

Importance of Zinc in Human Health: A Comprehensive Review

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Abstract

Zinc is an indispensable trace mineral that plays a fundamental role in human physiology. It modulates numerous biological processes in the human body. It is found to be involved in cellular metabolism, maintaining immunity, linear growth, development of reproductive organs, repair mechanisms, structural integrity in proteins and cell membranes and many more. Zinc is present as a catalytic, structural, and regulatory component in more than 300 enzymes and numerous transcription factors for DNA synthesis, protein synthesis, wound healing, and immune defense mechanisms. Generally, malnutrition and a cereal-based plant diet result in zinc deficiency in humans due to lower bioavailability. Zinc deficiency affects nearly two billion people worldwide. Deficiency of zinc has been associated with growth retardation, impaired immune response, cognitive dysfunction, reproductive disorders, and increased susceptibility to infections. This review discusses the biological importance of zinc, its physiological roles, dietary sources, consequences of deficiency and measures to prevent zinc related disorders that might be a useful guide.

Keywords: Trace Element; Zinc Containing Enzymes; Zinc Fingers; Zinc Sources; Zinc

Introduction

Zinc is an essential trace element required for the proper functioning of numerous biological processes in the human body. In earth's crust it is the 24th most abundant element and in the human body it is second most abundant element after iron. Zinc has filled 3d electronic configuration with two electrons in the outer 4s shell. The Zn^{2+} state is highly stable with respect to redox reactions and so does not participate in physiological redox reactions. Due to the d^{10} electronic configuration, Zn^{2+} does not have any crystal field stabilization energy and thus has no preference towards octahedral or tetrahedral sites. Thus, Zn^{2+} is found in both tetra-coordinated and hexa-coordinated forms in biological medium and also can toggle easily between different geometrical forms during its course of action. It is present on the borderline of hard and soft acids and acts as a Lewis acid, lowering the pKa of the medium while avoiding the chance of electron transfer.

French physiologist Raulin first considered zinc to be an essential nutrient in the mid-nineteenth century while observing the growth of a fungus. In early twentieth century in Boston, a series of patients with liver cirrhosis were found to have a very low level of zinc. Nearly simultaneously, a distinct form of dwarfism was identified in Egypt and Iran, along with hypogonadism and delayed sexual development. A zinc supplement and balanced diet containing adequate animal protein initiated their rapid recovery. In 1973, the WHO published an estimated dietary requirement for different nutrients, which included zinc as an essential micronutrient. Many recent reviews (Consales *et al.*, 2024; Pratama *et al.*, 2026; Pavić Vulinović *et al.*, 2026) highlight the indispensable role of zinc for infants and also to prevent different diseases in adults.

Zinc has an exceptional ability to form strong bonds with ligands and can exchange ligands easily. The metal's flexibility towards coordination geometry makes it useful in biosystems. Zn^{2+} is ubiquitous within cells. Zinc is present in all tissues and body fluids and is required for the activity of many enzymes and transcription factors involved in cellular metabolism, immune regulation, and genetic expression.

However, it is not stored within cells, unlike other minerals, viz., iron, copper, etc., to reach a level of toxicity, so regular intake through a balanced diet is necessary. Approximately 10% of the human proteome is associated with expression of ~3000 zinc-containing proteins, including transcription factors. A healthy human body contains ~2-3 g of zinc mainly in the skeletal muscles and bones. Zinc helps to maintain cellular integrity, stability of cell membranes, defense mechanisms for immunity, metabolism of carbohydrates, proteins, lipids, and nucleic acids and involvement in cellular signaling pathways. The role of the mineral can be classified in three major categories: catalytic, structural and regulatory (Roohani *et al.*, 2013).

Biological Functions of Zinc

Zinc plays an indispensable role in a wide range of biological processes essential for human health. These functions can generally be classified into catalytic, structural, and regulatory roles (Lippard & Berg, 1997).

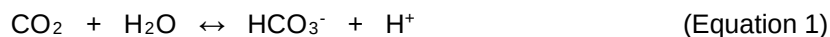
Catalytic Functions of Zinc

Zinc appears in the active site of many hydrolytic enzymes like carboxy peptidase A (for digestion of proteins by cleaving it from C-terminal side), carbonic anhydrase (a lyase hydrating CO₂), thermolysin (hydrolyzes peptide bonds specifically having hydrophobic amino acid side chain and endopeptidase), alcohol dehydrogenase (an oxidoreductase where Zn activates the substrate for redox reactions involving the cofactor NAD⁺), alkaline phosphatase, adenosine deaminase, etc.

