

SELENIUM: ITS POTENTIAL ROLE IN MALE INFERTILITY

OO Oguntibeju¹, JS Esterhuyse², EJ Truter³

ABSTRACT

Currently, biomedical research is showing interest in the anti-oxidant activity of selenium. This could be due to compelling evidence that reported that oxidative damage to cells and cell membranes is one of the causative agents in the pathogenesis of many disease states including male infertility. Selenium is a trace element which may be found in soil, water and some foods and is considered to be an essential element which plays an active role in several metabolic pathways and is believed to perform several important roles in the human body. These roles include anti-oxidative activities at cellular level and participating in different enzyme systems. Selenium also serves as a vital component in the maintenance of muscle cell and red blood cell integrity, playing a role in the synthesis of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). It has also been reported that selenium is essential in the detoxification of toxic metals in the human system, foetal respiration and energy transfer reactions as well as in the production of sperm cells. It is thought that male infertility can be the result of a selenium deficiency as the absence of selenium in the testicular tissues induces degeneration which results in the active impairment of sperm motility as the first indication of impending infertility. This review paper investigates the role of selenium in male infertility.

KEY WORDS: Selenium, Male infertility.

Pak J Med Sci April - June 2009 Vol. 25 No. 2 332-337

How to cite this article:

Oguntibeju OO, Esterhuyse JS, Truter EJ. Selenium: its potential role in male infertility. Pak J Med Sci 2009;25(2): 332-337

-
1. OO Oguntibeju,
 2. JS Esterhuyse,
 3. EJ Truter
- 1-3: Oxidative Stress Research Unit
Faculty of Health & Wellness Sciences,
Cape Peninsula University of Technology,
Bellville 7535,
South Africa.

Correspondence

Dr. OO Oguntibeju
Department of Biomedical Sciences
Faculty of Health & Wellness Sciences
Cape Peninsula University of Technology (CPUT)
Bellville 7535,
South Africa.
Email: oguntibejuo@cput.ac.za
bejufemi@yahoo.co.uk

* Received for Publication: October 17, 2008

* Revision Received: January 22, 2009

* Revision Accepted: February 16, 2009

INTRODUCTION

Reports have shown that about 6% of adult males are believed to be infertile.¹ According to Griffin and Wilson,² infertility could be defined as the inability to achieve a pregnancy after one year of unprotected intercourse. It is also believed that conception should normally be achieved within 12 months in about 80% of couples without contraceptive measures whereas about 20% of couples attempting their first pregnancy have a problem achieving it within the same period.^{1,2} It is further known that certain cases of male infertility may be due to anatomical abnormalities. However, about 40-90% of male infertility is considered to be due to deficient sperm production to which selenium deficiency has been linked.

The biological functions associated with selenium besides male fertility include prevention of cancer, cardiovascular disease, viral mutation, endocrine and immune function as well as modulating inflammatory response.^{3,4} It is important to note that the biological actions of selenium are mediated via the expression of 30 selenoproteins. This review therefore examines the potential role of selenium in male infertility.

Selenium and male infertility: Limited data is available on the effects of selenium on male reproduction. Hurst *et al.* reported that fertile males had significantly higher selenium levels in their seminal fluid than infertile men.⁵ This study shows the importance of selenium in male reproduction and the probable relationship between male infertility and selenium. According to Boitani & Puglisi selenium is considered to be essential for normal spermatogenesis of mammals and the critical role it plays is principally mediated by two selenoproteins, namely phospholipid hydroperoxide glutathione peroxidase (PHGPx) and selenoprotein P.⁶ Laboratory evidence has shown that PHGPx is the major selenoprotein expressed by germ cells in the testis, having multiple functions and representing an important link between selenium, sperm quality and male fertility.⁶

Selenoprotein P, a plasma protein is said to be required to serve as a selenium supply to the testis. In the past years, nutritional studies and experimental animal models on cells lacking/over-expressing a specific PHGPx isoform and selenoprotein P have provided a better understanding of the selenium dependency of the male reproductive system. Available clinical data have pointed to a correlation between lack or over-expression of PHGPx gene, a low serum selenium level and male infertility. However, more evidence is needed to draw any definitive conclusions about therapeutic strategies for improving fertility by selenium administration.

