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ZINC AND HUMAN HEALTH: IMPLICATIONS OF ZINC DEFICIENCY IN IMMUNE, GASTROINTESTINAL, DERMATOLOGICAL, AND METABOLIC DISORDERS

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ABSTRACT

Zinc is an essential trace element involved in key biological processes, including enzymatic activity, gene expression, and immune regulation. Zinc deficiency remains a relevant health issue in specific populations and has been associated with the development and progression of several disease states.

This narrative review summarizes current evidence on the role of zinc in selected immune-related, gastrointestinal, dermatological, and metabolic disorders. Data from clinical and observational studies are discussed in relation to disease-specific outcomes, dosage, formulation, and population characteristics. The aim of this review is to provide an evidence-based overview of the clinical relevance of zinc supplementation in the context of human health and disease.

Methodology: This narrative review was conducted using a structured literature search to identify and analyze scientific publications addressing the role of zinc in human health and disease. The PubMed and Google Scholar databases were searched for relevant articles.

The search strategy included the following keywords: “zinc”, “zinc supplementation”, “zinc deficiency”, “human health”, “immune function”, “gastrointestinal disorders”, “dermatological conditions”, and “metabolic disorders”. Additional publications were identified through manual screening of reference lists of selected articles.

Clinical studies, observational studies, and relevant reviews published in English were considered for inclusion based on their relevance to the selected disease states and clinical outcomes.

KEYWORDS

Zinc, Zinc Supplementation, Zinc Deficiency, Human Health, Immune Function, Gastrointestinal Disorders, Dermatological Conditions, Metabolic Disorders

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Introduction

Zinc is a key micronutrient that contributes to the structural integrity and activity of numerous proteins, enzymes, and transcription factors, while inadequate zinc status is associated with diverse clinical manifestations.[1] Substantial evidence indicates that zinc deficiency represents a significant global health issue and is more prevalent than health problems related to excessive zinc exposure. Both acute and chronic zinc deficiency occur in human populations and are likely more widespread than is commonly acknowledged.[2] Due to its role in numerous physiological processes, zinc deficiency has been associated with the development and progression of various disease conditions.[3]

Disrupted zinc homeostasis has been associated with dysfunction across multiple physiological systems, including immune, gastrointestinal, dermatological, and metabolic pathways, with clinical and observational studies indicating a potential impact of zinc status on disease outcomes in these conditions. [1,4]. This narrative review aims to critically evaluate existing evidence on the involvement of zinc in immune-related, gastrointestinal, dermatological, and metabolic conditions, emphasizing clinical outcomes and therapeutic implications.

Biological functions of zinc

Zinc and immune regulation

Zinc plays an important role in the regulation of the immune system, which is particularly sensitive to changes in zinc status. Zinc deficiency affects both innate and adaptive immunity, leading to impaired first-line defense mechanisms against invading pathogens. In innate immune responses, zinc deficiency is associated with reduced chemotaxis, phagocytosis, and pathogen elimination by immune cells, as well as dysregulation of inflammatory responses through increased production of proinflammatory cytokines. [5]

With regard to adaptive immunity, inadequate zinc levels are linked to thymic atrophy, decreased numbers of T and B lymphocytes, and reduced antibody production, resulting in a weakened immune response.[6]

Zinc and epithelial barrier function

Zinc is a key element involved in the maintenance of epithelial barrier integrity and proper barrier function, with particular importance for the gastrointestinal tract and the skin. Adequate zinc availability is necessary for normal epithelial cell proliferation and differentiation, as well as for the preservation of tight junction structures, which play a central role in ensuring barrier stability and supporting tissue repair processes. [7,8]

Within the skin, zinc contributes to keratinocyte activity, collagen formation, and wound repair, thereby playing an important role in maintaining structural integrity and supporting regenerative processes. Consequently, disturbances in zinc status may impair epithelial barrier function in both gastrointestinal and dermatological tissues. [9,10]