Through its catalytic role, the positively charged Zn²⁺ lowers the pKa of coordinated water and provides a local high concentration of OH⁻, which is unavailable at physiological pH. In a similar manner, the positively charged metal center serves as a general Lewis acid for activation of substrate molecules, mostly by changing coordination. E.g., in carboxypeptidase, Zn²⁺ is coordinated to two imidazole side chains of two histidine residues and bidentate carboxylate residues of glutamic acid. The fifth coordination is to a water molecule, which is activated by Zn²⁺ and is the key feature of the enzyme mechanism. Protein side chains greatly assist the assembly of activated complexes interacting with metal centers. The rate of catalytic reaction is accelerated by internal attack within the coordination sphere of the metal ion or by rearranging the substrate ligand at the active site. The Zn²⁺ ion is uniquely suitable among biological transition metal ions to serve as a Lewis acid without participating in electron transfer reactions.

Zinc in Lyase Enzyme

The specific function of zinc in biological pathways was first recognized in 1939 while studying the catalytic reaction of carbonic anhydrase. At physiological pH the rate of reaction (Equation 1) is slow (~10⁻² s⁻¹) in the absence of a catalyst, while the rate is as high as ~10⁶ s⁻¹ in the presence of the enzyme. The Zn(II) is coordinated to three histidine imidazole side chains. The fourth coordinating site is occupied by a water or hydroxide to complete a distorted tetrahedral coordination sphere. Once the metal hydroxide unit is formed, binding of CO₂ can occur, followed by nucleophilic attack of hydroxide to produce a metal-bound bicarbonate. Then the product is displaced by water molecules.



Zinc in Hydrolytic Enzyme

In 1955 another zinc-containing protein was discovered carboxy peptidase A and then B, synthesized in pancreas. The zinc atom is situated well inside the surface of protein coordinated by two imidazole side chains of histidine residues and a bidentate carboxylate group of glutamic acid. In the fifth coordination site of Zn(II), a water molecule is attached, which is activated by the metal, giving a penta coordinated metal center. This step is the key feature of the enzyme mechanism. In the presence of a substrate, the carboxylate group of glutamic acid becomes nearly unidentate and rearranges to keep the coordination

number constant. This kind of mechanism is common to zinc as it does not have any structural preference.

Other well-known zinc-containing hydrolase enzymes are alkaline phosphatase that promote the reaction (Equation 2).

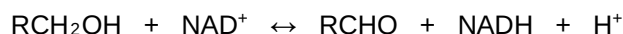


Here also a pair of Zn(II) ions serve as a general Lewis acid, polarizing the substrate and rendering it a better electrophile.

In addition to carboxypeptidases, zinc-dependent aminopeptidases that cleave N-terminal residues are also important in peptide hormone regulation and peptide homeostasis (Bhat, 2026).

Zinc in Oxidoreductase Enzyme

Generally, zinc is present in enzymes that do not undergo any redox reaction. However, there are few enzymes, like alcohol dehydrogenase, super dismutase, etc., where zinc is present as an activator but not participating in redox reactions. Liver alcohol dehydrogenase converts primary alcohols to aldehydes.



Alcohol is oxidized to aldehyde by essential coenzyme NAD^+ . Two zinc ions are found in different environments in the enzyme. One Zn(II) in the active site is coordinated to two cysteinate sulphur atoms, one histidine nitrogen atom and a water molecule. The other Zn(II) is bonded to four cysteine thiolate ligands and is inaccessible to solvent and plays a structural role. The zinc in the active site binds directly with alcohol substrate by loss of bound water and deprotonation of ligand to form RO^- . However, binding of coenzyme NAD^+ does not need the presence of Zn(II); rather, a change in conformation of the protein occurs from open to close form. This conformational change helps to position the substrate-binding pocket at an appropriate distance and orientation with respect to the coenzyme. This facilitates the crucial step in the enzyme mechanism, namely, the transfer of a hydride ion from α -carbon of the alcohol to the nicotinamide ring of NAD^+ to form NADH. Following hydride transfer, NADH dissociates from the enzyme. The role of zinc is twofold: firstly, deprotonation of alcohol substrate rendering it better hydride ion donor and secondly, positioning the substrate in the active site in a suitable way leading to direct hydride transfer to the coenzyme.

Superoxide dismutase is another oxidoreductase that contains Zn^{2+} along with copper. The copper toggles between +1 and +2 states to catalyze the disproportionation of superoxide, while Zn^{2+} is also essential for its activity. Coordination of a histidine ring nitrogen atom to Zn^{2+} lowers the pKa of other ring nitrogen atom and it prefers to bind to a proton rather than Cu^{2+} , which was initially bonded. Cu^+ reduces superoxide and itself turns to Cu^{2+} . Zn^{2+} helps to create the electric field gradient that attracts superoxide. Another possible role of Zn^{2+} is to confer thermal stability to superoxide dismutase. This suggests that zinc also has some anti-inflammatory properties that help to reduce oxidative stress.

