Importance of Few Trace Elements in Male Reproductive Health – A Comprehensive Review

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Abstract:

The normal functioning of sperm is very crucial for the successful fertilization of the oocyte, to develop into a potent embryo. For the proper functioning, sperm may seek assistance from trace elements present in seminal fluid. Semen contains several trace elements, mainly calcium (Ca), Iron (Fe), magnesium (mg), zinc (Zn), and selenium (Se), and these elements can also be linked to DNA, capable of altering gene expression patterns. Low levels of these trace elements can affect, normal sperm function, sperm maturation, motility, and capacitation. In this review article the role of the trace elements in male infertility is explored. The main objective of this review article is to highlight the impact of the trace elements on sperm and the consequences of deficiencies. The importance of maintaining the optimal level to achieve successful fertilization and implantation should be considered while treating infertility.

Introduction:

Infertility affects approximately 15% of couples, with male factor infertility accounting for 30–50% (31). Infertility leads to a stressful life for couples trying to conceive despite trying for an extended period. It can have emotional, psychological, and social implications. Understanding the cause of infertility is very important to begin treatment effectively. Over the past 70 years, both sperm parameters and fertility rates have decreased. Toxic exposures from the environment, lifestyle, and workplace may contribute to these occurrences.

The basic cause of male infertility is sperm abnormalities, which include poor sperm motility (asthenozoospermia) and poor sperm morphology (teratozoospermia). An imbalance in the levels of hormones such as testosterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) can affect sperm production as well as the quality of the sperm (32). Chromosomal defects, or Y chromosome microdeletions, are some of the genetic abnormalities that may lead to infertility. Varicocele is one of the factors that can impair sperm production (33). Lifestyle factors such as advanced age, smoking, excessive alcohol consumption, drug use, obesity, and exposure to environmental toxins can negatively impact sperm quality and fertility.

Key Words: Infertility, Sperm, Zinc, Calcium, Iron, Magnesium, Selenium.

Material and Methods:

The review was done using PubMed, Research Rabbit, Google Scholar, and Semantic Scholar, which showed vast research papers on in vivo and in vitro studies related to the influence of essential elements or trace elements like zinc, iron, calcium, magnesium, and phosphorous on male infertility or spermatozoa quality. The literature review was done using key words like “male infertility," “sperm quality," “trace elements," “levels of trace elements in human seminal plasma," and “trace elements and male infertility." Several methods were used by different researchers to assess the levels of trace elements in the seminal plasma. A few methods are inductively coupled plasma optical emission spectrometry (ICP-OES) (5) and electrothermal-atomic absorption spectrometry (AAS).

Importance of trace elements in female:

Trace minerals are micronutrients that have roles in various physiological functions, particularly in supporting women’s reproductive wellbeing (34). Understanding how different trace minerals impact fertilization and implantation rates is crucial for health. A recent analysis underscored the significance of trace minerals in the fertilization process, fertility, and pregnancy. The study stressed the need to maintain levels of trace minerals, as excessive or insufficient levels could signal toxicity or interfere with functions (1). Iron is crucial for making haemoglobin, a protein that helps carry oxygen to body tissues like the ovaries and uterus. Having iron is important for maintaining menstrual cycles and fertility. When there’s a lack of iron, it can lead to anaemia, which can disrupt ovulation and lower fertility rates (35).

Zinc plays a role in aspects of women’s reproductive health, such as follicle growth, ovulation, and hormone balance (37). It also supports the system and DNA production, which are essential for a functioning reproductive system. Selenium acts as an antioxidant that shields cells from damage caused by oxidation. Selenium could potentially aid in improving function, egg quality, and embryonic development. All beneficial for reproductive health. Additionally, it plays a part in thyroid hormone regulation, which influences regularity and fertility levels (37). Magnesium plays a role in biochemical processes within the body, such as regulating hormones, supporting muscle function, and facilitating nerve transmission. When it comes to women’s health, magnesium could potentially ease premenstrual syndrome (PMS) symptoms. Promote fertility overall.

