Austin Andrology

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Review Article

Reactive Oxygen Species Turns Men Infertile but Vitamin C Prohibits - Behind the Scene

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Received: September 30, 2016; **Accepted:** October 19, 2016; **Published:** October 21, 2016

Abstract

Now-a-days, a fair number of the married couples are worried about the menace of infertility where the male partner is almost a concerned part of the "problem. Modern advances in this field of study have directed mankind to" search for the causes of the problem leading to infertility. The present review is focused on the causes and factors of sperm dysfunction related to the problem. The quality and quantity of the sperm is one of the causes of sperm infertility. Besides, ROS also plays an important role in infertility resulting in the failure of the sperm to fertilize. The use of antioxidants especially vitamin C helps to curb this sort of complications. The present review has been penned down through some basic steps that lead to infertility, which need to be understood to facilitate a solution towards the menace of infertility.

Keywords: Reactive Oxygen Species; Infertility; Vitamin C

Abbreviations

ROS: Reactive Oxygen Species; SOD: Superoxide Dismutase; GPX: Glutathione Peroxidase; NADPH oxidase: Nicotinamide Adenine Dinucleotide Phosphate-oxidase

Introduction

Infertility is a big word linked with the inability to procreate a new individual, as offspring, being produced by their parents, involving two distinct types of specialized reproductive cells as gametes, coming both from female as well as male. The menace of infertility, in question, is not involved with the females only; rather males also play a pivotal role in true sense of term. The global prevalence rates in infertility are very difficult to determine due to their occurrences in both males and females but they affect one in four couples of developing countries [1]. In the global scenarios (Figure 1), where 15% of the couples are infertile, [2] out of which 50% of the cases are the end results of the male infertility. The main problems underlining the male infertility are either restricted sperm production or blockage of sperm transport. If the production is less or the quality of the sperm is poor, the fertility cannot be achieved. Besides these, obstructions in the tubes that help to pass sperm from the testis to the penis also account for a condition of lack of sperm causing infertility. Less common causes of infertility also include sexual problems, low hormonal levels and sperm antibodies [3]. Besides, the sperms, as main reproductive cells, get damaged due to the production of too much of free radicals or reactive oxygen species (ROS) and those are the main subjects of discussion in the present review. Further, the rationale of this review is to explore the impacts of ROS on the function of the sperm, reasons for generation of ROS and the possibility of the use of vitamin C as an antioxidant that recovers the damage to sperm.

Understanding Oxidative Stress, Free Radicals and Antioxidants

An imbalance between free radical productions and the capacity of the body to detoxify harmful effects produced by the free radical through antioxidants is essentially identified as oxidative stress. A free radical otherwise is a molecule containing oxygen having one or more unpaired electrons that makes other molecules highly reactive by undergoing metabolism within the biological system. This free radical chemically works together with cellular components like DNA, proteins or lipids and by taking electrons from one molecule to other molecule consecutively generates a large chain of free radical reactions. Cells containing antioxidants molecules stop these reactions by donating an electron to the free radicals without becoming destabilized themselves. Thus it is an imbalance between oxidants and antioxidants which is the core criterion for oxidative stress.

Identification of Factors Affecting the Normal Functioning of Sperms

The sperms are vulnerable to excessive reactive oxygen species (ROS) assault which has been extensively studied [4-6] to get an idea about mechanism of infertility. The most common causes of male infertility are the malfunctioning of the sperms. Many more factors are associated with the functioning of the sperms. Among others, oxidative stress is one of the factors that have been considered to have an effect on the fertility functioning of the spermatozoa. The productions of ROS are the main negative effects of oxidative stress comprising of free radicals and peroxides [7]. It is a normal physiological process that a sperm produces ROS, but the negative perspective is the imbalance between the production of ROS and the scavenging activity which are linked with male infertility [8]. Side by side the sperm cells also get ready to fight with a powerful defense system of antioxidants those are considered as defense factors against free radical induced oxidative stress [9].

Connection of ROS with Sperm

25 % of the infertile men have high levels of ROS in their semen [10] which are linked with the damages of DNA of sperm; although

Citation: Sahu CR. Reactive Oxygen Species Turns Men Infertile but Vitamin C Prohibits - Behind the Scene. Austin Andrology. 2016; 1(2): 1009.

