L'impatto del trattamento del varicocele sulla frammentazione del DNA spermatico … e sullo stress ossidativo

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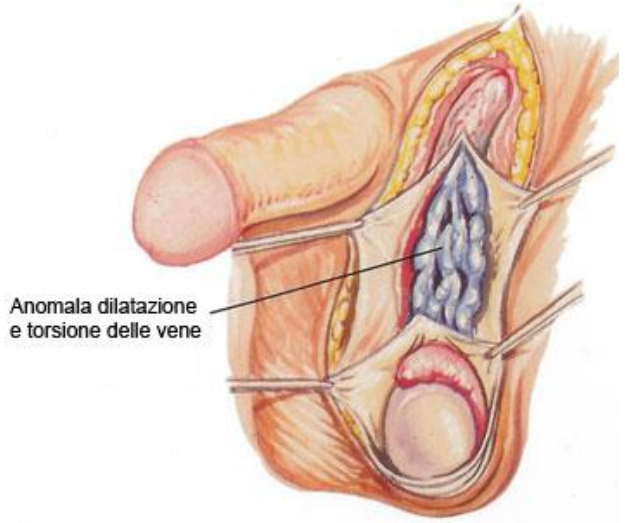
Next Fertility
GynePro

VARICOCELE e FERTILITA' MASCHILE - 1

Il Varicocele, "anomala dilatazione e tortuosità delle vene nel plesso pampiniforme", presente soprattutto a carico del didimo sinistro, è una delle più frequenti cause di infertilità maschile.

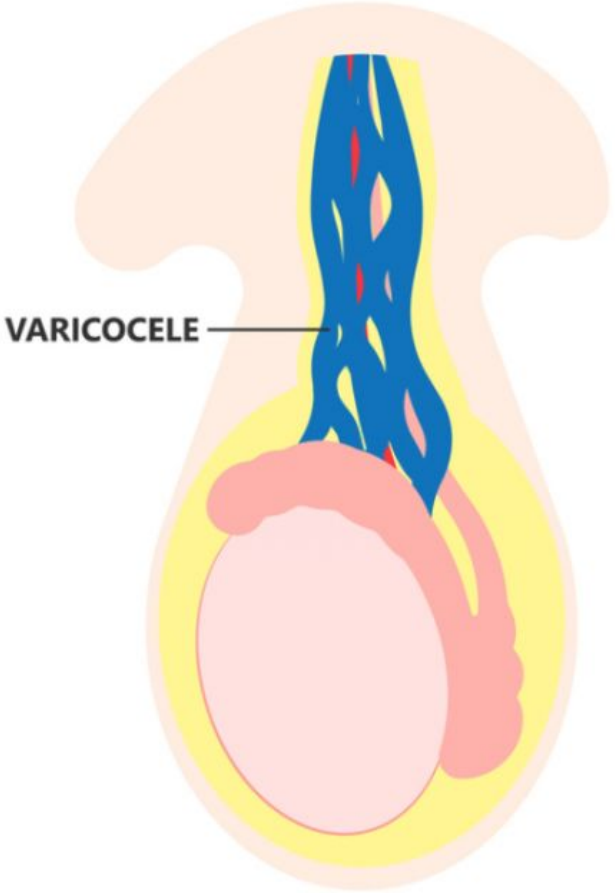


La sua **prevalenza**: 15% in maschi sani, 35-44% nell'infertilità primaria, 45-80% nell'infertilità secondaria

Può alterare la fertilità maschile attraverso svariati **meccanismi**; i più noti:

- ✔ aumento della T scrotale,
- ✔ ipossia testicolare,
- ✔ anomalo reflusso metaboliti surrenalici.

VARICOCELE e FERTILITA' MASCHILE - 2



Alterazione parametri seminali:
oligo-asteno-teratozoospermia

Aumento della *FRAMMENTAZIONE DEL DNA SPERMATICO*

↕

Aumento dello stress ossidativo

Agarwal A, Sharma RK, Desai NR, Prabakaran S, Tavares A, Sabanegh E. Urology 2009;73:461-9.
Agarwal A, Hamada A, Esteves SC. Nat Rev Urol 2012;9:678-90.
Smit M, Romijn JC, Wildhagen MF, Veldhoven JL, Weber RF, Dohle GR. J Urol 2010; 183:270-4.

FRAMMENTAZIONE DEL DNA SPERMATICO – “SDF”

FRAMMENTAZIONE DEL DNA SPERMATICO – "SDF"

			Negative influence of DNA damage on				
Author	**n**	**Assay**	**Fertilization**	**Embryo quality**	**Pregnancy**	**pregnancy loss**	**P-value**
Lopes et al. (1998)	131	TUNEL	Yes	No	na	na	<0.05
Sun et al. (1997)	143	TUNEL	Yes	Yes	na	na	<0.01
Tomlinson et al. (2001)	140	NT	No	No	Yes	na	<0.05
Morris et al. (2002)	60	Comet	No	No	No	No	
Tomsu et al. (2002)	40	Comet	No	Yes	Yes	na	<0.05
Virant-Klun et al. (2003)	18[illegible]	AO	Yes	Yes	No	No	<0.05
Benchaib et al. (2003)	10[illegible]	TUNEL	Yes	No	Yes	na	<0.05
Larson-Cook et al. (2003)	89	SCSA	No	No	Yes	na	<0.01
Bungum et al. (2004; 2007; 2008)	12[illegible]96	SCSA	na	na	No	No	
Gandini et al. (2004)	3[illegible]	SCSA	No	No	No	No	
Henkel et al. (2004)	2[illegible]9	TUNEL	No	nd	Yes	nd	<0.05
Seli et al. (2004)	4[illegible]	TUNEL	No	Yes	No	na	<0.05
Virro et al. (2004)	2[illegible]9	SCSA	No	Yes	Yes	No	<0.01
Huang et al. (2005)	3[illegible]3	TUNEL	Yes	na	No	na	<0.05
Payne et al. (2005)	10[illegible]0	SCSA	Yes	No	No	No	<0.05
Borini et al. (2006)	13[illegible]2	TUNEL	na	na	Yes	Yes	<0.01
Muriel et al. (2006)	85	SCD	Yes	Yes	No	na	<0.05
Frydman et al. (2008)	11[illegible]	TUNEL	No	No	Yes	Yes	<0.001; <0.01
Lin et al. (2008)	223	SCSA	No	No	No	Yes	<0.05
Avendaño et al. (2010)	36	TUNEL	na	Yes	Yes	na	<0.001; <0.05
Simon et al. (2010)	360	Comet	Yes	Yes	Yes	No	<0.05
Speyer et al. (2010)	347	SCSA	No	No	Yes	No	<0.01
Meseguer et al. (2011)	210	SCD	na	na	Yes	No	<0.05

AO: acridin orange staining; n: number of cycles; NT: in-situ nick translation; SCD: sperm chromatin dispersion test; SCSA: sperm chromatin structure assay; TUNEL: TdT-mediated-dUTP nick-end labelling;
Table 3 followed reviews of Sharma et al. (2004), Zini and Libman,(2006) and Zini and Zigman (2009).

