

ARTICLE (1)
ANTIOXIDANTS SUPPLEMENTATION AND SPERM PARAMETERS
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During recent years, functional foods have attracted a great attention because of consumers' increasing concerns about their health. One of the functional foods properties is their antioxidant capacity, which contributes to the prevention of certain illnesses, including cardiovascular diseases, cancer and infertility.

It has been reported that between 30% to 80% of male subfertility cases are due to the damaging effects of oxidative stress on sperm and one man in 20 will be affected by subfertility. Antioxidants products are very available and inexpensive when compared to other fertility treatments and many men are already using these to improve their fertility. It is thought that oral supplementation with antioxidants may improve sperm quality by reducing oxidative stress.

Oxidative stress results from the imbalance between production of the Reactive Oxygen Species (ROS) and the protective effect of the antioxidant system responsible for their neutralization and removal. An excess of ROS causes a pathological reaction resulting in damage to cells and tissues.

Spermatozoa are particularly vulnerable to the harmful effects of ROS. Oxidative stress affects their activity, damages DNA structure, and accelerates apoptosis, all of which consequently decrease their numbers, hinders motility and development of normal morphology, and impairs function. This leads to disturbances in fertility or embryo development disorder. The main cellular source of ROS in the semen are immature sperm cells and white blood cells. The increase in the number of leukocytes may be due to infection and inflammation, but can also be due to long sexual abstinence, or varicocele (an enlargement of the veins within the bag of skin that holds the testicles).

DID YOU KNOW THAT

1. *Reactive oxygen species represent a broad category of molecules including:*
 - a) *Oxygen free radicals, such as superoxide anion (O_2^-), hydroxyl radical (OH) and peroxy radical (HO_2).*
 - b) *Non-radical species, such as hypochlorous acid (HOCl) and hydrogen peroxide (H_2O_2).*
 - c) *Reactive nitrogen species and free nitrogen radicals such as nitroxylion, nitrous oxide, peroxy nitrite, etc*
2. *Antioxidants are compounds that can delay or inhibit the oxidation of lipids or other molecules by inhibiting the initiation or circulation of oxidative chain reactions*
3. *In normal conditions, there is a balance between ROS production and antioxidant activity in male reproductive system. But high production of ROS in semen can affect sperm or seminal plasma antioxidant defense mechanisms and cause oxidative stress.*
4. *The body has developed antioxidant defense system by minimizing the formation of oxygen derived radicals to protect itself from oxidative damage*

The protective antioxidant system in the semen is composed of enzymes, as well as non-enzymatic substances, which closely interact with each other to ensure optimal protection against ROS. Non-enzymatic antioxidants include vitamins A, E, C, and B complex, coenzyme Q10 and carnitine, and micronutrients such as zinc, selenium, and copper. It seems that a deficiency of any of them can cause a decrease in total antioxidant status. *In vitro* and *in vivo*, studies demonstrate that many antioxidants possess a beneficial effect on fertility and, therefore, their use is recommended as supportive therapy for the treatment of infertility in men. In this article, we present the conclusions of few key publications on the subject.

1. A SYSTEMATIC REVIEW

This Cochrane review aimed to evaluate the effectiveness and safety of oral supplementation with antioxidants for sub fertile male partners in couples seeking fertility assistance. Workers included randomised controlled trials.

The results for the clinical pregnancy rate showed an expected clinical pregnancy for 6 out of 100 sub fertile men who did not take any antioxidants, compared to between 11 and 28 out of 100 men who were taking antioxidants.

Reference: Showell MG et al. Antioxidants for male subfertility. Cochrane Database of Systematic Reviews 2014, Issue 12. Art. No.: CD007411. (www.cochranelibrary.com)

2. A SYSTEMATIC REVIEW

A systematic review of randomized studies was conducted to evaluate the effects of oral antioxidants (vitamins C and E, zinc, selenium, folate, carnitine and carotenoids) on sperm quality and pregnancy rate in infertile men. 14 of the 17 (82%) trials showed an improvement in either sperm quality or pregnancy rate after antioxidant therapy. Ten trials examined pregnancy rate and six showed a significant improvement after antioxidant therapy. The use of oral antioxidants in infertile men could improve sperm quality and pregnancy rates.

