Role of Zinc in Male Infertility: Review of Literature

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Abstract

Infertility is a worldwide problem with male factor contributing equally to infertility as females. Zinc is one of essential trace elements required for normal physiology of male reproduction and plays important role in spermatogenesis. The process of spermatogenesis is well studied and understood, but studies related to role of essential nutritional elements like zinc; necessary for normal spermatogenesis are not yet covered thoroughly in detail. The present review throws light on role of zinc in human spermatogenesis as well as its effect on male infertility. Method: The literature regarding male infertility and role of zinc in male reproduction was searched from various journals and published peer-reviewed articles on Pubmed, MEDLINE, Embase and Google Scholar till 2015.

Key words: Contraception; Infertility; Spermatogenesis; Sperm count; Testosterone.

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Introduction

According to International Committee for Monitoring Assisted Reproductive Technology, World Health Organization (WHO), infertility is defined as failure to achieve clinical pregnancy after 12 months or more of regular unprotected sexual intercourse[1]. It can be further defined as failure of couple to conceive after 12 months of regular intercourse without contraception in women <35 years; and after 6 months of regular intercourse without contraception in women ≥35 years[2]. Infertility affects 15% of couples globally, amounting to 48.5 million couples annually. Males solely account for 20-30% of infertility cases and are responsible for 50% of all infertile cases[3]. One of the commonest causes of male infertility is sperm dysfunction[4]. This can be due to many risk factors leading to defective spermatogenesis, like varicocele, obstructive lesions, cryptorchidism, cystic fibrosis, trauma, genitourinary infection, environmental factors, and nutritional deficiency of trace elements especially zinc, selenium, vitamins and oxidative stress[5,6].

Incidence

Recent figures reveal that male infertility is responsible for approximately 30-55% of infertility cases[4]. Furthermore according to Sharlip, 50% of infertility cases are solely due to female factor, male factor accounts for 20-30% of cases, and remaining 20-30% results from combination of two[7]. A major portion of these sub-fertile men are classified as having unexplained male infertility[8]. Globally information regarding male infertility rates is acutely lacking, and has not been accurately reported as male infertility remains under-reported, especially in countries where cultural factors and societal pressures prevent accurate statistics from being collected and compiled[3]. According to recent global figures rate of male infertility ranges from 2.5% to 12%[9] with a worldwide estimate of 30,625,864 to 30,641,262 infertile men[3]. Moreover, incidence of male infertility varies in developed and developing regions of world (Table 1 and Fig. 1[9]). The epidemiologic reports indicate that infertility rates range from 3.5% to 16.7% in developed countries and 6.9% to 9.3% in developing countries[10].

The etiology of male infertility is mainly unknown and unexplained, although various environmental, occupational, and lifestyle factors are known to play role[11]. Moreover nutritional factors were found to be crucial determinants of normal reproductive function[11-13]. High intake of antioxidants, fruits, vegetables, sea food, milk as well as low intake of fat full dairy products, sweets, processed meat, especially with high-saturated fatty acid, have significant association with sperm quality[14,15]. Furthermore, dramatic changes in semen quality have been noticed in past three decades[16]. In 90% of infertile men, it is the sperm count which is low[17]. Role of trace elements in maintaining quality of human semen is receiving much of interest now-a-days[18]. Although the role of trace elements in male fertility has been realized, but biological role of these elements is yet not fully understood[19]. One such trace element is Zinc which is found in high concentration in mammalian semen, and is responsible to play an important role in human spermatogenesis.

Role of Zinc in Male Reproduction

Zinc is a trace mineral, essential for normal functioning of male reproductive system. In human body > 200 enzymes in various biochemical processes are dependent on zinc[28]. It is also involved in several cell functions like signal transduction, transcription and replication[29]. Further, about 3-10% of all proteins in mammalian genomes bind zinc for holding, activity and conformational changes[30]. Also since, zinc concentration is so high in male sex organs like prostate[31], testicles and in spermatozoa itself, its role in male reproduction is undeniable[32]. Many studies reveal high concentration of zinc in human seminal plasma, mean ranges from 78.9 to 274.6 mg/L[33-35].

Zinc is not only involved in anatomical development and normal functioning of male reproductive organs, but also increases spermatogenesis by actively participating in spermatozoa maturation and preservation of germinal epithelium[28]. It also plays a role in production and secretion of testosterone from Leydig cells, which, along with follicle stimulating hormone, is a key regulator of spermatogenesis[36]. Further, zinc is also known for antibacterial function[37]. Zinc content of prostate gland, seminal fluid and ejaculated sperm are very high and testicular zinc is essential for spermatogenesis[38]. Studies report that zinc concentration in blood closely affects spermatogenesis, as zinc deficiency leads to gonadal dysfunction, decrease in testicular weight and shrinkage of seminiferous tubules[12].

The daily Recommended Dietary Allowances of zinc is 11 and 8 mg/day for men and women respectively[39]. Adult human body contains around 1–3 g of zinc, of which 0.1% is replenished daily[40]. It is also reported that Zinc supplementation protects against deleterious effects of lead which causes degenerative changes in sperm maturation. Table 2 represents the functions of Zinc in male reproduction[40].