The selenoprotein phospholipid hydroperoxide glutathione peroxidase (PHGPx) accounts for almost the entire selenium content of the

mammalian testis. It is quantitatively expressed in spermatids as active peroxidase but is transformed to an oxidatively inactivated protein in the mature sperm cell, where it is considered to be a major constituent of the mitochondrial capsule in the mid-piece. Male infertility in selenium-deficient animals, which is characterized by impaired sperm motility and morphological mid-piece alterations, is considered to result from insufficient PHGPx content. In a study carried out by Foresta *et al.* the relationship between sperm PHGPx, measured as rescued activity and human fertility, was investigated.⁷ Sperm specimens from 75 infertile men and 37 controls were analyzed for fertility-related parameters according to World Health Organization criteria and the PHGPx protein content was estimated after reductive solubilization of the spermatozoa by measuring the rescued PHGPx activity. Rescued PHGPx activity of infertile men ranged significantly below that of controls (93.2 ± 60.1 units/mg sperm protein vs. 187.5 ± 55.3 units/mg respectively) and was found to be particularly low in oligoasthenozoospermic specimens (61.93 ± 45.42 units/mg; $P < 0.001$) when compared with controls and asthenozoospermic samples. Rescued PHGPx activity was found to correlate positively with viability, morphological integrity, and most profoundly forward motility ($r = 0.35, 0.44, \text{ and } 0.45$, respectively). In isolated motile sperm samples, motility decreased faster with decreasing PHGPx content. The authors concluded that in humans, PHGPx appears to be indispensable for the structural integrity of spermatozoa and that it co-determines sperm motility and viability. Because the content of PHGPx, irrespective of the cause of alteration, correlated with fertility-related parameters, PHGPx can therefore be considered to be a predictive measure for fertilization capacity.

In a study conducted in Zagreb, Croatia between 1988 and 1990, Krsnjavi *et al.* investigated the potential role of selenium in male infertility.⁸ Blood and semen samples were collected from 18 men with low sperm counts and from 23 controls which were matched for age,

smoking, alcohol and coffee consumption. After adjusting for confounders, the authors reported that serum selenium was significantly lower in men with oligospermia and azoospermia than in controls (fertile men). They also observed a significant difference in serum selenium levels in men with oligospermia and azoospermia, being higher in men with oligospermia than azoospermia. It was suggested that additional studies on supplementation could contribute to solving the enigma of male idiopathic infertility.

In a Canadian study, Vezina *et al.* reported evidence supporting the beneficial effect of selenium in infertile male patients.⁹ The patients were given 400 mg of vitamin E and 100 µg of selenium daily, in divided doses for one month, followed by 200 µg of selenium and 400 mg of vitamin E daily for the next five months of the study. This study showed a significant improvement in sperm motility, viability and morphology following supplementation in nine infertile men when treated with selenium and vitamin E. The authors believe that prevention of oxidative damage by seleno-enzymes and vitamin E may be the underlying reason for the improvement in sperm motility, viability and morphology. In our opinion certain questions need to be asked. What will the effect of selenium be if taken alone by the same men in the above-mentioned study? Will it yield the same positive effect to the same degree? Is it not possible that the observed positive effect may be due to the vitamin E and not necessarily that of selenium? It is possible that the observed positive effect observed following supplementation with selenium and vitamin E is a combined effect rather than that of selenium alone. Further study is suggested to examine the effect of selenium either alone or in combination with vitamin E.

As mentioned earlier in this review, glutathione and selenium are essential to the formation of phospholipid hydroperoxide glutathione peroxidase (selenium is a component of PHGx), an enzyme present in spermatids which becomes a structural protein comprising more than fifty percent of the mitochon-

drial capsule in the mid-piece of matured spermatozoa. In a study by Lenzi *et al.* glutathione therapy was used in a two-month, placebo-controlled, double-blind, cross-over trial in 20 infertile men.¹⁰ The subjects were given either a daily 600 mg intra-muscular injection of glutathione or an equal volume of placebo. Glutathione demonstrated a significant effect on sperm motility, particularly with reference to the percentage of forward motility.

