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REVIEW

Microsurgical varicocelectomy effects on sperm DNA fragmentation and sperm parameters in infertile male patients: A systematic review and meta-analysis of more recent evidence

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Summary

Background: Varicocele is known to have impacts in infertility cases and sperm quality. This review aimed to evaluate the effects of microsurgical varicocelectomy on sperm DNA fragmentation index (DFI) and sperm parameters.

Methods: Open full English text articles from January 2017 to October 2021 were searched from online database including PubMed, EMBASE, Scopus, Cochrane Library and Google Scholar.

Results: Systematic search resulted in 277 potential papers. After throughout paper analysis, 5 studies were included in this review. From all five analyzed studies, microsurgical varicocelectomy was statistically proven to reduce DNA fragmentation index by 5.46% (mean difference -5.46; 95% CI: -4.79, -6.13; p < 0.00001). Moreover, the procedure also significantly improved other sperm parameters (sperm concentration +8.23%, sperm motility +7.17%, sperm progressive motility +2.77%, sperm morphology +0.64%).

Conclusion: Microsurgical varicocelectomy significantly improves spermatogenesis as reflected by biomarkers of infertile men including semen parameters and sperm DNA fragmentation (SDF).

KEY WORDS: *Microsurgical varicocelectomy; Sperm DNA fragmentation; DNA fragmentation index; Progressive sperm motility; Sperm concentration; Sperm morphology; Total sperm motility.*

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INTRODUCTION

Varicocele is an abnormal dilatation of pampiniform plexus veins in the spermatic cord that commonly correlates to infertility and bad sperm quality. Its incidence reaches up to 15% among normal population while its prevalence varies from 30-80% in primary and secondary infertile patients (1). The etiopathogenesis of varicocele remains unclear. The common hypothesis believes the condition is caused by the lack of oxygen in the scrotum, small vessel obstruction and imbalance of *reactive oxygen species* (ROS) and antioxidant production. The imbalance in specific leads to lipid, protein and nucleic acids damage of the living sperm cells due to high oxidative stress, hence altering their its motility and ability to fuse with oocyte. ROS also impair sperm chromatin structure by breaking DNA strands that negatively affecting development and embryo implantation negatively (2). Sperm integrity, DNA damage and genetic material are reflected by DNA fragmentation index (SDF) parameter that is suggested as a crucial biomarker for semen quality (3).

The *sperm DNA fragmentation* index (SDF) is a potential parameter for the study of fertility. Previous studies hinted the possibility of using DNA fragmentation with the clinical limit of 25% (4). Men with higher DFI are more susceptible to have reproductive problems. A more Recent studies claim surgical repair of varicocele can help improve sperm DNA quality. This theory is supported as reviewed by the *Schauer et al.* (5) meta-analysis result, stating that regardless of the chosen surgical technique (high ligation, inguinal or subinguinal approach), improvements can be seen. Moreover, microsurgical methods offer adequate simplified anatomic visualization with a lower recurrence and complication rate (6). High SDF coupled with normal sperm parameters has yet to be considered as varicocelectomy indication due to the limited studies regarding the impact of such intervention on SDF (4). Studies have shown that varicocele repair can improve sperm quality and pregnancy rates of people with clinical varicocele. Varicocelectomy may also result in the development of testicular regrowth and improve the sperm DNA integrity in up to 80% of cases. Considering the impact of untreated varicocele cases, especially on male fertility, it is important to evaluate and provide physicians with the most updated knowledge. A recent meta-analysis (7) evaluated the effect of varicocelectomy, including microsurgical varicocelectomy, on sperm DNA integrity, but other studies were more recently published targeted on specific populations with infertility associated to varicocele and with longer follow-up. Therefore, this paper aims to update the review of current literature regarding the effects of microsurgical varicocelectomy on sperm DNA fragmentation index and sperm parameters.

MATERIAL AND METHODS

Eligibility criteria

Inclusion criteria of the chosen studies were: study written in English, available online in full-text, published

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between January 2017 to October 2021, designed as *randomized controlled trials* (RCTs) or cohort prospective studies, reporting DFI and sperm parameters after microsurgical varicocelectomy.