FRAMMENTAZIONE DEL DNA SPERMATICO

i test:

SCD= *Sperm Chromatin Dispersion test*

TUNEL= *Terminal deoxynucleotidyl transferase dUTP nick end labelling*

COMET assay

SCSA= *Sperm Chromatin Structure Assay*

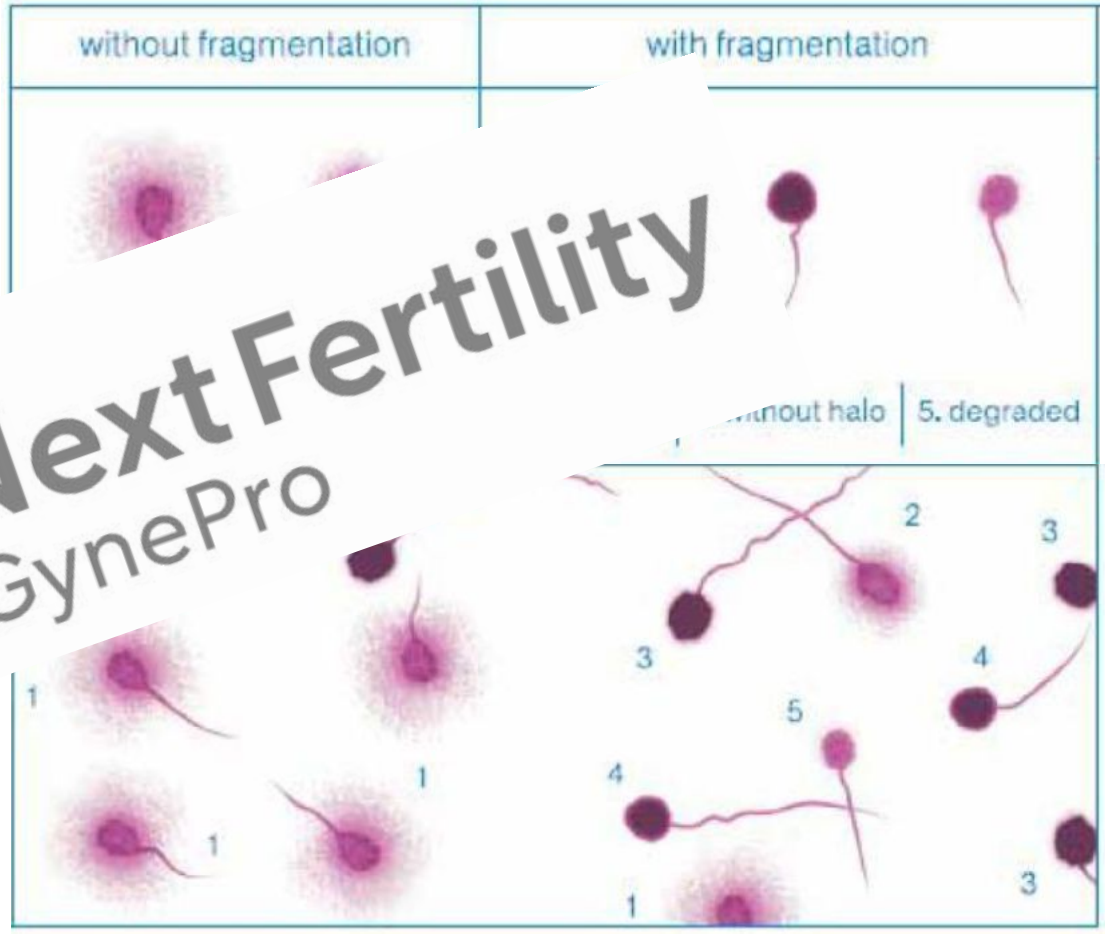
AOT= *Acridine Orange Test*

FRAMMENTAZIONE DEL DNA SPERMATICO – "SDF"

i test: **SCD**, TUNEL, COMET, SCSA, AOT

SCD= Sperm Chromatin Dispersion test

- il DNA non frammentato si dispiega in anse che formano aloni
- il DNA fra produce gl

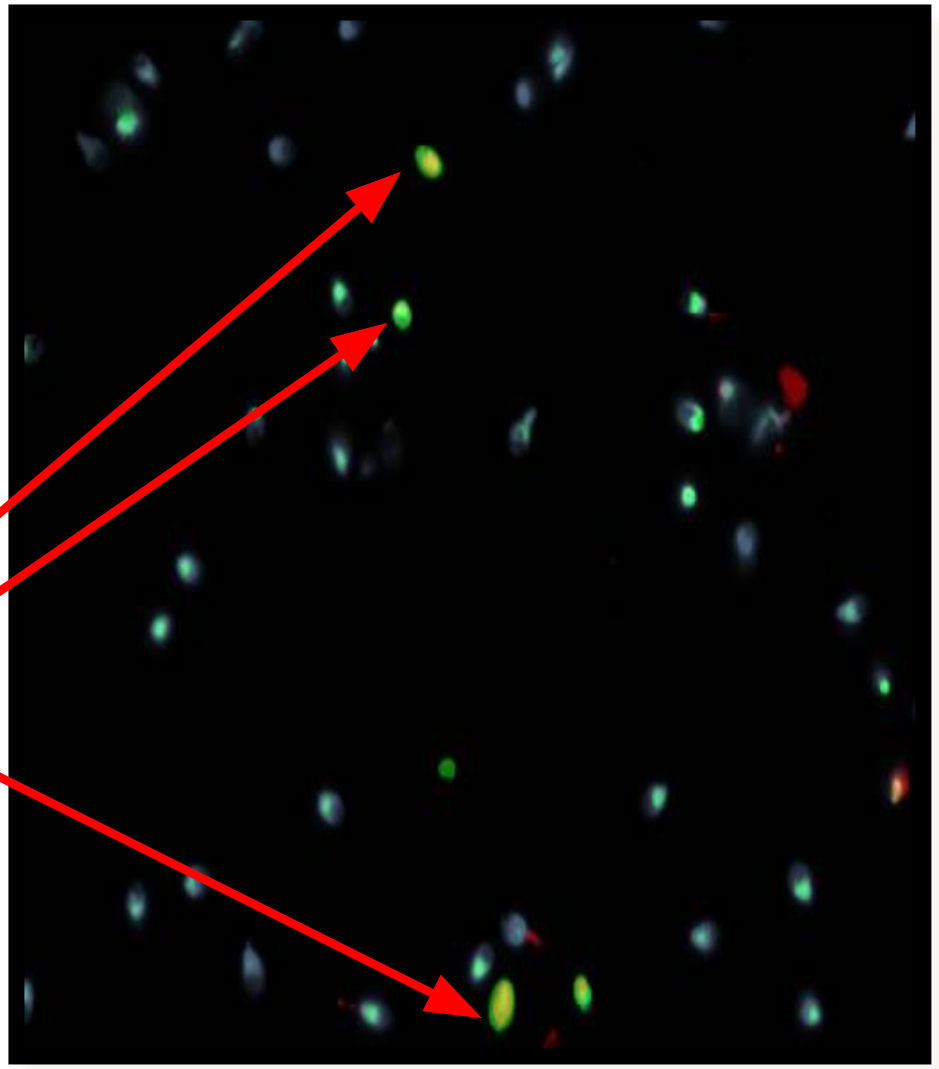


FRAMMENTAZIONE DEL DNA SPERMATICO – "SDF"

i test: SCD, **TUNEL**, COMET, SCSA, AOT

TUNEL

- impiego di una desossinucleotidil transferasi –OH terminale
- analisi microscopica o citofluorimetrica



