

Infertile Men with Varicocele Have Increased Nuclear DNA Damage in Spermatozoa

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The incidence of varicocele is high in infertile men—in 19 to 41 percent who present for an infertility exam and in an estimated 60 to 80 percent of those diagnosed with secondary infertility. Research has documented that varicoceles adversely affect sperm function, but the exact mechanism of this negative effect has not yet been elucidated. The Cleveland Clinic evaluated the role of oxidative stress (OS) on sperm function and found that men with varicoceles have sperm with high levels of nuclear DNA damage.

High levels of seminal OS have been correlated with sperm dysfunction through different mechanisms that include lipid peroxidation of sperm plasma membrane and impairment of sperm metabolism, motility and fertilizing capacity. In addition, OS has been shown to affect the integrity of the sperm chromatin and to cause high frequencies of single and double DNA strand breaks. Recent data indicate that increased sperm nuclear DNA damage negatively impacts natural and assisted reproduction. Also, sperm chromatin/DNA is an independent measure of sperm quality that may have better diagnostic and prognostic capabilities than the standard sperm parameters.

Researchers here hypothesized that spermatozoal dysfunction associated with varicoceles may be related, in part, to increased levels of sperm DNA damage caused

by high levels of OS. A study was designed to examine and compare levels of sperm nuclear DNA damage using the sperm chromatin structure assay (SCSA) and OS among a group of infertile men clinically diagnosed with varicocele, a group of infertile men with normal genital examination, and fertile donors.

sperm parameters and infertility status. Also, levels of reactive oxygen species were positively correlated with DNA damage ($P = .02$; $r = .57$) in men with varicoceles (see table below).

The median (interquartile range) DNA fragmentation index (percent DFI) was significantly higher in the patients

OS may be attributed to an increase in nitric oxide (NO) and the release of NO synthase and xanthine oxidase within the dilated spermatic veins of men affected with varicoceles. Another factor could be the significant decrease of the antioxidant defenses normally present in seminal and blood plasma. Because there is strong

Seminal Oxidative Stress Parameters in Fertile Donors and in Infertile Men with (Group 1) or Without Varicocele (Group 2)

Parameters	Fertile Donors (n = 16)	Group 1 (n = 16)	Group 2 (n = 15)	A	P value B	C
ROS (X 10 ⁶ cpm)	0.36 (0.1, 2)	12 (1.3, 53.4)	1.7 (0.1, 5.4)	0.01	0.38	0.06
TAC (Trolox Equivalent)	871 (699, 1288)	693 (499, 882)	904 (693, 978)	0.03	0.74	0.08
ROS-TAC Score	40.3 (38, 44)	21 (9.5, 31)	34 (28, 42)	0.002	0.10	0.02
DFI (percent)	15 (10, 22)	25 (20, 35)	20 (13, 28)	0.002	0.08	0.12

Values are median and interquartile range (25% & 75%). ROS = reactive oxygen species; TAC= total antioxidant capacity; OS= oxidative stress; DFI= DNA fragmentation index. A= P-value between fertile donors and group 1; B= P-value between fertile donors and group 2; C= P-value between groups 1 and 2. Wilcoxon rank-sum test was used for the analysis and $P < 0.05$ was significant.

The study included 31 men attending our male infertility clinic with a history of infertility that had persisted for at least 1 year. Sixteen of the 31 patients had a left varicocele (Group 1), confirmed by clinical examination and scrotal color Doppler ultrasound, and 15 men who had normal genital examinations (Group 2). A group of healthy fertile volunteers (n = 16) who had initiated a natural pregnancy within the past 12 months and had a normal genital examination served as a control group.

The presence of a varicocele was significantly correlated with reduced levels of antioxidant activity ($P = .03$) after adjusting for standard

with varicoceles as compared to the fertile controls [25 (20, 35) versus 15 (10, 22); $P = .002$]. In addition, infertile patients with varicoceles had higher DFI values than infertile patients with a normal genital examination. The difference between these 2 groups, however, was not statistically significant. The presence of a varicocele was significantly correlated with DFI ($P = .04$) after adjusting for standard sperm parameters and infertility status.

Results of the study indicate that infertile men with varicoceles have sperm with significantly high levels of nuclear DNA damage. The association of varicoceles with

evidence suggesting that high levels of OS mediate the DNA fragmentation in spermatozoa of infertile men, we speculate that increased DNA damage in spermatozoa from varicocele patients is related, at least in part, to OS.

Further research in this area is needed to understand the exact mechanism(s) by which DNA damage increases in spermatozoa from infertile men with varicoceles and to determine whether correction of the varicocele can reduce such damage. Men with varicoceles should be counseled about the potential negative effects of increased sperm DNA damage on their fertility potential.