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Beneficial effect of  
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# Beneficial effect of lycopene against lifestyle induced male infertility

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## Introduction

Statistical analysis shows that in the present scenario, one in six couples have an infertility problem and the male member is responsible for 50 percent of the cases<sup>1</sup>. 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<sup>2</sup>.

Semen is ejaculated from the male reproductive organ, which contains sperm. A mature sperm cell or spermatozoa is a key element of male fertility. But the functionality of spermatozoa is compromised by elevation of reactive oxygen species level<sup>2</sup>. It is well known that oxygen is essential for life, but due to its strong oxidizing property, it causes free radicals formation within the cellular structures and consequences of this lead to series of structural and functional changes in the organs. Various external factors, including unhealthy lifestyle and exposure to environmental toxic chemicals, often influence free radicals formation within the cellular structures. The most common free radicals like superoxide anions, hydroxyl radicals, and hypochlorite radicals are collectively known as reactive oxygen species (ROS). Research

findings supported that increased burden of ROS plays an important role in male infertility<sup>2</sup>.

The metabolic process generates free radicals and redox homeostasis in human physiology which is diminished with decreased physical activity<sup>3</sup> and the consequences of the sedentary lifestyle increases the burden of ROS<sup>4</sup>. The study findings support that like other non-enzymatic antioxidants, lycopene, which is a natural carotenoid ingredient of tomato has a potent antioxidant property and can be a therapeutic benefit in oxidative stress-induced male infertility<sup>2</sup>.

The aim of this article is to discuss how the lifestyle factors influence male infertility, how oxidative stress damages male fertility, how the antioxidant property of lycopene can combat male infertility and also discuss some basic lifestyle management to prevent male infertility.

## How lifestyle factors negatively influence male fertility?

In recent days, optimum semen quality is only found in 1 in 4 men<sup>5</sup>. Certain identified lifestyle factors, which have a negative influence on male fertility, are as follows:

- Today almost every male individual prefer to wear tight outfits and undergarments and do office jobs. In the office, prolonged seating on the desk with wearing tight undergarments and outfits increase the temperature in the male genital organs<sup>6</sup>.
- Male workers in glass, metal,

and ceramic industry are often exposed to high temperature due to their occupational reasons, which also causes excess heat exposure to the male genital organs<sup>6</sup>.

- Most of the male members prefer to take shower rather than a bath, which also alter scrotal temperature<sup>6</sup>.
- Pesticides application in harvesting and agriculture sector increases the tendency to harmful chemicals exposure by ingesting the foods<sup>6</sup>.
- Male members prefer to eat more animal fats containing foods than plant-based foods, which also influence several metabolic disorders<sup>6</sup>.
- The distance of workplace from residential area and traffic queues influence prolonged driving, which not only disturbs body temperature but also increases the atmospheric pollutant exposure timing<sup>6</sup>.
- Diet also has maximum influence on fertility issues; like the hormonal treatment of animals to alter the reproduction process, which can further alter the food value of the nutrients, as hormonal residues are present in animal fats and that provide negative impact in the human fertility process<sup>6</sup>.
- The increasing trend of soy-containing foods also alters fertility, as soybeans contain phytoestrogens and that alter human hormonal homeostasis<sup>6</sup>.
- In recent days, people are inclined to take readily to eat

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foods or packaged foods due to their fast and sedentary lifestyle. This packaged food is also a source of trans fat and can cause several metabolic disorders and decrease sperm generation ability and poor semen quality<sup>6</sup>.

- Males have a tendency to drug abuse for recreational purposes or sports activities or to develop muscle growth. This unnecessary exposure of the body to foreign materials can increase the tendency of infertility<sup>6</sup>.
- Medical science advancement has given us several chemotherapeutic agents to combat cancer and infections. Cancer chemotherapeutic agents, radiation therapy, and antibiotics can adversely affect sperm production<sup>6</sup>.

The above-mentioned factors alter scrotal thermoregulation and sex steroidal activities in male, which poorly regulate spermatogenesis and semen quality. In addition, increased oxidative stress due to adverse environmental and lifestyle factors causes DNA damage and break down of the cell membranes of spermatozoa. This leads to a large number of abnormal spermatozoa production, impaired sperm motility, and viability<sup>2</sup>.

