبيعي أعلى بشكل ملحوظ في مرضى العقم الذين يعانون من دوالي الخصية مقارنة مع أولئك الذين ليس لديهم دوالي الخصية، (12.63 ± 39.56 مقابل 4.541 ± 28.07) و (23.00 ± 51.59 مقابل 15.72 ± 34.79) على التوالي ($P < 0.0001$) ما فيما يتعلق بمستويات تلف الحمض النووي للحيوانات المنوية، أظهرت الصور المجهرية الفلورية للحمض النووي للحيوانات المنوية لمرضى العقم المصابين بدوالي الخصية هجرة واضحة إلى ذيل الحمض النووي (تلف الحمض النووي) مقارنة مع الحمض النووي للحيوانات المنوية لأولئك الذين ليس لديهم دوالي الخصية (0.3799 ± 8.195 مقابل 0.2186 ± 4.794) على التوالي. ترتبط درجة تلف الحمض النووي للحيوانات المنوية ارتباطاً مباشراً بدرجة دوالي الخصية وكانت معنوية ($P < 0.0001$).

الاستنتاجات: يكون تلف الحمض النووي للحيوانات المنوية وقلة التشكل والحركة أعلى في مرضى العقم المصابين بدوالي الخصية مقارنة بمن لا يعانون من دوالي الخصية ودرجتها مرتبطة مباشرة بدرجة دوالي الخصية.