



Zinc as a Modulator of Male Fertility: Interplay Between Lipid Metabolism, Oxidative Stress, and Sperm Function

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Abstract

Infertility is a multifaceted and pressing global health challenge, with male reproductive impairment playing a significant role in its overall burden. Zinc (Zn), a biologically indispensable trace element, is fundamental to spermatogenesis and overall male reproductive function. This narrative review explores the following aspects: (1) the mechanistic function of Zn in spermatogenesis, (2) the impact of oxidative stress on Zn status and male infertility, (3) the interplay between Zn and lipid metabolism in male reproductive physiology, (4) the relationship between Zn concentrations and semen parameters, and (5) the effects of Zn supplementation on sperm quality, alongside relevant institutional recommendations. The molecular pathways underlying Zn deficiency-induced enzymatic dysfunction, oxidative stress, and lipid homeostasis disruption remain partially elucidated, warranting further investigation into their interdependent effects on male infertility. While accumulating evidence suggests that Zn supplementation may have therapeutic potential in male infertility management, guidelines for its clinical application vary considerably across institutions and regions. To establish a clear and evidence-based framework for the function of Zn in male reproductive health, future research should prioritize determining of optimal Zn levels, the mechanistic links between Zn and lipid metabolism, and the long-term clinical outcomes of Zn supplementation in infertile populations.

Keywords Zinc · Spermatogenesis · Lipid profile · Oxidative stress · Supplementation

Abbreviations

Zn	Zinc	Mg	Magnesium
Cu	Copper	Ca	Calcium
Mn	Manganese	FA	Fatty acids
Se	Selenium	PUFA	Polyunsaturated fatty acids
		OS	Oxidative stress
		ZnT proteins	Zinc transporter proteins
		ZIP	Zrt- and Irt-like proteins

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ZFP	Zinc finger protein
SOD	Superoxide dismutase
MTF- 1	Metal regulatory transcription factor
Nrf2	Nuclear factor erythroid 2
ROS	Reactive oxygen species
Bcl- 2	B-cell lymphoma 2
Bax	Bcl- 2-associated X protein
PRM1	Protamine 1
PRM2	Protamine 2
ZFY	Zinc Finger Protein Y-linked
ZFX	Zinc Finger Protein X-linked
KRAB	Kruppel-associated box
KAP- 1	KRAB-associated protein 1
O ₂ –	Superoxide anion radical
H ₂ O ₂	Hydrogen peroxide
SFA	Saturated fatty acids
MUFAs	Monounsaturated fatty acids
DHA	Docosahexaenoic acid
AA	Arachidonic acid
EPA	Eicosapentaenoic acid
GLA	Gamma-linolenic acid
DGLA	Dihomo-γ-linolenic acid

Introduction

As a complex and pressing global health issue, infertility has far-reaching implications for individuals, societies, and healthcare infrastructures. Recent estimates indicate that infertility affects 17–26% of married couples of reproductive age, with 56% requiring medical treatment [1]. The intricate and diverse etiological spectrum of infertility poses challenges to its epidemiological characterization and the identification of contributing factors. While a definitive cause is identified in approximately 85% of infertile couples, the remaining cases are considered idiopathic, as no clear physiological or biochemical abnormalities are detected despite extensive clinical investigation [1]. Male-factor infertility accounts for nearly half of all cases, acting as the sole determinant in approximately 20% and contributing to an additional 30–40% [2]. Within this subset, impairments including hormonal dysregulation and deficiencies in sperm production or function have been identified in roughly 35% of infertile men. Given the frequent co-existence of male and female infertility factors, a comprehensive evaluation of both partners is essential for accurate diagnosis and effective management [3]. In this context, an array of exogenous and endogenous factors may contribute to the rising incidence of reproductive disorders, including environmental stressors, lifestyle alterations, poor nutrition, genetic predispositions, and endocrine imbalances [4]. Yet, in many instances, the precise pathophysiological mechanisms remain insufficiently characterized, warranting further research into how these

factors influence spermatogenesis and overall male reproductive function at the molecular and systemic levels.

Trace elements are essential for male reproductive health, affecting key processes such as spermatogenesis, hormonal regulation, and sperm function. However, their biological significance extends far beyond reproduction, as they play indispensable roles in cellular metabolism, immune defense, and overall physiological homeostasis, despite constituting only 0.1% of total body mass [5]. Human semen contains several trace elements, copper (Cu), manganese (Mn), Zn, and selenium (Se), as well as macroelements, primarily magnesium (Mg) and calcium (Ca). Trace elements have been extensively studied for their potential implications in male infertility, with particular attention given to Zn, due to its significant impact on reproductive health [6, 7].

Zinc is the second most abundant trace element in the human body, where it serves a multifaceted role in biochemical pathways and physiological processes, including oxidative stress defense, homeostatic balance regulation, immune response, and cell-mediated functions [8]. Zn exerts its biological effects through three primary enzymatic functions: (1) the catalytic function, wherein it directly facilitates biochemical reactions; (2) the coactive function, in which Zn modulates enzymatic activity by either enhancing or attenuating its effects; and (3) the structural function, where Zn contributes to maintaining the stability of the quaternary structure of enzymes, ensuring their proper conformation and functionality [9, 10].

The World Health Organization estimates that approximately one-third of the global population may be affected by Zn deficiency [11]. This is corroborated by findings from a recent large-scale cohort study by Hibi et al. (2022), which reported that normal serum Zn concentrations (800–1300 µg/L) were present in 53.2% of individuals, while 42.0% exhibited subclinical deficiency, and 3.9% had overt Zn deficiency [12]. An adult human body contains approximately 1.4 to 2.3 g of Zn, distributed across various tissues and organs [13]. Specifically, almost 50% of Zn is stored in muscles, 37% in the bones, 7.60% in the skin, and 6.20% in all other organs [14]. However, only a small fraction of the body Zn circulates in the bloodstream [15]. Beyond its systemic distribution, Zn is highly concentrated in seminal plasma, where its levels surpass those in blood by 85- to 90-fold, highlighting its vital importance in male reproductive physiology. Zn is essential for protecting sperm from bacterial invasion and maintaining sperm integrity [16].