Zinc and Metabolic Regulation

Zinc contributes to the control of various metabolic pathways by acting as a structural and catalytic element of numerous enzymes. Both experimental and clinical studies indicate that disruptions in zinc homeostasis may affect metabolic function, especially in disorders associated with chronic inflammation and increased oxidative stress. [11]

Adequate zinc status is required for proper glucose metabolism, insulin synthesis, and insulin signaling, indicating its importance in metabolic homeostasis. Zinc deficiency has been associated with impaired insulin sensitivity, altered lipid metabolism, and increased oxidative stress, which may contribute to the development of metabolic disturbances.[12]

Role of Zinc in Selected Diseases

Zinc and Immune-Related Disorders

Several randomized and observational studies suggest that correcting zinc deficiency can improve selected immune parameters and clinical outcomes in immune-related disorders, although the magnitude of effect varies depending on baseline zinc status and disease context.[13]

During infection, circulating zinc levels are significantly decreased as part of the inflammatory response. This process is largely mediated by proinflammatory cytokines, particularly interleukin-6, which induces the expression of the zinc transporter ZIP14 in hepatocytes, resulting in hepatic sequestration of zinc bound to metallothionein.[14] Neutrophils also release calprotectin, a heterodimer composed of S100A8 and S100A9, which contributes to antimicrobial defense by limiting zinc availability and thereby inhibiting the growth of *Staphylococcus aureus*. In addition, neutrophils form neutrophil extracellular traps (NETs) consisting of DNA, chromatin, and granular proteins that serve to capture and eliminate invading microorganisms. During NETosis, calprotectin is released in high concentrations and may be incorporated into NET structures or remain in the surrounding extracellular environment.[15,16]**.**Administration of zinc in the form of lozenges at daily doses of at least 75 mg has been shown to shorten the duration of common cold symptoms in otherwise healthy individuals.[17]

Tuberculosis, lepromatous leprosy and leishmaniasis are examples of diseases caused by intracellular pathogens.

Th1 cells stimulate the generation of reactive oxygen species in phagocytes to facilitate the elimination of intracellular pathogens, while zinc-dependent antioxidant enzymes act to neutralize these reactive species and protect phagocytes from oxidative damage.[18] Macrophages are capable of eliminating pathogens such as *Histoplasma capsulatum* by limiting zinc availability within the phagosome, thereby restricting microbial growth through nutritional deprivation.[19] The significance of zinc becomes particularly evident in states of deficiency, which are associated with increased susceptibility to viral infections and more severe disease courses. Zinc deficiency has been frequently observed in patients with chronic viral infections, including human papillomavirus (HPV), human immunodeficiency virus (HIV), and hepatitis C virus (HCV).[20]

A substantial body of research has examined the potential role of zinc in inflammatory diseases, and multiple high-quality reviews have summarized outcomes from recent supplementation studies employing diverse therapeutic approaches. [21,5] Available evidence indicates that the appropriate dose and duration of zinc supplementation depend on both the underlying disease and the individual's baseline zinc status. Current data suggest that addressing zinc deficiency before disease onset is particularly important, as untreated

deficiency has been associated with poorer clinical outcomes and increased disease severity. In contrast, existing zinc deficiency itself may represent an independent risk factor for adverse disease progression. While zinc supplementation is generally considered beneficial in populations at risk of deficiency or infection, its timing in relation to disease activity appears to be critical. The effects of zinc administration during active inflammatory states and recovery phases remain insufficiently characterized and warrant further investigation. Overall, ensuring adequate zinc status in vulnerable populations is widely regarded as a reasonable and clinically relevant strategy.[22,23]

Zinc and Gastrointestinal disordes

Zinc is a trace element with antioxidant properties that contributes to cellular growth, immune function, and the regulation of intestinal epithelial cells. Available evidence indicates that zinc deficiency impairs intestinal barrier integrity.[7] Zinc supplementation during episodes of diarrhoea has been shown to support the restoration of tight junctions between intestinal epithelial cells, thereby limiting fluid and electrolyte loss. Moreover, through its immunomodulatory effects, zinc plays an important role in the management of diarrhoeal disease, with clinical evidence indicating reductions in symptom duration, stool volume, and the likelihood of progression to persistent diarrhoea in pediatric populations.[24]

