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REVIEW ARTICLE

Impact of Dietary Nutrients and Antioxidants in Boosting Male Fertility: A Comprehensive Review

Noor-ul-ain Irfan, Shemaila Saleem
Department of Physiology, Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad

ABSTRACT

Various nutrients play a crucial role in enhancing reproductive health and have shown promise in treating male infertility. Omega 3 fatty acids present in diets have been noted for their ability to boost sperm quality by maintaining the integrity of sperm membranes and the stability of mitochondria. Phytochemicals have also displayed a potential to improve sperm function and reduce damage caused by oxygen free radicals. Certain dietary phytochemicals influence sperm movement, mitochondrial function and seminal fluid quality with effects varying based on concentration levels.

Furthermore, nutrients and minerals play a role in minimising oxidative damage and enhancing sperm health by improving mitochondrial function. This review delves into how various dietary nutrients enhance mitochondrial function resulting in improved reproductive health. Understanding how nutrients support sperm mitochondria and modulate epigenetic variables linked to sperm quality could pave the way for effective treatments, for male fertility issues by targeting mitochondrial function. It elucidates how different dietary nutrients enhance sperm functionality and overall fertility.

Keywords: Antioxidants, Dietary nutrients, Male infertility, Sperm mitochondria

Authors' Contribution:
Both authors contributed equally to the conception, literature search, manuscript drafting, editing and review

Correspondence:
Noor-ul-ain Irfan
Email: noorulainirfan@gmail.com

Article info:
Received: November 24, 2024
Accepted: December 28, 2024

Cite this article. Irfan NA, Saleem S The Impact of Dietary Nutrients and Antioxidants in Boosting Male Fertility: A Comprehensive Review. J Islamabad Med Dental Coll. 2024; 13(4): 685-695. DOI: https://doi.org/10.35787/jimdc.v13i4.1330

Funding Source: Nil
Conflict of interest: Nil

Introduction

Globally, infertility affects 10–15% of couples, with the male aspect contributing to 20–30% of the cases.[1] Male infertility is characterized by the inability to produce enough sperms for fertilization of an oocyte. From a personal perspective, male infertility can lead to emotional distress, anxiety, and strained relationships, particularly for couples trying to conceive. Addressing male infertility is essential not only for improving individual health outcomes but also for fostering healthy family dynamics and contributing to the stability of society at large.[1] Male-related factors such as semen quality issues (low sperm count, abnormal morphology, poor motility), hormonal imbalances (testosterone and FSH), genetic factors (chromosomal abnormalities), medical conditions (diabetes, cystic fibrosis, autoimmune diseases), age-related decline in sperm quality, lifestyle factors (obesity, tobacco and alcohol use, drug use, diet), environmental exposures (toxins, heavy metals, pesticides), medical treatments (chemotherapy, radiation) and infections (sexually transmitted

and other genital infections) account for 20- 30% of cases. [2]

Some nutrients such as omega-3 fatty acids, vitamins, minerals and phytochemicals enhance semen quality, sperm energy levels and overall sperm function [3]

They also improve membrane integrity, mitochondrial stability and motility which offers promising avenues for the prevention and treatment of infertility. [4]

Balancing diet and being physically active is key to staying healthy.[5] Adding antioxidants to the diet has shown positive effects on fertility by alleviating male infertility caused by oxidative stress. [6] However, additional research is needed to confirm the effectiveness and safety of using dietary supplements to reduce male infertility. Changes in patterns could be linked to an increase in sperm counts raising public health alarms. [4] For instance cutting down on saturated fats might have effects on both health and reproductive well-being. Current research is focused on exploring how dietary nutrients can impact male fertility. Antioxidants are currently being marketed to treat male infertility. In semen, antioxidants may decrease oxidative stress and potentially improve sperm parameters. [7]

Methodology

The research, for this review was base upon the modified 'Preferred Reporting Items for Systematic Reviews and Meta Analyses' (PRISMA) guidelines. The search was made across PubMed, Medline and Cochrane databases to find studies on the impact of dietary changes and effect of dietary nutrients and antioxidants on fertility. By selecting keywords such as antioxidants, sperm parameters, male infertility, rate of pregnancy, rate of births and sperm function' we curated our research diligently.

Our process for selecting studies started with reviewing the titles and abstracts of the articles, followed by an examination of the relevant articles. We carefully screened the original and reviewed articles to find sources. To ensure the integrity and focus of our research, we set exclusion criteria, such, as gender (females) species (animals), and languages (non-English). Data collection was carried out meticulously including extraction, verification and cross-checking. With this selection process as depicted in figure 01, a total of seven papers were short listed from amongst 225 papers.

