Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Der Pharmacia Lettre, 2016, 8 (8):167-172
(http://scholarsresearchlibrary.com/archive.html)

Scholars Research Library
ISSN 0975-5071
USA CODEN: DPLEB4

Antioxidants in the Treatment of Male Infertility

Mitra Sotoudeh[1] and Azizollah Arbabisarjou*[2]

[1]*MSc, Faculty Member, Iranshahr University of Medical Sciences, Iranshahr, Iran.(IR. Iran).*
[2]*Pregnancy Health Research Center, Zahedan University of Medical Sciences, Zahedan, IR Iran*

ABSTRACT

By affecting the process of spermatogenesis, several genetic, environmental, physiological and nutritional factors can reduce sperm quality and quantity and cause male infertility. The present study aimed to summarize studies conducted on the epidemiological and pathophysiological causes of male infertility, the effects of oxidative stress on poor sperm function and the role of antioxidants in the treatment of male infertility. In the present meta-analysis, the following key words were searched on PubMed, Google scholar, Scopus and Web of Science (1993-2013): male reproductive, male infertility, treatment for male infertility, antioxidant, role of antioxidant therapy, oxidative stress, antioxidant treatment in male fertility, oxidative stress and male infertility and effects of oral antioxidants on sperm quality. Oxidative stress is created by Reactive Oxygen Species (ROS) or free radicals. Although small amounts of ROS are required for sperm functioning, high levels of ROS can affect semen quality which is responsible for %25 of male infertility cases. However, there are antioxidants that have control over the production of ROS and the process of lipid peroxidation by collecting ROS and balancing useful oxidants creating oxidative stress. Thus, using these antioxidants has been recommended for the treatment of male infertility. the administration of L-Carnitine, Selenium, Vitamin E, Vitamin C, Glutathione and coenzyme Q10, as antioxidants, has been proven effective for improving sperm parameters.

Key words Male Infertility, Antioxidant, Oxidant stress, Sperm

---

INTRODUCTION

According to the World Health Organization (WHO), infertility is defined as 'failure to achieve pregnancy after a year of regular unprotected sexual intercourse' [1,2]. Statistics have shown that infertility can be seen in almost %15 of couples and that in %25 of male infertility cases, the reason is reduced semen quality [1- 3].By affecting the process of spermatogenesis, several genetic, environmental, physiological and nutritional factors (e.g. oxidative stress) can reduce sperm quality and quantity and lead to male infertility [4].

Male fertility depends on different factors, including sperm count, motility and morphology. According to studies, the mentioned factors are considerably vulnerable to free radicals [5]. Free radicals are oxygen molecules containing one or more unpaired electrons [2]. Reactive Oxygen Species (ROS) are among the most powerful free radicals [5]. ROS are produced in a normal cell metabolism and during the process of enzymatic regeneration of O_2 for energy production[2]. ROS can be seen in different forms, including the primary superoxide anion radical ($-O_2$) that can finally turn into secondary forms such as hydroxyl peroxide (H_2O_2), peroxyl radicals and hydroxyl radicals[2, 6 , 7]. Although small amounts of ROS are needed for capacitation, hyper activation and oocyte-sperm fusion, elevated rates of ROS can lead to low sperm motility, high sperm DNA damage, lipid peroxidation of sperm membranes and

reduced oocyte-sperm fusion [2]. High levels of ROS in semen impair antioxidant defense mechanisms in sperm and seminal plasma and lead to oxidative stress [5, 8]. Oxidative stress is the main cause of male infertility in %30 to %80 of cases [2].

MATERIALS AND METHODS

Methodology

In this review study, key words including antioxidants (antioxidant therapy, oral antioxidants, folate, folic acid, selenium, zinc, vitamin C, vitamin E, ascorbic acid, tocopherel and Carnitine) and male infertility (male infertility, male reproductive system, treatment for male infertility, oxidative stress, male Infertility, oxidative stress and effects of oral antioxidants on sperm quality)were searched on PubMed, Google scholar, Scopus and Web of Science (1993-2013). Among the obtained studies, those related to male infertility and treatment with oral antioxidants were included in the analysis.