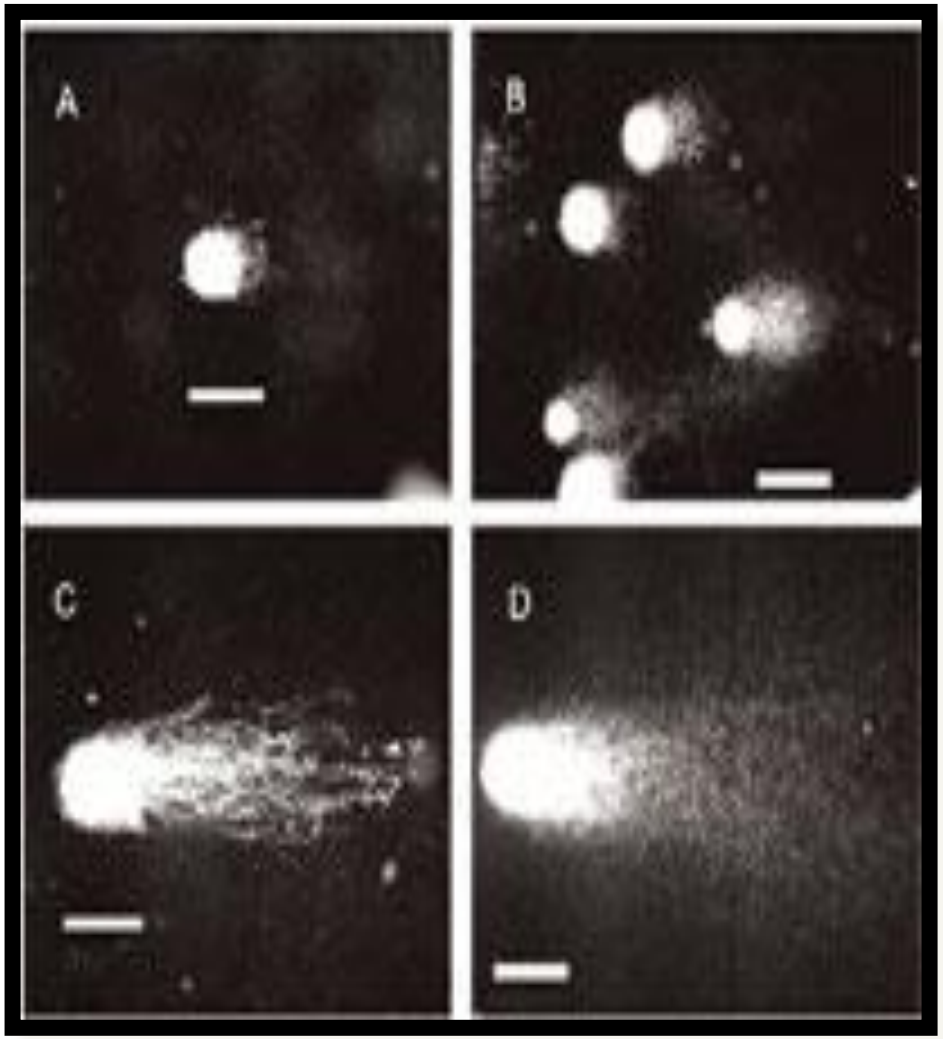
- Il risultato è espresso come percentuale: cellule TUNEL positive/cellule totali

FRAMMENTAZIONE DEL DNA SPERMATICO – “SDF”

i test: SCD, TUNEL, **COMET**, SCSA, AOT

COMET assay

- differente velocità di migrazione elettroforetica del DNA danneggiato: le cellule con DNA danneggiato appaiono come “comete” con una coda di DNA frammentato e decondensato

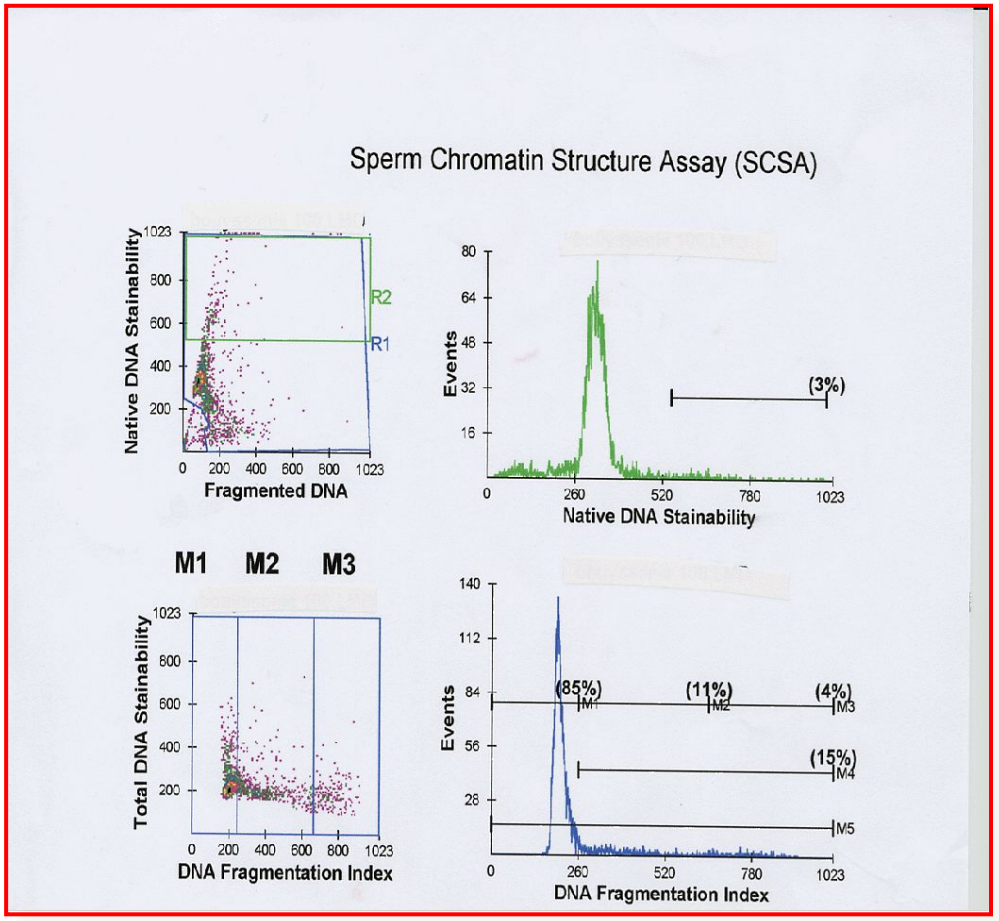


FRAMMENTAZIONE DEL DNA SPERMATICO – "SDF"

i test: SCD, TUNEL, COMET, **SCSA**, AOT

SCSA= Sperm Chromatin Structure Assay

- proprietà metacromatiche dell'arancio di acridinina (AO):
- fluorescenza verde quando l'AO si lega al DNA nativo
- fluorescenza rossa quando l'AO si lega al DNA danneggiato