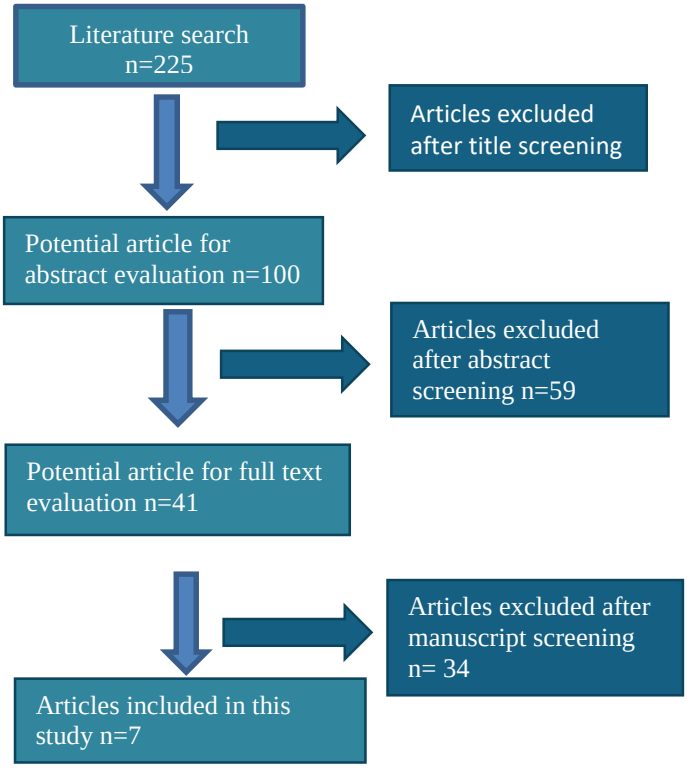

Figure: 1 PRISMA flow chart of study selection

Results and Discussion

The impact of dietary nutrients and antioxidants results in boosting of male reproductive health.

Omega-3 fatty acids

Omega 3 fatty acids help maintain cell structure, influence hormone production, and affect enzymes related to male fertility.[8] Following a fatty diet could lower testosterone levels in Caucasian men and different types of fats like

saturated fats, trans fats, and polyunsaturated fats can affect reproductive functions.[9] Saturated fats may have an impact on sperm count. At the same time, higher levels of omega-3 acids such as Dehydroepiandrosterone (DHEA) and Epiandrostendione (EPA) are linked to improved testosterone levels, sperm movement, and semen quality. Another study suggests that polyunsaturated fatty acids can benefit fertility robustly and evidence is needed for a conclusive link.[10] A Study indicates that a daily intake of 0.5–2 grams of DHA can enhance sperm mobility and reduce stress markers in men with poor sperm motility. [11] Moreover supplementing with omega-3 fatty acids has been shown to decrease DNA damage in sperm, improve mobility and reduce effects, on sperm cells.[12]

Vitamins

Essential micronutrients are generally classified as water-soluble and fat-soluble vitamins.[13]

Vitamin E (Alpha-tocopherol)

This vitamin is found in foods, like leafy greens, avocados, potatoes and almonds. A trial studied infertile men revealed a reduction in sperm DNA impairments following an eight-week supplementation of vitamins E and C (1 g/day for each). Vitamin E can stimulate ATP synthesis, enhancing sperm motility and reproductive competence.[15,16] Antioxidant property of vitamin E helps neutralize free radicals, protect cell membranes, and prevent lipid peroxidation. According to the European Commission Directive 2008/100/EC, 12 mg of vitamin E has been recommended as a daily intake [17] It is essential to explore the effects of adequate vitamin E intake on human fertility through further research.[8, 14]

Vitamin C

This water-soluble vitamin is rich in antioxidants. Berries and fruits of the citrus family are a comprehensive source of vitamin C.[18] Its supplementation has been extensively studied for its impacts on sperm function. A study by Lewis and Simon has shown that male rats that were administered vitamin C were able to alleviate damage to the testicles caused by cyclophosphamide. The association of reduced vitamin C levels and increased ROS concentrations found in semen with the occurrence of asthenozoospermia has highlighted the importance of vitamin C in healthy fertility in males.[19]