Sources of ROS

High concentration of PUFA in sperm membrane makes sperm to be more vulnerable to lipid peroxidation. On the other hand, a relative lack of intracellular antioxidant defense mechanism increases spontaneous generation of ROS by sperms [2].

The main sources of ROS generation in semen are leukocytes and sperms [2, 6, 9]; however, antioxidant defense mechanism in seminal plasma compensates for limited intracellular antioxidant defense to protect plasma membrane around the sperm tail and head (acrosome) [2 , 6].

There are also external sources of ROS generation in addition to the internal sources (leukocytes & sperms). Environmental factors, infections and lifestyles are among the main external sources of ROS. Moreover, industrial compounds, smoking, alcohol consumption, extreme exercises and high temperature can have negative impacts on male fertility [2].

Internal sources of ROS

Leukocytes

Peroxidase positive leukocytes are the main sources of ROS generation in the semen. These leukocytes contain polymorphonuclear leukocytes (neutrophils) (%50-%60)and macrophages (%20-%30) mainly produced by prostate and seminal vesicles. The ability of these leukocytes for ROS generation depends on their activity and increases by infection, inflammation or any other stimulation. When leukocytes are active, the amount of Nicotinamide Adenine Dinucleotide Phosphate-Oxidase (NADPH)secretion increases and the myeloperoxidase system becomes activated; these processes finally lead to a respiratory burst with the generation of a large amount of ROS. Respiratory burst acts as the first effective defense system that kills infection [6].

When transferring seminal plasma in the capacitation stage, the produced ROS damage the sperm cells. On the other hand, leukocytospermia (i.e. an abnormal increase in the concentration of seminal leukocytes) leads to ROS generation followed by low sperm count and motility and abnormal sperm shapes [2 , 6].

Spontaneous sperm production

ROS production by sperm is independent of ROS production by leukocytes. The ability of sperms to produce ROS depends on their maturity level. When sperms are being produced, cytoplasm naturally leaves spermatogenesis and the remaining cytoplasm contains high levels of Glucose-6-phosphate dehydrogenase (G6PD) enzyme that controls glucose flow speed (through Hexose Monophosphate Shunt) and NADPH intracellular bioavailability.

NADPH produces ROS through oxidase available in the sperm membrane. Impaired sperm maturation may increase the level of residual sperm cytoplasm that leads to increased seminal ROS and secondary damages [2, 6]. Results of recent studies have shown significant differences in ROS generation in various stages of sperm maturation; so that, the maximum amount of ROS is produced by immature sperms with abnormal head and high cytoplasm concentration and the minimum amount of ROS is produced by mature sperms and immature progenitor cells [6 ,9].

RESULTS

The results showed that oxidative damage of mature sperms, done by ROS-producing immature sperms when co-migrating from seminiferous tubules to the epididymis, may be an important cause of male infertility [2].It was also indicated that the amount of damage caused by ROS depends not only on the type and quantity of sperm cells, but also on the time and duration of exposure to ROS, intracellular factors (e.g. temperature &O_2 pressure) and the composition of sperm surrounding environment (e.g. ions, pros and scavengers) [6].

ROS effects

Impaired sperm motility

H_2O_2 radical penetrates sperm and inhibits the activity of G6PD that reduces NADPH bioavailability, accumulates oxidized glutathione, reduces restored glutathione level and eventually leads to peroxidation of phospholipid membrane (NADPH provides the energy needed for sperm functioning) [2].

Mechanism of G6PD action

Sperm DNA damage

ROS can damage sperm DNA by breaking DNA strands [2 , 6]. Both leukocytes and sperms are sources of ROS generation; however, the concentration of ROS produced by leukocytes is 1000 times greater than ROS produced by sperms indicating that leukocytes are the most important causes of oxidative damage. Evidence also suggests that oxidative stress damage in sperm is more related to sperm position than its concentration [2].