In addition, Zn plays a variety of roles in the male reproductive system, including regulation of the process of spermatogenesis (from germ cells to sperm), maturation of epididymal sperm, sperm structure and function, sperm motility, capacitation, pre-fertilization events, and fertilization itself and embryonic development [16, 17]. Due to its high concentration in seminal plasma, Zn is often regarded

as a macroelement in human semen [18]. Variations in Zn concentration within seminal plasma have been shown to affect sperm count, motility, viability, pH, and viscosity, with low Zn levels being associated with reduced fertility potential [6]. Furthermore, Zn-mediated mechanisms have been closely linked to oxidative stress (OS) regulation and fatty acid (FA) metabolism, underscoring its broader importance in maintaining sperm function and integrity [19].

Current literature provides limited evidence on the interactions of Zn with other micronutrients in the context of male fertility [20–22]. Moreover, the precise mechanisms through which Zn influences polyunsaturated fatty acids (PUFA) metabolism and OS, as well as its broader impact on reproductive function, remain incompletely understood. Several studies indicate that the relationship between seminal plasma Zn concentrations and male infertility warrants further investigation [6, 17, 23], along with the determination of optimal Zn supplementation doses to enhance fertility outcomes [24].

Accordingly, this review aimed to explore the mechanistic underpinnings of Zn's involvement in spermatogenesis, its intricate interplay with lipid metabolism, and the impact of OS on Zn homeostasis. Additionally, we discussed the correlation between zinc concentrations in seminal plasma and semen quality parameters. We also examined the therapeutic potential of zinc supplementation encompassing optimal dosing strategies and evidence-based recommendations from relevant health authorities in improving male fertility.

Literature Search

A systematic approach was employed in this narrative review to comprehensively identify relevant literature on Zn's contribution in male fertility. Searches were conducted across major scientific databases, PubMed, Scopus, and Embase, utilizing a combination of controlled vocabulary, i.e., Medical Subject Headings (MeSH) terms and free-text keywords to ensure both the breadth and specificity of retrieved publications. Search terms were categorized into four primary domains: (1) zinc-related terms (e.g., “zinc metabolism,” “zinc deficiency,” “zinc supplementation,” “zinc transporters,” “zinc-binding proteins”), (2) male reproductive health (e.g., “spermatogenesis,” “sperm quality,” “male infertility”), (3) oxidative stress and redox biology (e.g., “reactive oxygen species,” “oxidative stress,” “antioxidant defense”), (4) and lipid metabolism and membrane integrity (e.g., “fatty acids,” “lipid peroxidation,” “phospholipid composition,” “polyunsaturated fatty acids,” “desaturase enzymes,” “elongase enzymes”). Boolean operators (AND, OR) were applied to refine search queries and establish logical relationships between terms, thereby minimizing redundancy and optimizing the retrieval of relevant studies. Additional

filters were applied to restrict results to peer-reviewed journal articles published in English between 2000 and 2024, ensuring both methodological rigor and contemporary relevance. The initial search results were systematically screened based on titles and abstracts to exclude irrelevant or duplicate studies. Full-text articles were retrieved for further assessment if they met predefined inclusion criteria. Eligible studies were required to focus on the biochemical, physiological, or clinical aspects of Zn in male reproductive health, including its involvement in sperm function, enzymatic activity, OS modulation, and lipid metabolism. Case reports, conference abstracts, editorials, and non-peer-reviewed sources were excluded to maintain methodological robustness and reliability. Furthermore, the reference lists of included studies were manually screened to identify additional relevant publications that may have been overlooked in the initial database search. Study selection was conducted independently by two reviewers (MZ and AV) to minimize bias, with discrepancies resolved through consensus.

The Role of Zn in the Male Reproductive System and Fertility

Zinc is essential for various stages of spermatogenesis and sperm maturation, impacting genomic integrity, membrane stability, and metabolic activity. Throughout the progression of spermatogenesis, Zn contributes to ribonuclease-mediated regulatory processes essential for both the mitotic proliferation of spermatogonia and the meiotic division of spermatocytes. It stabilizes sperm chromatin, modulates the histone-to-protamine transition, and ensures proper nuclear condensation, which are all fundamental for sperm viability and function [6]. As a highly coordinated process, spermatogenesis involves a series of complex morphological and biochemical transformations, predominantly occurring within the seminiferous tubules. These transitions—including chromatin remodeling, tail elongation, and midpiece formation—are critically dependent on Zn availability [25]. Zinc homeostasis is regulated by two major transporter families: ZIP (Zrt- and Irt-like proteins) proteins, which mediate Zn influx into Sertoli cells, and ZnT (zinc transporter proteins) proteins, which facilitate its intracellular trafficking and targeted export to developing germ cells [26, 27]. The functional significance of ZIP-mediated Zn transport extends beyond the seminiferous tubules, as Zn also plays a pivotal function in the post-testicular maturation of spermatozoa [28]. According to Protić et al. (2022), ZIP transporters exhibit heterogeneous expression patterns in ejaculated spermatozoa from normozoospermic and asthenozoospermic samples, with distinct compartmental and sub-compartmental immunolocalization. This may reflect

their different functions in sperm integrity, motility, and overall post-testicular functional competence in humans [29]. Veselinović et al. (2025) reported no significant differences in serum and seminal plasma Zn levels between normozoospermic and teratozoospermic men, as well as comparable ZIP6 and ZIP14 immunoexpression in ejaculated spermatozoa of men whose female partners achieved pregnancies, highlighting the need for larger studies to further investigate the significance of Zn transporters in reproductive outcomes [30]. Zn plays a pivotal part in the terminal differentiation of spermatids, where it facilitates nuclear DNA condensation and stabilization. By binding to protamines, Zn promotes the formation of disulfide bonds that reinforce chromatin architecture, ensuring proper genomic packaging and structural integrity during sperm maturation [27, 31]. A decline in testicular Zn levels has been associated with pathological alterations, including compromised Leydig cell populations, reduced testicular mass, and increased susceptibility to oxidative lipid damage. Furthermore, Zn depletion disrupts key transcriptional and translational processes, leading to impaired DNA integrity and defective spermatogenesis [27]. This underscores the indispensable role of Zn in maintaining protein homeostasis, nucleic acid synthesis, and overall sperm viability, all of which are critical determinants of fertilization success [32].