Importance of trace elements in male:

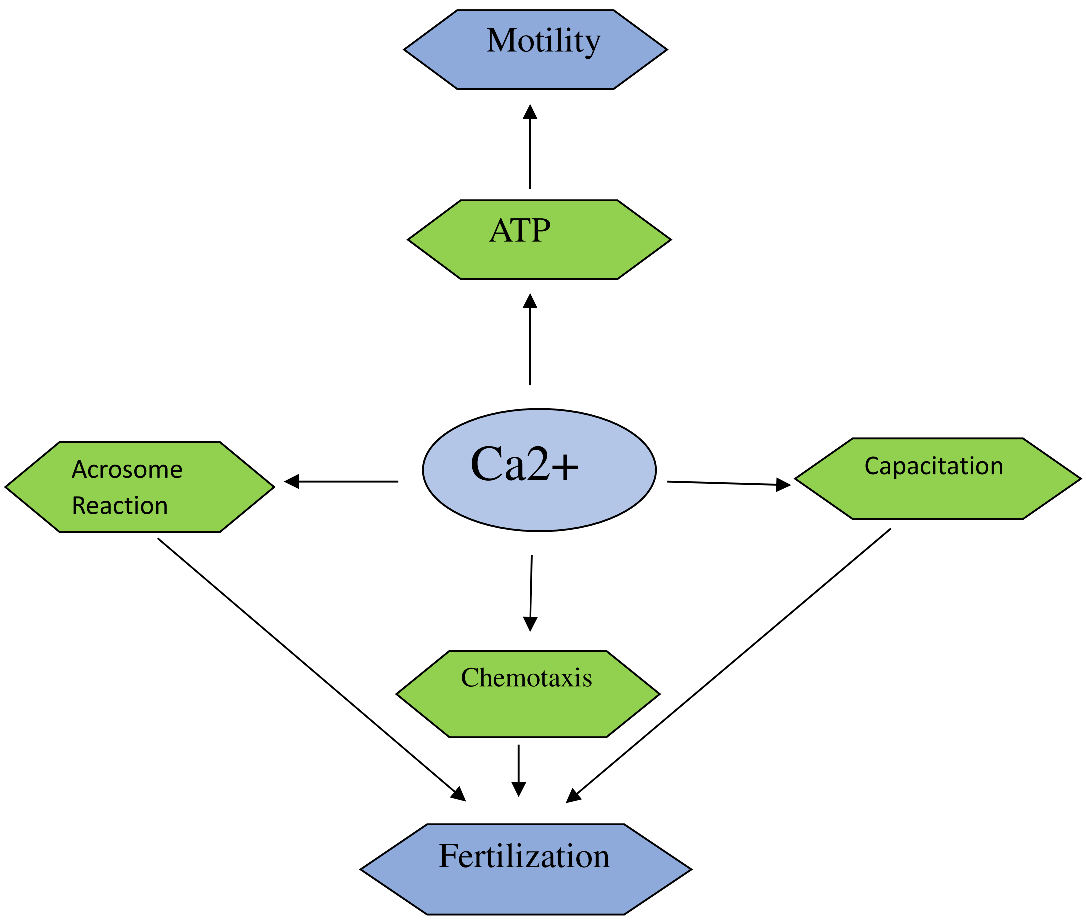
Calcium (Ca) and male infertility:

Ca is one of the most important trace elements in mammalian sperm, essential for sperm motility, maturation, sperm capacitation, and acrosome reactions, as well as sperm chemotaxis (1) and (2). Nishida S et al. reported that increasing the fertilizing potency of human Ca is necessary for sperm chemotaxis, sperm capacitation and acrosome reactions, and sperm motility and hyperactivation. The level of calcium concentration was low in the hypomotility group (0.19 + 0.01 mmol/L) while 0.24 + 0.01 mmol/L($p<0.001$) were noted in the control group with normal motility.