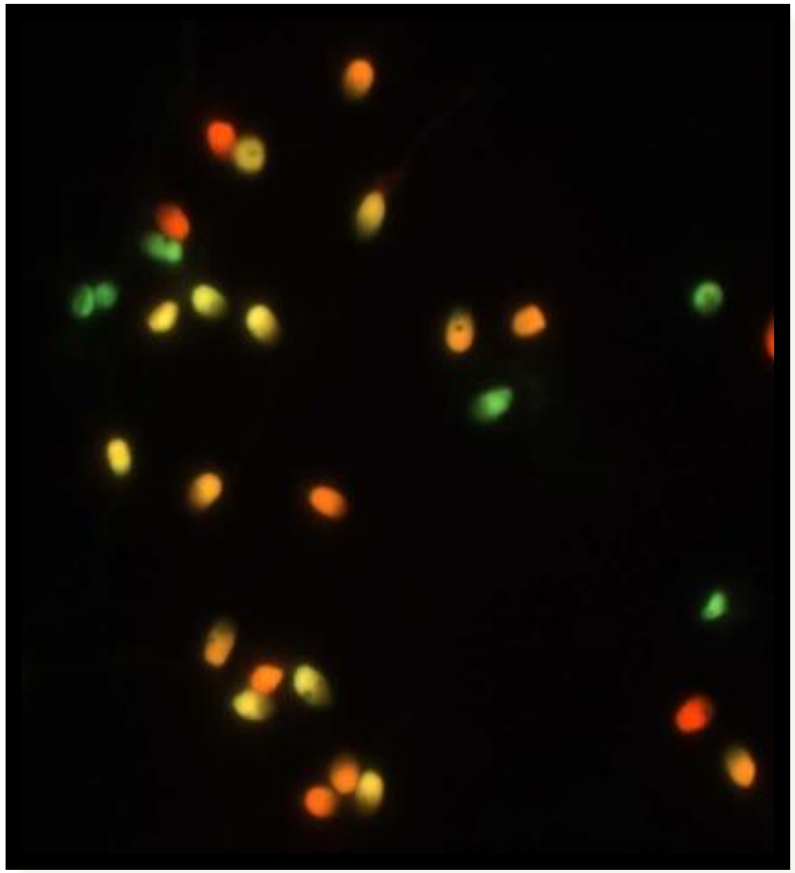


FRAMMENTAZIONE DEL DNA SPERMATICO – "SDF"

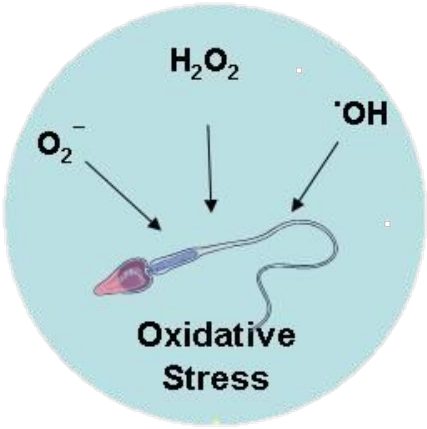
i test: SCD, TUNEL, COMET, SCSA, **AOT**

AOT=Acridine Orange Test

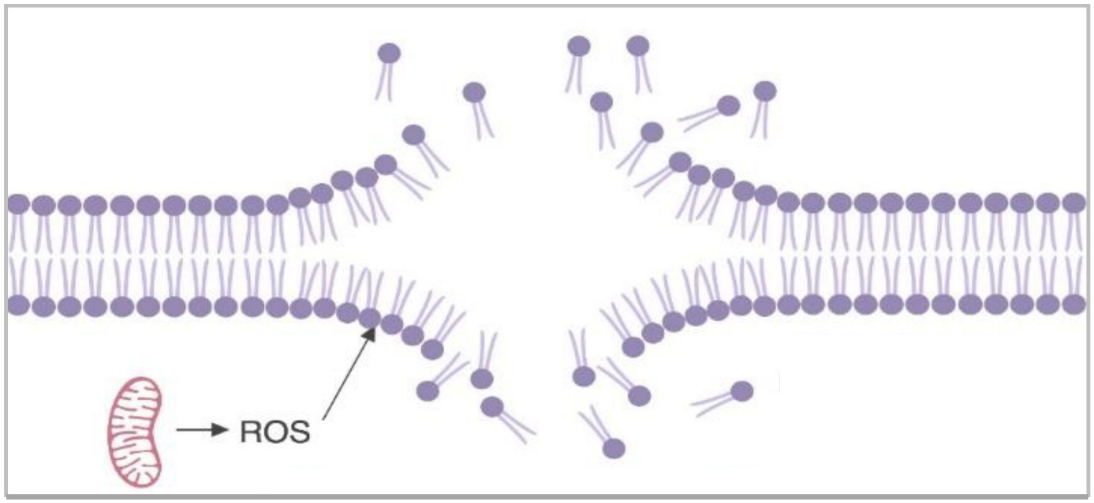
- stesso principio dello SCSA (proprietà metacromatiche dell'AO)
- limiti: scarsa riproducibilità



STRESS OSSIDATIVO “OS”



Lo Stress Ossidativo è il risultato di un alterato equilibrio tra a generazione dei ROS e l’attività antiossidante. Gli spermatozoi sono vulnerabili allo stress ossidativo poiché i ROS possono alterare la loro membrana plasmatica mediante lipoperossidazione, determinando danno a strutture proteiche e al DNA.



DOMANDA:

Quale è l'impatto del <u>trattamento del varicocele</u> sulla *frammentazione del DNA spermatico* e sui livelli di *stress ossidativo*?

***RISPOSTE**, ad oggi:*

Study (publication year)	No. of studies/ patients (total)	Study designs included in SRMA	The measure of sperm DNA damage	Outcomes
Lira Neto et al (2021) [76]	19/1,070	Prospective and retrospective	SCSA, TUNEL, SCD, Comet	Varicocele repair reduces sperm DNA damage.
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Wang et al (2012) [74]	6/177	Prospective, retrospective, and unspecified	SCSA, TUNEL, Comet	Varicocele repair reduces sperm DNA damage.
Baazeem et al (2011) [72]	3/84	Prospective	SCSA	Varicocele repair reduces sperm DNA damage.

SRMA: systematic review and meta-analysis, SCSA: sperm chromatin structure assay, SCD: Sperm Chromatin Dispersion, TUNEL: terminal deoxy-nucleotidyl transferase-mediated deoxyuridine triphosphate-nick end labeling, 8OHDG: 8-hydroxydeoxyguanosine, AOT: acridine orange test.

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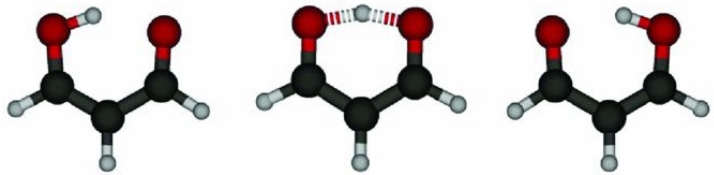
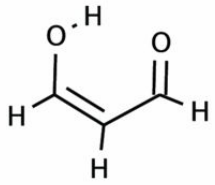
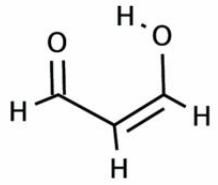
MALONDIALDEIDE SEMINALE, **"MDA":**
biomarcatore dello stress ossidativo, già coinvolta in "recurrent pregnancy loss".