Zn deficiency impairs testicular development and endocrine function by disrupting steroidogenesis and increasing susceptibility to reactive species, thereby compromising the stability of membrane lipids, DNA, and intracellular proteins. These disruptions can precipitate a cascade of molecular imbalances, further exacerbating spermatogenic defects and diminishing male reproductive potential [33]. Additionally, studies highlight the competitive interplay between Zn and cadmium in the testes, revealing that reduced Zn uptake by spermatogonia allows cadmium to substitute Zn, thereby altering Zn-dependent enzymatic activity and compromising sperm differentiation and function [16].

At the peak of spermatogenesis, sperm maturation and storage occur in the epididymis and seminal vesicles, where Zn concentrations progressively increase within the surrounding tissue [34]. As a result, Zn becomes highly concentrated in the tail region of mature spermatozoa, where it plays an integral part in facilitating motility [6, 35]. Following their release from the testes, spermatozoa remain functionally immature and lack intrinsic defense mechanisms. Their progressive maturation, which confers full motility and fertilization competence, is orchestrated within the epididymal tubule, a tightly regulated microenvironment that governs biochemical and structural modifications. Beyond its function in sperm storage, the epididymis serves as a protective niche, safeguarding sperm from OS and preserving their viability between successive ejaculations. The

regulated decline in sperm Zn levels throughout epididymal transit is essential for the acquisition of progressive motility and chromatin decondensation, both of which are prerequisites for fertilization [17, 36].

Given their exceptionally high content of PUFAs, spermatozoa are particularly susceptible to oxidative damage, which can compromise membrane integrity, chromatin stability, and overall functionality. Notably, oxidative processes play a paradoxical part in sperm maturation—while controlled levels of oxidation are essential for epididymal remodeling, excessive OS disrupts key maturational events. This requires a finely tuned balance between beneficial redox signaling and peroxidative damage within the epididymal milieu. Zn is a pivotal modulator of oxidative equilibrium, mitigating lipid peroxidation and stabilizing sperm membrane integrity through direct interactions with sulfhydryl groups. By integrating into sperm membranes, Zn fortifies structural resilience, enhances antioxidant defense, and contributes to the preservation of fertilization potential. Additionally, Zn works in concert with enzymatic antioxidants, particularly glutathione peroxidases, to neutralize reactive species and prevent oxidative damage during epididymal transit. The intricate interplay between Zn homeostasis and the antioxidant defense system underscores its indispensable contribution in sustaining sperm viability and optimizing reproductive outcomes. At the same time, sperms are particularly susceptible to the effects of free radicals and lipid peroxidation due to the high concentrations of PUFAs in their plasma membranes. This susceptibility can impair their ability to mature, affecting the development of motility and chromatin condensation. In addition, Zn reduces lipid peroxidation in sperm [27, 37, 38]. Zn plays a key function by integrating into the sperm membrane through interaction with sulfhydryl groups, helping to stabilize the sperm membrane, form a protective barrier, and enhance fertilization potential [16].

The mechanism of Zn deficiency effect on male reproduction is shown in Fig. 1.

Seminal plasma is the liquid component of seminal fluid that serves as a medium facilitating sperm transport through the male reproductive tract and ultimately enables successful fertilization. Seminal Zn acts as a cofactor for the semenogelin, a primary structural protein responsible for seminal coagulation and subsequent liquefaction, processes essential for post-ejaculatory sperm release and motility. Both semenogelin and Zn are implicated in the modulation of sperm capacitation, a fundamental process that primes spermatozoa for oocyte recognition and gamete fusion [39]. In addition, Zn facilitates prostasome-spermatozoa membrane fusion, thereby promoting the efficient transfer of essential biomolecules that contribute to sperm motility and functional competence [16]. Beyond its direct influence on sperm physiology, Zn plays an important role

