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Effects of Lycopene on Sperm Parameter in Healthy Male: A Review

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Abstract:

Infertility is an ability of couple to have a baby after one year of unprotected intercourse affects 48.5million couple in worldwide. Out one of four couple are affected by infertility. A minimum 30 million men world-wide are infertile and male factor are responsible for approximately 20-30% in all infertile cases. It is now understood that oxidative stress plays a significant role in the aetiology of male infertility. Reactive oxygen species (ROS) in excess lead to an oxidative stress condition that reduces sperm viability and motility by causing DNA damage, apoptosis, and lipid peroxidation of the sperm membrane. Increased ROS levels are a crucial role in idiopathic male factor infertility, which is a disease that is becoming more prevalent in society today. Due to its antioxidant qualities, lycopene, the most effective singlet oxygen quencher of all carotenoids, may be used to treat male infertility. Lycopene may minimise the occurrence of oxidative stress and, consequently, the harm that would otherwise be done to spermatozoa by interacting with and neutralising free radicals. We have analysed data from a number of sources and provided information regarding lycopene and its impact on male infertility in this review paper. The focus of this review is on how lycopene affects sperm parameters in healthy men.

Keywords: Lycopene, Oxidative stress, Antioxidants, infertility.

Introduction:

Infertility is a disease of male or female reproductive system defined by the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse. Infertility affects millions of people of reproductive age worldwide and having an impact on their families and communities [1]. Every year, 60-80 million couple around the world are affected by infertility, with India accounting for 15-20 million (25%) [2]. Infertility affects one out of every six couples in developing nations, according to world health organisation research [3].

In the world wide infertility affect around 8-12% of couples, with male factor identified as a primary cause in 50%-60% of cases [4] but is solely responsible in only 20% of couples [5]. Overall the world, 7% men are affected by male infertility. Almost 35 percent cases have varicocele and in 25 percent cases, idiopathic infertility is the reason behind the male infertility. However, urogenital infections, endocrine disorders, immunologic factors, genetic abnormalities, and congenital disorders are other causes of male infertility [6].

One of the main causes of infertility is stress, which can work as an influencer to have a negative effect on both sexes' reproductive strength [6]. It has been established that oxidative stress plays a significant role in the aetiology of male idiopathic infertility [7]. Spermatozoons contain a significant amount of unsaturated fatty acids, making them very susceptible to oxidation [8]. Oxidative stress can be the outcome of free radical formation which bears unpaired electrons in their outer orbit with strong capability to react with any compound and excess development of free radical can trigger destruction [9].

Oxidative stress and its effects on male reproduction

A molecule is referred to as a free radical if it possesses at least one unpaired electron [10-11] which is responsible for the molecule's unstable, highly reactive, and short-lived high energy state [12]. Until two of these radicals react and the unpaired electrons are neutralised, these radicals will participate in propagative chain reactions and produce even more radicals. Free radicals will target and oxidise membrane lipids, amino acids, and carbohydrates in nucleic acids during this process [11].

Reactive oxygen species (ROS) are unpaired electrons that produce free radicals such as superoxide anion (O2 -) and hydroxyl radicals (-OH), which are known as oxidative stress (ROS).These attack the fatty acid membrane and resultant of this generates lipid peroxidation. Unsaturated fatty acids on human spermatozoa penetrate the membrane, which lipid peroxidation can harm. The results of the investigation also showed that participants who were fertile men had no ROS found in their seminal plasma, whereas the levels of ROS in infertile men's seminal plasma were rather high [13]. The sperm nuclear structure, including the DNA, can be harmed by the chemical and structural changes brought on by ROS. Reduced sperm motility results from the breakdown of seminal fluidity brought on by the increasing load of ROS. In order to have minimal possibilities of male infertility, antioxidant capacity improvement to protect spermatozoa from oxidative stress may be necessary [14].

The seminal plasma naturally contains both enzymatic and non-enzymatic antioxidants to keep ROS concentrations low under normal conditions. While catalase, glutathione reductase, and superoxide dismutase are enzyme-based antioxidants, vitamins C, E, and B, carotenoids, and carnitines are non-enzymatic oxidants. Oxidative stress happens when the delicate equilibrium between ROS and antioxidants is disturbed, either by a significant increase in ROS levels or a significant drop in antioxidant levels [10]. Oxidative stress affects spermatozoa in three main ways membrane lipid peroxidation, DNA damage and induction of apoptosis [15].