Exclusion criteria
Studies were excluded if studies were case reports, reviews and other than microsurgical varicocelectomy therapy was performed.

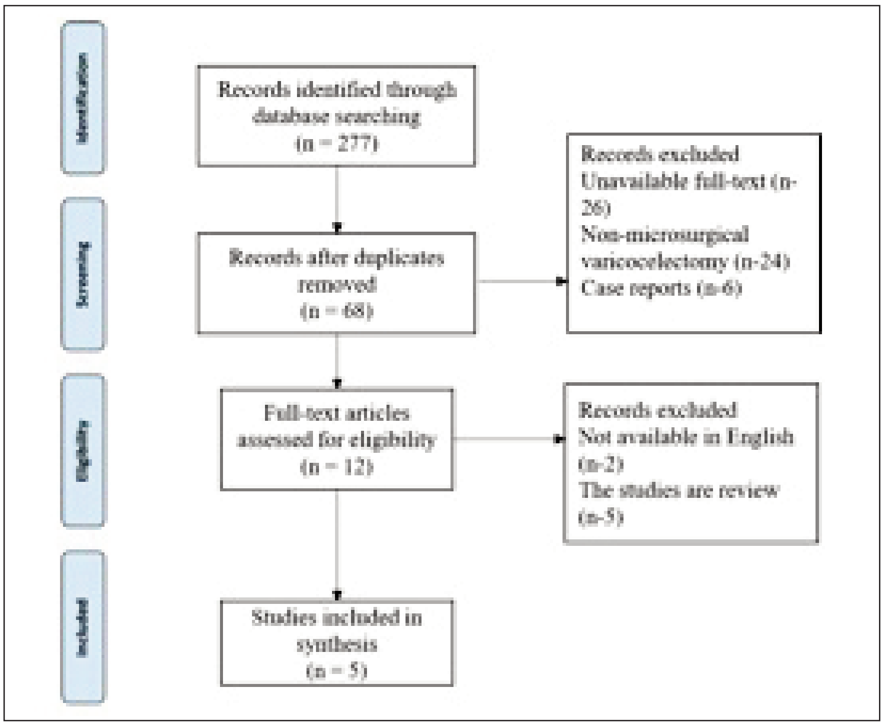
Guidelines
We used the *Preferred Reporting Items for Systematic Reviews and Meta-Analysis* (PRISMA) guidelines in reporting this study (8) (Figure 1).

Search strategy
Literature search was performed on *PubMed*, *EMBASE*, *Scopus*, *Cochrane Library*, and *Google Scholar* following PRISMA guidelines. The search was conducted on September 23^{rd}, 2021 using the search term ("*microsurgical varicocelectomy*" OR "*microscopic varicocelectomy*" OR "*microsurgery of varicocele*" OR "*varicocele repair*") AND ("*sperm parameter*" OR "*sperm analysis*" OR "SDF".

Data extraction and quality assessment
One reviewer selected literature and inputted data into an Excel database. Two independent reviewers screened titles and abstracts to determine their eligibility. Then, a full-text review was done to obtain detailed information. Risk of bias assessment was done based on PRISMA Guidelines.

Statistical analysis
Meta-analysis compared preoperative vs. postoperative sperm parameters and SDF using the *Review Manager 5.4.1 software*. The main outcome was the mean difference with 95% CI before and after varicocelectomy. If the p value of heterogeneity chi-squared test was less than 0.10 or I2 > 50%, the random-effect model was used. The fixed-effect model was then used if p ≥ 0.10 or I2 ≤ 50%.

Figure 1.
PRISMA Flow Diagram.



RESULTS

Study selection
Systematic search for studies from all available databases resulted in 277 potential papers. After screening and duplicate exclusion, 68 studies were chosen. After second evaluation regarding topic relevance, 12 studies were evaluated. Finally, after throughout paper analysis, 5 studies were included in this review (Figure 1). Three more studies were retrieved with respect to the previous review of *Qiu et al.* (7). They were specifically targeted on patients with infertility associated to varicocele and one of them reported data at a longer follow up period.

