

Review Article

Nutraceuticals in Sperm Abnormalities

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Introduction

Male factor infertility is an important cause of a barren marriage. Semen abnormalities constitute the most important cause of the same. These could be abnormalities in sperm concentration, motility or morphology. Several medical and surgical methods have been introduced in the past and several more are currently being tried to improve the sperm abnormalities. These methods have not yielded much benefit except in established cases of obstruction. To evolve methods to improve sperm abnormalities, a proper understanding of sperm physiology and a deeper perspective of pathophysiology of sperm abnormalities are important. The paper describes the current role of nutraceuticals in male infertility. Nutraceuticals are widely used in an attempt to combat the effect of free radicals in male reproductive system.

Nutraceuticals

Nutraceuticals is a portmanteau of the words Nutrition and Pharmaceuticals. Stephen Defelice in 1989, first coined the word 'Nutraceuticals', from the two words nutrition and pharmaceuticals. He was the founder and chairman of the Foundation for Innovation of Medicine, (FIM) in New Jersey. According to him, nutraceutical can be defined as "a food or a part of food that provides medical or health benefits including the prevention and or treatment of a disease"¹. The term indicates several products like isolated nutrients, dietary supplements, herbal products, specific diets, genetically modified food, processed foods such as cereals, soups and beverages².

While nutrition plays a crucial role in health and disease, it is not exactly clear what role nutraceuticals play. Nutritional deficiencies have been implicated in the pathogenesis of several diseases. For example, deficiencies in Vitamin C, Vitamin B and Vitamin D give rise to scurvy, beriberi and rickets, respectively. Although there seems to be no clear association between nutritional deficiency and infertility, inadequacy of certain nutrients such as folic acid, L-carnitine and selenium have been claimed to cause infertility^{3,4}.

Spermatogenesis

Nutrition plays an important role in spermatogenesis. There is a definitive role of micronutrients such as zinc, folate and antioxidants for the normal maintenance of spermatogenesis and sperm maturation, DNA synthesis, repair and transcription. However, knowledge about the effect of paternal malnutrition on sperm aneuploidy is scarce. Environmental factors such as exposure to pesticides and chemotherapy have been associated with aneuploidy in spermatozoa of humans⁵.

Nutraceuticals commonly used are:

- 1) Nutritional factors: Arginine, VitB 12, Folic acid
- 2) Motility enhancers: L-carnitine, Acetyl carnitine, Co enzyme Q10
- 3) Antioxidants: Vit C, Vit E, Glutathione, Lycopene, Selenium, Zinc

Male infertility

Infertility affects 15% of the married, eligible couples. Male factor accounts for about 50% of the cause for infertility. Nutraceuticals, which are readily available in the market, offer an easy alternative to the couples against Assisted Reproductive Technologies. These include those that offer improvement in sperm function, semen parameters, sexual function and erectile function. However, there is no clear evidence that support these claims. The benefits of nutraceuticals in male infertility are yet to be proven. More importantly, the side effects of these supplementations are unknown and very often used by common population as a substitute for lack of nutrition in the diet.

Free radicals in health and disease

Oxidative metabolism in all the cells, tissues and organs leads to the production of free radicals - reactive oxygen species and reactive nitrogen species. These molecules have an unpaired electron in the outer orbit. They are unstable and very reactive. Free radicals are effectively counteracted by several natural antioxidants⁶.



Fig 1 : Source of free radicals and oxidative stress

Free radicals also serve a physiological function. Reactive oxygen species (ROS) are produced during a variety of biological processes. These molecules in small concentrations are essential for cell growth, differentiation or proliferation. They are involved in physiological processes such as signal transduction, regulation of protein kinases or transcription factors⁷. They also regulate redox balance, immune responses, activate macrophages and neutrophils. Cell adhesion and relaxation of smooth muscle are controlled by free radicals. Reactive Oxygen species are essential for apoptosis⁷. These molecules are very important for the correct function and life of the cell⁸.

Oxidative stress in male reproductive system

The cells in the male reproductive system are vulnerable to the effects of free radicals like any other cell in the body. The male reproductive system has an inherent antioxidant system to protect the cells from the detrimental effects of free radicals and ROS. In addition to enzymes, substances such as zinc and carnitine make up the antioxidant system.

The spermatozoan has high content of polyunsaturated fatty acids (PUFA) in its plasma membrane and is highly susceptible to oxidative damage. Thus to maintain viable reproductive ability, a protective mechanism against oxidative stress is of importance. Although the body employs a number of mechanisms to minimize ROS induced damage, antioxidants in seminal plasma provide substantial protection to spermatozoa against ROS insult starting from spermiogenesis (during the loss of cytoplasm).