Treatment strategies

Sperm production disorders are the leading causes of male infertility; therefore, the treatment of these disorders is very important. The best way to assess male fertility is sperm analysis. Doing so, at least two samples of sperm must be collected in an at least a 4-weak interval. Unfortunately, the reasons behind most of male infertility cases are still idiopathic reflecting the current little knowledge about the mechanisms governing testicular functions and spermatogenesis process. Assisted reproduction techniques such as ICSI, ZIFT, IVF and other methods of fertilization have solved many infertility problems; however, the average cost of such treatments is high. Medication is mostly available and less costly for a wider range of couples. Some oral treatments improve sperm count and sperm motility [1, 2].

Methods of oxidative stress treatment

1. The elimination of ROS sources in human including:
- ✓ Lifestyle modification
- ✓ Varicocelectomy

2. The use of antioxidant vitamin supplements [2 , 6].

Elimination of ROS sources in humans

Understanding the differences between sperms and leukocytes, as ROS sources, can significantly affect the treatment of oxidative stress. Moreover, factors influencing the penetration of abnormal leukocytes (e.g. inflammation, infection and smoking) should be identified and treated. The interference of seminal ROS-generating cells (leukocytes & abnormal sperms) with normal sperms must be minimized [6].

Antioxidant supplements

Against free radicals, there are antioxidants that control ROS generation and lipid peroxidation processes [3].

In order to neutralize cell damages caused by ROS generation, enzymatic and non-enzymatic antioxidant systems create a balance between useful oxidants and oxidative stress-generating oxidants by collecting excessive ROS [2].

Seminal plasma contains enzymatic antioxidants (e.g. Superoxide dismutase (SOD), Glutathione Reductase (GR), Glutathione Peroxidase (GPx) and Catalase) plus non-enzymatic antioxidants (e.g. Vitamin E, Vitamin C, Vitamin A, Carnitine and Selenium) [2, 6 , 7].

The administration of L-Carnitine, Selenium, Vitamin E, Vitamin C, Vitamin B-12, Glutathione and coenzyme Q10, as antioxidants, has been proven effective for improving sperm parameters [1].

Antioxidant defense mechanism includes three levels of prevention, cessation and modification [6].

Preventing ROS generation is the most important antioxidant defense mechanism; for example, the binding of Fe metal ions, particularly Cu, can prevent a series of chain reactions. When the binding of metal ions to ROS is loosen, the generation of active oxidants, especially –OH, increases. Through the process of ROS deactivation, antioxidants prevent the formation of free radicals and the final products will be non-radical. The third antioxidant defense mechanism is the modification of damages. Damages can be fixed for the first time. The sperms cannot modify damages due to the lack of enzymatic system in cytoplasm needed for the modification of damages [6].

Vitamin E (Tocopherol) is a fat-soluble vitamin that acts as the main defense of cell phospholipid membrane and mitochondrial sheath against oxidative stress. Vitamin E cuts reaction chains involved in lipid peroxidation and increases the production of ROS-collecting enzymatic antioxidants [12].

Vitamin E acts by collecting –RO and –ROO radicals and connecting hydrogen to radicals and converting them to harmless metabolites. This function of Vitamin E is called clearing up free radicals [13]. Maintenance of steady states of –RO and –ROO radicals depends on regenerative agents such as Vitamin C; therefore, Vitamin E becomes able to continue its activities against free radicals [6]. Vitamin E significantly decreases the concentration of Malondialdehyde (MDA) increased during the process of lipid peroxidation in seminal plasma and sperm; thus, Vitamin E is effective in improving sperm motility [3].

Vitamin C is a powerful ROS scavenger that can be effective in the expression of genes involved in the intracellular pathway to regeneration [15]. Vitamin C ALSO plays a role in restoring oxidized Vitamin E [3, 6].

Selenium plays its vital role by increasing Glutathione Peroxidase. Selenium is also an essential factor in normal testicular functioning, spermatogenesis process and sperm motility. Selenium is important in testosterone metabolism and acts as a major component of capsule selenoprotein of sperm. Selenoprotein helps in the perseverance of membrane continuity. Selenium is involved in the production of Glutathione Peroxidase that decreases ROS, improves men fertility and acts as a defense factor against oxidative stress [3].Glutathione Peroxidase acts like hydrogen peroxidase and destructs peroxidase [14].