Study characteristics
The general characteristics of reviewed prospective studies are listed in Table 1. Varicocele repair through microsurgical varicocelectomy was done in 95, 141, 67, 120 and 60 patients, respectively. Three out of five studies evaluated SDF after three months from the procedure, whereas the other two did the test after 6 and 12 months of operation. The SDF data by varicocele grade was provided by two studies.
Sperm parameters such as sperm concentration, total and progressive sperm motility and sperm morphology are listed in Table 2. Only one study didn't measure sperm concentration. The rest showed massive improvement in both concentration and morphology after the intervention. Other than that, two studies reported total and progressive sperm motility, respectively. In general, all included studies resulted in the improvement of sperm parameters after the surgery.

Pre-and post-operative SDF
The SDF was evaluated preoperatively, 3 months or 6 months postoperatively in all of the included studies. The result of meta-analysis for 5 studies were presented in Figure 2. The heterogeneity test was statistically significant (chi-squared = 108.39, df = 4, p < .00001, I-squared = 96%), hence the random effect model was used otherwise. On average, SDF percentage among clinical varicocele patients showed -5,61% reduction after the procedure (mean difference -5.61; 95% CI: -6.28, -4.94; p < 0.00001).

Sperm concentration
Four studies reported sperm con-

centration before and after surgery. It was showed an increase of sperm concentration by 8.23% after surgery (mean difference: 8.23; 95% CI: 6.62, 9.85; $p < 0.00001$) (Figure 3).

Table 1.
Study characteristics and SDF findings.

Reference	Design	Patients	Follow up month after surgery	SDF assay	Surgical technique	Main SDF results
Fathi et al. (9)	Prospective cohort	95 male patients with a 1-year history of male subfertility	12 months	SCD	Microsurgical subinguinal	SDF% decreased from 34.93% ± 5.56% preoperatively to 25.75% ± 5.15% postoperatively (p < 0.001)
Kavoussi et al. (10)	Prospective cohort	141 male patients who underwent varicocele repair for infertility	3 months	SCD	Microsurgical subinguinal	SDF% decreased from 29.7% ± 5.0% preoperatively to 22% ± 0% postoperatively (p < 0.38)
Vahidi et al. (1)	Prospective cohort	67 infertile male patients with varicocele	3 months	TUNEL test	Microsurgical subinguinal	SDF& decreased from 15.93 ± 4.96% preoperative to 10.86 ± 4.44% postoperative (p < 0.001)
Zaazaa et al. (11)	Prospective cohort	120 male patients associated with varicocele grade II and III	3 months	SCD	Microsurgical subinguinal	SDF% decreased from 34.6 ± 4.1% preoperative to 28.3 ± 5.2% postoperative (p < 0.05)
Abdelbaki et al. (12)	Prospective cohort	60 male patients with varicocele	3-6 months	SCSA	Microsurgical subinguinal	SDF% decreased from 29.49% preoperative to 18.78% postoperative (p < 0.001)

SDF = sperm DNA fragmentation; SCD = sperm chromatin dispersion; TUNEL = terminal deoxynucleotidyl transferase- mediated dUTP nick end-labelling.

Table 2.
Sperm parameters.

