Zinc Supplementation in Pediatric Gastrointestinal Diseases

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Children with inflammatory bowel disease (IBD), celiac disease, and those receiving long-term proton pump inhibitor treatments are particularly susceptible to zinc deficiency (ZD). ZD in children with celiac disease and IBD is attributed to insufficient intake, reduced absorption, and increased intestinal loss as a result of the inflammatory process. Zinc plays a crucial role in maintaining the integrity of the gastric mucosa and exerts a gastroprotective action against gastric lesions.

zinc infectious diarrhea IBD celiac disease peptic ulcer disease GERD children

1. Introduction

For over two decades, researchers have explored the correlation between zinc and gastrointestinal (GI) diseases, as well as the potential benefits of zinc supplementation for specific GI conditions. In the last century, Semrad emphasized the crucial role of zinc in intestinal function, particularly in managing diarrhea [1]. Zinc plays a vital role in various cellular and systemic functions, including DNA repair, apoptosis, cell cycle progression, p53 activation, and the prevention of oxidative stress-induced DNA damage [2][3]. Zinc is considered a functional food for preserving GI mucosal function [4]. In terms of its epithelial barrier function, zinc could be used as an alternative to the use of steroids and anti-tumor necrosis factor modalities for treating inflammatory bowel disease (IBD) [5]. The intestinal mucosa not only experiences degeneration but also suffers severe effects from zinc deficiency (ZD). This results in a thinner mucus layer and changes in mucus composition, which were observed in both animal studies and human goblet cells [6][7].

ZD compromises GI epithelial function and is linked to various GI diseases, such as diarrhea, malabsorption, celiac disease, IBD, peptic ulcer disease (PUD), and gastroesophageal reflux disease (GERD) [8]. Zinc supplementation positively impacts many aspects of GI mucosa at both molecular and cellular levels, enhancing GI barrier function [9][10]. Numerous studies have shown that zinc supplementation improves epithelial barrier function, particularly via tight junction modifications [11][12]. Epithelial and endothelial tight junctions (zonula occludens) selectively seal the gap between adjacent cells, preventing unregulated paracellular exchange across the epithelial or endothelial barrier via zinc supplementation [13][14]. In addition to tight junction modification, epithelial barrier leak can be induced more significantly via induction of apoptosis and detachment [12].

2. Infectious Diarrhea

ZD can lead to intestinal hyperpermeability (leaky gut), resulting in increased nitric oxide and oxidative stress, which can cause diarrhea [15][16][17]. Studies in rats have shown that ZD upregulates the expression of intestinal uroguanylin, a peptide that stimulates chloride secretion driving fluid secretion, decreases the absorption of triglycerides by changing chylomicron development, and decreases the absorption of proteins by changing enterocyte peptidase activity, which can cause diarrhea [18][19][20][21].

In individuals with ZD, the GI tract may perhaps be one of the initially involved areas where symptoms manifest [22]. Such individuals are more susceptible to toxin-producing bacteria or enteroviral pathogens that activate guanylate and adenylate cyclases, stimulating chloride secretion and leading to diarrhea while also diminishing nutrient absorption. Additionally, ZD impairs the absorption of water and electrolytes, prolonging the duration of normally self-limiting GI disease episodes, and can exacerbate diarrhea caused by Vibrio cholera [23][24]. Notably, ZD can not only cause diarrhea but chronic diarrheal illnesses can also lead to ZD, thereby worsening diarrhea [25]. Studies have demonstrated that zinc supplementation influences lactulose excretion in children with stool isolates of *E. coli*, *Shigella* sp., and *Campylobacter jejuni*. The greatest reduction in lactulose excretion was observed in zinc-supplemented children who were lighter (weight-for-age less than 80%), thinner (weight-for-height less than 85%), and undernourished [middle upper arm circumference less than 12.5 cm], or with hypozincemia (less than 14 µmol/L) [26]. Zinc has also exhibited a direct antimicrobial effect on pathogenic enteric bacteria such as Salmonella and Shigella [27]. Children with acute diarrhea treated with zinc have shown a decrease in the duration and rate of diarrhea, as well as a reduced need for antibiotic therapy compared to controls [28].

A systematic review investigating the therapeutic value of zinc supplementation in acute and persistent diarrhea found evidence supporting the use of zinc to treat diarrhea in children; however, there was some uncertainty due to heterogeneity across the studies regarding zinc supplementation's effect on diarrhea outcomes [29]. Zinc supplementation reduced the mean duration of diarrhea by 19.7% but had no significant effect on stool frequency or output while increasing the risk of vomiting [29]. Nevertheless, zinc supplementation has proven effective in decreasing the prevalence, morbidity, and mortality of diarrhea in healthy children in developing countries [29][30]. In cases of infectious diarrhea where there is typically increased intestinal permeability (lactulose/mannitol ratio), zinc supplementation has shown improvement [29][30][31]. Another systematic review of clinical trials involving 6165 children (aged >6 months) with diarrhea found that zinc supplementation reduced diarrhea duration and lessened diarrhea at days 3 and 7 in children with acute diarrhea, and also reduced the duration of persistent diarrhea. No serious adverse events were reported, but vomiting was more common in zinc-treated children with acute diarrhea [32]. A 1-year observational study of 20,246 children (aged 3–59 months) with diarrhea observed that regurgitation and/or vomiting occurred in 4392 (21.8%) cases. However, this phenomenon was transient and did not affect the continuation of zinc treatment [33]. According to meta-analyses of randomized, controlled intervention trials on children, the World Health Organization (WHO) and United Nations Children's Fund (UNICEF) advocate for the regular use of zinc in treating children under the age of five with acute diarrhea, irrespective of its cause. They also advise diligent monitoring for any adverse events linked to zinc administration, with a specific focus on excessive or unusual vomiting.