In a study, Moslemi et al. (2011) examined the effects of consuming Selenium and Vitamin E supplements on sperm parameters and found that both antioxidants can improve sperm motility and sperm morphology ($p<0.001$) [3].

Carnitine is an amino acid produced in the liver and kidneys via the metabolism of methionine and lysine. Carnitine is widely distributed in the body and normally acts as a supplement in transporting fatty acids into the mitochondria. Together with fructose and lactate, Carnitine is an important source of energy in sperm. Carnitine also plays a vital role as an energy substrate for sperm in the epididymis. More than %94 of free Carnitine in seminal plasma originates from the epididymis. Carnitine is effective in sperm motility and sperm maturation. The effectiveness of Carnitine in sperm motility and sperm generation is due to the oxidation of fatty acid as the main source of sperm energy in epididymis. Furthermore, Carnitine protects DNA and cell membrane against damages caused by oxygen free radicals [1,4]. Numerous studies have shown reduced levels of Carnitine in semen of infertile men.

In a study conducted between the years 2006 and 2007 on 40 patients with as then ospermia who were treated with 750 mg Carnitine per day, Amiri et al. have found that Carnitine significantly increases sperm count and improves sperm morphology ($p<0.05$) [4].

DISCUSSION AND CONCLUSION

Significant developments have been made in understanding the process of male reproductive performance and the importance of factors affecting male infertility [1]. One of the factors affecting male infertility is oxidative stress; so that, high levels of ROS and oxidative stress negatively affect the pathophysiology of infertility, sperm DNA, fertilization and embryo growth, pregnancy and proper placement of embryo in the womb [7]. In case of proper diagnosis and treatment, many of infertile men can be treated by medication [1]. The treatment of male infertility by oral antioxidants decreases oxidative stress and improves sperm motility and morphology [7]. Studies conducted on the effectiveness of pomegranate juice in improving sperm parameters and fertility rate in adult male rats showed that consuming pomegranate juice can significantly affect sperm count ($p=0.014$), sperm morphology ($p=0.01$) and

sperm fertility ($p<0.05$) [5 , 15]. Analysis of the effectiveness of consuming Carnitine in improving sperm parameters in infertile men showed that daily consumption of Carnitine (750 mg) , (2 gr) can significantly improve sperm count and sperm motility ($p<0.05$) [1,4]; however, studies did not show any improvement in sperm morphology ($p=0.0005$) ,($p=0.04$) as a result of daily consumption of Carnitine[1,16]. The effectiveness of Carnitine consumption in improving sperm count and sperm motility was more obvious in patients with severe infertility disorders [17]. In another study, Carnitine consumption was not statistically and clinically effective in overall sperm motility and sperm count [18]. Studies have shown that the use of Vitamin E can improve sperm motility ($p=0.003$) [17]. It has been shown that consuming a daily 200 mg dose of Vitamin E can significantly decrease lipid peroxidation after 3 months and increase fertility rate after 1 month[19]. Simultaneous use of Vitamin C and Vitamin E can positively affect sperm count and the percentage of normal sperms [20]. Moreover, consuming a daily 200 mg dose of Selenium supplement plus a daily 400 mg dose of Vitamin E significantly affect sperm motility and sperm morphology ($p<0.001$) [3].Self-care education is emphasized because it leads in active role in treatment process and accepting responsibility for individual health [22]. Social networks are used for behavior improvement, educational performance and other self-care education [23]. Infertility and menstruation are accompanied with natural menopause or surgery may influence health of women, then it can say that these women needed special education and training [24].

Results of studies conducted on animals and humans showed that:

✓ Compared to fruits such as blackberry, raspberry and orange, pomegranate contains higher amounts of Vitamin E and Vitamin C and is more effective in improving sperm parameters; accordingly, consuming pomegranate juice is highly recommend, especially for men with infertility problems [1].