Reference	Sperm concentration	Total sperm motility	Progressive sperm motility	Sperm morphology	Pregnancy rate
Fathi et al. (9)	Increased from 26.1 ± 8.5 millions/mL preoperative to 32.5 ± 8.6 millions/mL postoperative (p = 0.002)	N/A	Increased from 33.9 ± 1.6% preoperative to 36.1 ± 6.3% postoperative (p = 0.82)	Increased from 4.3 ± 0.5 preoperative to 5.2 ± 1.8% postoperative (p = 0.09)	Higher pregnancy rate of varicocelectomy group (31.1%) compared to control group (13.3%) (p = 0.10)
Kavoussi et al. (10)	Increased from 25.5 ± 32.4 millions/mL preoperative to 36.0 ± 37.0 millions/mL postoperative (p = 0.25)	Increased from 47.5 ± 20.3% preoperative to 53.4 ± 14.5% postoperative (p = 0.25)	Increased from 25.8 ± 3.8% preoperative to 30.6 ± 14.3% postoperative (p = 0.38)	N/A	N/A
Vahidi et al. (1)	N/A	N/A	N/A	Increased from 13.86 ± 7.85% preoperative to 18.53 ± 7.36% postoperative (p = 0.016)	N/A
Zaazaa et al. (11)	Increased from 20.8 ± 18.4 millions/mL preoperative to 28.0 ± 22.9 millions/mL postoperative (p < 0.05)	Increased from 24.3 ± 10.8% preoperative to 32.1 ± 12.1% post operative (p < 0.05)	N/A	Increased from 1.5 ± 0.5% preoperative to 2.2 ± 0.9% postoperative (p < 0.05)	N/A
Abdelbaki et al. (12)	Increased from 10.9 ± 2.8 millions/mL preoperative to 21.04 ± 8.9 millions/mL postoperative (p < 0.001)	Increased from 36.4 ± 10.7% preoperative to 53.6 ± 18.9% postoperative (p < 0.001)	Increased from 10.8 ± 4.6% preoperative to 19.1 ± 8.1% post operative (p < 0.001)	Increased from 2.3 ± 0.7% preoperative to 2.7 ± 0.6% postoperative (p < 0.001)	N/A

Figure 2.
Forest plot of meta-analysis on the efficacy of varicocelectomy for sperm DNA fragmentation improvement (random-effect model of 5 studies).

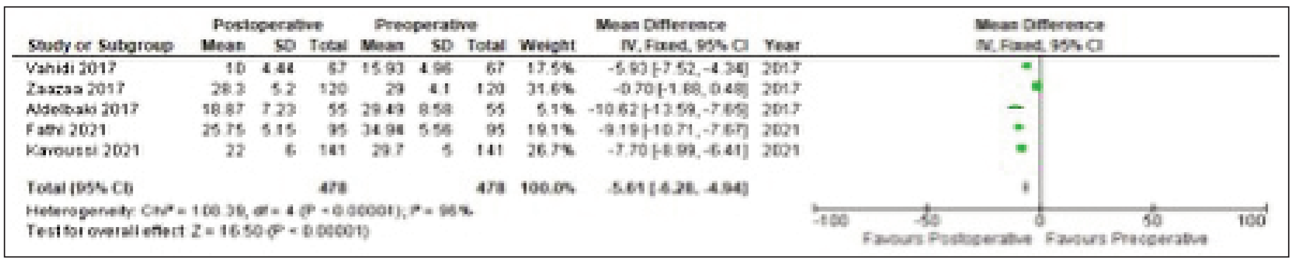


Figure 3.
Forest plot of sperm concentration (fixed-effect model).

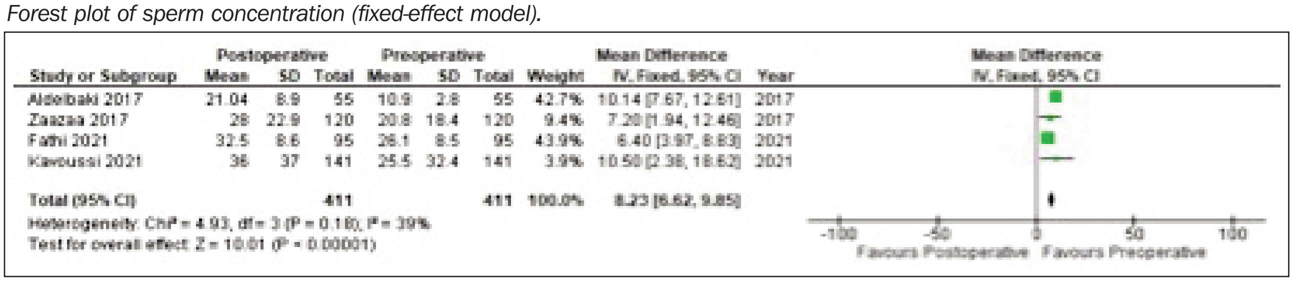


Figure 4.
Forest plot of total sperm motility (fixed-effect model).