#### **How increased oxidative stress contributes male infertility by damaging sperm structure?**

Oxidative stress is the increased burden of free radicals which is generated by unpaired electrons like  $O_2^-$  (superoxide anion) or  $-OH$  (hydroxyl radicals), which are termed as reactive oxygen species (ROS). Reactive oxygen species attack the fatty acid membrane and resultant of this generates lipid peroxidation<sup>7</sup>. Human spermatozoa covered with unsaturated fatty

acids reach membrane, which can be damaged by lipid peroxidation<sup>8</sup>. Investigative study result also provided the evidence that ROS level is comparatively high in seminal plasma of infertile male, while no ROS detected in fertile male participants<sup>8</sup>.

The ROS induced chemical and structural changes can damage the sperm nuclear structure including DNA. The increased load of ROS leads to disruption of seminal fluidity, which causes reduced sperm motility. In addition, the detrimental reaction of sperm membrane leads to abnormal reactions, which are responsible for impaired sperm-oocyte fusion and acrosome reaction<sup>9</sup>.

The significant DNA damage of human sperm is induced by ROS, which affects both nuclear and mitochondrial genomes. At the initial stage, ROS attacks guanine base of the DNA and gradually the detrimental effect spreads to phosphodiester backbones. The consequence of this leads to deterioration of the molecular and cellular structure of the DNA and progressive damage causes DNA destruction. The evidential study has been conducted by different techniques including TUNEL (terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling), SCSA (sperm chromatin structure assay) and 8-OHdG (8-hydroxydeoxyguanosine), which are reinforcing the association of oxidative stress and DNA structural damage of sperm cells<sup>9</sup>. Therefore, it is suspected that elevation of ROS level is a considerable factor for idiopathic male infertility<sup>8</sup>. However, the sperm cells damage intensity due to oxidative stress is not same for every individual, because the endogenous and exogenous factors can modify the stress generated

by ROS<sup>9</sup>. The endogenous factors involve the physiological condition of the individuals, as ROS level increases with association with pathological conditions like increasing age, infection, cancer, poor nutrition etc. Whereas, environmental factors trigger ROS elevation in exposure to the toxic environment, alcohol consumption, smoking, drug addiction, administration of medication, exposure to radiation etc<sup>9</sup>. It has been also observed that disease conditions and aging also increase oxidative stress condition<sup>10</sup>.

Increased ROS generation triggers the elevation of advanced glycation end products (AGEs) levels and activates receptor for AGEs (RAGE). RAGE influences organ-specific oxidative stressors and causes tissue damage, increase aging process, DNA fragmentation and hold back the restoration of homeostasis. Increased level of ROS in the male genital tract contributes to activating RAGE and damages sperm DNA<sup>11</sup>.

#### **What is the beneficial role of Lycopene on male infertility?**

Before we discuss the role of lycopene against male infertility, it is imperative to know the details about lycopene.

#### **Overview of Lycopene**

Lycopene is a red pigmented carotenoid naturally present in red colored fruits and vegetable sources, including tomatoes, watermelons, papayas, rosehips, pink grapefruits, apricots, and guavas. Differently processed tomato products are also rich sources of lycopene. However, all the red colored foods are not a source of lycopene<sup>2</sup>.

The chemical structure of carotenoid is  $C_{40}H_{56}$ , which is not attached to the beta-ionic ring. The cis and trans isomeric

transformation of the structure of the lycopene is possible in exposure to light, heat and chemical reactions. Like other carotenoids, lycopene unable to perform as a source of vitamin A as the chemical structure of the lycopene does not contain beta-ionone ring at the terminal end. But extended half-life (almost 2 to 3 days) of the lycopene in human body and interaction with other dietary ingredients provide an extensive and additive antioxidant effect. There is no lycopene related adverse effect reported and researchers considered lycopene is safe for human use. The antioxidant property of lycopene is one of the primary reasons for health benefits obtained from this ingredient<sup>2</sup>.

#### **Mechanism of action of Lycopene to treat and prevent oxidative stress induced male infertility?**

Lycopene promotes redox mechanism and quenches single oxygen ions. Both of these mechanisms are possible due to the presence of many free electrons in the chemical structure of the lycopene. They can neutralize oxidative free radicals by donating free radicals. The strong antioxidant property of lycopene not only stabilizes single oxygen molecule, but it can able to neutralize other free radicals, including hydroxyl radicals, hydrogen peroxide, and nitrogen dioxide. Thus, it reduces the overall burden of oxidative stress. In addition, Lycopene can bind with cellular membrane and provide extended anti-oxidation reaction, because of its lipophilic nature<sup>2</sup>.