✓ Considering metabolic activities of Carnitine in energy production processes and antioxidant activities, consuming Carnitine, as a supplement or medicine, is highly recommended to increase sperm count and improve sperm motility and sperm morphology [1, 4].

✓ Considering the essential role of Selenium in the structure of Glutathione Peroxidase and the importance of Vitamin E as a scavenger, consuming Selenium and Vitamin E supplements can improve semen quality and sperm parameters, especially sperm motility [3].

REFERENCES

[1]Peyvandi S; Karimpour AA; Moslemizadeh N. *Journal of reproduction and infertility*,**2009**, 10, 4, 245-251.
[2] Kefer J; Agarwal A;Sabanegh E. *Int j Urology*,**2009**, 16, 449-457.
[3] Moslemi KM; Tavan Baksh S.*Int j Gera General Medicine*,**2001**, 4, 99-104.
[4]Amiri I; Mahmodi R; Babalhavaeji H; Sheikh N;Najafi R. *Armaghane Danesh Journal*, **2007**, 12, 4, 66-71.
[5]Amini Rad O; Khalili M; Soltani Gord Faramarzi H.*Hormozgan Medical Journal*, **2009**, 13, 3,182-188.
[6]Agarwal A;Saleh R. *urologic clinics of North America*, **2002**, 29, 4,817-827.
[7] Ross C; Morris A; Khairy M; Khalaf Y Braude P; Coomarasamy A; EL – Toukhy T. *Reproductive Biomedicine* online ,**2010**, 20,711-723.
[8]Agarwal A; Sharma RK; Desai NR; Prabakaran S; Tavares A;Sabanegh E.*Urology*, **2009**, 73, 461-469.
[9]Aitken Rj ; Harkiss D; Knox W . *J cell sci* ,**1998**, 83,95-103.
[10]Henkel R, Kierspel E, Stalf T, Mehnert C, Menkveld R, Tinneberg HR, Schill WB, Kruger TF.*Fertil Steril*, **2005** ,83,3,635-42.
[11] Buettner GR.*Arch Biochem Biophys*, **1993**, 300,535-453.
[12] Mahan L. Kathleen;Scott – stump Silvia. Krause's food, nutrition and Diet therapy, Salami, Tehran, **2012**; pp.1388:88-89.
[13] Scott R; Macpherson A; Yates R.W.S. *Br j urol* , **1998**, 82,76-89.
[14]Türk G, Sönmez M, Aydin M, Yüce A, Gür S, Yüksel M, Aksu EH, Aksoy H.*Clin Nutr*, **2008**, 27, 2, 289-96.
[15]Lenzi A;Sgro O; Salacone P; Paoli D; Gilio B; Lombardo F . *Fertility and Sterility*, **2004**,8, 16, 1578-84.
[16]Lenzi A;Sro P; Salacone P; PaoliD; Glio B; Lombardo F; etal. *Fertility and Sterility*,**2003**,79,2, 22-300.
[17] Sigman M; Glass S;Campagnone J;Jryor Jl. *Fertil Steril*, **2006** ,85,5, 1409-14.
[18] Suleiman SA; Ali M ; Zaki ZM; el – Malik EM;Nasr MA .*J Androl* ,**1996**, 17,5,530-537.
[19] Greco E; Roman o; Lacobell M. *HVM Reported*, **2005**, 20,2590-94.
[20] Greco E; Lacobelli M; Rienzi L. *J Androl* ,**2005**, 29, 349 – 353.
[21] Khosrowbeygi A. *Arak Medical University Journal* (AMUJ), **2013**, 15,68, 94-103.
[22]Raufmehrpour Z. & Arbabisarjou A. *Transplant International* (online ISSN: 1432-2277) P :267 , E 71.

[23]Arbabisarjou Azizollah , Balouchi A., Balouchi M. Application of Social Networks among high schools students in Sisitan and Balouchestan,Iran, **2015**, 7(9): 161-167.
[24]Kiani F. Arbabisarjou A. General health and its related factors in postmenopausal women, **2013**; 10(S_1), 141-144.