Chen CS, et al: Biochem Mol Biol Int 1997;43:291-303
Mohanty G, et al: Syst Biol Reprod Med 2016;62:201-12

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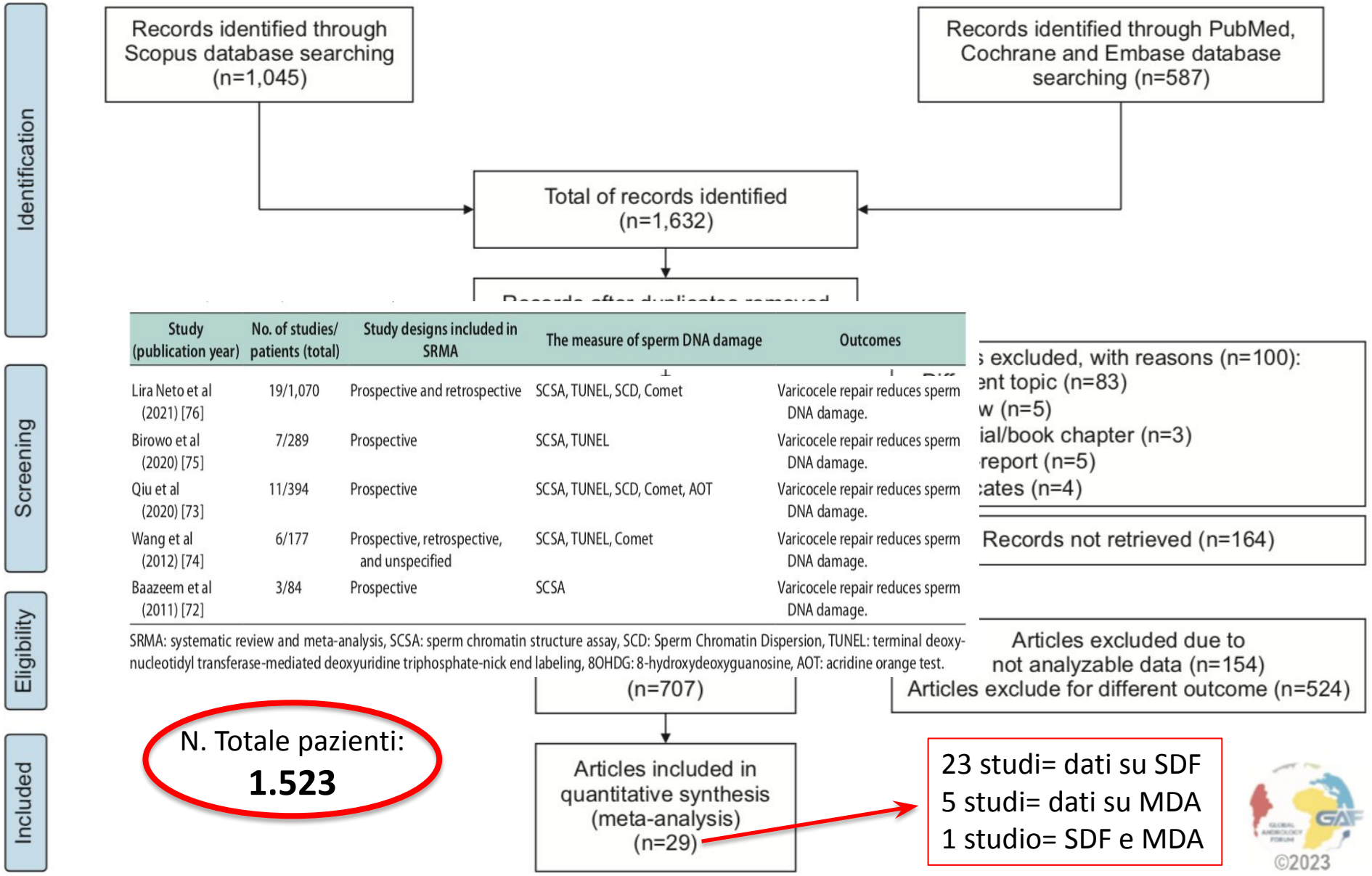

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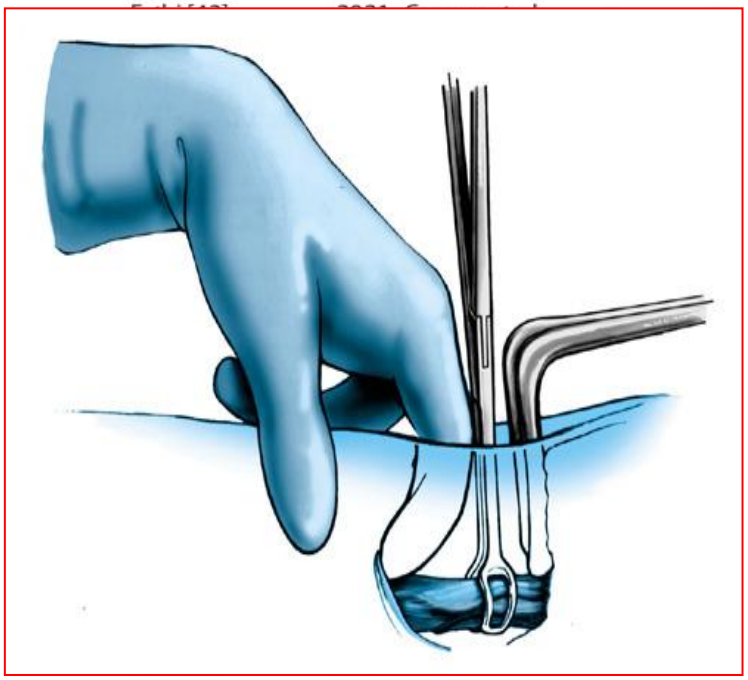
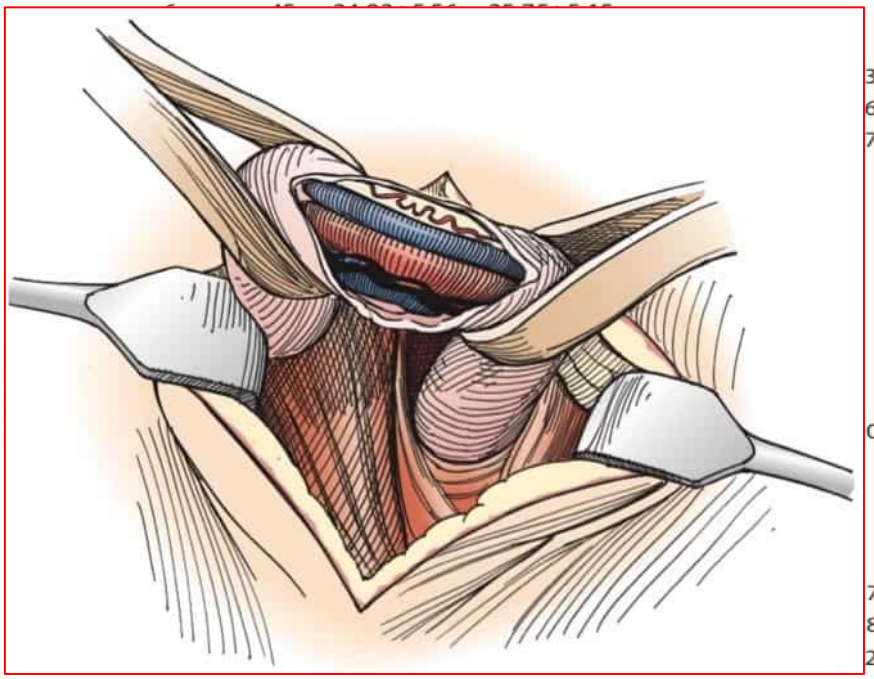
Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P) flow-chart for inclusion/exclusion of studies.