This is now considered to be the underlying pathological consequence. A wide range of conditions including testicular torsion and diabetes, may ultimately lead to the production of free radicals¹⁰. Excessive amounts of free radicals may cause peroxidative damage to the spermatozoa, however the amount at which free radicals can cause damage is unknown.

Deficiency of these substances may lead to a reduction in the sperm quality and it is yet to be answered if antioxidants need to be supplemented to treat this condition. As discussed earlier, ROS also has physiological role. In reproduction they are involved in vascular tone regulation, gene regulation, fertilization, sperm capacitation, hyper-activation, motility and acrosome reaction⁹. Free radicals act as signals for various physiological processes. It is unclear as to whether ROS present in excess in the body is physiological or pathological.

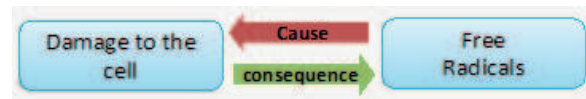


Fig 2: Free radicals: cause or consequence?

Antioxidants in the male reproductive system

Antioxidants, which can be enzymatic or non-enzymatic, prevents or delays the oxidation of the substrate, which can be any molecule found in any biological material.

Seminal plasma also contains several naturally occurring antioxidants like catalase, glutathione peroxidase, superoxide dismutase, beta-carotene, ascorbate, etc. They are involved in continuously inactivating the reactive oxygen species leaving behind a small physiological level of reactive oxygen species to maintain normal cell function. It is possible that free radicals are associated with several disease states without being causative.

Nutraceuticals in male infertility

Nutraceuticals are a group of substances, which are claimed to improve sperm parameters. Commonly used nutraceuticals in male infertility are:

- 1) Arginine
- 2) Vitamin B
- 3) Vitamin C
- 4) Vitamin D
- 5) Vitamin E
- 6) Folic acid
- 7) Glutathione
- 8) Vitamin K
- 9) Pyridoxine
- 10) Retinol
- 11) Selenium
- 12) Zinc

Treatment with nutraceuticals is widespread for a variety of conditions like atherosclerosis. The efficacy of nutraceuticals in the treatment of these conditions has not been proved¹¹. Folic acid seems to have an apparent benefit in reducing aneuploidy in spermatozoa⁵.

Normal and abnormal semen

Attempts to define normal semen have been recent. The first world report from World Health Organization (WHO) was available in 1980. Four further editions have been published. Each new edition have been redefining and down staging normal parameters and the current WHO manual does not even call it normal parameters but as Reference values or Standard

parameters¹². There are too many parameters listed. We will confine this paper to concentration, motility and morphology.

Azoospermia

Azoospermia defined as absence of spermatozoa in the ejaculate, both in a neat semen sample and in a centrifuged resuspended semen sample. This may be obstructive or non obstructive¹². Obstructive azoospermia requires surgical correction or sperm retrieval techniques. Nutraceuticals are of no value.

In non-obstructive Azoospermia - gonadotrophins are of immense value in hypogonadotrophic hypogonadism. Nutraceuticals have been tried with no proven benefit. Anti oxidants are the primary group of drugs used in other non-obstructive azoospermia patients. The results are conflicting. Significant number of men with non-obstructive azoospermia have chromosomal anomalies or Y chromosome micro deletions. It is unlikely that nutraceuticals would be of any value to these patients.

Oligoasthenoteratozoospermia

These conditions are difficult to define except in the total state as in Total asthenozoospermia. The definition of these conditions have been changed 5 times in the last 30 years .For example the lower reference limit for normal morphology is 4% (WHO 2010) which has come down from 80.5% while the motility has come down from 60% to 40% (WHO 1980). It is not clear if the increased DNA fragmentation and increased ROS levels found in some of these men is the cause or consequence of the sperm abnormalities⁵.

Risks of antioxidants

Treatment with antioxidants is not required in all situations. Antioxidants do not seem to have any short-term risks. The long-term risks are unknown. Some studies found that cancer patients who took antioxidants had worse outcomes¹³. Fertility treatment studies show that 40% of men seeking fertility treatment are fertile and devoid of sperm oxidative damage. Supplements given to improve fertility may cause harm than cause good which is the actual purpose they are taken for. For example, selenium given alone or in combination with other antioxidants reduces the number of motile spermatozoa. Vitamin-C and Vitamin-E supplementation causes an increase in DNA damage and plasma membrane damage of spermatozoa¹⁴.