Spermatozoa cell membranes contain a high concentration of polyunsaturated fatty acids, particularly docosahexaenoic acid, which makes them more vulnerable to the oxidative damage caused by free radicals [16]. Multiple unconjugated double bonds containing a lot of electrons make up polyunsaturated fatty acids. Lipid peroxides are produced when these electrons are transferred from ROS to them during the process [12]. As a result, the spermatozoal cell membrane's fluidity is compromised, which has an adverse effect on the viability and motility of sperm. Sperm viability will decline due to modification of critical membrane proteins and abnormal acrosome reaction, which impairs the sperm's ability to fuse with the oocyte. Sperm motility will be affected by the decline in axonemal protein phosphorylation [15], while viability will decrease due to modification of key membrane proteins [10].

DNA damage is another ROS-related impact on spermatozoa [15]. This happens when the bases (particularly guanine) or the phosphodiester backbones are directly attacked, which destabilises the

DNA molecule and results in anomalies such as point mutations, polymorphisms, deletions, translocations, and even double-stranded breaks [12]. DNA fragmentation will cause improper fertilisation, decreased implantation, and poor embryonic development, which will likely result in a shorter life span and a higher chance of acquiring cancer in the progeny [17]. In more serious cases of damage, spermatozoa may experience apoptosis, leading to the low sperm counts typical of idiopathic male factor infertility [15].

Lycopene

One of the many substances that make up the carotenoid family is lycopene. Fruits and vegetables naturally contain carotenoids, which are responsible for the bright yellow, orange, and red colours that plants exhibit [18].They protect us from too much light and are necessary for photosynthesis. As a result, only plants and bacteria can produce them; humans cannot. Humans can only consume fruits and vegetables to obtain carotenoids. Not only are carotenoids providers of vitamin A, but they also having antioxidant capabilities, making them essential components of the human diet [6].

Lycopene ($C_{40}H_{56}$) is a red-pigmented unsaturated linear carotenoid with a molecular weight of 536.85Da, containing 11 conjugated and two non-conjugated double bonds [19]. It is more soluble in organic solvents because it is lipophilic [20]. Because double bonds are present, both cis- and trans-isomeric forms are possible, and exposure to light, heat, or chemical reactions can cause the forms to change [21]. Lycopene is a frequent dietary component found in foods like tomatoes, processed tomato products, pink grapefruits, watermelons, apricots, guavas, papayas, and rosehips. The highest concentration of lycopene is found in processed tomato products [22].

Mechanism of action

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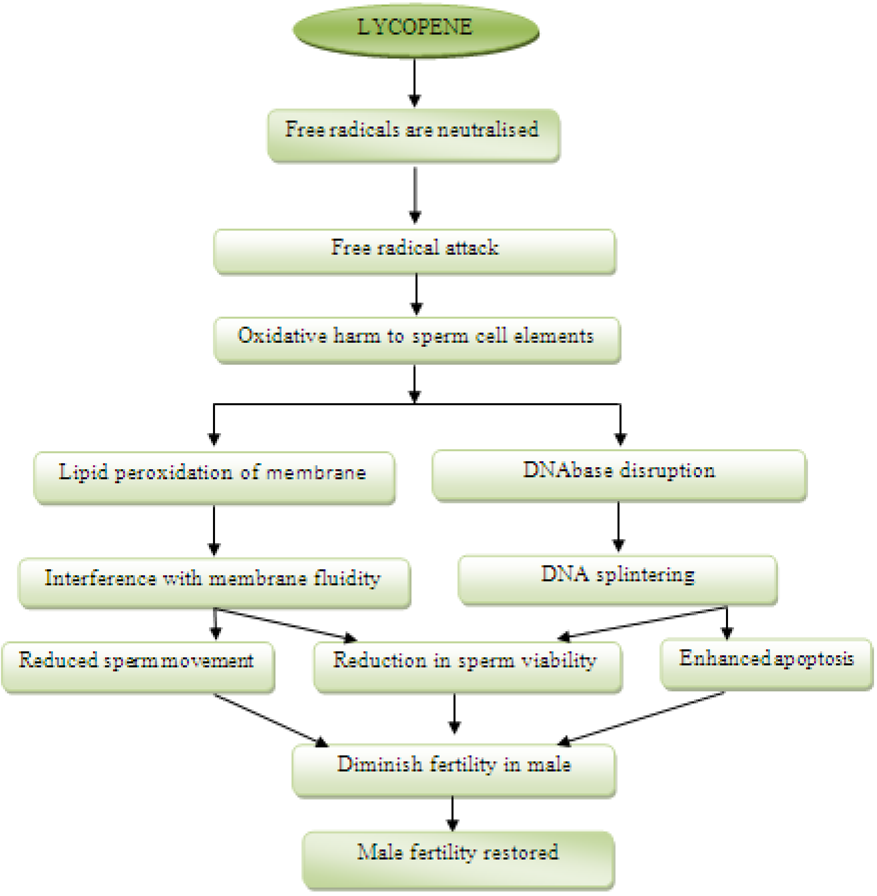
Figure 1: Mechanism of lycopene in male fertility