In another study, 69 infertile Scottish men were given either selenium or selenium in combination with vitamins A, C and E for three months. At the end of the clinical trial, all the patients showed significant improvements in sperm motility. It was further observed that 11% of the subjects in the treated patients impregnated their partners during the course of the study.¹¹

Another study compared the effects of selenium supplementation in 33 infertile men.¹² The men were given either a 200 mg/day dose of selenium as sodium selenite or selenium-rich yeast for 12 weeks. The level of selenium increased in both groups but was found to be higher in the selenium-rich yeast group which indicated a positive effect on semen biophysical and physiological parameters. We suggest that further studies be conducted with larger sample sizes in order that it might provide supportive evidence to the interpretation of the results of this study.

In a study conducted by Keskes-Ammar *et al.*,¹³ it was observed that vitamin E and selenium supplementation significantly decreased malondialdehyde (MDA) concentrations and also improved sperm motility while Lerda¹⁴ reported that selenium by itself protected against oxidative DNA damage in human sperm thereby enhancing sperm motility and viability.

Akinloye *et al.* examined the selenium status of idiopathic infertile Nigerian males.¹⁵ In this study, selenium concentrations in the sera and seminal plasma of 60 infertile males (40 oligospermia and 20 azoospermia) and 40 males with proven evidence of fertility (normospermia; control group) were estimated

by atomic absorption spectrophotometry. The results of the study were correlated with spermatogram and hormonal levels in order to determine their relationship to male infertility. The mean serum concentrations of selenium were found to be significantly higher in cases of oligospermia when compared to cases of azoospermia and a significant inverse correlation was also observed between serum selenium levels and sperm count. It was also observed that seminal plasma selenium levels correlated with sperm motility, viability and morphology while serum selenium levels showed a positive correlation with serum testosterone levels. The authors concluded that selenium appears to have a positive influence on Leydig cells, thus influencing the secretion of testosterone.

Bleau *et al.* studied semen samples of 125 men of couples consulting for infertility.¹⁶ Of the 125 men, relevant information of 101 couples was collected in a follow-up study for 4.5 to 5 years. In these men, a positive correlation was observed between sperm count and semen selenium concentration. Sperm motility was maximal at semen selenium levels between 50 and 60 ng/ml. It was observed that below and above this range, sperm motility was lower and the incidence of asthenozoospermia was higher. Low serum selenium levels were therefore associated with a low pregnancy rate while a high selenium level was associated with a high abortion rate and female reproductive failures.

Takasaki *et al.* examined semen samples of 32 healthy fertile and 73 infertile males.¹⁷ It was observed that selenium concentrations in whole semen and seminal fluid were not significantly different between the fertile and infertile groups. Semen selenium concentrations were found to be significantly higher in the infertile men and a negative correlation was observed between semen selenium levels and sperm motility. These results suggest that an abnormally high selenium level in semen can be related to male infertility, especially as regards the deterioration of sperm motility and spermatogenesis.

Roy *et al.* measured selenium concentrations in seminal plasma of 211 healthy men attending a male infertility clinic and observed no significant correlation between the selenium levels in the seminal plasma and sperm count or motility.¹⁸

Research over the last five decades has reported a decline in sperm count and its association with dietary factors which includes selenium. Carlsen *et al.* analyzed a total of 61 studies including 14, 947 men from the years 1938 to 1991, for mean sperm density and mean seminal volume.¹⁹ The results show a significant decline in mean sperm density from 113 million/ml in 1940 to 66 million/ml in 1990 with p value < 0.001. It was observed that seminal volume decreased (1940-1990) from an average of 3.40 ml to 2.75 ml (p= 0.027).^{20, 21} This demonstrates a 20-percent decline in volume and a significant 58-percent decline in sperm production over the last five decades. Van Waeleghem *et al.* also reported a possible link between a decline in sperm quality and selenium deficiency, although in combination with other dietary factors.^{22,23}