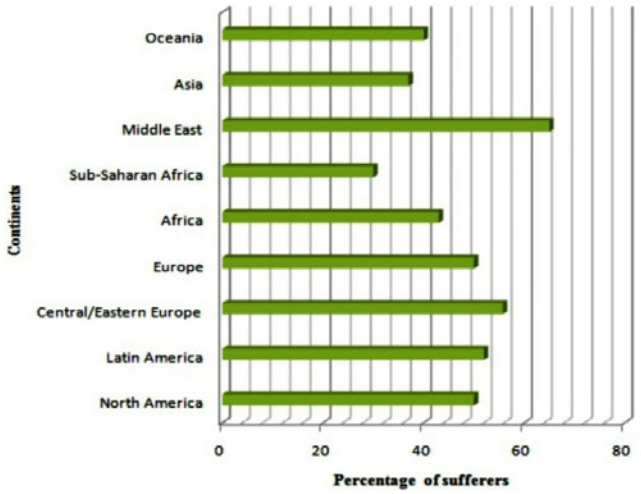

Figure 1: Global picture of male infertility.

studies [11-13] have confirmed there is no ROS threshold level above which such DNA damage occurs. However, further studies [14,15] have established the fact that the infertile men have a higher sperm DNA oxidation level in comparison to fertile men. Free radical or the ROS are present in the seminal plasma and can change the functionality of a cell [16] and simultaneously can put the cell in danger, thus making up for both the functions as a metabolite of the oxygen. That's why, to uphold the normal functioning of the cell the excess production of the ROS must be stopped by the activity of the antioxidants present in the seminal plasma. The disparity in production of ROS and the weakened antioxidant defense result in oxidative stress (OS).

Origin of ROS and its Affectability

The defective and/or immature spermatozoa produce semen ROS and even semen leucocytes have a role in its production [17-20]. It is a well established fact that the sperm cannot execute normal function due to the release of excessive ROS [20] but shows a reverse phenomenon on its release in a controlled manner. The effect of ROS on the sperm function is also dependent on its place of origin and the period of exposure [21]. The nature of and the concentration of ROS are also the determining factors for sperm functioning, whether it is useful or harmful. The basis for the ROS reaction depends on the availability of the large quantity of unsaturated fatty acids in the sperm plasma membrane that offers fluidity which is essential for sperm motility, sperm-egg interaction and the acrosomal reaction during fertilization processes. It is the nature of the unsaturated fatty acid that persuades free radical attack in the sperm plasma membrane with a stable lipid per oxidation. The built up lipid peroxidase in this process [22] helps in rendering damage to the sperm. Various studies [23-25] have proved the role of ROS in damaging the sperm function.

Excessive Production of ROS

As mentioned, the plasma membrane and the cytoplasm of the sperm contain ROS which put the sperm in danger because of the presence of unsaturated fatty acids that leads to a stage of infertility. One of the components of ROS, hydrogen peroxide, derived from the sperm can act differentially. In a moderate concentration it arrests sperm through diminution of intracellular ATP [26,27] but not the viability, whereas high concentrations lead to cell death. The excessive production of ROS has an impact in differentiation of sperm during spermatogenesis process and the sperm does not differentiate as a functional one from its pre-existing stage. The sperms are immature and defective due to faulty cytoplasmic extrusion system. Report of Aitken [28] suggests that there is a positive correlation between ROS generation and retention of residual cytoplasm by spermatozoa which are mediated by cytosolic enzyme glucose -6-phosphate dehydrogenase. Aitken et.al [29] further proposed that the generation of the ROS by spermatozoa takes place due to NADPH oxidase system at the point of sperm plasma membrane while the mitochondrial level is subjected to NADPH-dependent oxidoreductase (diaphorase) system [30].

Antioxidants Saving Fertility

Various antioxidants and antioxidant enzymes available in the seminal plasma or in spermatozoa itself give protection against oxidative damages. The management of male infertility is thus possible if the motility of the sperms can be improved by reducing the oxidative stress by breaking the oxidative chain reaction. It is an established fact that sperms are damaged by production of ROS resulting in cell death, but the intensity of production of ROS by spermatozoa is negatively correlated with the sperm quality in original semen [31]. In a published report [32] it has been observed that the infertile men have a significantly lower level of antioxidant in seminal plasma than a fertile control. It is obvious that an increased ROS production is linked with semen of infertile men having pathological detection levels of ROS but not with reduced capability of antioxidant in seminal plasma [33]. Various antioxidants in question remove the excess ROS and prevent them from oxidative stress. Thus rational use of antioxidants is desired to maintain a steady state of ROS in the seminal plasma as it is also essential for sperm physiology. The antioxidants include SOD, catalase and GPX (Glutathione peroxidase) and a variety of non-enzymatic antioxidant molecules as vitamin C, vitamin E, pyruvate, glutathione and carnitine in semen [21], acting as free radical scavengers for protection of sperm from ROS. These antioxidants facilitate in balancing the loss of cytoplasmic enzymes during spermiogenesis when a re-organization process removes excess cytoplasm of spermatid and forms a tail resulting in a sperm with other functional structures.