Oxidative mechanisms

Lycopene has 11 conjugated double bonds, which means it has a lot of electrons available to donate to free radicals, neutralising them [23]. In doing so, lycopene reduces the load of ROS, alleviates oxidative stress, and prevents oxidative damage to lipids, proteins, and DNA. Lycopene also serves as an antioxidant to capture free radicals and stop the propagation of chain reactions [24]. Lycopene is thought to be one of the most effective singlet oxygen quenchers in the carotenoid family [25], being twice as effective as -carotene and up to ten times more effective than –tocopherol [24].

A combination of carotenoids has been found to have a more strong effect than any single one, and this synergism was most prominent when lycopene or lutein were added to the mixture [25]. Lycopene is known to work on additional free radicals such hydrogen peroxide, nitrogen dioxide, and hydroxyl radicals in addition to quenching singlet molecular oxygen [19]. Because lycopene is lipophilic and has a tendency to accumulate in cell membranes and lipoproteins, it has a more direct influence on these parts of the cell [22].

Non oxidative mechanisms

Lycopene may also affect cells through non-oxidative methods such as improving gap junction communication, altering gene expression, regulating the cell cycle, and boosting the immune system [23].

Tumor cells are predicted to lack gap junction communication and, as a result, continue to proliferate without inhibition [26]. Lycopene may be able to prevent tumour development and subsequently cancer by enhancing cell-to-cell communication, especially in the prostate, breast, and lung [25]. By interfering with insulin-like growth factor-1 signalling and stopping cell cycle progression, lycopene also inhibits unwanted cell proliferation [27].

A naturally occurring carotenoid found in fruits and vegetables is lycopene. As it has the strongest quenching ability against singlet oxygen, a high-energy form of oxygen, it is essential to the human redox defence mechanism [28]. High quantities of lycopene have been found in human testes and seminal plasma; although they are often lower in infertile males [29].

Turk *et al.*, (2010) studies demonstrated that testes were shielded by lycopene, which increased sperm motility and decreased apoptosis. Unexpectedly, lycopene administration not only markedly decreased BAX and elevated Bcl-2 expression, but also decreased the number of TUNEL-positive cells in the seminiferous tubules, suggesting that lycopene markedly controlled and decreased apoptotic process [30]. Singlet molecular oxygen and peroxyl radicals are two reactive oxygen species (ROS) that are scavenged by lycopene [31].

Mangiagalli *et al.*, (2012) experiment show that in rabbit buck lycopene enhances the production of semen, the volume and total quantity of spermatozoa, and improves sperm kinetic properties and viability during semen storage at 5°C when added to drinking water. As a result, lycopene could be employed as an antioxidant instead of other compounds like the highly researched and utilised vitamins E and C in animal production. The use of lycopene supplements in rabbit farming could be very useful [32].