Likewise, zinc deficiency has been frequently reported in patients with inflammatory bowel disease (IBD), both during active disease and remission. [25,26]. Both preclinical evidence and human studies indicate that zinc deficiency may play a role in promoting mucosal inflammation in patients with inflammatory bowel disease (IBD). Experimental models have shown that inadequate zinc status worsens colitis and enhances the production of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α). Beyond its immunomodulatory effects, research in animal models of colitis as well as in patients with Crohn's disease has demonstrated that zinc supplementation can improve intestinal mucosal permeability.[27]

Zinc homeostasis is primarily maintained through regulatory mechanisms involving gastrointestinal absorption and excretion, with the liver serving a central role in controlling systemic zinc balance.[28]

Zinc serves as a cofactor for the activation of ornithine transcarbamylase, a key enzyme of the urea cycle that plays an essential role in ammonia detoxification. Consequently, zinc deficiency has been associated with impaired ammonia metabolism and has been implicated in the pathophysiology of hepatic encephalopathy in certain patients. In addition, inadequate zinc status is known to compromise immune function and reduce resistance to infections. Zinc deficiency has also been frequently reported in individuals with liver cirrhosis.[29] In patients with liver cirrhosis, zinc deficiency has been linked to a range of clinical manifestations, including muscle cramps, dermatological lesions such as erythema necroticans migrans and acrodermatitis enteropathica, taste disturbances, hepatic encephalopathy, and increased susceptibility to infections. Moreover, low zinc status has been shown to correlate with greater disease severity, higher infection rates, and reduced transplant-free survival.[30]

Zinc deficiency creates a biological environment that predisposes individuals to the development of multiple gastrointestinal disorders, largely due to its detrimental impact on epithelial barrier integrity. Moreover, adequate zinc status may contribute to reduced morbidity in certain established gastrointestinal diseases.[7]

Zinc and Dermatological Conditions

The skin represents the third largest zinc-rich tissue in the human body.[10]

Acquired zinc deficiency remains a global health issue, affecting a substantial proportion of the population, particularly individuals with malnutrition, chronic illness, alcohol dependence, as well as infants, older adults, and pregnant women. [31-33] Zinc deficiency may lead to acquired acrodermatitis enteropathica and is frequently observed in disorders associated with other nutritional deficiencies, which often present with similar dermatological manifestations. In these conditions, alterations in epidermal immune cells and zinc-dependent skin abnormalities can often be reversed with zinc supplementation, underscoring the central role of zinc deficiency in the pathogenesis of various skin disorders.

Necrolytic migratory erythema (NME) is regarded as a characteristic dermatological manifestation of pancreatic glucagonoma, as the associated skin lesions often resolve following surgical removal of the tumor. Current evidence indicates that NME may also arise in association with other conditions, including elevated inflammatory mediators, hepatic dysfunction, and metabolic or nutritional deficiencies, particularly involving zinc as well as essential amino acids and fatty acids.[34] Reduced serum zinc concentrations have been reported in patients with NME in the context of inflammatory bowel disease, celiac disease, liver dysfunction,

and malignancies other than glucagonoma. [35,36] Clinical observations indicate that zinc supplementation can lead to resolution of NME-associated skin lesions, suggesting that low serum zinc levels contribute to the pathogenesis of this condition.[10]

Niacin refers to a group of compounds with anti-pellagra activity, primarily nicotinamide and nicotinic acid. Nicotinamide can be produced via two main pathways: first, dietary nicotinic acid is rapidly taken up by the liver and converted into nicotinamide; second, nicotinamide is synthesized endogenously from the essential amino acid tryptophan through the tryptophan–nicotinamide metabolic pathway. [37]

Individuals with pellagra commonly present with acrodermatitis enteropathica–like erythema, diarrhea, and neurological symptoms consistent with dementia.[10]