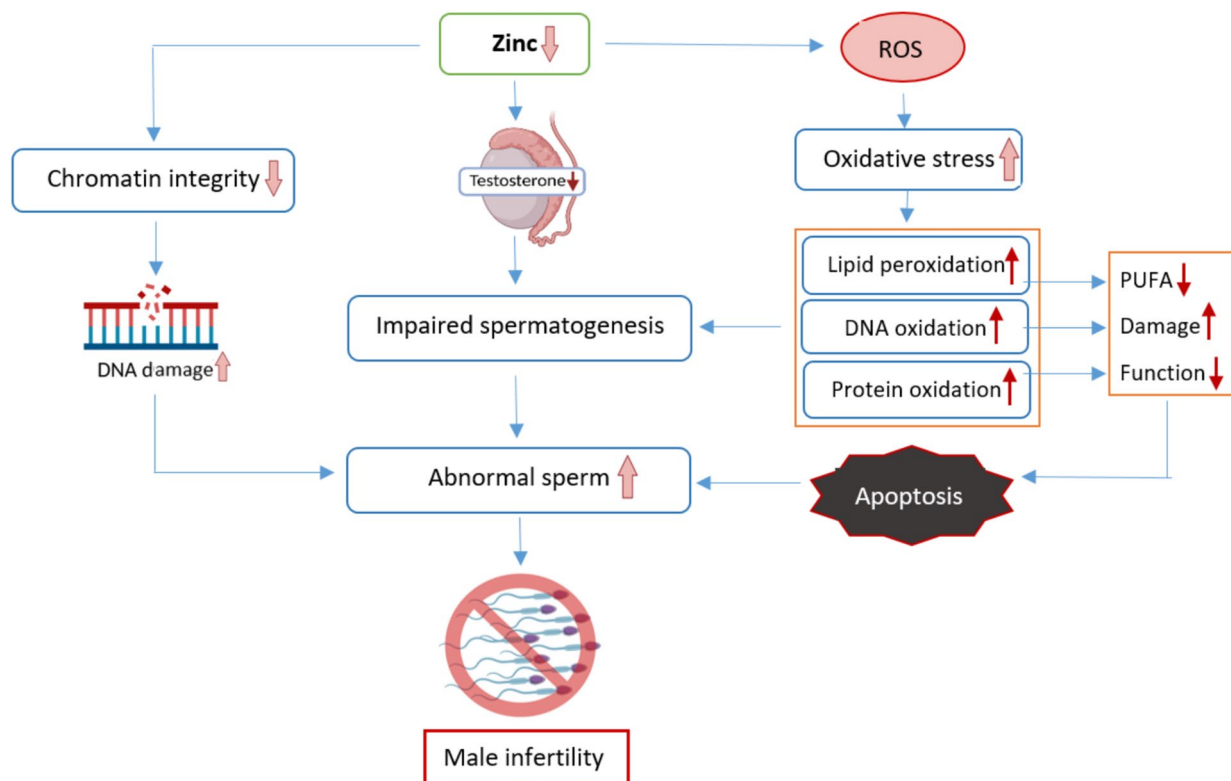


Fig. 1 The effects of seminal Zn deficiency on male reproduction

in the immune defense mechanisms of the male reproductive system. Within the prostate, Zn exhibits potent antimicrobial properties, mitigating the risk of bacterial colonization and infection during ejaculation [40]. This protective function is further reinforced through Zn-mediated stimulation of antimicrobial peptides, including kallikreins and lysozymes, which enhance the innate immune response of the prostate and seminal plasma [41]. The prostate serves as the primary source of seminal Zn, with prostatic secretions containing exceptionally high Zn concentrations, reaching approximately 500 µg/mL [27]. Studies have reported that Zn concentrations in seminal plasma are higher than those in blood serum [18, 42, 43]. The pronounced disparity between Zn levels in seminal plasma and those in blood serum, where Zn concentrations are substantially lower, suggests an active prostate-specific regulatory mechanism that governs Zn absorption and secretion. Prostatic epithelial cells efficiently extract Zn from circulation and incorporate it into seminal plasma, thereby creating an optimal biochemical microenvironment essential for sperm function [44]. Maintaining balanced Zn levels in seminal plasma is essential, as insufficient Zn can impair spermatogenesis, whereas excessive Zn may induce OS and other disruptions contributing to male infertility [45]. Moreover, ejaculation serves as a significant route for Zn excretion, underscoring

the importance of maintaining adequate Zn homeostasis to support reproductive function [18].

Despite its well-established role in male fertility, the precise mechanisms by which Zn deficiency disrupts spermatogenesis remain only partially elucidated. Several inter-related pathways have been proposed, including heightened reactive species generation and OS, diminished activity of key Zn-dependent enzymes such as carbonic anhydrase and zinc finger proteins (ZFP), dysregulation of tyrosine kinase activity (an enzyme essential for DNA synthesis), structural and functional damage to testicular cells, impaired steroidogenesis leading to reduced testosterone production and secretion, and increased rates of apoptosis within the testes [33]. These multifaceted disruptions collectively underscore the critical importance of Zn in sustaining optimal testicular function and overall male reproductive potential.

The Impact of OS on Zn Status and Male Infertility

OS, arising from an imbalance between reactive oxygen species (ROS) production and the capacity of endogenous antioxidant defenses, is strongly associated with sperm abnormalities and male subfertility [46]. Due to their unique biochemical composition and structural constraints,

spermatozoa exhibit heightened vulnerability to oxidative damage. Several intrinsic factors contribute to this susceptibility: (1) their plasma membranes are rich in PUFAs, rendering them highly prone to lipid peroxidation [47]; (2) their compacted chromatin architecture limits access to DNA repair mechanisms, thereby exacerbating the impact of oxidative DNA lesions; (3) they exhibit inherent deficiencies in intracellular antioxidant enzymes, further compromising their ability to counteract ROS-induced damage [48, 49].

Experimental evidence from Omu et al. (2015) [50] highlights the detrimental consequences of Zn deficiency on testicular function and spermatogenesis. Zn depletion caused a notable reduction in testicular volume in a Sprague–Dawley rat model, along with significant decreases in circulating levels of Zn, selenium, and magnesium, all essential for redox balance and the maintenance of spermatogenic homeostasis. In addition, the activity of the antioxidant enzymes was remarkably impaired as indicated by reduced levels of superoxide dismutase and glutathione peroxidase, alongside diminished concentration of vital regulatory molecules, including interleukin-4, Bcl-2 (B-cell lymphoma 2), and testosterone. Simultaneously, the levels of OS and apoptotic dysregulation markers were significantly elevated, including serum cadmium, malondialdehyde (a byproduct of lipid peroxidation), tumor necrosis factor- α , Bax (Bcl-2-associated X protein), caspase-3, and the rate of germ cell apoptosis. Another study by Sun et al. (2023) determined that a Zn-deficient diet leads to structural damage in spermatozoa in mice, increased DNA fragmentation, chromatin damage, elevated levels of malondialdehyde, and reduced levels of antioxidant enzymes, including superoxide dismutase, glutathione peroxidase, and Nrf2 factor. However, the authors found that these effects were partially reversible upon the restoration of a diet with adequate Zn intake, suggesting a potential for the recovery of reproductive function with proper Zn supplementation [51]. Collectively, these findings suggest that Zn deficiency compromises male reproductive potential via interrelated pathways involving oxidative damage, disrupted steroidogenesis, and apoptotic dysregulation.

Although Zn is redox-inactive, its pivotal role in oxidative defense is mediated through its interactions with a vast array of proteins and enzymes involved in cellular homeostasis [27]. Zn-containing proteins, broadly classified as metalloproteins, play crucial roles in antioxidant regulation and cellular protection. These proteins can be categorized into three principal groups: (1) gene regulatory proteins, (2) metallothioneins, and (3) metalloenzymes [52].

Gene regulatory proteins are a class of nucleoproteins that govern gene expression across diverse cellular processes, including spermatogenesis. From a structural perspective, they can be divided into three major classes: zinc fingers, zinc clusters, and zinc twists [52]. These transcriptional regulators are essential in modulating chromatin architecture

and gene accessibility. As mature spermatozoa are transcriptionally inactive, the transition from histone-based chromatin to a protamine-enriched structure is crucial for DNA condensation/packaging and transcriptional silencing. Protamines are the principal nuclear sperm proteins, comprising two types: protamine 1 (PRM1), encoded by a single-copy gene, and protamine 2 (PRM2), which plays a paramount role in maintaining sperm nuclear integrity [53]. Disruptions in this tightly regulated process have been implicated in male infertility. A review by Aliakbari et al. (2019) highlighted that the PRM1/PRM2 mRNA ratio was significantly elevated in infertile men compared to fertile controls, suggesting disrupted chromatin remodeling as a potential contributory factor [54]. In normal spermatogenesis, sperm chromatin undergoes a complex sequential remodeling process: testis-specific nuclear proteins are initially replaced by transitional proteins, which are subsequently displaced by protamines. Any deviation from this hierarchical transition may compromise DNA integrity, leading to defective sperm development and impaired fertilization potential. Studies have further shown that inadequate protamine incorporation results in aberrant chromatin packaging, rendering sperm DNA more susceptible to fragmentation and oxidative damage [55].