Zinc and Male Infertility

Zinc is an essential trace element required for normal spermatogenesis and steroidogenesis; its deficiency is one of factors responsible for decreased testicular function in infertile males[43]. It was found that males with asthenospermia/ teratazoospermia had a significantly lower intake of zinc in comparison to normal fertile males[44]. Studies also report a positive correlation between seminal plasma zinc concentration with sperm count, motility and serum testosterone levels[45,46]. Most important effect of zinc is on sperm motility. It helps in stiffening of outer dense fibers by formation of disulfide bridges during sperm maturation in epididymus, which is an essential step for generation of sperm motility; especially progressive motility[47]. Severe zinc depletion causes a 50% decrease in amount of zinc per ejaculate, resulting in pathozoospermia[48]. In a trial of 37 males with idiopathic infertility, 24 mg of elemental zinc was supplemented for 45 to 50 days[49] which resulted in a substantial increase in testosterone level and sperm count from eight million to 20 million/ ml, leading to nine successful conceptions. Similar results were reported by another study which found a significant increase in total normal sperm count after zinc supplementation in both sub-fertile and fertile men[31]. A recent study reported that seminal zinc levels in fertile and infertile (smokers or nonsmokers) males correlated significantly with sperm count and normal sperm morphology[50]. Another study reported that seminal plasma zinc concentration was significantly correlated with sperm count[51], density, motility, and viability[33,52].

Some other authors have shown that there is no correlation between total amount of zinc and semen characteristics[35,53]. Another study reported decline in human sperm motility in association with increased zinc concentrations in seminal plasma[54]. A similar study reported that zinc intake was not associated with improved semen quality[55]. A study also reported a positive correlation between concentrations of seminal plasma selenium and zinc with sperm density in normospermic men but not in oligozoospermic men[56]. In addition, another study demonstrated a weak association between blood plasma zinc concentrations and sperm count, motility, and abnormal sperm morphology[51].

Hence, zinc is found to play important role in physiology of male reproduction. Though many more studies on human population are required to exactly know the effect of zinc on spermatogenesis, so that it can be utilized in future in an attempt to reduce the overall burden of male factor infertility.

Table 1: **Global male and female infertility rates based on various studies**

Country	Infertile Males	Infertile Couples	Couples in which male factor is one of multiple factors involved
North America	4.5-6%a	15%	50%
Middle East	Unknown	Unknown	60%-70%b[20]
Sub-Saharan Africa	2.5%-4.8%a	12.5%-16%[21]	20-40%[21]
Europe	7.5%a[22]	15%[22]	50% of all infertile couples
Australia	8%; 9%b[23]	15%	40%[24]
Central/Eastern, Europe	8%-12%[25,26]	20%[26]	56%[25]
Asia	Unknown	Unknown	37%[27]
Latin America	Unknown	Unknown	52%[27]
Africa	Unknown	Unknown	43%[27]

- aPercentages were calculated from data reported on female infertility, using assumption that 50% of infertility cases are due to females only, and 20-30% due to male factor only.
- bStudy states that 60-70% of all men presenting to IVF clinics in the Middle East have some involvement in cause of infertility.

Table 2: Functions on Zinc in Male Reproduction

Stages of Spermatogenesis	Functions of Zinc
Initiation of spermatogenesis	Involves in ribonuclease activity[41].
During spermatogenesis	Spermatozoa maturation[41]. Preserve germinative epithelium and seminiferous Tubule[42].
End of spermatogenesis	Enhance sperm motility[41].

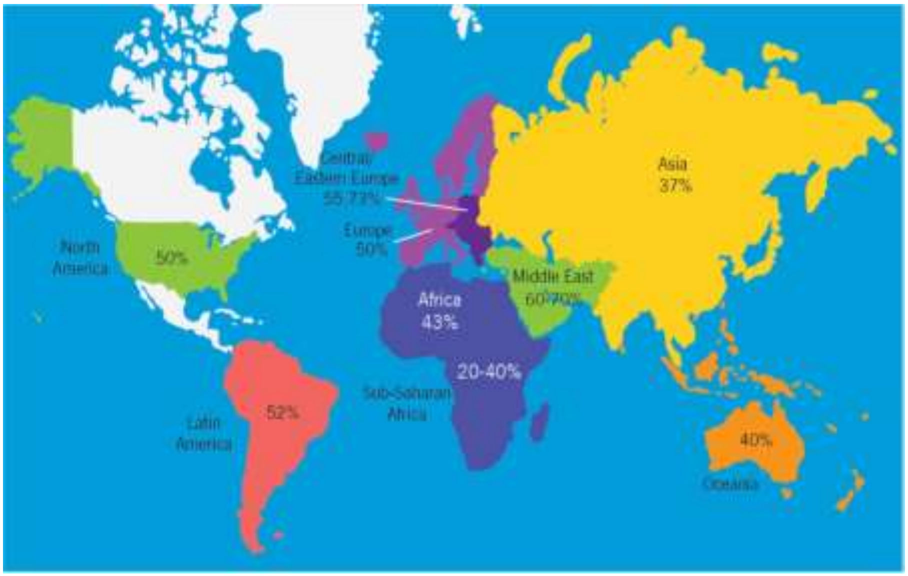

Fig. 1: World map showing percentages of male factor infertility cases per region

Source: Mascarenhas MN, Flaxman SR, Boerma T, Vanderpoel S, Stevens GA. National, regional, and global trends in infertility prevalence since 1990: a systematic analysis of 277 health surveys. PLoS Med. 2012;9:e1001356.

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