Nucleotide Activation

Several zinc enzymes are involved in nucleic acid metabolism, especially phosphodiesterases and nucleases. Zn^{2+} is present in DNA and RNA polymerases, which catalyze the polymerization of mononucleotide triphosphate building blocks to form polymers. The exact mechanism is yet to be established. Additionally, zinc plays an important role in the synthesis and degradation of nucleic acids, which are essential for cellular replication and gene expression.

Structural Functions of Zinc

Zinc is found to be contained in transcription factor IIIA (TFIIIA) and plays a vital structural role, the central core of small nucleic acid binding domains, referred to as 'zinc fingers'. In TFIIIA the metal binding domain directly interacts with DNA. Many other classes of zinc-containing proteins are found to be involved in gene regulation. Most DNA and RNA polymerases contain Zn^{2+} ions.

TFIIIA is a site-specific DNA-binding protein that plays a central role in controlling the transcription of 5S ribosomal RNA genes in African clawed toad *Xenopus*. The role of Zn is twofold. The protein isolated from *Xenopus* oocytes contains two to three equivalents of zinc, which are much more tightly bound to the protein and are resistant to removal by dialysis of TFIIIA-5SRNA complex against chelating agent EDTA solution. However, when RNA is destroyed using a nuclease, then only Zn^{2+} can be replaced. Moreover, the protein binds DNA to a specific sequence of ~45 base pairs, which upon binding remain resistant to nuclease activity.

Analysis of amino acid sequence of TFIIIA led to an exciting hypothesis that amino acid sequence remains nearly constant, having two cysteine and two histidine residues, which are considered to be potential zinc-binding sites. These domains are called zinc fingers. The EXAF study reveals that two S atoms are 2.30 Å apart and two N atoms are at 2.00 Å apart, consistent with the tetrahedral structure of Zn^{2+} .

Regulatory Functions of Zinc

In addition to its catalytic and structural roles, zinc serves as an important regulator of cellular signaling pathways. Zn^{2+} ions are detected in synaptic vesicles that release upon stimulation outside the cell (Costa *et al.*, 2023). This suggests that perhaps Zn^{2+} acts as a carrier of information between the cells. Cells allow Zn^{2+} ions via transmitter-gated ion channels and regulate intracellular targets. Extracellular Zn^{2+} activates growth factor receptors that decide cell proliferation, differentiation, growth and apoptosis. These processes are essential for tissue development, immune responses, and the maintenance of overall physiological balance. Intracellular Zn^{2+} also participates in various signaling pathways. Intracellular zinc ions remain mostly bound to metallothionein and glutathione. It influences hormone release, nerve signal transmission, and immune system responses.

Versatile Role of Zinc and Its Source

One of the remarkable functions of zinc is that it has antiviral property and it plays an important role in maintaining a healthy immune system. Zinc influences both innate and adaptive immune responses and plays a crucial role in protecting the body against infections. Zinc is required for the normal development and function of immune cells such as neutrophils, macrophages, natural killer cells, and lymphocytes. Zinc acts as a key regulator in various organelles in the cell as its concentration in different cellular organelles varies in normal as well as stressed condition and the micronutrient helps in inter-organelle communications (Brito *et al.*, 2026). These cells form the primary defense mechanisms against invading pathogens. Zinc deficiency causes inefficient immune function and reduces the activity of immune cells that alter cytokine production, which leads to increased susceptibility to infections, e.g., respiratory illnesses like pneumonia, gastrointestinal infections like diarrhea, and viral diseases and also reduces neuropsychological performance. Recently a zinc supplement was found to result in a better healing response for COVID-19-affected patients (Pal *et al.*, 2020; Jin *et al.*, 2024).

Zinc regulates many important cellular events. It is used as a potential therapeutic agent against several diseases. It plays a crucial role in both intra and extracellular signaling pathways. Intracellular zinc is found mostly bound to sulfur-containing amino acids like methionine and glutathione and the concentration of free zinc varies from picomolar to nanomolar range. Intracellular zinc signaling can be classified into three kinds depending on their duration. The first one is an immediate or rapid response

where zinc is released from cells on stimulation and does not last long. The second kind of signal gets increased for nearly an hour after stimulation and the third type of signal is where zinc levels are altered several hours after the external stimulation. This last kind of signal is a late, non-immediate signal, dependent on the transcriptional regulation of zinc transporters, where intracellular concentration of zinc varies through one or more days. Zinc ions are detected in the presynaptic vesicles of neurons and released upon exocytic stimulation. The Zn^{2+} released is taken up by postsynaptic cells. Zn^{2+} can also enter the cell via transmitter-gated ion channels. Different secretory cells like endocrine and exocrine pancreas, mammary glands, prostate glands, intestine and platelet cells contain Zn ions in their vesicles.