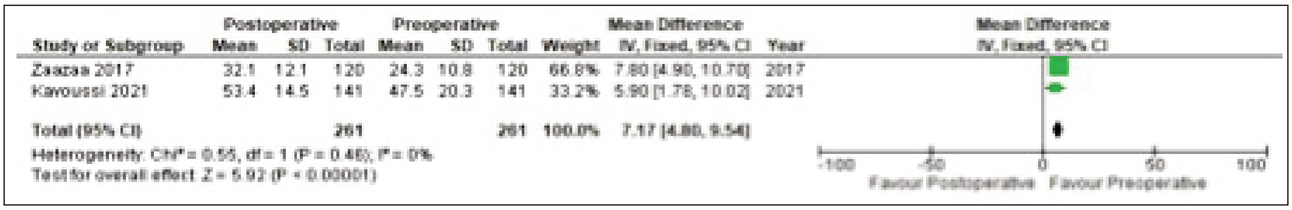


Figure 5.
Forest plot of progressive sperm motility (random-effect model).

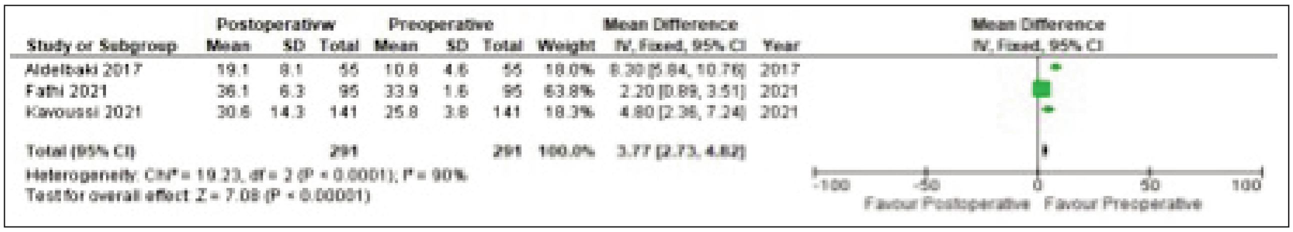
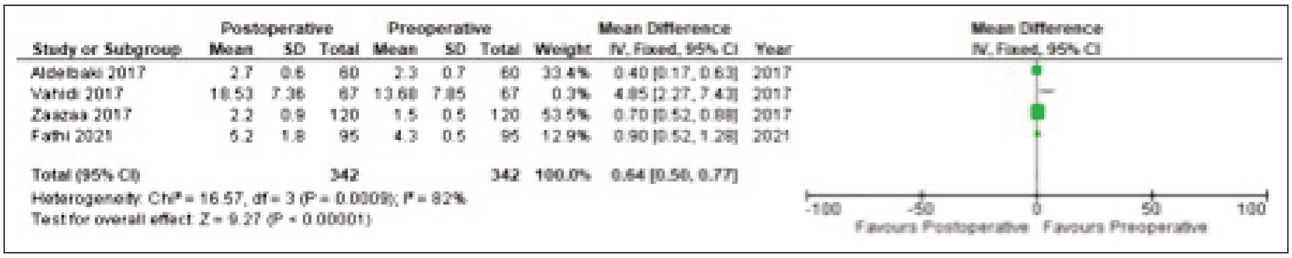


Figure 6.
Forest plot of sperm morphology (random-effect model).



Total sperm motility

Both *Kavoussi et al.* and *Zaazaa et al.* evaluated total sperm motility 3 and 6 months post-varicocelectomy. There was meaningful increase by 7.17% (mean difference: 7.17; 95% CI: 4.80, 9.54; p < 0.00001) (Figure 4).

Progressive sperm motility

Progressive sperm motility was evaluated in three studies comparing pre- and post-varicocelectomy results, showing a significant increase by 3.77% (mean difference: 3.77; 95% CI: 2.73, 4.82; p < 0.00001) (Figure 5).