Selenium deficiency and health: It has been reported that selenium deficiency induced in experimental animals resulted in abnormalities such as defective growth, hepatic necrosis, myocardial degeneration and muscular dystrophy in sheep, cattle, chickens and horses.²⁴ In the human, it is recognized that selenium plays an important role in various physiological and biochemical processes and its altered blood or tissue level has a direct or indirect impact on health which may lead to development of disease.²⁵ Dietary deficiency is considered to be the most common cause of selenium deficiency. Many countries including the United Kingdom have selenium intakes that are significantly below the current recommended intake of 40 mg/day, leading to sub-optimal expression of glutathione peroxidase and other seleno-proteins in blood and tissues.^{26,27} Its deficiency can occur in areas where the soil content of selenium is found to be low such as Africa, Russia, New Zealand and China and it may affect thyroid function and cause conditions such as

Keshan disease. Selenium deficiency is also commonly seen in patients on total parenteral nutrition (TPN) as their sole source of nutrition. Gastrointestinal disorders may decrease the absorption of selenium resulting in a depletion or deficiency. Selenium may also be destroyed when foods are refined or processed and both iron and copper deficiency appear to increase the risk of selenium deficiency. There is evidence that selenium deficiency does not usually cause illness but makes the biological system more susceptible to illnesses induced by other nutritional, biochemical or infectious stresses.²⁷

Dietary sources of selenium: Dietary selenium intakes and serum selenium levels vary widely in different parts of the world and there is increasing evidence that these differences influence patterns of disease risk. In a survey carried out in Styria, Austria by Titan, selenium levels were measured in serum samples from 630 healthy volunteers aged 1-89 years.²⁸ The mean selenium level was found to be 67 µg/l which represents one of the lowest in Europe. Selenium levels were particularly low in young children and the levels found in milk samples from 34 nursing mothers were also found to be very low. The authors concluded that it may therefore be necessary for people with low serum selenium levels to modify their diet or to supplement their diet with selenium.

Selenium is widely available from a variety of foods and mother's milk usually contains higher selenium levels than cow's milk. Specific dietary sources of selenium include brewer's yeast, wheat germ, butter, garlic, grains, sunflower seeds, Brazil nuts, walnuts, raisins, liver, kidney, shellfish (lobster, oyster, shrimp, scallops), fresh-water and salt-water fish (red snapper, salmon, swordfish, tuna, mackerel, halibut, flounder, herring, smelts). Selenium is also found in alfalfa, burdock root, catnip, fennel seed, ginseng, raspberry leaf, radish, horseradish, onion, chives, medicinal mushrooms and yarrow. In some foods, where a greater percentage of selenium is found in a water-soluble form and contact with water is high, losses of selenium can occur. It has been

observed that gross deficiencies of selenium are quite rare in Western countries although intake by most people via their diet is probably not sufficient to maintain optimal levels.

CONCLUSION

As shown in this review, research has indicated that optimal selenium levels play a major role in male fertility and we are therefore of the opinion that low selenium levels could potentially contribute to cases of male infertility in humans. Based on the important biological function of selenium in male reproduction in particular and health in general, it is suggested that there should be daily increased consumption of a selenium-rich diet with increasing age and also by those individuals with high oxidative stress conditions such as chronic diseases (diabetes, cardiovascular disease, HIV) and alcoholics and smokers. It is known that infertility is one of the most stressful conditions amongst married couples and further research is suggested in this field to provide more scientific information on the role of selenium in male infertility.

REFERENCES

1. Purvis K, Christiansen E. Male infertility: current concepts. *Ann Med* 1992;24:258-72.
2. Griffin E, Wilson D. Disorders of the testes. In: Isselbacher K, Braunwald E, Wilson J, Martin B editors. *Harrison's Principles of Internal Med.* 13 Edition New York, McGraw Hill: 1994;2006-2017.
3. Arthur JR, McKenzie RC & Beckett GT. Selenium in the immune response. *J Nutr* 2003;133:1457S-9S.
4. Beckett GJ, Arthur JR, Millier SM, McKenzie RC. Minerals and immune responses-selenium in diet and human immune function. Eds. DA Hughes, LG Darlington, A Bendich, WR Beisel, Totoro, NJ: Humana Press 2004;217-40.
5. Hurst R, Bao YP, Ridley S. Phospholipid hydroperoxide cysteine peroxidase activity in human serum. *Biochem J* 1999;338(3):723.
6. Boitani, Puglisi. Molecular mechanisms in spermatogenesis. 2007 edited by C Yan Cheng www.landesbioscience.com.
7. Foresta C, Flohe L, Garolla A, Roveri A, Ursini F, Maiorino M. Male Fertility Is Linked to the Selenoprotein Phospholipid Hydroperoxide Glutathione Peroxidase. *Biol Reproduction* 2002;67:967-71.

