

# Zinc as a Modulator of Chronic, Inflammatory Intestinal Disorders with Focus on Celiac Disease, Inflammatory Bowel Syndrome and Crohn's Disease

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Zinc (Zn) is an essential trace element, sometimes referred to as a micro mineral. Among numerous catalytic, regulatory and structural functions of Zn, its role in the highly proliferating human cells, like those of the immune system, is critical. Importance of Zn in the immune system is supported by evidence from reports where even mild Zn-deficient diets resulted in decreased function of various kinds of immune cells and overall impaired immunity, as reviewed earlier [1]. Although Zn is primarily an intracellular ion, recent research indicates the existence of a labile Zn pool, acting as a signaling agent in some physiological processes [2]. In that capacity, Zn may act as a second messenger and when activated by extracellular stimuli, like cytokines and growth factors, it transduces the signal and promotes the intracellular response. This groundbreaking discovery of Zn as a second messenger and particularly its signaling in the immune system is attracting a lot of recent interest [3]. Widespread chronic intestinal disorders may result in part from an unregulated immune response caused by altered inflammatory pathways, leading to impaired intestinal barriers, propagated inflammation, and subsequent impaired immune function [4,5]. Studies have demonstrated that Zn has a strong role in these immune processes, although specific cellular mechanisms are still being explored [6,7]. Low Zn consumption and deficiency may lead to the damage of intestinal mucosa on multiple levels, including the mediation of tumor necrosis factor  $\alpha$  (TNF  $\alpha$ ) expression [8]. TNF  $\alpha$  is a primary biomarker in inflammatory bowel diseases and its unregulated production has been confirmed as a consequence of Zn deficient diets administered to rats induced with colitis [9]. These findings suggest that disruption of the immune response may be a result of alterations in Zn status of various tissues [9], further relating Zn to specific chronic disorders marked by intestinal inflammation. New findings show that the anti-inflammatory functions of Zn may ameliorate celiac disease (CCD) symptoms [10], as well as other chronic disorders such as irritable bowel syndrome (IBS) and Crohn's disease (CD) [11], as discussed in the following sections.

Celiac disease is an autoimmune disorder characterized by a permanent intolerance to protein found in foods containing gluten and its development is believed to be a result of three factors: human leukocyte antigen genetic predisposition; specific humoral response to the antigen tissue transglutaminase; and exposure to a gliadin, protein within gluten, acting as an initiation factor in the disease [12]. Intestinal biopsy results have revealed an inverse relationship between higher intestinal-cells atrophy and their concentration of Zn in children with CCD [13]. These results point to Zn as a possible contributing factor in preservation and healing of the intestinal mucosa and in CCD progression. However, there are limitations in current research regarding Zn supplementation with subsequent gluten free diet and intestinal repair in CCD [14]. Further research is warranted to establish its role and potential need for supplementation in CCD.

Although the exact etiology of IBS is unknown, its development is a result of multiple causes, including genetic defects, impaired gut motility, changes in the intestinal mucosa, as well as the heightened inflammation,

with Zn as a key micronutrient involved [15]. Gene polymorphisms that code for some of the proinflammatory cytokines, like interleukin-6, interleukin-10 and TNF  $\alpha$  have been reported in individuals with IBS. Under normal conditions, these proinflammatory cytokines regulate the immune inflammatory response, but their impaired release may be involved in IBS proliferation and increased susceptibility to the disease in some individuals. Specifically, a high production of interleukin-10 has been observed in IBS patients [16]. Studies in mice with Zn-restricted diets have shown aggravated cytokine levels and heightened mucosal permeation as a result of inflammation from lipopolysaccharide endotoxin injection [17], while Zn supplementation resulted in increased occluding and zonulaoccludin (intestinal tight-junction membrane proteins) expression and production in weaning piglets [18]. These findings imply that Zn could be a promising agent for prevention of altered intestinal permeability and possible enterocyte aggravation as a result of exacerbated inflammation.

Crohn's disease is a specific form of inflammatory bowel diseases that can affect the entire gastrointestinal tract and it is thought to occur from multiple factors, including poor nutrition, mal absorption and inflammation. Therefore, malnutrition is a primary concern for individuals with CD. Since Zn promotes tissue repair and plays an important role in immune functioning, it is not surprising that serum Zn and iron were reported to be lower in the newly diagnosed CD cases compared to those without the disease [19], although this could have also been a response to inflammation. Studies have also reported decreased levels of metallothionein, a Zn-binding protein, thought to be an important factor in cellular defense in patients with severe disease activity [20]. Additionally, patients with CD may have issues with intestinal barrier permeability related to disturbances in functionality of tight-junctions. Altered intestinal permeability may further allow bacteria and pathogenic agents to pass, contributing to the disease progression. It has been shown that Zn deficiency may play an integral role in the disruption of this altered barrier permeability [11]. Further investigation is warranted to determine a protective role of Zn in the maintenance of tight-junction permeability in inflammatory

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conditions, as well as to determine a specific relationship between Zn supplementation and modulation of intestinal inflammation.

It is important to mention in this context the role of the enteric nervous system (ENS) that reciprocates the activity between the gastrointestinal (GI) tract and the central nervous system [21]. The pathophysiology of functional GI disorders may be dependent on neurotransmitter activity because the receptors in the brain are interdependent with the receptors in the GI tract. It has been shown that the ENS feedback system modulates the GI motility, electrolyte balance, immunity, secretion and inflammation [21]. The glutamatergic system is one of the CNS modulators and is Zn-dependent by way of N-methyl-D-aspartate (NMDA) receptor antagonist function. The NMDA antagonists inhibit the production of reactive oxygen species associated with inflammatory bowel disorders. Zn as a signaling agent is an NMDA antagonist and through glutamate inhibition modulates inflammation by down regulating TNF $\alpha$  production and collectively behaves as an antioxidant [21].

In conclusion, it is obvious that Zn regulates the development of chronic intestinal inflammatory conditions, although the understanding of its role in the mediation of inflammatory damage to the mucosal lining is still incomplete. Zn regulates immunity by modulating receptors on the enterocytes of the GI tract. This effect has been observed with TNF $\alpha$  regulation during experimental colitis, exacerbated intestinal atrophy in CCD, and increased intestinal permeation with Zn depletion in IBS. Numerous factors including genetics, environmental toxins, and depression of the immune system, may lead to decreased mucosal barrier function and trigger the autoimmune response and inflammatory intestinal disorders. Integrity of the gastrointestinal tract is maintained by the permeability of the enterocytes, which is regulated by Zn-dependent transcription factors, thus affecting inflammatory intestinal disorders. The human neurochemical network modulates GI motility, secretion, electrolyte balance, immunity and inflammation. This concept is further supported by the reports of potential therapeutic and preventative role that Zn may play in specific inflammatory conditions. Even though human clinical trials are needed to affirm existing concepts, current research suggests that Zn therapy may improve clinical outcomes of inflammatory intestinal disorders.

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