Vitamin D

This fat-soluble vitamin has limited dietary sources and usually has to be supplemented.[20] Its synthesis is endogenously stimulated in the skin by ultraviolet rays from sunlight. Many important functions of vitamin D have been identified, including its role in regulating calcium and phosphorus balance in the body and maintaining the health of bones, muscles, and teeth.[21] A study showed that the number of spontaneous pregnancies is increased if men with infertility received a dosage of vitamin D (300,000 IU) and calcium (0.5 g/day) for 5 months. Sperm counts also began to differ from untreated individuals. The administration of vitamin D in sub-fertile men improved semen quality, sperm motility, vitro fertility competence and sperm function. Vitamin D deficiency effects can be measured on fertility in both genders as made evident by trials.[22] However, there is a lack of substantial evidence from interventional research, as most trials had small sample sizes and focused mainly on vitamin D intake levels and duration. [23] A deficiency of vitamin D has been shown to increase oxidative stress markers, which can lead to alterations in sperm variables and pose a significant risk for reduced fertility. [24] Hussein et al. pointed out that vitamin D deficiency and methylation of the vitamin D receptor (VitDR) gene could complicate male infertility. [4]

Cobalamin (vitamin B12)

It is a water-soluble vitamin. It acts as a co-factor in both DNA synthesis, amino acid and fatty acid

metabolism.[25] The effects of vitamin B12 on sperm function and semen quality are an increment of sperm motility and count and the reduction of damage to sperm DNA.[26]

Folic acid

It improves various sperm function parameters to improve fertility.[27] Folate is involved in the synthesis of nucleic acids and proteins through the synthesis of S-adenosylmethionine through the one-carbon metabolic pathway. Thus, folate deficiency can influence spermatogenesis by altering gene expression.[28]

Trace element

Trace element play crucial roles in cellular function.

Zinc (Zn)

Zn is one of the most common trace elements.[29] Naturally present in our diet, it promotes DNA and protein synthesis amongst other functions. It has immunomodulatory effects and plays an important role in cell development and mitosis. It also possesses strong antioxidant abilities which enable it to protect the testicular system. Lower Zn levels in the seminal plasma of infertile males have a positive association with fertility outcomes, indicating the importance of Zn in fertility and infertility treatment.[30] Furthermore, Zn supplementation has been observed to significantly improve spermatogenesis, emphasizing its role in sperm DNA formation.[31]

Iron

Iron is an integral part of Hb molecule, and its deficiency causes anemia. A study involving 209 healthy Spanish students revealed a significant inverse correlation between dietary iron consumption and sperm quality.[4] Iron consumption has also been associated with fertility, suggesting potential positive effects on fertility among women with iron insufficiency.[32]

Selenium (Se)

This trace mineral has many essential roles in the cellular and organismal levels in human health. The biological effects of Se are mainly carried out by selenoproteins. Se is required for spermatogenesis and male fertility, due to its role in the modulation of antioxidant defense mechanisms.[33] In a randomized placebo-controlled study, 468 men with idiopathic Oligoasthenoteratozoospermia were divided into groups receiving daily doses of 200 µg selenium, 600 mg N-acetylcysteine, or 200 mg selenium + 600 mg N-acetylcysteine for 26 weeks followed by 30 weeks off treatment. All sperm parameters (motility— concentration— morphology) improved significantly in the group receiving the combination therapy. A positive correlation was found between the plasma concentrations of selenium and N-acetyl-cysteine and the improvement of sperm motility, morphology and concentration.[32,34]

Antioxidants

Carotenoids

These are found in various colorful vegetable dyes and are indispensable for human health. [35] These are vital for antioxidant protection and play a significant role in ensuring the proper function and development of sperm. Inadequate intake of carotenoids can lead to male infertility leading to reduced sperm motility and functionality.

Astaxanthin

It is a powerful antioxidant derived from natural sources, and may hold a key role in addressing fertility issues like sperm characteristics.[36,37] It also impacts on mitochondrial membrane potential, and functionality, and aids in the synthesis of ATP. Astaxanthin is found in plants, microbes, and marine organisms. It is also 100–500 times more active than vitamin E in combating oxidative stress with its considerable antioxidative properties. It also reduces lipid peroxidation.[38]

Coenzyme Q10 (CoQ10)

CoQ10 is vital in the electron-transport chain, facilitating the production of ATP particles through aerobic cellular respiration.[39] It also acts

as a powerful scavenger of free radicals, an energizing mediator, and a stabilizer of cell membranes, thus effectively preventing lipid peroxidation.