Sperm morphology

Evaluation of sperm morphology before and after the intervention was done in 4 studies showing an increase of sperm morphology by 0.64% (mean difference: 0.64; 95% CI: 0.50, 0.77; p < 0.00001) (Figure 6).

Table 3.
Risk of Bias Assessment.

Author	Year	Random Sequence	Allocation Concealment	Blinding Generation	Incomplete Outcome Data	Other Bias	Overall Risk Bias
Fathi et al.	2021	No	No	No	Yes	No	High
Kavoussi et al.	2019	No	No	No	Yes	No	High
Vahidi et al.	2018	Unclear	No	No	Yes	No	High
Zaazaa et al.	2018	Yes	Unclear	No	Yes	No	Moderate
Abdelbaki et al.	2017	No	No	No	No	No	High

Table 4.
Summary of Findings.

Patient or population: Varicocele patients
Intervention: Microsurgical varicocelectomy
Comparison: Standard varicocelectomy
Outcomes; Sperm DNA Fragmentation Index and other sperm parameters with mean differences (95%CI)
SDF -5.61 95% CI -6.28 to -4.94
Sperm concentration 8.23 95% CI 6.62 to 9.85
Total sperm motility 7.17 95% CI 4.8 to 9.54
Progressive sperm motility 3.77 95% CI 2.73 to 4.82
Sperm morphology 0.64 95% CI 0.5 to 0.77
Total participants: 483 infertile males [5 studies]
Follow up: 3-12 months

Risk of bias and summary of findings

Results of Risk of Bias assessment and Summary of Findings are reported in Tables 3, 4.

Discussion

Varicocele has long been associated to higher SDF index damage (13). Newer studies has started to include SDF index as a new indicator for varicocelectomy since a prior study had suggested it as a diagnostic tool for clinical varicocele patients (16). The average value of SDF is 15-30% and is regarded as high when detected DFI reaches more than 30%. Majority of men with grade II and III varicocele have SDF level of more than 30%. Moreover, a group of scientists has claimed lower embryo implantation and pregnancy rate happened if SDF threshold was more than 30% (14). This even more suggests a connection between ROS level in spermatozoa and SDF.

For more than a century, varicocelectomy has always been the first treatment option for subfertile male with palpable varicocele. This procedure is performed through three surgical approaches such as retroperitoneal, inguinal and subinguinal varicocele repair with or without magnification (15). In general, sperm DNA integrity in patients improved after the procedure (7). Based on EAU guideline, varicocelectomy in infertility cases has been shown to enhance semen parameters including sperm motility, concentration, and morphology (16). It also significantly decreases testosterone levels, natural and assisted pregnancy rates. Varicocelectomy in infertility cases with absence of semen parameters abnormality and subclinical varicocele is not recommended (16).

SDF

From meta-analysis of all the 5 analyzed studies, varicocelectomy decreased DNA fragmentation index by 5,61% (mean difference -5.61; 95% CI: -6.28, -4.94; $p < 0.00001$). This result was confirmed in three studies using different methods of assessment ($p < 0.001$); from 34.93% ± 5.56% preoperatively to 25.75% ± 5.15% postoperatively using SDF assay of SCD9, from 15.93 ± 4.96% preoperatively to 10.86 ± 4.44% postoperatively using TUNEL test1, and from 29.49% preoperatively to 18.78% postoperatively using SCSA (12). Moreover, a lower SDF index from 34.6 ± 4.1% preoperatively to 28.3 ± 5.2% postoperatively ($p < 0.05$) was also seen in 120 grade II and III varicocele patients (11). Similar results of lower DNA fragmentation index from 29.7% ± 5.0% to 22% ± 0% ($p < 0.38$) after varicocele repair among 141 infertile male patients were also observed (4).

Prior meta-analysis by *Qiu et al.* observed a reduction of SDF percentage after varicocelectomy of -6.14 [95% CI, -6.90 to -5.37].7 Results from *Birowo et al.* and *Wang et al.* also supported this finding (4, 13). Both studies had demonstrated the impact of varicocele repair in decreasing SDF index, leading to the halt of varicocele progression by downregulating systemic *oxidative stress* (OS) (2). Study by *Neto et al.* added that varicocelectomy improved SDF count in all varicocele condition regardless of its grade without much different in treatment duration (17). Furthermore, a review of 20 studies reported great reduction of SDF after varicocelectomy during 3-12 months follow up time (2). The findings in this study has been constant with previous literatures (4, 13, 17) concluding that varicocelectomy does bring improvement in sperm DNA characteristics in clinical varicocele patients.