Beyond its structural role, protamine plays a role in epigenetic regulation, DNA repair, and genome integrity. According to Oliva (2006) [56], sperm chromatin condensation serves multiple functions beyond compaction, including protection of the paternal genetic material, epigenetic imprinting, and facilitating post-fertilization processes. Aberrations in protamine levels have been associated with an increased susceptibility to DNA damage, potentially compromising sperm viability and early embryonic development. Protamine deficiencies, whether arising from mutations in protamine genes or disruptions in their expression, have been linked to various forms of male infertility, as evidenced in transgenic mouse models exhibiting defective sperm morphology and compromised reproductive outcomes [57]. The significance of protamine balance is further underscored by Spiess et al. (2016) [55], who emphasized its relevance in assisted reproduction, particularly in intracytoplasmic sperm injection. The meta-analysis showed that subfertile men have significantly altered PRM1/PRM2 ratios, which correlate positively with increased sperm DNA fragmentation. Dysregulation of protamines causes chromatin disarray, rendering spermatozoa unable to protect themselves against OS, ultimately exacerbating male reproductive dysfunction. Moreover, a study by Zalata et al. (2016) found that PRM2 gene expression, encoding a protein essential for sperm chromatin stability, was markedly reduced in immature sperm from both fertile and infertile men. Concurrently, caspase-9 activity was significantly elevated, suggesting an association between altered protamine expression and

apoptotic initiation. Given its critical involvement in chromatin remodeling, PRM2 has been proposed as a potential biomarker for assessing sperm quality and predicting fertilization success [58]. These insights highlight the pivotal role of gene regulatory proteins, particularly protamines, in maintaining chromatin organization and ensuring sperm DNA stability. Given their reliance on Zn-dependent transcriptional regulators, proper Zn homeostasis emerges as a crucial factor in modulating nuclear architecture and sustaining the functional integrity of male gametes.

Zn plays a fundamental role in the structure and function of ZFPs, a vast family of transcription factors essential for gene regulation, DNA binding, RNA packaging, and the expression of genes critical for sperm development and quality [16, 33]. These proteins contain highly conserved cysteine- and histidine-rich domains that facilitate Zn binding, enabling their structural stability and interaction with DNA [59]. ZFPs are categorized into multiple subfamilies, including C₂H₂-type ZFPs, glucocorticoid receptor-associated Zn fingers, ring finger proteins, and GATA-type factors, each implicated in distinct regulatory processes. Within the context of male reproductive biology, over 20 ZFPs have been identified as key modulators of spermatogenesis, with functions spanning from meiosis to postmeiotic differentiation. Notably, C₂H₂-type Zn finger genes such as ZFY (Zinc Finger Protein, Y-linked) and ZFX (Zinc Finger Protein, X-linked) reside on the Y and X chromosomes, respectively, while autosomal counterparts, including Zfp-35, Zfp-29, and Zfp-37, are predominantly expressed during pachytene spermatocyte and round spermatid stages, highlighting their involvement in meiotic and postmeiotic sperm development [59, 60].

The KRAB (Krüppel-associated box) domain, positioned at the NH₂ terminus of KRAB-ZFPs, functions as a potent transcriptional repression module. It exerts its regulatory effects by interacting with the scaffold KRAB-associated protein 1 (KAP-1), which serves as a recruitment platform for chromatin-modifying complexes, including histone deacetylases and heterochromatin-associated proteins. This interaction facilitates gene silencing at target loci, thereby modulating developmental and differentiation processes. The widespread presence of KRAB-ZFP genes in the human genome underscores their evolutionary significance in transcriptional regulation and epigenetic control, particularly in tissues with high cellular turnover, such as the testis. Among the KRAB-ZFP subfamily, several members have been implicated in male fertility [61]. ZNF230 (one of Zinc finger proteins), for example, encodes two transcript variants: a ubiquitously expressed 4.4-kb isoform and a testis-specific 1-kb isoform. The latter is notably absent in fetal testes and azoospermic patients, suggesting a specialized role in sustaining normal spermatogenic progression [59]. These findings suggest that members of the KRAB-ZFP

family may exert transcriptional control over genes critical for germ cell differentiation and maturation.

Zn²⁺ is present in all six classes of enzymes (i.e., oxidoreductases, transferases, hydrolases, lyases, isomerases, and ligases) and is required for the function of more than 300 enzymes [52]. A significant example is the metalloenzyme superoxide dismutase (SOD), a key homodimeric antioxidant enzyme that catalyzes the conversion of superoxide anion (O₂⁻) into hydrogen peroxide (H₂O₂) and molecular oxygen (O₂), thereby reducing the toxicity of ROS [62, 63]. In mammals, three distinct SOD isoforms have been identified: cytosolic Cu/Zn-SOD (SOD1), mitochondrial SOD (SOD2), and extracellular SOD (SOD3) [52]. Zn is an essential cofactor for the Cu/Zn-SOD enzyme, which has antioxidative properties critical for sperm survival and function [64]. Moreover, Zn helps mitigate OS by binding to SH groups in proteins and occupying Cu-binding sites in lipids and DNA [33, 65]. Veselinovic et al. (in press, 2025) examined OS biomarkers between pregnancy and non-pregnancy groups of both male and female patients undergoing the assisted reproductive technology process and found that prooxidant, antioxidant, and oxy scores were similar in the groups [66]. However, some studies on this topic indicate a predominantly negative role of OS markers in semen quality and male fertility [67].

Zn has a strong affinity for metallothioneins which are primarily located in the cytoplasm. Marin de Jesus et al. (2024) [27] described the antioxidant mechanism of Zn as follows: Zn enters the cell through ZIP and binds to thioneins to form metallothioneins. Then, free Zn is recognized by the metal regulatory transcription factor (MTF-1), a protein with six Zn-finger domains. Zn binding to MTF-1 enables its translocation to the nucleus, where it binds to metal response elements in promoter regions [68] to perform important functions, such as protecting DNA from oxidative damage and interacting with transcription factors [69], particularly thioneins and some Zn transporters, like ZnT-1 [62, 68]. Additionally, nuclear factor erythroid 2 (Nrf2) is a Zn-sensitive transcription factor with a Zn-finger structure. When Zn binds to Nrf2, the complex translocates to the nucleus and interacts with antioxidant response elements, upregulating the expression and transcription of various antioxidant proteins. Thus, both MTF-1 and Nrf2 rely on Zn to regulate the expression of MTs, antioxidants, and other proteins that directly neutralize free radicals [27].