A study assessing serum zinc concentrations in patients with pellagra demonstrated significantly lower zinc levels compared with healthy individuals. Although average zinc concentrations were within the range of latent zinc deficiency, the findings suggest that zinc deficiency may be involved in the pathogenesis of pellagra.[38]

Alopecia observed in patients with acrodermatitis enteropathica (AE) typically exhibits features of telogen effluvium, a non-scarring form of hair loss characterized by a premature shift of hair follicles from the anagen to the telogen phase. Patients with telogen effluvium in the absence of acrodermatitis enteropathica have also been shown to exhibit reduced serum zinc levels compared with healthy controls, and zinc supplementation has been reported to promote recovery in these cases.[39]

In summary, zinc deficiency is associated with the development of telogen effluvium and disturbances in normal hair keratinization.[10]

Overall, zinc deficiency is strongly associated with various dermatological manifestations, particularly acrodermatitis-like skin changes observed in conditions related to nutritional deficiencies. These findings highlight the importance of adequate zinc status for maintaining normal skin structure and function.

Zinc and Metabolic Disorders

Pancreatic β cells are characterized by high zinc content, as zinc plays a crucial role in insulin storage by facilitating the formation of insulin hexamers composed of six insulin molecules coordinated by two zinc ions within secretory granules.[40] Owing to its essential contribution to insulin structure, zinc is also required during the formulation of insulin analogs to ensure their stability and biological activity.[41]

An early cross-sectional study in adults demonstrated that low zinc intake was associated with higher postprandial insulin levels, indicating insulin resistance. After adjustment for age, low zinc intake was linked to central obesity, glucose intolerance, and diabetes among urban participants, whereas these associations were not observed in rural populations.[42]

Another study indicates that zinc deficiency may contribute to insulin resistance and the development of hepatic fibrosis in patients with primary biliary cirrhosis, although insulin resistance in advanced primary biliary cirrhosis appears to be less pronounced than in hepatitis C–related liver cirrhosis.[43]

Given the essential role of zinc in insulin synthesis, storage, secretion, and stabilization of its hexameric structure, zinc deficiency may contribute to the pathogenesis of diabetes.[44]

Studies have demonstrated that low zinc concentrations in drinking water are associated with an increased risk of developing type 1 diabetes during childhood. [45,46] In contrast, one study failed to confirm these associations. A population-based study conducted in Finland found no significant relationship between zinc levels, nitrate exposure, or urban–rural differences and the incidence of childhood insulin-dependent diabetes mellitus, highlighting inconsistencies in the available epidemiological evidence.[47]

Experimental studies in animal models have shown that zinc deficiency induced by chelating agents can lead to diabetes in several mammalian species, including rabbits, mice, and hamsters, primarily through β-cell damage. Moreover, zinc deficiency has been reported to increase diabetes susceptibility in genetically diabetes-prone animals. Collectively, these findings from animal models support the concept that zinc deficiency represents a risk factor for the development of diabetes.[48-50]

A human study in patients with type 2 diabetes demonstrated that individuals with lower serum zinc levels had a higher risk of cardiovascular events compared with those exhibiting relatively higher zinc concentrations.[51]

Conclusions

Zinc is a key micronutrient involved in numerous biological processes essential for maintaining human health. The evidence discussed in this review highlights the multifaceted role of zinc in immune regulation, preservation of gastrointestinal and skin barrier integrity, and metabolic function.

Across the disease groups addressed in this work, including immune-related conditions, gastrointestinal disorders, dermatological manifestations, and metabolic diseases, zinc deficiency has been consistently associated with impaired physiological function, dysregulated inflammatory responses, and unfavorable clinical outcomes. Both experimental and human studies indicate that inadequate zinc status may contribute to disease development and progression, while correction of zinc deficiency is frequently linked to improvements in functional and clinical parameters.

Although the strength and consistency of evidence vary between disease categories and study designs, the overall findings emphasize the clinical relevance of maintaining adequate zinc status, particularly in populations at increased risk of deficiency. Further well-designed clinical studies are warranted to clarify disease-specific mechanisms and to optimize strategies for the assessment and management of zinc deficiency in clinical practice.

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