Vitamin C as an Antioxidant Representation

As of now, there are no much studies about the relationship between vitamin deficiency and the male infertility. Though there is no direct relationship between dietary intake of antioxidants as vitamins C, E or β–carotene and in fertile men but has an implication to the infertile men where they are at risk of antioxidant insufficiency [34], particularly vitamin C. Vitamin C holds for a much more powerful antioxidant than others by supplying up to 65% of the seminal plasma and 10 times of which go above than that of blood plasma [35]. It is well established that a high number of sperms with DNA fragmentation leads to an infertility condition but a supplementation with vitamin C decreases DNA fragmentation rates in sperm and thus making them fertile. Deficiency of vitamin C has been associated with low sperm count, their morphology and even the motility. To make sure of healthy sperm to fertilize, vitamin C

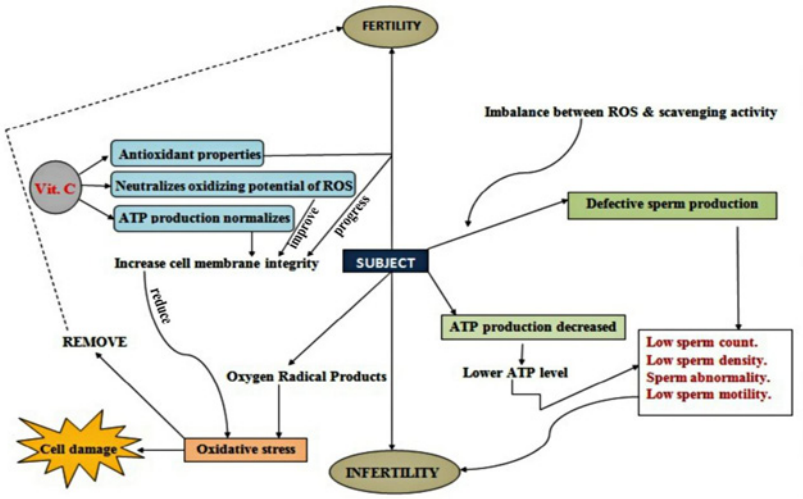

Figure 2: Possible mechanism of ROS action and their removal by vitamin C.

is essential for its normal function as it recovers sperm quality and guards sperm from DNA damages and also from oxidative damage due to free radicals. In a report it has been shown that dietary Vitamin C has a direct connection with the ascorbic acid content in the male seminal fluid. When the dietary vitamin C intake is reduced to 5 mg instead of 250 mg a day, the ascorbic acid level in the seminal fluid is reduced by 50% and simultaneously in the increase of the number of sperms with DNA damage by 91% thus indicating the importance of nutritional Vitamin C in preventing infertility in men. In our laboratory, the use of vitamin C in the form of aqueous extract of *Emblica officinalis* in sperm morphology and sperm motility in rats [36,37] shows a fruitful result against toxicity, thus proving to have a strong antioxidant capacity of vitamin C .Our results further confirm that the agent which induces oxidative stress that lessens male fertility in rats is remodeled by the extract of *Emblica officinalis* formulation. Since the extract is very rich in vitamin C and contains antioxidants, several flavonoids and steroids, hence it reduces the oxidative stress, acting as a first-rate scavenger of oxygen free radical within the cells where cells are liable to produce reactive metabolites. This helps to make progress of the testicular damage by just counteracting with the oxidizing potential of ROS induced by the agent. The vitamin C through some possible actions (Figure 2) maintains cell membrane integrity and viability. The report of Fraga et.al [38] confirms not only the improvement of sperm DNA integrity in men using dietary vitamin C but also the increased level of vitamin C in semen. It keeps the sperm from de-clumping and makes them motile. The sperm motility has also been affected by the dose and has a positive effect at a dose of 1000 mg/L; not above the level but a dose lesser than 200 mg has no effect on motility [39]. Not only dose but duration of the treatment also has an impact on sperm parameters. It is very unlikely that not showing the effectiveness of the antioxidant is either due to the short period of study or poor sample size. In future, longer period of study or large sample size will be of greater help in better understanding the approach of infertility menace.

Conclusion

The male infertility is now posing a great problem to the society. The management of the male infertility is possible only through good knowledge of the cause and concern for the problem which has been discussed in the present assessment. Next to sperm count, the sperm motility is one of the important factors to predict their fertilizing capacity and is highly correlated with fertility. While full ATP pool is crucial for the movement of the normal spermatozoa, a slight deficiency of ATP causes the spermatozoa immotile which counts for the major cause of infertility. A definitive conclusion can only be drawn if anyone gets acquainted with the factors like ROS and OS in male infertility; and it is the high OS status that gives a clue for the antioxidant therapy. The dose for antioxidant is crucial to note since ROS also plays a vital role in physiological processes. Further studies through different angles in this regard would help in solving the essential problems in male infertility.

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Austin Andrology - Volume 1 Issue 2 - 2016
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Citation: Sahu CR. Reactive Oxygen Species Turns Men Infertile but Vitamin C Prohibits - Behind the Scene. Austin Andrology. 2016; 1(2): 1009.