8. Krsnjavi H, Grgurevic-batinica A, Beker D, Romic Z, Krsnjavi A. Selenium and fertility in men. *Trace Elem Med* 1992;9:107-8.
9. Vezina D, Maufette F, Roberts KD, Bleau G. Selenium-vitamin E supplementation in infertile men. *Biol Trace Elem Res* 1996;53:65-83.
10. Lenzi A, Culasso F, Gandini L. Placebo-controlled, double blind, cross-over trial of glutathione therapy in male infertility. *Hum Reprod* 1996;8:1657-62.
11. Scott R, MacPherson A, Yates RW. The effect of oral selenium supplementation on human sperm motility. *Br J Urol* 1998;82:76-80.
12. Iwanier K, Zachara BA. Selenium supplementation enhances the element concentration in blood and seminal fluid but does not change the spermatozoal quality characteristics in subfertile men. *J Androl* 1995;16:441-7.
13. Keskes-Ammar L, Feki-Chakroun N, Rebai T, Sahnoun Z, Ghozzi H, Hammani S. Sperm oxidative stress and the effect of an oral vitamin E and selenium supplement on semen quality in infertile men. *Arch Androl* 2003;49:83-94.
14. Lerda D. Study of sperm characteristics in persons occupationally exposed to lead. *Am J Ind Med* 1992;22:567-71.
15. Akinloye O, Arowololu AO, Shittu OB, Adejuwon CA, Osotimehin B. Selenium status of idiopathic infertile Nigerian males. *Biol Trace Ele Res* 2005;104(1):9-18.
16. Bleau G, Lemarbre J, Faucher G, Roberts KD, Chapdelaine A. Serum selenium and human fertility. *Fert & Sterility* 1984;42:890-4.
17. Takasaki N, Tonami H, Simizu A, Ueno N, Ogita T, Okada S, Miyazaki S. Serum selenium in male fertility. *Bul Osaka Med Sch* 1987;33:87-96.
18. Roy AC, Karunanithy R, Ratham SS. Correlation of serum level in human semen with sperm count/motility. *Arch Androl* 1990;25:59-62.
19. Carlsen E, Giwercman AJ, Keiding N, Skakkebaek NE. Declining semen quality and increasing incidence of testicular cancer: is there a common cause? *Environ Health Perspect* 1995;103:137-9.
20. Carlsen E, Giwercman AJ, Keiding N, Skakkebaek NE. Evidence for decreasing quality of semen during past 50 years. *BMJ* 1992;305:609-613.
21. Carlsen E, Giwercman AJ, Keiding N, Skakkebaek NE. Decline in semen quality from 1930 to 1991. *Ugeskr Laeger* 1993;155:2230-35.
22. Van Waelegheem K, De Clercq N, Vermeulen L. Deterioration of sperm quality in young healthy Belgian men. *Hum Reprod* 1996;11:325-9.
23. Comhaire FH, Dhooge W, Mahmoud A, Depuydt C. A strategy for the prevention of male infertility. *Verh K Acad Geneesk Belg* 1996;61:441-52.
24. Hoekstra WG. Biochemical role of selenium. In: Hoekstra WC, Suttie JW, editors. *Trace element metabolism in animals* 2nd Edition: Baltimore Uni Park Press: 1974;61-90.
25. Saxena R, Jaiswal G. Selenium and its role in health and disease. *Kuwait Med J* 2007;39(1):10-18.
26. Rayman MP. The importance of selenium to human health. *Lancet* 2000;356:233-41.
27. Caribbean Food & Nutrition Institute. Selenium, nutrition and health. *Nyam News* 2005;1 & 2:1-5.
28. Titan B. Selenium status of healthy children and adults in Styria, Austria. *Trace Elem Med* 1992;9(2):75-9.