C Ross a et al. A systematic review of the effect of oral antioxidants on male infertility. Reproductive Bio Medicine (Published by Elsevier Ltd.), Online (2010) 20, 711- 723

3. REVIEW

Despite the controversial findings in the existing literature, there is now enough evidence to show that sperm DNA damage is detrimental to reproductive outcomes. In addition, spermatozoa of infertile men are suggested to carry more DNA damage than do the spermatozoa from fertile men. Besides impairment of fertility such damage is likely to increase the transmission of genetic diseases during the assisted reproductive procedures. Standardization of protocols to assess reactive oxygen species and DNA damage is very important in introducing these tests in such clinical practice. Thus,

evaluation of seminal ROS levels and extent of sperm DNA damage in an infertile male may help develop new therapeutic strategies and improve success of assisted reproductive techniques

Reference: Marcello Cocuzza et al. Clinical Relevance of Oxidative Stress and Sperm Chromatin Damage in Male Infertility: An Evidence Based Analysis. *Int Braz J Urol.* 2007; 33: 603-21

4. REVIEW

Administration of antioxidants to infertile men has been assessed in numerous clinical studies with at least 20 reports highlighting its effect on measures of oxidative stress in human spermatozoa. A qualitative but detailed review of the results revealed that 19 of the 20 studies conclusively showed a significant reduction relating to some measure of oxidative stress in these cells. Strong evidence also supports improved motility, particularly in asthenospermic patients. However, of these studies, only 10 reported pregnancy-related outcomes, with 6 reporting positive associations.

Reference: Parviz Gharagozloo and R. John Aitken. The role of sperm oxidative stress in male infertility and the significance of oral antioxidant therapy. *Human Reproduction*, Vol.26, No.7 pp. 1628-1640, 2011

5. REVIEW

This paper was to review the literature on clinical trials studying the effects of various types of antioxidant supplements on basic and other sperm parameters and pregnancy rates in sub fertile males due to oligoasthenoteratozoospermia-(OAT). Most of studies confirmed beneficial effect of antioxidants on at least one of the semen parameters; the biggest effect was determined on sperm motility. Authors concluded that antioxidants play an important role in protecting semen from ROS and can improve basic sperm parameters in case of idiopathic OAT.

Reference: Senka Imamovic Kumalic and Bojana Pinter. Review of Clinical Trials on Effects of Oral Antioxidants on Basic Semen and Other Parameters in Idiopathic Oligoasthenoteratozoospermia. *BioMed Research International*, Volume 2014, Article ID 426951, 11 pages

6. REVIEW

This review on the effects of oral antioxidant supplements on improving major semen parameters. Authors found that supplements such as CoQ10 and alpha-tocopherol, significantly improve sperm count. Also, carnitine has positive effects on sperm motility and morphology. Simultaneous administration of vitamin E and vitamin C reduces the sperm DNA damage. However, in some studies, one or more factors have not changed substantially. In most of the studies, antioxidant supplementation improved the number, motility, morphology and sometimes DNA integrity of sperm. The present study showed

that antioxidant supplements, especially a combination of antioxidants such as vitamin C, vitamin E, and CoQ10 intake can effectively improve semen parameters in infertile men.

Reference: Sedigheh Ahmadi et al. Antioxidant supplements and semen parameters: An evidence-based review. Int J Reprod BioMed Vol. 14. No. 12. pp: 729-736, December 2016

POINTS TO REMEMBER

1. Reactive Oxygen Species (ROS) are being constantly produced in small controlled amounts in the reproductive tract and by a variety of semen components.
2. Limited amounts of free radicals and oxidative stress have an important role in controlling many physiological functions in reproduction.
3. Many searching enzymes and molecules (antioxidants) control the damaging effects of ROS to keep the normal physiological balance.
4. When ROS production exceeds the scavenging capacity of the antioxidants, a state referred to as **oxidative stress** is generated that becomes toxic to sperm.
5. High levels of ROS and OS in reproductive tract and semen are associated with sperm dysfunction and damage to sperm nuclear DNA.
6. Sperm DNA damage is more common in infertile men and has been correlated with poor reproductive outcomes.
7. A significant percentage of couples, even after extensive infertility evaluation, show no apparent male or female factor and are still unable to conceive. Increased oxidative stress and DNA damage may be responsible for the poor fertility in these patients.
8. Although routine semen analysis remains the backbone of evaluating male infertility, determining the levels and sources of excessive ROS generation in semen may be useful in developing future therapeutic strategies for male infertility.
9. Current methods for evaluating sperm DNA integrity are not standardized and are not routinely used in clinical laboratories.
10. To date, no treatment for abnormal DNA integrity has proven to be of clinical value.
11. Current evidence suggests the use of systemic antioxidants for the management of selective cases of male infertility as well as in vitro supplements during various sperm preparation techniques.