Durairajanayagam et al., (2014) state that lycopene is the most potent singlet oxygen quencher of all carotenoids, is a possible treatment option for male infertility because of its antioxidant properties. Lycopene may minimize the occurrence of oxidative stress and, consequently, the harm that would otherwise be done to spermatozoa by interacting with and neutralising free radicals. In the testis, nonoxidative mechanisms like gap junction communication, gene expression regulation, cell cycle control, and immunological stimulation are hypothesised to play a role in the therapeutic effects of lycopene. Numerous lycopene supplementation studies carried out on both humans and animals have demonstrated promising results in reducing male infertility - lipid peroxidation and DNA damage were lowered, while sperm count and viability and general immunity were raised [23].

Yilmaz *et al.*, (2018) study the beneficial effects of lycopene against aflatoxin B1-induced renal and cardiac damage in rats. They found a significant decrease in the activities of antioxidant enzymes (GST, GPx, superoxide dismutase (SOD) and catalase (CAT)) and the non enzymatic antioxidant system in these rats and lycopene had protective effects against these unwanted changes [33].

Moslemi *et al.*, (2019) study shown that Lycopene has a significant effect on the number, motility, and morphology of sperm in most clinical trials, and significant changes have also been seen with changes in antioxidant capacity and oxidative factors that play a significant role in changing sperm parameters.

Among the other observations were changes in the surface of the receptors as well as oxidative enzymes such as glutathione peroxidase, superoxide dismutase and catalyse [34].

Williams *et al.*, (2020) examined in his studies Oral antioxidant therapy may help several sperm parameters, according to data from controlled studies and the effect of dietary variables. In this article, they investigate how lycopene supplementation has potential health advantages for treating sperm quality issues. In this study, healthy men's semen quality was examined after receiving 14 mg of lactolycopene daily for a period of 12 weeks [35].
According to Pietro *et al.* (2020), experimentally generated varicocele causes hormonal disruption and subsequent infertility. Lycopene treatment significantly increased testosterone levels in varicocele-treated rats, demonstrating the usefulness of lycopene in treating this disease. In fact, there experimental findings offer new insight into how carotenoids, primarily lycopene, function biologically by supporting the critical role of steroid hormones and molecular signalling processes, such as insulin-like growth factor [36].

Antonuccio *et al.*, 2020 experimental study show the effects of lycopene given intraperitoneally at a dose of 1 mg/kg on rat varicocele. They discovered that in mice with varicocele, lycopene treatment markedly increased testicular weight and decreased MDA. The contralateral testis varicocele served as a control for the varicocele-operated testis in this study, despite the fact that the study's design is ambiguous [36].

Babaei *et al.*, 2021 state that the administration of lycopene, particularly at a level of 10 mg/kg, shielded sperms from the degradation of membrane integrity, testicular injury, and consequences of varicocele induction. Numerous researchs on the impact of lycopene on male and animal reproduction have shown favourable findings. They hypothesised that lycopene could protect human sperm from OS by reducing plasma membrane LPO and sperm DNA breakage [37]. They added that lycopene has the ability to improve concentration, motility, viability, and morphology by reducing sperm DNA fragmentation and LPO of the plasma membrane [38].

According to Babaei study from 2022, administering lycopene especially at a level of 10 mg/kg—a powerful antioxidant—was more successful at enhancing sperm functional features in varicocele-affected rats. Lycopene shielded sperm and testicular tissue against oxidative stress-induced death. In contrast to varicocele groups, lycopene groups had higher concentrations, higher survivability rates, and more intact membranes [39].

Conclusion:
As shown by the analysis of the numerous researches above, the only factors that are indisputable improved with lycopene supplementation are: a decrease in lipid peroxidation and DNA damage, an increase in antioxidants and therefore general immunity, and better sperm count and viability. These improvements are crucial in addressing the condition of oxidative stress, which impairs sperm viability, motility, and DNA and eventually result in infertility. The findings of several researches may be caused by the absence of defined protocols and outcome measurements, which is compounded by the small sample sizes of the studies, which may have added some bias into the outcomes. Although the findings

are generally encouraging, it is clear that more thorough investigation is required to determine whether lycopene, a prominent singlet oxygen quencher, is effective in treating idiopathic male factor infertility. Therefore, a large placebo-controlled clinical study must be conducted for statistically significant outcomes in order to demonstrate this. Over a specified time period, patients should be assigned at random to receive various lycopene dosages provided daily. In addition to sperm parameters, pregnancy rates should also be measured as an outcome.

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