Spermatozoa concentration and motility correlate with the level of calcium ions but not with total calcium (6). In the oligozoospermic and asthenozoospermic semen samples, the level of calcium is low when compared to the normozoospermic semen samples. Since the difference is statistically highly significant, it is well known that the level of calcium in the semen sample is very important for sperm production and sperm motility (9). A study conducted in 1997 by Logoglu et al. says that the level of calcium is lower in infertile men with normozoospermia when compared to fertile men. Sperm concentration and motility have no significant correlation with the level of calcium.

The level of calcium should be measured even for normozoospermic infertile men. The concentration of seminal calcium in fertile men is 152±9.9 and in normozoospermic infertile and oligo and azoospermic infertile men is 113±15.2 and 137±14.5, respectively (13). Mechanisms such as spermatogenesis failure, impaired steroidogenesis, chemotactic failure, impaired sperm motility, capacitation, and acrosome reactions are activated due to the deficiency of calcium (17).

The main role of calcium ions in male infertility is given in Fig.1(29).



Zinc (Zn) and male infertility:

Zn is one of the most significant nutrients in human semen. It acts as a biological marker and an antioxidant, which is necessary for good sperm count, motility, and morphology (3). Zinc is involved in sperm cell membrane and nuclear chromatin stability. It also controls energy utilization and phospholipid regulation. Khan et al. assessed the level of zinc and its role in male infertility. The study concluded that the sperm count is affected by the decreased concentration of seminal Zn, and sperm motility is affected by the increased level of seminal plasma Zn. Sperm morphology is directly affected due to the decreased level of zinc (10).

Andrea Molistic Srb et al. conducted a study to determine if there was any significant correlation between the zinc concentration and the sperm parameters in infertile men and how it affected motility and morphology. The study results state that the level of zinc is low in the low-sperm count semen sample. Similarly, another study confirmed that the level of seminal plasma zinc significantly correlates with all the parameters such as sperm concentration, motility, and morphology ($p<0.05$, r = 0.86, 0.87, 0.86) (4). The sperm concentration, motility, and normal morphology are positively correlated with the level of Zn in the seminal fluid. The level of Zn in azoospermia and oilgozoospermia is significantly lower in infertile males than in fertile males (14). A significant improvement has been noted in semen parameters after oral zinc supplementation in infertile men in a study conducted by Fatima et al. Mainly in Oligoasthenozoospermia men, improvement was seen in sperm total count, motility, and rapid linear morphology (28).

Table 1: Effect of Zinc Supplementation on Sperm Parameters (Fatima, P. et al.)

Parameters	**Group A (n-38)**	**Group B (n-37)**
Sperm count Million/ml	+14.83**	+5.44
Sperm motility %	+16.30**	+13.70*
Sperm rapid motility %	+11.96**	+6.78
Normal Sperm morphology %	+4.26***	+2.22

*p<0.05, **p<0.01, ***p<0.001

Group A: Oligozoospermia, zinc supplementation

Group B: Oligozoospermia, placebo

Iron (Fe) and male infertility:

High levels of iron and lipid peroxidation in seminal plasma can disturb the sperm nuclear integrity, which causes DNA breaks, resulting in poor sperm morphology. Iron plays a significant role in sperm motility since the enzyme that is dependent on iron generates ATP (adenosine triphosphate) for sperm movement. Hence, energy metabolism is dependent on the level of iron in semen. DNA integrity and stability are very important for normal sperm function. A low level of iron may lead to DNA damage and decreased fertility. Sperm motility is decreased in semen samples with a low level of Fe (10, 21). There is a significant correlation between the level of iron and seminal parameters such as abnormal morphology ($r = 0.445$, $p<0.001$) and total motility ($r = -0.296$, $p = 0.002$) (11). Recent findings say that a high level of iron is associated with sexual dysfunction and infertility in men. Also, an overload of iron decreases testosterone levels (15). The concentration of iron in the seminal plasma of normozoospermic males is between 1.0 and 3.7 µg/ml (10). Human seminal iron concentration is 2.59±0.21 mg/kg. There was a negative correlation between iron and pathological forms of spermatozoa ($r = -0.32$). If the level of iron is increased in the testes, oxidative damage to lipids, proteins, and DNA may occur.