Less antioxidant level and increased ROS level in seminal fluid causes abnormal spermatogenesis because of increase ROS and oxidative stress influences lipid peroxidation,

damages sperm DNA and promotes apoptosis. The investigative test report showed that lycopene promotes antioxidant level in seminal fluid and reduces the ROS level and oxidative stress. This protective effect of lycopene against oxidative stress and ROS due to its potent antioxidant property provides therapeutic benefits against male infertility, which induces by stress<sup>2</sup>. In brief, the following mechanisms are followed by lycopene against oxidative-stress induced male infertility:

- The ROS load reduction by ingesting lycopene can decrease the risk of lipid peroxidation reaction persuade spermatozoal cell membrane damage. In addition, administration of lycopene can uphold the integrity of the cellular structure<sup>2</sup>.
- The lipophilic nature of lycopene assists to retain sufficient amount of lycopene in the cell membranes and provide a protective effect on spermatozoa against oxidative damage<sup>2</sup>.
- Lycopene may also interact with other antioxidant enzymes present in the human physiological system and activate them. Thus, the overall anti-oxidative effect in the human physiology is increased which further decreases the scope of an inflammatory condition and reduces the risk of male infertility<sup>2</sup>.
- Prostate gland present in male reproductive tract can selectively absorb lycopene. Lycopene can decrease soluble receptor for advanced glycation end products (sRAGE) levels in semen plasma. The decreased level of the sRAGE level by administering Lycopene improve male fertility<sup>12</sup>.

#### **Scientific evidence supports effect of Lycopene against male infertility**

Several clinical trials are conducted to check the efficacy of lycopene; following are some of the evidence:

- A clinical trial conducted on 75 human subjects treating them with lycopene obtained from tomato containing diet or synthetic lycopene containing supplements showed that experimental group members had decreased lipid peroxidation and oxidative stress levels than control group under placebo treatment arm<sup>2</sup>.
- In vitro and in vivo studies also reported that administration of lycopene (30mg daily) can decrease the DNA damage of the spermatozoa<sup>2</sup>.
- Investigative test performed by different scientists have also reported lycopene supplementation (30mg daily) increase other antioxidant enzymes like glutathione peroxidase and catalase activities<sup>2</sup>.
- A clinical study conducted in Spain reported that dietary intake of lycopene improves semen quality<sup>10</sup>.
- Other significant test reports obtained from different research studies also reported that daily administration of a particular dose of lycopene can significantly increase sperm count (60 - 70 percent), sperm motility (53 - 54 percent), sperm viability (6 percent) and also improves 10 percent sperm morphology. The resultant of this leads to 23 percent participants expected parenthood after completion of the therapy. The author of this study concluded that lycopene may be a good therapeutic

agent to treat oligospermia (a condition, in which sperm density is less than 5 million per ml of semen) <sup>13</sup>.

- A clinical study conducted on 28 male participants showed that 20 mg lycopene treatment for 12 weeks can suppress sRAGE in seminal plasma and improve male fertility<sup>12</sup>.

#### **The dose of lycopene to treat male infertility:**

The daily recommended dose of lycopene is not yet discussed officially, but several investigative studies performed to check the efficacy of lycopene against male infertility reported that daily lycopene supplementation with a dose of 4 to 8 mg for 3 months to one year treatment period provides the effective result to treat male infertility. Instead of supplementation, 150 gm of raw tomato or 80 gm of watermelon can accomplish the lycopene requirement to combat male infertility<sup>2</sup>.

#### **Interesting facts about lycopene<sup>2</sup>**

- It has been observed that processed tomato products or cooked tomato are a rich source of lycopene than a raw tomato. Because the chemical structure of the lycopene present in raw tomato is in the trans-form, but the chemical reaction persuade during processing can change them to cis-form. This isoform interchanging increases the bioavailability of the lycopene.
- In cooked tomatoes the bioavailability of lycopene is more due to heat interchange the trans-isoform to cis-form of lycopene.
- Cooking the tomatoes in oil medium is more acceptable than aqueous preparation like tomato soup, because the presence of oil in the tomato preparation increase the lycopene cellular

absorption due to its lipophilic nature.

- The absorbed lycopene is mainly accumulated in the organs, which have extensive lipoprotein receptors and involve in metabolic reactions like testis, prostate, liver and adrenal gland. This also explains that lycopene improves genital organ functioning by accumulating in these tissues.
- Lycopene absorption is decreased with increasing age, as aging alters the gastrointestinal absorption pattern. In addition, smoking, alcohol consumption also decrease the physiological concentration of lycopene by decreasing its dietary absorption.
- The antioxidant property of lycopene is comparatively higher than other natural antioxidants, including  $\beta$ -carotene and  $\alpha$ -tocopherol. The antioxidant potency of lycopene is double than  $\beta$ -carotene, whereas ten times more than  $\alpha$ -tocopherol.
- Combination therapy with other antioxidants, lycopene provides a synergistic effect.