The Role of Zn in Lipid Profile and Male Infertility

Sperm quality and fertility are closely associated with the composition of fatty acids (FAs) in the sperm membrane [70, 71]. Human sperm contain approximately 30 distinct

FAs, including saturated fatty acids (SFAs), monounsaturated fatty acids (MUFAs), and PUFAs, predominantly omega-6 and omega-3 PUFAs [72]. Previous studies on sperm FA content in men with abnormal seminal parameters [73, 74] reported negative correlations between the ratios of arachidonic acid to docosahexaenoic acid (AA:DHA) and between arachidonic acid to eicosapentaenoic acid (AA:EPA) and total sperm count, motility, and morphology. These findings suggest that infertile men had lower omega-3 FAs concentrations in spermatozoa compared to their fertile counterparts. A recent study indicated that normozoospermic samples contained significantly higher total omega-3 PUFA content than samples from men with oligozoospermia, asthenozoospermia, or oligoasthenozoospermia [75]. Similar observations have demonstrated that infertile men generally exhibit lower omega-3 PUFA levels and higher omega-6/omega-3 PUFA ratios in their sperm compared to fertile men [76]. According to Zerbinati et al. (2016), DHA content in sperm is about six times higher than in seminal plasma [70]. Moreover, several studies have reported that normozoospermic individuals tend to have high levels of DHA in their sperm [70, 73, 74]. A correlation between the ratio of SFAs to MUFAs and sperm quality has been established, particularly with regard to progressive motility and sperm concentration. This is likely attributed to the higher proportion of SFAs, which are less prone to oxidative damage due to their lack of double bonds, compared to MUFAs, which contain a single double bond in their aliphatic chain. Furthermore, it is well established that the susceptibility of FAs to radical formation increases with the degree of unsaturation [72]. In a study by Collodel et al. (2020), higher levels of oleic acid, total MUFAs, and palmitic acid were associated with increased sperm necrosis and a reduced fertility index, as well as a decline in sperm concentration, progressive motility, normal morphology, and vitality in both fertile and infertile populations [77]. Given the synergistic relationship between Zn and essential FAs, deficiencies in both can lead to similar clinical manifestations [78], highlighting the importance of Zn in PUFA metabolism. Zn contributes to membrane flexibility, and studies have shown a positive association between Zn supplementation and increased PUFA content in red blood cell membranes [78]. Dietary patterns rich in Zn and PUFAs have been linked to the serum ratio of linoleic acid (LA) to dihomo- γ -linolenic acid (DGLA), which is proposed as a biomarker for Zn status [79]. In the study investigating an association between Zn intake and PUFAs profiles in dyslipidemic subjects, an inverse correlation was observed between the LA:DGLA ratio and dietary Zn status [80]. The metabolism of endogenous FAs is regulated by desaturase enzymes (D5, D6, and D9), for which Zn acts as a cofactor, as well as for elongases involved in FA synthesis. Consequently, Zn deficiency can impair enzyme activity disrupting

FA metabolism [80]. The conversion of LA to its metabolites, gamma-linolenic acid and DGLA, is influenced by the availability of trace elements, with higher Zn levels generally promoting enhanced desaturase enzyme activity [81]. Additionally, low levels of omega-3 PUFA have been shown to reduce mitochondrial RNA expression, which is important for regulating mechanisms that protect against obesity [80].

However, the synergistic interplay between Zn and lipid status in male infertility remains largely underexplored. While some studies have investigated the relationship between blood Zn levels and lipid status in obese men and their impact on sperm quality, this specific interaction between Zn status and male infertility requires further investigation.

In infertile overweight men, notable reductions in sperm motility, viability, and seminal Zn levels have been observed [82]. Calderon et al. (2020) investigated the correlation between serum Zn levels and sperm quality in obese male patients following metabolic surgery. The study found that 33% of the men exhibited serum Zn deficiency, and serum Zn levels were positively correlated with progressive sperm motility. The authors suggested that the lack of improvement in sperm quality may be due to nutrient malabsorption, particularly Zn [83]. In overweight and obese men, elevated seminal Zn levels in semen appear to exert a protective role by mitigating oxidative stress caused by excess body fat [84]. These findings suggest that Zn deficiency may disrupt enzyme activity and interfere with PUFA metabolism, leading to lower PUFA levels and diminished Zn status in infertile men. However, research in this area is limited and further studies are required to elucidate the underlying mechanisms.

Deficiency in Serum and Seminal Plasma Zn Concentrations and Seminogram Parameters

Our review of studies examining serum Zn concentrations in men with normozoospermic and altered seminograms reveals conflicting results. Despite only 1% of the body's total Zn being present in circulation, serum Zn concentrations are widely recognized as a biomarker for assessing dietary Zn intake, supplementation, and clinical deficiency [85]. Blood plasma/serum Zn, regarded as the most widely accepted and reliable indicator of population-level Zn status, is particularly responsive to severe Zn deficiency, though mild to moderate Zn deficiency often remains undetected [86]. The study by Wang et al. (2024) provided a comprehensive review of biomarkers used to assess Zn nutritional status (body fluid Zn levels, tissue Zn levels, Zn dependent proteins, Zn containing enzymes), highlighting the challenges of diagnosing mild Zn deficiency due to nonspecific symptoms and biomarker limitations [87]. Takić et al. (2021)