There is evidence showing a strong inverse relationship between CoQ10 levels and sperm motility in infertile men, suggesting a potential link between CoQ10 levels and infertility. Sperm quality significantly improved after supplementing with CoQ10 (120 mg/day for 3–6 months) in infertile males.[40] Supplementation with CoQ10 enhances sperm parameters such as sperm concentration, motility, and morphology, and improves OS markers in men with idiopathic infertility.[41] This assists cellular metabolisms, including cytochrome C and NADH production and ATP levels in sperm also improve.[41]

L-Carnitine (LCN)

It is a non-protein amino acid that offers numerous nutraceutical properties.[42] It acts as a crucial co-factor in the oxidation of fatty acids within the mitochondria and facilitates the transport of fatty acids, thereby contributing to cellular energy supply. The adequate levels of LCN in sperm are linked to increased ATP production, which is essential for sperm function and cellular metabolism. LCN was found to have protective effects during cryopreservation due to its significant antioxidant properties.[43] Research has also demonstrated that oral administration of LCN can reduce DNA damage in sperm and enhance sperm function and quality. There is evidence to suggest that LCN may have a positive impact on testicular Leydig cells, potentially aiding in the treatment of male infertility.[44]

Quercetin

The most used flavonoid Quercetin (QUR) is a natural bioactive molecule.[45,46] It is found in several foods and its daily intake ranges from 0.01 to 0.1 g. Quercetin uptake can extend up to 0.5–1 g/day due to its production quality.[47] Animal studies have also shown that quercetin has valuable impact in protecting the testicular system against toxic elements and diseases like diabetes.[48] Moreover, quercetin has the potential to boost sperm function in men having infertility issues, along with benefits for sperm health, semen quality and reproductive outcomes. Animals consuming quercetin also exhibit protection against oxidative stressor substances and diabetes affecting their testicular tissues.[49] Recent findings suggest that quercetin could be a tool in addressing infertility related to diets, which may be high in processed foods and low in essential nutrients and can negatively impact reproductive health.[50]

Quercetin has been demonstrated to play a role in protecting rat sperm from stress leading to improved quality and fewer abnormalities.[51] Quercetin causes enhanced viability, DNA integrity and increased sperm motility. Mitochondrial function was observed to improve.[52] It exhibits promise in shielding testicular tissues from toxic elements like cadmium lead nitrate and diabetes in animal testes.[53] It may potentially influence ATP synthesis.[54] There is also a growing interest in the potential of quercetin along with whey protein as an innovative, biocompatible antioxidant medicine for infertility associated with the Western diet.[55]

Curcumin

Curcumin increases the percentage of motile and viable spermatozoa but decreases and prevents the intracellular overproduction of free radicals within the sperm mitochondrial membrane. Experimental in vivo evidence in rats suggests that curcumin reverses the decreased sperm motility and teratozoospermia observed in response to UV exposure in rats, a feature associated with its antioxidant capacity.[56]

Kallikrein

In a prospective study, 31 infertile men with idiopathic oligozoospermia were given a daily oral

Table I. Original researches with nutrients and their effect on sperm parameters for male fertility					
Study authors (Yr)	**Nutrients/ Antioxidants used**	**No of participants**	**Characteristics (Kind of infertility)**	**Duration of intervention**	**Outcome**
Boussabbeh M et al (2024)[65]	Crocin	10	oligospermia	3 hours in vitro in semen sample	Increased motility of sperm. [65]
De Ligny et al (2022)[66]	Various combinations of Zinc and folic acid	303	Asthenospermia	In vitro before IVF	Increase in live birth rates. [66]
Shahid M et al (2021)[67]	Vitamin D	150	Altered sperm parameters	6 months	Vitamin D deficient and insufficient patients had increased oxidative stress markers which altered sperm parameters.[67]
Schisterman, E. F (2020)[68]	5 mg folic acid, 30 mg zinc once daily	1773	1773 men planning to undergo infertility treatment with a spouse	6 months	No improvement in Sperm motility and morphology. [68]
Micic, S (2019)[69]	L-carnitine = 1 g, L-acetylcarnitine = 0.5 g, fumarate = 0.725 g, fructose = 1 g, citric acid = 50 mg, zinc = 10 mg, coenzyme Q10 = 20 mg, selenium = 50 µg, Vit C = 90 mg, folic acid = 200 µg, Vit B12 = 1.5 µg daily		Idiopathic oligoasthenozoospermia (Placebo group n= 50, Treatment group n= 50)	3 months	Increase in semen volume, progressive motility, and vitality in the placebo group. Decrease in sperm DNA fragmentation index in the treatment group. [69]
Diao R et al (2019)[70]	Quercetin incubation of sperms	56	Leuko-cyto-spermic infertile men	2 months	Improved sperm motility.[70]
Stenqvist A (2018)[71]	30 mg vitamin C, 5 mg vitamin E, 0.5 µg vitamin B12, 750 mg L-carnitine, 10 mg coenzyme Q10, 100 µg folic acid, 5 mg zinc 25 µg selenium twice daily	7	7 infertile men with sperm DFI >25%Treatment group (37 patients) Placebo group (40 patients)	6 months	No change in SC, DFI. [71]

dose of 600 units of pancreatic kallikrein (Padutin(R) 100) for 3 months. Total sperm output increased significantly peaking 3 months after initiation of therapy.