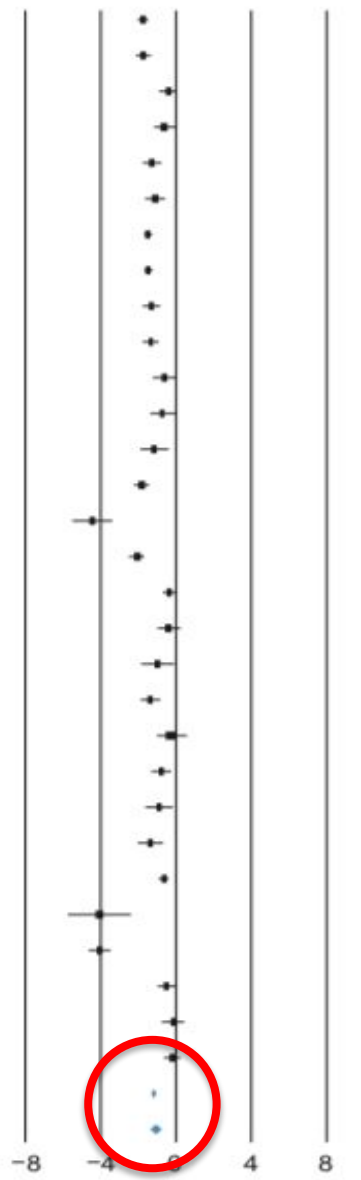
First author	Year	Study design	Varicocele		Varicocele repair		Time to evaluation (mo)	Patients (n)	SDF (%)		MDA (nmol/mL)	
			Side	Grade	Type	Side			Before	After	Before	After
Kavoussi [42]	2021	Observational	-	-	MS	-	3	121	35.3±11.6	19.6±5.3		
					MS							
					MS							
					NMI							3
					MS							6
					NMI							7
					MS							
					-							
					MS							
					MS							
					MS							
					MS							
					MS							
					MS							06
					MS							
					MS							
					MS							
					NMI							
					MS							73
					MS							83
					MS							28
Telli [56]	2015	Observational	-	-	NMI		3	72	34.5±3.3	28.2±3.5		
Tavalaee [57]	2015	Observational	1	-	-							
Mohammed [58]	2015	Observational	-	-	NMI							
Smit [59]	2013	Observational	-	-	-							
Li [60]	2012	Observational	-	-	MS							
Gabriel [61]	2012	Observational	-	-	MS							
La Vignera [62]	2012	Observational	Left	3	MS							
Sadek [63]	2011	Case-control	Bilateral	-	NMI							
Zini [64]	2011	Observational	-	-	MS							
Ghazi [65]	2011	Observational	Bilateral	-	MS							
Dada [66]	2010	Observational	-	-	-							
Nasr Esfahani [67]	2010	Case-control	-	3	-							
Smit [34]	2010	Observational	-	-	-							
Zini [68]	2005	Observational	-	-	MS							
Yeşilli [69]	2005	Observational	-	-	MS						9	0.58±0.06





Sperm DNA fragmentation change after varicocele repair

Model	Study name	Year	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-value	p-value
	Kavoussi et al [42]	2021	−1.741	0.151	0.023	−2.037	−1.445	−11.532	0.000
	Fathi et al [43]	2021	−1.713	0.246	0.061	−2.196	−1.230	−6.950	0.000
	Abbasi et al [44]	2020	−0.375	0.304	0.093	−0.971	0.222	−1.231	0.218
	Camargo et al [48]	2019	−0.611	0.289	0.084	−1.178	−0.044	−2.112	0.035
	Afsin et al [49]	2018	−1.272	0.245	0.060	−1.752	−0.791	−5.188	0.000
	Vahidi et al [50]	2018	−1.077	0.276	0.076	−1.619	−0.536	−3.898	0.000
	Sun et al [51] (1)	2018	−1.484	0.123	0.015	−1.725	−1.243	−12.083	0.000
	Sun et al [51] (2)	2018	−1.453	0.121	0.015	−1.690	−1.216	−12.016	0.000
	Zaazaa et al [53]	2018	−1.345	0.248	0.061	−1.831	−0.860	−5.434	0.000
	Abdelbaki et al [54]	2017	−1.305	0.211	0.045	−1.764	−0.936	−6.389	0.000
	Ni et al [ ] (1)	2016	−0.609	0.332	0.110	−1.260	0.041	−1.836	0.066
	Ni et al [ ] (2)	2016	−0.750	0.345	0.119	−1.426	−0.074	−2.175	0.030
	Ni et al [ ] (3)	2016	−1.140	0.407	0.166	−1.938	−0.341	−2.797	0.005
	Telli et al [56]	2015	−1.852	0.199	0.040	−2.243	−1.462	−9.297	0.000
	Tavalaee et al [57]	2015	−4.431	0.548	0.300	−5.505	−3.356	−8.085	0.000
	Mohammed et al [58]	2015	−2.073	0.202	0.041	−2.470	−1.676	−10.238	0.000
	Smit et al [59]	2013	−0.359	0.204	0.041	−0.758	0.040	−1.763	0.078
	Li et al [60]	2012	−0.419	0.328	0.108	−1.062	0.224	−1.278	0.201
	Gabriel et al [61]	2012	−1.040	0.403	0.162	−1.829	−0.251	−2.582	0.010
	La Vignera et al [62]	2012	−1.355	0.286	0.082	−1.916	−0.794	−4.733	0.000
	Sadek et al [63]	2011	−0.724	0.172	0.030	−1.061	−0.386	−4.206	0.000
	Zini et al [64] (1)	2011	−0.790	0.294	0.086	−1.366	−0.214	−2.690	0.007
	Zini et al [64] (2)	2011	−0.936	0.342	0.117	−1.606	−0.266	−2.740	0.006
	Zini et al [64] (3)	2011	−1.364	0.360	0.130	−2.070	−0.658	−3.788	0.000
	Ghazi and Abdelfattah [65]	2011	−0.662	0.160	0.026	−0.976	−0.347	−4.126	0.000
	Dada et al [66]	2010	−4.151	0.874	0.764	−5.865	−2.438	−4.748	0.000
	Nasr Esfahani et al [67]	2010	−4.054	0.295	0.087	−4.633	−3.475	−13.723	0.000
	Smit et al [34] (1)	2010	−0.462	0.257	0.066	−0.966	0.042	−1.795	0.073
	Smit et al [34] (2)	2010	−0.152	0.334	0.111	−0.807	0.502	−0.457	0.648
	Zini et al [68]	2005	−0.182	0.233	0.054	−0.639	0.275	−0.781	0.435
Fixed			**−1.243**	**0.042**	**0.002**	**−1.325**	**−1.161**	**−29.681**	**0.000**
Random			**−1.256**	**0.139**	**0.019**	**−1.529**	**−0.982**	**−9.013**	**0.000**