reported a negative correlation between dietary Zn intake, serum Zn status, and the ratio of certain micronutrients in a cohort of 40 adult Serbian patients undergoing hemodialysis [71]. Telišman et al. (2000) observed a positive correlation between serum Zn concentration ($971 \pm 125 \mu\text{g/L}$) and sperm count in healthy controls [88]. Similarly, Muhamadamin et al. (2011) found a positive correlation between serum Zn concentration and both sperm count and motility, with serum Zn levels being significantly higher in the normozoospermic control group ($921.2 \pm 17.65 \mu\text{g/L}$) compared to infertile men ($506.7 \pm 11.77 \mu\text{g/L}$) [89]. Wong et al. (2001) also reported weak positive correlations between serum Zn levels and sperm concentration, motility, and morphology in both fertile ($1359 \pm 222 \mu\text{g/L}$) and subfertile men ($1314 \pm 196 \mu\text{g/L}$) combined [90]. Similarly, Chia et al. (2000) reported no significant differences in serum Zn concentrations between fertile ($7570 \pm 1000 \mu\text{g/L}$) and infertile ($7130 \pm 1000 \mu\text{g/L}$) men [91]. In contrast, a study by Hibi et al. (2022) found significantly higher serum Zn concentrations in normozoospermic subjects compared to azoospermic and cryptozoospermic subjects [12]. In contrast, Fatima et al. (2017) reported lower serum Zn concentrations in fertile men ($683.9 \pm 143.7 \mu\text{g/L}$) compared to infertile men ($758.3 \pm 174.1 \mu\text{g/L}$) [92]. Osadchuk et al. (2021) found no significant correlation between serum Zn levels and sperm parameters, including total sperm count, sperm concentration, progressive motility, and normal morphology [43]. Evaluations of blood plasma Zn concentrations in the study by Hibi et al. (2022) showed that normozoospermic subjects had significantly higher serum Zn concentrations than azoospermic and cryptozoospermic subjects; however, in the study by Hibi et al. (2022), the serum Zn concentrations were not correlated with the sperm parameters (sperm concentration and motility) [12].

The results concerning serum Zn concentrations remain inconclusive, as serum samples provide only transient information regarding blood Zn levels. While serum Zn concentrations may offer some insights into Zn status, they may not serve as reliable biomarkers of dietary Zn intake in infertile men, primarily due to the body's regulatory mechanisms and the influence of various external factors. For more robust data, it is essential to assess Zn concentrations in seminal plasma, as it serves as a more accurate indicator of male reproductive health. Future, comprehensive studies focusing on the relationship between serum Zn concentrations and semen parameters are required to resolve the existing uncertainties.

Several studies have reported elevated Zn concentrations in the seminal plasma of healthy individuals, with values ranging from 78.9 to 274.6 mg/dL [23, 64, 93]. However, a recent review from Zečević et al. (2025) highlighted that seminal plasma Zn levels ranging from 100 to 200 mg/L can generally be considered indicative of adequate Zn status

in fertile men globally [45]. Numerous studies have found lower seminal plasma Zn concentrations in infertile men compared to their fertile counterparts [64, 91, 94–96]. Specifically, Altaher et al. (2015) observed a significant reduction in seminal plasma Zn levels in oligozoospermic and azoospermic infertile males compared to fertile controls [97]. A meta-analysis by Taravati et al. (2015) found that seminal plasma Zn concentrations were reduced in asthenozoospermic infertile men [96]. Similarly, a systematic review and meta-analysis by Zhao et al. (2016) concluded that Zn concentrations were significantly lower in infertile men compared to fertile men. Notably, this review highlighted that Zn deficiency is a contributing factor to sperm dysfunction and male infertility [23]. Chia et al. (2000) investigated the relationships between seminal plasma Zn concentrations and sperm quality in fertile men ($274.6 \pm 1.4 \text{ mg/L}$) and infertile men ($183.6 \pm 1.6 \text{ mg/L}$) and found that all sperm parameters (sperm density, motility, and viability) except semen volume were significantly lower in the infertile men than in the fertile men [91]. The same authors found the mean level of seminal plasma Zn in fertile men (275 mg/L), which is a much higher finding than in other reviewed studies.

Several studies have reported higher seminal plasma Zn concentrations in normal semen samples, with positive correlations to seminogram parameters, including sperm count, concentration, motility, and morphology [90, 98]. Osadchuk et al. (2021) found that men with normal semen quality ($n = 375$) had higher seminal Zn concentrations ($113.1 \pm 67.99 \text{ mg/L}$) compared to those with lower semen quality ($n = 251$, $87.3 \pm 56.6 \text{ mg/L}$), with a positive correlation to sperm count, concentration, motility, and morphology [43]. Mankad et al. (2006) observed a significant positive correlation between seminal Zn levels and sperm count in both fertile ($n = 55$) and infertile ($n = 20$) men [99]. Fatima et al. (2017) found a positive correlation between seminal plasma Zn and all semen parameters in fertile men, while in infertile men, Zn was negatively correlated with semen parameters, except sperm morphology [92].

Conversely, Dissanayake et al. (2010) reported higher seminal Zn levels in asthenozoospermic patients ($142.98 \pm 92.98 \text{ mg/L}$) compared to normal motility groups, but no significant differences in Zn levels were observed between normal and subnormal semen quality groups [93]. Similarly, Hashemi et al. (2018) found no significant differences in Zn levels between normozoospermic and asthenozoospermic men, suggesting that Zn does not impact sperm quality or motility [100]. Abudl-Rasheed (2009) and Eggert-Krusse et al. (2002) also found no significant correlation between seminal Zn and semen quality parameters such as sperm count, motility, or morphology [101, 102]. Marzec et al. (2010) similarly found no significant differences in seminal Zn between normozoospermic and pathological seminogram groups [103].

Atig et al. (2012) found a significant negative correlation between Zn concentrations and the percentage of abnormal sperm in asthenozoospermic and oligoasthenoteratozoospermic men. They suggested that physiological Zn levels improve sperm motility and concentration, while excessively high Zn concentrations may adversely affect sperm morphology [104]. Chen et al. (2024) identified a positive relationship between Zn concentrations and sperm motility but noted that both Zn deficiency and excess can impair motility, possibly due to cytotoxicity induced by high Zn levels in Germ Cell- 2 cells [105].

In summary, the existing literature highlights inconsistencies in the relationship between seminal plasma Zn concentrations and sperm quality, indicating the need for further studies to resolve these discrepancies. Current evidence suggests that both Zn deficiency and excess can negatively affect sperm integrity and quality, underscoring the importance of maintaining optimal Zn levels for male reproductive health. Future research is important to better understand the precise role of Zn in semen quality and its potential as a therapeutic target for male infertility.

Effect of Zinc Supplementation in the Treatment of Male Infertility

The effectiveness of Zn supplementation in improving pregnancy rates in humans remains inconclusive [6]. A human *in vitro* study involving semen samples from 24 normozoospermic and 20 oligozoospermic men demonstrated a direct protective effect of Zn, D-aspartate, and coenzyme Q10 in mitigating motility decline, DNA fragmentation, and lipid peroxidation [49]. Multiple studies suggest that men with adequate Zn intake exhibit fewer sperm abnormalities compared to those with lower Zn levels [22, 49, 106]. Table 1 provides an overview of studies conducted between 2000 and 2024, summarizing the effects of Zn supplementation on sperm parameters, including Zn dosages, treatment durations, and the results obtained.