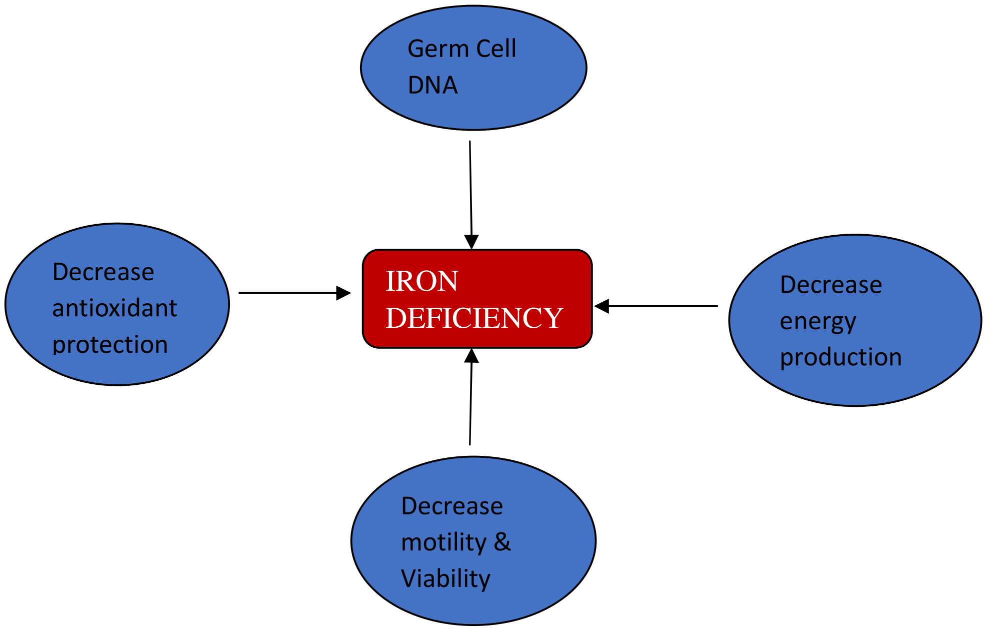


Fig.2: Effect of Iron Deficiency in Sperm (36)

Magnesium (Mg) and male infertility:

For spermatogenesis, sperm motility, and regular ejaculation, magnesium is required (18). Magnesium influences sperm motility and overall plays an important role in male infertility since it is involved in more than 300 enzymatic reactions in the body, including reproductive health. Like other trace elements, magnesium in seminal fluid plays a vital role in fertility. A low level of magnesium concentration in semen increases nitric oxide production and vasoconstriction, which results in premature ejaculation (19). Enzymes involved in ATP production for sperm motility required magnesium for the process. A decreased level of seminal Mg can be associated with defects in the prostate gland since Mg in semen is produced from the prostate gland (1). The concentration of Mg is low in infertile patients. It plays a vital role in enzymatic reactions and ejaculatory functions. A study on the level of magnesium in seminal plasma in the group having genuine premature ejaculation was conducted by Nikoubakht, M.R. et al. Both serum magnesium and seminal plasma were evaluated. The study concluded that there is a significant relationship with the decreased level of magnesium in genuine premature ejaculation men compared to controls (23).

Table.2 shows the Magnesium levels in Oligozoospermia semen samples (low count), Azoospermia (no sperms), and Normozoospermia (normal count, motility, and morphology).

Table- 2: Mean Seminal Plasma Magnesium levels

	Oligozoospermia (n=43)	***p* value**	**Azoospermia (n=35)**	***p* value**	**Normozoospermia (n=41)**
Magnesium (mg/dL)	5.70±0.65	0.000	5.59±0.69	0.000	12.62±2.28

Selenium (Se) and male infertility:

Selenium deficiency leads to a low sperm motility rate, defects in the sperm head, and damage to the midpiece. Se is present in sialoproteins, from which the enzyme Glutathione Peroxidase (GPxs) is secreted, which is present in the midpiece of the sperm (25). Selenium supplementation shows a positive outcome on sperm parameters in men with infertility. Thus, while treating infertile men, analyzing the level of Se and supplementing with the same could be considered (26). Selenium, or Selenoproteins, plays an important role in normal sperm structure integrity.