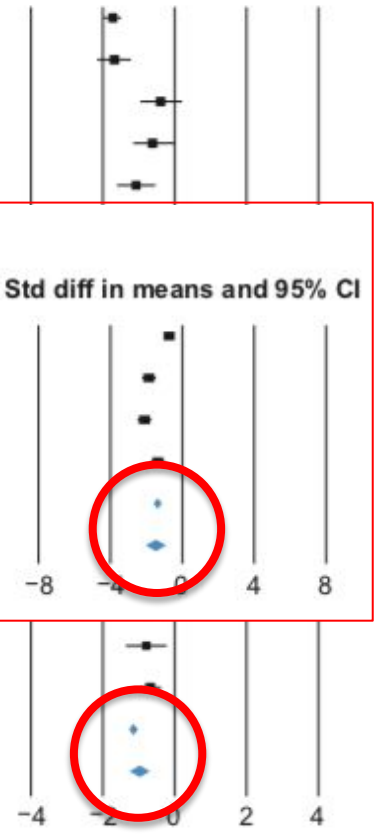
SDF subgroup analysis 1:
tecnica microchirurgica *versus* non-microchirurgica

Microchirurgia

Model	Study name	Year	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-value	p-value
	Kavoussi et al [42]	2021	−1.741	0.151	0.023	−2.037	−1.445	−11.532	0.000
	Fathi et al [43]	2021	−1.713	0.246	0.061	−2.196	−1.230	−6.950	0.000
	Abbasi et al [44]	2020	−0.375	0.304	0.093	−0.971	0.222	−1.232	0.218
	Camargo et al [48]	2019	−0.611	0.289	0.084	−1.178	−0.044	−2.112	0.035
	Vahidi et al [50]	2018	−1.077	0.276	0.076	−1.619	−0.536	−3.898	0.000

NON-microchirurgia

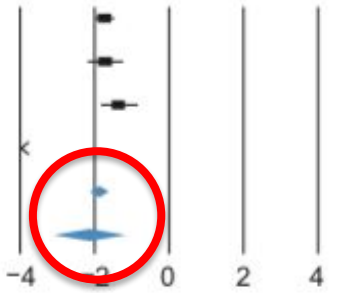
Model	Study name	Year	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-value	p-value
	Sadek et al [63]	2011	−0.724	0.172	0.030	−1.061	−0.386	−4.206	0.000
	Telli et al [56]	2015	−1.852	0.199	0.040	−2.243	−1.462	−9.297	0.000
	Mohammed et al [58]	2015	−2.073	0.202	0.041	−2.470	−1.676	−10.238	0.000
	Abdelbaki et al [54]	2017	−1.350	0.211	0.045	−1.764	−0.936	−6.389	0.000
Fixed			**−1.436**	**0.097**	**0.009**	**−1.627**	**−1.246**	**−14.771**	**0.000**
Random			**−1.495**	**0.317**	**0.101**	**−2.116**	**−0.873**	**−4.714**	**0.000**
	Zini et al [64]	2011	−0.790	0.294	0.086	−1.366	−0.214	−2.690	0.007
	Ghazi and Abdelfattah [65]	2011	−0.662	0.160	0.026	−0.976	−0.347	−4.126	0.000
Fixed			**−1.180**	**0.052**	**0.003**	**−1.283**	**−1.078**	**−22.622**	**0.000**
Random			**−1.014**	**0.127**	**0.016**	**−1.263**	**−0.765**	**−7.994**	**0.000**



SDF subgroup analysis 2: indagini diagnostiche

SCD

Model	Study name	Year	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-value	p-value
	Kavoussi et al [42]	2021	−1.741	0.151	0.023	−2.037	−1.445	−11.532	0.000
	Fathi et al [43]	2021	−1.713	0.246	0.061	−2.196	−1.230	−6.950	0.000
	Zaazaa et al [53]	2018	−1.345	0.248	0.061	−1.831	−0.860	−5.434	0.000
	Nasr Esfahani et al [67]	2010	−4.054	0.295	0.087	−4.633	−3.475	−13.723	0.000
Fixed			**−1.963**	**0.107**	**0.011**	**−2.127**	**−1.755**	**−18.429**	**0.000**
Random			**−2.197**	**0.505**	**0.255**	**−3.187**	**−1.207**	**−4.350**	**0.000**



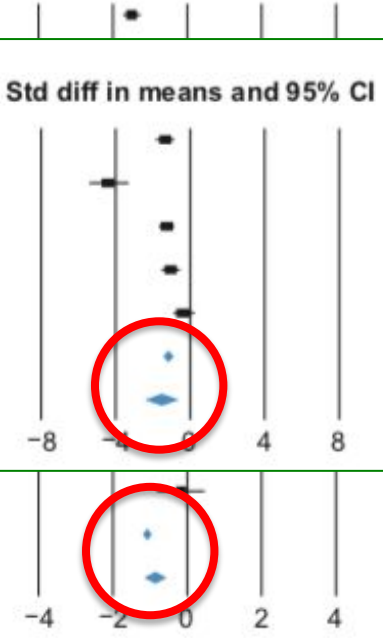
SCSA

Model	Study name	Year	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-value	p-value
	Sun et al [51] (1)	2018	−1.484	0.123	0.015	−1.725	−1.243	−12.083	0.000