The DNA damage in varicocele can be one of the causes in lower SDF count after varicocelectomy. DNA fragmentation happens during sperm synthesis and maturation (3). During the sperm maturation, histones are replaced by smaller arginine- and cysteine- rich protamine (HP). The replacement hinders sperm DNA ability to repair itself when being exposed to internal and external modifications. The misfolding of DNA supercoil structures in the chromosome due to the tension twist by the double stranded DNA helix that supposed to restore DNA actually caused SDF or abnormalities inside the chromatin structure.18 Furthermore, external genital tracts inflammation, venous statis and reflux increase risk of SDF by promoting hypoxia, inducing and increasing *reactive oxygen species* (ROS) within the sperm DNA. All those changes lead to worse DNA damage and fragmentation (3, 13, 19). Other than resolving venous stasis and reflux problem, varicocelectomy also reduce ROS synthesis, leading to less DNA damage (4).

Sperm parameters

Schauer et al. evaluated semen parameters after procedures such as high ligation or inguinal or subinguinal were performed. Regardless of the methods, meaningful comparable improvements were observed in sperm concentration and motility (5). Furthermore, surgical methods (77.5%) had been perceived to give better results in sperm parameter compared to radiological approach (62.5%) ($p = 0.032$) (20). The measured parameters showed improvement after 3 months of varicocelectomy (21). Sperm DNA fragmentation was not linked to sperm concentration, morphology and progressive motility.3 Result of this review regarding better sperm parameters were similar with prior studies (4, 5, 20).

Sperm concentration

Different results were seen from previous studies. *Li et al.* study showed different sperm concentration between control and varicocele group (22). However, *Nguyen et al.* claimed sperm concentration between two groups were alike (14). Sperm concentration was evaluated before and after surgery. An elevation of 8,23% were gained after procedure (mean difference: 8.23; 95% CI: 6.62,9.85; $p < 0.00001$). Comparison between pre- and post-intervention proved there are meaningful rise in sperm concentration ($p = 0.009$) (22). Further statistical analysis exhibited no significant relationship between sperm DNA integrity and sperm concentration (22).

Total sperm motility

Result of this review goes in accordance with previous study that assessed various varicocelectomy methods and sperm motility. In that study, sperm motility was higher by 6.80% after suprainguinal approach (95% CI 3.95 to 9.66, $p < 0.00001$), 9.44% after inguinal approach (95% CI 3.72 to 15.16, $p = 0.001$) and 12.25% by subinguinal approach (95% CI 4.76 to 19.75, $p = 0.001$) (5).

Progressive sperm motility

Higher progressive sperm motility was observed in current and prior studies. Study by *Kadioglu et al*. had showed better progressive sperm motility after six months of microsurgical varicocelectomy when compared to baseline ($p < 0.05$) (23). This study also had similar result with no association found between progressive motility and sperm SDF (3).

Sperm morphology

Most of studies showed improvement of sperm morphology after intervention, including result gained in this

study. Sperm morphology was 2.73% higher after varicocelectomy (mean difference: 2.73; 95% CI: 0.65, 4.80; p = 0.01) (4).
Only one study by *Li et al.* that had failed to establish such result (p = 0.028) (22).

Conclusions

Microsurgical varicocelectomy is not simply the best therapy approach for varicocele repair. It can also benefit in enhancing fertility by lowering SDF as seen in infertility biomarkers including semen parameters and pregnancy rates. Among the evaluated studies, only one paper showed better pregnancy rate after surgical procedure. Our data supported the hypothesis of spermatogenesis restoration after varicocelectomy in infertile patients. However, further studies using more related publications is needed to prevent publication bias. In this study, only RCT prospective studies were included.

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