Interestingly, quantitative and qualitative improvement in sperm motility was still evident 2 months after the withdrawal of therapy.[57]

Continued research is essential to establish clear guidelines for its safe and effective use.[58]

Cinnoxicam

In a randomized control study of 156 infertile men with Garde III varicoceles treated per rectum with 30 mg of the nonsteroidal anti-inflammatory drug Cinnoxicam once every 4 days over 12 months

improved sperm concentration, motility, and morphology.[58] The maximum benefit was observed after the 4 months with no further improvement after the 12 months.

Alpha Lipoic Acid

It prevents Reactive Oxygen Species-mediated damage to sperms, and NA fragmentation, improves sperm viability and motility, is reported to delay testicular lesions and to preserve the process of spermatogenesis in diabetes, restores glutathione, vitamin C and E levels in the testicular

Myoinositol

It is reported to control intracellular calcium concentration of sperms and is a key regulator of sperm mitochondrial events related to free radical generation and is known to improve mitochondrial functions and motility of sperm. Sperm parameters are improved and serum reproductive hormones in males having idiopathic infertility.[60]

Combinations

Combination of multiple antioxidants is believed to have a synergistic effect in combating infertility and increasing chances of pregnancy.[61] The benefit of combination therapy has been verified in a meta-analysis of 90 studies with a total population of 10,303 sub-fertile men, aged between 18 and 65 years. The results suggested that the chance following the use of antioxidants is estimated to be between 17 and 27%.[62] In another randomized control trial of 200 sub fertile couples, 100 men received a combination of Vitamin E, Vitamin C, and Zinc before assisted reproductive technology (ART), while the control arm received no treatment. Although sperm parameters improved significantly with combination therapy, the live birth rate was similar to the control group.[63] In a randomized double-blind control trial, 174 men were treated with 500 mg of vitamin C, 2000 IU of vitamin D3, 400 IU of vitamin E, 1 mg of folic acid, 20 mg of zinc, 200 mcg of selenium and 1000 mg of L carnitine daily for a period ranging from 3 to 6 months no improvement was found in sperm parameters, DNA fragmentation or pregnancy rates.[64]

Conclusion

World Health Organization (WHO) recognizes male infertility as a global concern, underscoring the urgency for effective diagnostic and therapeutic strategies.

Dietary nutrients and antioxidants play a pivotal role in male fertility by mitigating oxidative stress, promoting spermatogenesis, and enhancing sperm quality. This study emphasizes on current scientific research on the impact of diet on male fertility, providing crucial insights for preventive and therapeutic interventions in this field. The primary objective of this review is to explore the effects of dietary interventions, including omega-3 fatty acids, vitamins, minerals, and phytochemicals, on male reproductive health. However, further research is essential to fully elucidate the molecular mechanisms through which these nutrients exert their effects. This review outlines the potential of antioxidants such as selenium, L-carnitine, zinc, coenzyme Q10, and vitamins E and C either alone or in combination to enhance sperm quality and increase pregnancy rates in infertile men.

These nutrients have shown significant potential in enhancing antioxidant levels, reducing oxidative stress, improving sperm motility and function, and protecting sperm DNA integrity contributing to better overall sperm health and performance. Integrating dietary nutrients and antioxidants into fertility treatments represents a promising, non-invasive, and cost-effective strategy to improve male reproductive health.

Limitations:

Despite these promising findings, our study acknowledges certain limitations. Many of the reviewed studies suffer from poor design, small sample sizes, inconsistent dosages, varied

combinations of antioxidants, and a lack of live birth data as a primary endpoint. The heterogeneity in meta-analyses further complicates the interpretation of results. Therefore, it is crucial to conduct large, well-designed, randomized, placebo-controlled trials to generate more robust evidence, particularly concerning dosage, duration, precise combinations, and outcomes. Until such data are available, these treatments should be considered empirical.

Recommendations:

Future research must focus on conducting large-scale randomized controlled trials to establish definitive evidence for the efficacy of nutritional and antioxidant supplements in treating male infertility.

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