Table. 3: Changes in semen parameters before and after treatment with selenium. (Morbat, M.M et al)

Parameters	**Before ($)**	**After ($)**	**% Increase**
Sperm count Million/ml	39.24±27.4	*58.1±21.6	32.70%
Sperm motility %	22.14±12.9	*50.7±17.6	56.30%
Sperm viability %	32.14±12.2	*60±19.1	46.40%
Normal Sperm morphology %	68±5.7	*82.1±6.4	17.10%
Ejaculate volume ml	2.2±0.57	*3.61±0.32	39%

$=mean+/- standard deviation *=(p<0.01)

Table 3 describes the study done on the effect of selenium in treating male infertility by Morbat, M.M., et al. This study concludes that the supplementation of selenium in infertile men or selenium-deficient men with infertility may lead to a positive improvement in the semen parameter (27)**.**

Discussion:

Metabolic pathways use many enzymes that are dependent on trace elements. The appropriate level of trace elements plays a crucial role in spermatogenesis, sperm motility, and fertilization (16). The seminal plasma secreted by sexual accessory glands contains certain components that shield spermatozoa during ejaculation. Proteins, enzymes (acid phosphatase, alanine transaminase, alkaline phosphatase, aspartate transaminase), lipids, macroelements (sodium (Na+), potassium (K+), calcium (Ca2+), magnesium (Mg2+), phosphate (P), and chloride (Cl)), and microelements (copper (Cu), iron (Fe), and zinc (Zn)) make up this substance (38). Oxidative stress reduces sperm quality. Metal ions (e.g., copper, zinc, iron, and selenium) that act as co-factors for antioxidant enzymes are required to maintain the pro-antioxidant balance. Reduced concentrations of these trace elements can have a detrimental impact on sperm quality, human reproductive health, and, ultimately, male fertility potency (39). A study conducted by Sherif Salah Azab et al. showed that the Ca and Mg levels in infertile men with varicocele significantly decreased compared with the fertile group with a higher varicocele grade and varicocele bilaterally. Aso had a significantly positive correlation with sperm concentration, motility, and morphology. It is necessary for conception and embryonic implantation and plays a controlled role in sperm acrosome reactions and capacitation. There is a correlation between reduced fertility potential and low seminal zinc levels. High Zn concentrations have been linked by some authors to improved sperm parameters, such as sperm count, motility, and normal morphology. Seminal zinc had a strong positive correlation with sperm count and normal morphology in both fertile and infertile men (40). Calcium is an essential trace element of sperm and seminal parameters, including motility. It also has a vital role in metabolic function, acrosome reactions, and fertilization. The seminal calcium concentration is lower when compared to the seminal plasma calcium concentration. The mean level of calcium in semen is 38.9 mg/dl (7). The concentration of Mg, Cu, and Fe in normozoospermia males is significantly high. Zinc and calcium have the highest concentrations when compared to the other body fluids (10). Thomas E. et al. studied the elemental composition of human semen. According to the study, the concentration of zinc, copper, and calcium is high in sperm, and the level of sulphur is increased in the seminal plasma of older men (65–85 years old) when compared with the concentration of zinc, copper, calcium, and sulphur in younger men. DNA fragmentation is positively correlated with the concentration of calcium and copper in sperm. But sperm calcium is not correlated with sperm motility (22).

Conclusion:

Trace elements can be obtained by following a balanced diet including fruits, vegetables, whole grains, nuts, seeds, and lean proteins. But, in cases of very low or severe deficiency in trace elements or reproductive issues, consulting with a healthcare professional is advisable for proper evaluation and management. It is essential to measure these trace elements in men. This comprehensive review highlights the importance of trace elements in male fertility and urges the need for continued research to explore these relationships further.

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