Zinc has an important role in bone growth, too. Besides the main constituents of bone like calcium, magnesium and phosphorous, zinc is essential and its deficiency leads to linear growth retardation. Zn has a stimulatory effect on osteoblastic bone formation. Increased activity of a zinc-containing enzyme, alkaline phosphatase, is shown to increase calcium deposition. Zn^{2+} regulates both intracellular and extracellular Ca^{2+} ion concentration. Increase in Zn^{2+} ion concentration in cytoplasm controls Ca^{2+} concentration. The interaction between Zn^{2+} and Ca^{2+} seems to be bidirectional—the Zn^{2+} ion can alter Ca^{2+} and vice versa. Zinc also has a role to control diabetes. Insulin synthesis, storage and structural stability are controlled by zinc.

Human reproductive systems, both male and female, are highly controlled by zinc. It helps in development of male reproductive organs, testosterone hormone regulation, sperm cell production and hence fertility (Solomons, 2013). High zinc ion concentration is found in prostate gland and seminal fluid. In females zinc regulates ovarian function, menstrual cycle, different hormone secretion, egg development and fertilization. Zinc is proven to be very important during pregnancy for fetal growth and immune system development. Zinc oxide nanomaterials can be synthesized through various methods, viz., physical, chemical, biological or eco-friendly green methods and have been found to show antimicrobial, anti-inflammatory and anticancer activity (Maurya *et al.*, 2026). Even zinc-based bimetallic nanoparticles (with copper, silver, gold, and manganese) are found to show multiple biomedical activities (Fayed & Reda, 2026).

The main source of zinc is food found from animal proteins like red meat, chicken, eggs, fish, seafood and dairy products. The plant source includes legumes, whole grains, seeds, nuts, mushroom and leafy vegetables. However, presence of phytates in plant sources reduces zinc absorption in the intestine (Prasad, 1991). Fermentation, soaking, sprouting decrease phytates and improve zinc absorption. A recent review by Tokarczyk and Koch (2025) focuses on the bioavailability and corresponding bioaccessibility of zinc in various food materials. High temperature stress on rice can cause less bioavailability of zinc, which can be improved by using zinc oxide nanoparticles synthesized via a green method (Yadav *et al.*, 2026). Zinc ions and zinc-embedded carbon quantum dots are used recently to inhibit fumarase activity (Navaser & Kalhor, 2026).

Deficiency of Zinc and Supplementation

As zinc is an essential trace element, it is required throughout life, though in varied amounts, viz., the daily requirement for infants (2-3 mg), childhood (3-8 mg), adolescence (5-6 mg), pregnancy (11-12 mg), etc. Inadequate intake of food requires supplementation. Severity of common cold, respiratory infections, child diarrhea can be reduced using zinc supplementation (Alam *et al.*, 2023). Zinc supplements are widely used to improve health of pregnant women and infants (Diao *et al.*, 2025). Common symptoms of zinc deficiency are low birth weight, growth retardation, weak immunity, hair loss, skin problems, sexual impairment, etc (Hambidge, 2000). Moreover, zinc deficiency increases the possibility of heavy metal toxicity like cadmium, arsenic and lead (Wong *et al.*, 2025). Zinc oxide nanoparticles synthesized via an environmentally friendly green method are found to have prominent antimicrobial properties (Habtemariam *et al.*, 2026). Recent research on zinc supplementation in animals reveals that nano-ZnO

is much effective supplement than inorganic zinc oxide and Zn-lysine complex due to greater solubility in water and less precipitation in the gastrointestinal tract (Alipour *et al.*, 2026). Zinc dynamics across the trophic system have been investigated by a group of scientists to know the connection of its bioavailability in soil to plants and ultimately to human systems that might improve agriculture and hence health and nutrition (Mandal *et al.*, 2026).

Conclusion

The importance of zinc in human physiology is unquestionable. It is required for normal growth and development throughout the human life cycle. Starting from DNA synthesis, growth of new cells, survival, repair, proliferation, and even apoptosis—the participation of zinc is well established. The effect of zinc varies depending on cell type, its concentration, health condition and even under normal and pathological conditions. The demand of the body also varies depending on age, gender and physiological condition. Several disorders in humans appear due to deficiency of the mineral resulting from malnutrition that may induce other diseases. Zinc supplementation for much illness is observed to be lifesaving. The versatile role of zinc in preventing infection, diabetes, aging, neuropsychological impairment is well documented. Further research in this field will be helpful in exploring the therapeutic potential of the mineral for prevention and management of various diseases.

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