Is oxidative stress a missing piece in varicocele related infertility puzzle? - A meta-analytic approach

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Objective: Varicocele is one of the leading causes of male infertility present in almost 40% of infertile males. Controversy surrounds the exact cause of spermatozoal dysfunction in infertile varicocele patients. Recent understanding of the role of oxidative stress and free radicals in male reproduction has led some researchers to postulate oxidative stress as the possible cause of spermatozoal dysfunction in varicocele patients. The objective of our study was to carefully examine all published literature on the role of oxidative stress in patients with varicocele as the etiology of their infertility.

Design: Review of literature and meta-analysis

Materials and Methods: Comprehensive literature review through Medline (from 1988-2005), Ovid database (1988-2005) and abstracts from ASRM meetings (2001-2004) were done. The key search words were varicocele, oxidative stress, free radicals, reactive oxygen species (ROS), lipid peroxidation, antioxidants, DNA damage, male infertility etc. We identified 22 human studies after an extensive search related with the role of OS in varicocele associated infertility. Out of these 22 studies, 4 had measured similar type of ROS by a similar technique. We used meta-analysis statistical software for the analysis. Results: 1) Several studies (9/22) measured either ROS/ LPO levels in semen (n=7), serum (n=1) or testicular tissue (n=1) in infertile varicocele patients (17/22), but 5 failed to specify the fertility status; 2) the control group was used in 11/22 studies of which 10 employed normal donors; 3) most of the studies (n= 20) reported higher OS in patient groups compared to controls, irrespective of the type of OS indices measured, Four studies full-filled the inclusion criteria for meta-analysis with a total of 248 cases (169 cases were infertile varicocele patients and 79 controls). The estimated effect size (95% CI) using “random effect method” of Cohen’s d was 2.3 (-0.05, 4.5) and Hedges’s g 2.2 (0.27, 4.15). Similarly the estimated effect size (95% CI) using “fixed effect method” of Cohen’s d was 2.4 (2.13, 2.68) and Hedges’s g 1.6 (1.22, 1.90). The results were significant using fixed effect method (both Cohen’s and Hedges’s g) and random effect method (Hedges’s g). As p value for Q test (test of heterogeneity) was highly significant, so it is preferred to use
random effect method.

Conclusion: Our meta-analysis has validated the finding of significant increase in levels of oxidative stress parameters (such as reactive oxygen species, lipid peroxidation, and DNA damage) in infertile patients with varicocele compared to donors by combining 4 published studies with a large sample size and higher statistical power. Since these results were significant with Hedges’ g and not with Cohen’s d by random effects method we stipulate that oxidative stress is increased in varicocele patients but further research is needed to confirm this. Future research is needed to prove the etiological role of OS in varicocele by demonstrating a decrease in OS measures and an improvement in clinically relevant fertility outcomes (pregnancy and ART success) after therapeutic intervention such as antioxidants supplementation and varicocelectomy. Support: None

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