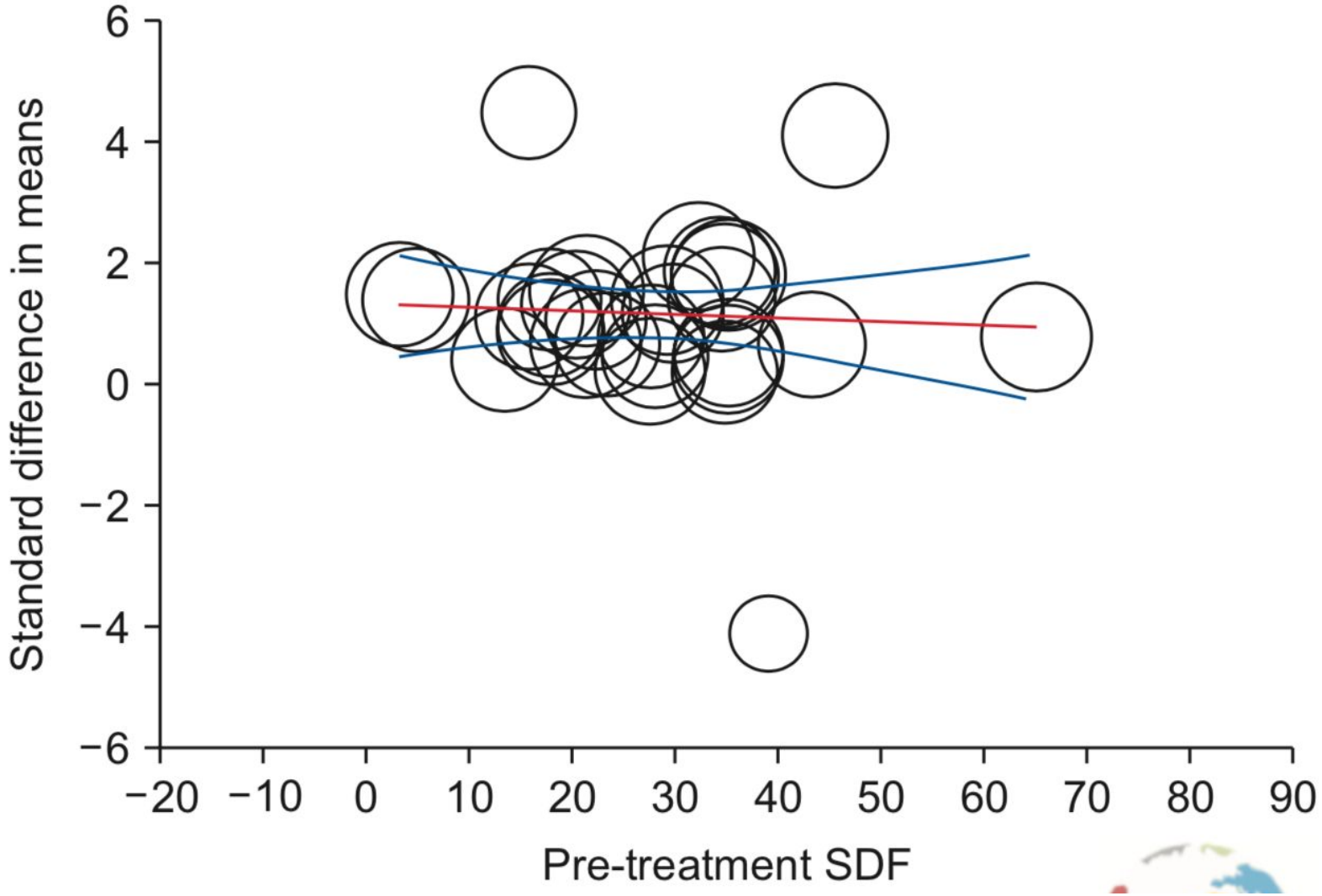
TUNEL

Model	Study name	Year	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-value	p-value
	La Vignera et al [62]	2012	−1.355	0.286	0.082	−1.916	−0.794	−4.733	0.000
	Tavalaee et al [57]	2015	−4.431	0.548	0.300	−5.505	−3.356	−8.085	0.000
	Afsin et al [49]	2018	−1.272	0.245	0.060	−1.752	−0.791	−5.188	0.000
	Vahidi et al [50]	2018	−1.077	0.276	0.076	−1.619	−0.536	−3.898	0.000
	Abbasi et al [44]	2020	−0.375	0.304	0.093	−0.971	0.222	−1.232	0.218
Fixed			**−1.259**	**0.134**	**0.018**	**−1.521**	**−0.997**	**−9.428**	**0.000**
Random			**−1.599**	**0.449**	**0.202**	**−2.478**	**−0.719**	**−3.561**	**0.000**

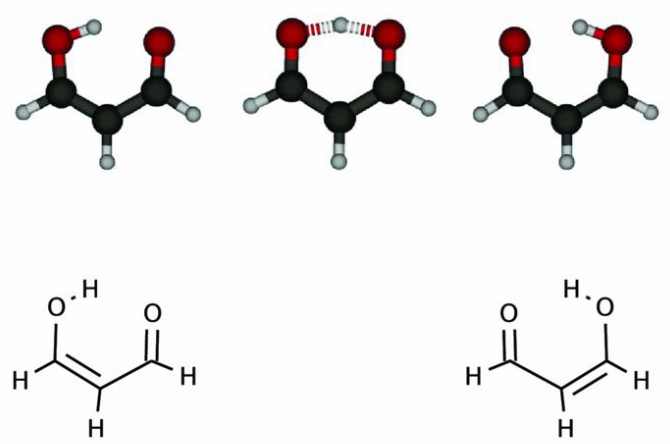
	Smit et al [34] (2)	2010	−0.152	0.334	0.111	−0.807	0.502	−0.457	0.648
Fixed			**−1.073**	**0.060**	**0.004**	**−1.191**	**−0.956**	**−17.898**	**0.000**
Random			**−0.857**	**0.152**	**0.023**	**−1.156**	**−0.559**	**−5.627**	**0.000**



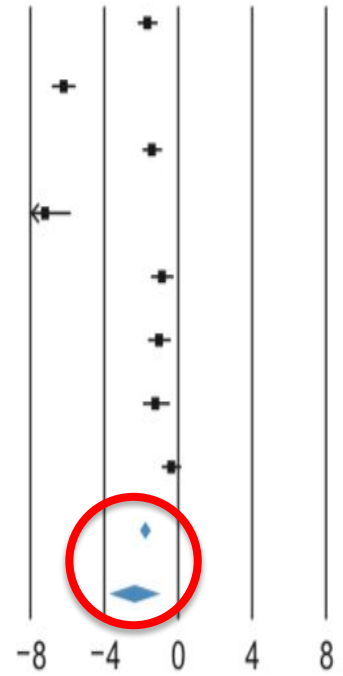
SDF meta-regression analysis



Malondialdehyde “MDA” (proxy di Stress Ossidativo)



Model	Study name	Year	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-value	p-value
	Kamal et al [45]	2020	−1.687	0.282	0.080	−2.240	−1.133	−5.973	0.000
	Omar et al [46]	2020	−6.208	0.341	0.116	−6.876	−5.539	−18.200	0.000
	Mostafa et al [47]	2020	−1.437	0.290	0.084	−2.004	−0.869	−4.961	0.000
	Lu et al [52]	2018	−7.256	0.749	0.562	−8.725	−5.787	−9.683	0.000
	Ni et al [ ] (1)	2016	−0.868	0.339	0.115	−1.533	−0.203	−2.557	0.011
	Ni et al [ ] (2)	2016	−1.020	0.354	0.126	−1.715	−0.326	−2.879	0.004
	Ni et al [ ] (3)	2016	−1.194	0.410	0.168	−1.998	−0.390	−2.911	0.004
	Yeşilli et al [69]	2005	−0.392	0.280	0.078	−0.941	0.157	−1.401	0.161
Fixed			**−1.885**	**0.119**	**0.014**	**−2.119**	**−1.651**	**−15.794**	**0.000**
Random			**−2.450**	**0.741**	**0.549**	**−3.903**	**−0.997**	**−3.306**	**0.001**



Study (publication year)	No. of studies/ patients (total)	Study designs included in SRMA	The measure of sperm DNA damage	Outcomes
Lira Neto et al (2021) [76]	19/1,070	Prospective and retrospective	SCSA, TUNEL, SCD, Comet	Varicocele repair reduces sperm DNA damage.
Birowo et al (2020) [75]	7/289	Prospective	SCSA, TUNEL	Varicocele repair reduces sperm DNA damage.
Qiu et al (2020) [73]	11/394	Prospective	SCSA, TUNEL, SCD, Comet, AOT	Varicocele repair reduces sperm DNA damage.
Wang et al (2012) [74]	6/177	Prospective, retrospective, and unspecified	SCSA, TUNEL, Comet	Varicocele repair reduces sperm DNA damage.
Baazeem et al (2011) [72]	3/84	Prospective	SCSA	Varicocele repair reduces sperm DNA damage.

SRMA: systematic review and meta-analysis, SCSA: sperm chromatin structure assay, SCD: Sperm Chromatin Dispersion, TUNEL: terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate-nick end labeling, 8OHDG: 8-hydroxydeoxyguanosine, AOT: acridine orange test.

CONCLUSIONI

- La nostra revisione sistematica e meta-analisi (SRMA) fornisce ulteriore evidenza che il trattamento del varicocele migliora la frammentazione del DNA spermatico

- La riduzione della percentuale di frammentazione è indipendente da: tecnica di correzione del varicocele, tipo di indagine per la valutazione della frammentazione, e dei valori preoperatori di frammentazione

- Questa SRMA è la prima a valutare l'impatto del trattamento del varicocele sullo stress ossidativo (mediante variazioni di livelli del suo biomarcatore MDA), dimostrandone una riduzione significativa dopo il trattamento


Grazie della
vostra attenzione