There are a large number of studies which emphasise on the beneficial effect of antioxidant supplementation and an equal number of studies which say that there is no effect,¹⁵ the duration of therapy, dose, and long term side effects needs to be established by larger studies before implementation of nutraceutical supplementation as a routine in male infertility treatment.

Conclusion

The role of nutraceuticals in sperm abnormalities is not

clear. A recent Cochrane study on Antioxidants in male infertility concluded that a well-designed large randomized placebo controlled trials are needed to confirm the usefulness of antioxidants in male infertility¹⁶. It may be prudent not to empirically use nutraceuticals in sperm anomalies except in a double blind randomized clinical trial setting. If clinical exigencies demand the need for a drug, folic acid may be used. Clinically randomized studies based on scientific evidence are required to standardize therapies with antioxidants. Currently, many drugs are used with minimal data showing any beneficial effect. A definitive conclusion cannot be drawn from the existing heterogeneous literature. Further randomized, controlled, clinical trials are needed to be able to fully understand the efficacy and safety of antioxidants and propose proper protocols for their use.

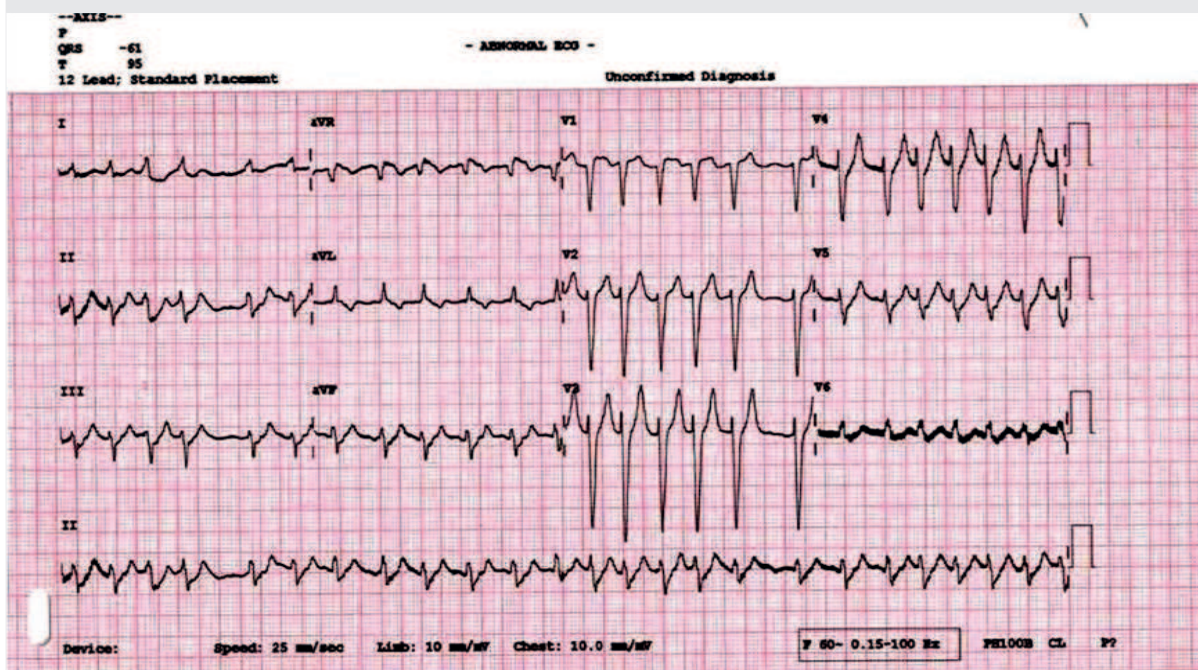
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Diagnose the condition

50 year old female presented to emergency with palpitation and breathlessness. Her ECG was taken.



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Answer in page: 147

Walk a Lot, to Keep Walking!

Walking briskly for about four hours a week apparently preserves your bone health and the muscle tone, and prevents hip fractures. That is the conclusion of a longitudinal study conducted at Brigham and Women's Hospital on 36000 men over a period of 24 years. The study relied on answers to questionnaires that the participants filled up once in every two years. The questions were designed to obtain information about how they spent their time in various activities including sitting, walking, playing, swimming etc. Information was also collected about the serious skeletal injuries suffered by the participants during that period. The results of the study suggest that the more a person walked, and more vigorously he walked, the lower the risk for hip fracture as he aged. To keep your bone healthy, just brisk walking is enough; no need for any strenuous exercise. The study is published online in Feb. 13th issue of the American Journal of Public Health.

- Dr. K. Ramesh Rao