A review article from Agarwal and Sekhon (2011) suggested that Zn therapy may benefit the treatment of idiopathic oligoasthenoteratozoospermia by reducing OS, sperm membrane damage, and DNA fragmentation [22]. Akbari et al. (2023) found Zn to be an effective supplement in counteracting the effects of diabetes on sperm parameters, and DNA integrity in diabetic infertile men [112]. A randomized clinical trial by Alsaman et al. (2020) showed that

Zn supplementation (ranging from 66 to 500 mg) improved semen quality in infertile men [111]. Ensuring adequate Zn intake through oral supplementation or food fortification is essential to prevent the adverse effects of Zn deficiency [113]. A combination of element-based antioxidants, including Zn and selenium, may help mitigate OS by inactivating ROS and reducing their production through enzymatic activity [32]. Studies on combined Zn and folic acid supplementation have yielded inconsistent results. For instance, a systematic review by Li et al. (2023) found no significant improvements in sperm characteristics with folic acid and Zn supplementation [21]. Similarly, Schisterman et al. (2020) found no improvement in sperm quality or pregnancy rates from folic acid and Zn supplementation in 2370 couples [114]. Raigani et al. (2014) also showed no benefit from Zn sulfate and folic acid supplementation in infertile men with severely impaired sperm parameters [109]. Current research suggests that taking Zn alone can improve the quality of seminal fluid. However, combinations of Zn with other vitamins, such as folic acid, have not consistently demonstrated similar benefits. To establish clear guidelines, well-designed randomized controlled trials are essential to evaluate the efficacy of Zn supplementation, both independently and in combination with other nutrients. Relevant institutions have provided validated recommendations on Zn supplementation dosages for adult men, as summarized in Table 2.

It can be observed that recommendations vary from region to region but generally fall within a certain range. It can be hypothesized that the most optimal effects would be achieved by formulating individualized dosages.

Conclusion

In conclusion, this review highlights that Zn deficiency can disrupt spermatogenesis and contribute to male infertility. Evidence suggests that Zn deficiency may impair enzyme activity and interfere with lipid metabolism; however, the synergistic relationship between Zn and FAs in infertility warrants further investigation. Measuring Zn levels in semen/seminal plasma and/or blood (whole blood, serum/plasma) in infertile men could provide valuable diagnostic and therapeutic insights. While Zn supplementation shows promise in improving male infertility, further well-designed, randomized, double-blind trials are necessary to better define Zn's role and optimize its therapeutic use in male infertility management.

Table 1 Studies investigating the effects of Zn supplementation on sperm parameters from 2000 to 2024

Study	Trial design	Country	Participants	Duration	Dose and treatment	Results
Wong, 2002 [107]	Double-blind placebo-controlled trial	The Netherlands	108 fertile and 103 infertile men	26 weeks	Treatments applied: folic acid and placebo, Zn sulfate and placebo, Zn sulfate and folic acid, and two placebos. Folic acid was given at a daily dose of 5 mg, and Zn sulfate was given at a daily dose of 66 mg	Total normal sperm count increased after combined Zn sulfate and folic acid treatment in both subfertile and fertile men
Ebisch, 2006 [108]	Double-blind placebo-controlled trial	The Netherlands	47 fertile and 40 subfertile men	26 weeks	A group receiving 5 mg/day folic acid and 66 mg/day ZnSO ₄ ; and placebo	Folic acid and Zn sulfate supplementation may have a beneficial effect on sperm characteristics, particularly motility and concentration, but the effects on hormone levels were less pronounced
Raigani, 2014 [109]	Double-blind trial	Iran	83 oligoasthenoteratozoospermic men	16 weeks	Folic acid (5 mg/day) and Zn sulfate (220 mg/day), or placebo	Zn sulphate and folic acid supplementation did not ameliorate sperm quality in severely compromised sperm parameters of infertile men
Hadwan, 2014 [110]	Randomized controlled trial	Iraq	60 fertile and 60 asthenozoospermic infertile men	3 months	Zn sulfate; 220 mg per day for subfertile group	Zn supplementation restored peroxynitrite levels, arginase activity and nitric oxide synthase activity and improved semen parameters
Alsalmán, 2020 [111]	Randomized controlled trial	Iraq	60 fertile and 60 asthenozoospermic subfertile men	13–26 weeks	Zn sulfate 66 to 500 mg	There were significant improvements in ejaculate properties in the group treated with Zn compared to the same group before treatment with Zn
Schisterman, 2020	Randomized controlled trial	United States	1185 in the intervention group, 1185 in the placebo group	6 months	5 mg/day of folic acid and 30 mg/day of elemental Zn or placebo	The supplementation did not result in any significant differences in live birth rates between the group receiving folic acid and Zn supplementation and the placebo group, nor did it result in substantial improvements in sperm count, motility, or morphology

Table 2 Relevant institutions recommendations for daily Zn intake for adult men

Organization/region	Recommended daily Zn intake (mg)	Reference
Europe		
European Food Safety Authority (EFSA)	9.4–16.3	[115]
British National Health Service (BNHS)	9.5	[116]
National Institutes of Health (NIH)	11	[117]
Centers for Disease Control and Prevention [118]	11	[118]
Asia		
China National Health and Family Planning Commission (NHFPC)	12.5	[119]
Ministry of Health, Labour and Welfare of Japan	10	[120]
Indian Council of Medical Research [121]	17	[121]
Australia		
National Health and Medical Research Council [122]	14	[122]
Global		
World Health Organization (WHO)	4.2–14.0	[123]
Food and Agriculture Organization [124]	11	[124]

Abbreviations: *EFSA*, European Food Safety Authority; *BNHS*, British National Health Service; *NIH*, National Institutes of Health; *CDC*, Centers for Disease Control and Prevention; *NHFPC*, China National Health and Family Planning Commission; *ICMR*, Indian Council of Medical Research; *NHMRC*, National Health and Medical Research Council; *WHO*, World Health Organization; *FAO*, Food and Agriculture Organization.

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Declarations

Conflict of Interest The authors declare no competing interests.

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