#### **Other important health benefits of lycopene**

- Lycopene can boost the immune system and maintain overall health<sup>2</sup>.
- The antioxidant property of lycopene is not only effective to treat male infertility, but also prevent oxidative stress-induced cancer, neurodegenerative conditions, cardiovascular disease and osteoporosis<sup>2</sup>.
- Lycopene assists in gap junction communication through non-antioxidative mechanism<sup>2</sup>. A gap junction is a communicating channel present

between the neighborhood cells. These communications are essential for life including embryogenesis, normal cardiovascular functioning<sup>14</sup>.

- Dysregulation of gene expression is the leading cause of tumorigenesis and cancer progression<sup>15</sup>. Lycopene assists in modulating gene expression and prevents tumorigenesis and cancer progression, especially in the prostate gland, liver, and breast<sup>2</sup>.
- Insulin-like growth factor-1 signaling can be disrupted by lycopene treatment and thus lycopene controlled unwanted cell cycle progression due to uncontrolled proliferation of the cell. This mechanism also important to prevent progression of inflammatory conditions<sup>2</sup>.
- Hypercholesterolemia is a condition, in which plasma lipid concentration is increased beyond its normal limit and one of the primary causes of plaque formation. The detrimental effect of plaque formation leads to atherosclerosis. Atherosclerosis hampers cardiovascular functioning. Lycopene can combat hypercholesterolemia by decreasing the hydroxyl-methyl-glutaryl coenzyme A reductase, which is essential for cholesterol synthesis. Thus, the hypocholesterolemic property of lycopene can regularize cholesterol level and cardiovascular functioning<sup>2</sup>.

#### **Lifestyle management to prevent male infertility**

Lifestyle management is the foremost important criteria for healthy living and to perform all the normal functioning, including sexual activity and fertility. The action of lycopene or any other

nutritional supplementation unable to provide optimum result in absence of good lifestyle. Following are some basic lifestyle management, which can assist to improve male fertility.

### Nutrition

Nutritional consideration is good to promote fertility along with good health. Fruits and vegetables obtained from different plant sources are a good source of macro and micronutrients along with several bioactive compounds like antioxidants. An increased consumption of these plant-based food items improves sperm motility in asthenospermic males due to their antioxidant property.

### Weight management

Obesity is one of the major causes of infertility, as erectile dysfunction is commonly associated with increasing weight. The increased adiposity due to obesity leads to increased serum estradiol levels and reduction of Inhibin B levels. Enhancement of increased serum estradiol levels is inversely related to androgen levels. Androgen plays a major role in penile erection. Inhibin B levels reduction leads to decreased sperm production.

However, underweight male individuals also have a higher risk towards low sperm count than the male with normal BMI. So it is very important to maintain proper weight according to the height of an individual.

### Physical exercise

The physically active male has a lower risk of infertility. It has been found that exercise improves sperm morphology. Although, the type of exercise is an important consideration, like prolonged bicycling negatively affects sperm count and motility. Both, diet and physical exercise

are important factors to prevent sperm DNA damage and improve sperm motility and concentration.

### Psychological relaxation

A sedentary lifestyle increases psychological stress levels, and depression is a common outcome of the overstressed condition. Depression and testosterone level suppression is inter-related; which also decreases other reproductive hormone secretion. The resultant of these can cause reduction of spermatogenesis and sperm parameters. Therefore, psychological relaxation is also important for sustaining fertility.

Apart from this lifestyle management, there are some bioactive compounds present in different plants that can also assist to improve male fertility. One of such evidential plant-based bioactive compound is lycopene<sup>16</sup>.

### Conclusion

In the present scenario, male members are equally responsible for infertility issues. One of the major causes of male infertility is increased level reactive oxygen species (ROS). Poor lifestyle is one of the primary causes, which initiates oxidative stressors and elevates ROS level. Lycopene is one of the natural potent antioxidants, which can prevent and treat ROS induced male infertility in association with healthy lifestyle measure. In this article, we elaborately discussed all the lifestyle issues and explained how lycopene exerts its effect against male infertility by providing different scientific evidence. But, the available data are collected from small-scale trial reports. This article may encourage conducting more dose specific multi-centered clinical trials to establish the precise efficacy of lycopene against male infertility treatment.

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