A systematic review investigating the disease-specific and all-cause mortality attributable to ZD in children <5 years old found that ZD contributes to morbidity and mortality, especially in cases of diarrheal illness. The findings specify that zinc supplementation, provided as an adjunct treatment for diarrhea, may be the best way to target children most at risk of ZD [34]. Another systematic review, with an emphasis on developing countries, found that zinc supplementation could reduce the average duration of childhood diarrhea by approximately 20% [29]. A Cochrane database systematic review (2016) concluded that zinc may be beneficial for children aged six months or more in areas where the prevalence of ZD or malnutrition is high, while evidence does not support the use of zinc supplementation in children less than six months of age, in well-nourished children, and children at low risk of ZD [32].

In light of this robust evidence, zinc supplementation is considered a cost-effective method to reduce the duration of acute diarrhea in children [35]. Guidelines suggest a dosage of 20 mg/day for children older than 6 months or 10 mg/day for children younger than 6 months for at least 10–14 days during diarrhea [36][37][38][39].

3. IBD

IBD is a chronic condition characterized by inflammation in the gut mucosa and may appear at a young age, persisting throughout life with phases of recurrence and remission. This condition significantly impacts the quality of life of affected individuals [40][41]. Patients with IBD are at a high risk of experiencing nutritional deficiencies due to long-term gut inflammation and reduced oral intake. ZD is common among patients with IBD, with a prevalence rate ranging from 15 to 45% [42]. Given the involvement of immune function in IBD, maintaining normal zinc levels in these patients appears to be crucial.

Most reports of ZD in IBD come from Western countries and primarily concern adult patients. ZD is more frequently observed in patients with CD compared to those with UC. This difference is likely because zinc is predominantly absorbed from the GI lumen in the small intestine, particularly in the distal duodenum and proximal jejunum, which is affected in CD [40][41][42][43]. On the other hand, UC characteristically does not manifest in the small bowel. Several studies have shown that well-nourished UC patients did not experience ZD. When comparing patients with moderate or severe UC to healthy controls or patients in remission, their serum zinc concentrations were found to be normal or even elevated [44][45].

Elevated serum zinc concentrations in UC are correlated with increased levels of complement component C3C and elevated antinuclear antibodies during flares. These are known predictors of UC flares and markers of steroid dependence in UC [46][47]. ZD in UC patients is generally associated with malnutrition resulting from poor oral intake due to systemic illness during active UC, rather than being solely caused by the damaged colon [48][49]. During active UC flares, there is a correlation between increased serum zinc concentrations, increased levels of complement component C3C, and elevated antinuclear antibodies, which are recognized predictors of UC flares. The elevated serum zinc concentrations may potentially result from zinc release triggered by the activated inflammatory cascade. Nevertheless, one study did not find a correlation between serum zinc levels and severe inflammation (indicated by elevated erythrocyte sedimentation rate or C-reactive protein) in patients with UC [50]. In

animal models of UC, ZD exacerbated the disease activity index, serum TNF-α levels, weight loss, and further shortening of the colon length. Several studies have explored the effects of zinc supplementation on inflammation in UC. For instance, Di Leo et al. reported improvements in diarrhea and weight gain in a rat colitis model when supplemented with zinc, although no effect was observed on neutrophil infiltration or visible inflammation [51]. On the other hand, Mulder et al. reported no change in the disease activity index or inflammation in human UC intestinal biopsies after zinc supplementation [52]. Zinc supplementation has the effect of suppressing colitis in a mouse model, as proved by lessened disease activity and histological severity, as well as decreased myeloperoxidase activity [53]. The effects of ZD on the development and progression of colitis were observed in mice; ZD can aggravate colonic inflammation via activation of the IL-23/Th17 axis [54].

ZD is a well-documented issue in individuals with CD due to a reduction in zinc absorption within the small intestine, as well as chronic dietary restrictions and intolerances [55][56]. In a substantial cohort of patients diagnosed with IBD, approximately 8.5% were estimated to have insufficient zinc intake, and as many as 29.3% exhibited deficient levels of serum zinc. Notably, ZD was even observed in individuals with CD during periods of remission [57]. ZD was even documented in CD patients during remission [58]. CD patients receiving total parenteral nutrition can develop acute ZD, resulting in acrodermatitis enteropathica and decreased vision [59]. More commonly, ZD in CD contributes to stunted growth in children and manifests as decreased taste sensation, visual acuity, and immune function [60][61] A positive correlation between increased mucosal permeability and CD disease activity was reported, as confirmed by the increased uptake of large molecular markers (such as lactulose) from the GI lumen into the bloodstream [62]. During periods of remission, heightened transmucosal permeability was employed as an indicator to predict the relapse of CD [63].

A high prevalence of micronutrient deficiencies, particularly zinc, was reported in pediatric IBD patients [64][65][66][67][68], with implications for poor clinical outcomes such as subsequent hospitalizations, disease-associated complications, and an increased risk of surgeries [67]. In a retrospective study that investigated the prevalence of ZD in children under 17 years with IBD, subjects were categorized into CD (n = 98), UC (n = 118), and normal controls (n = 43). The results revealed significantly lower serum zinc levels in CD (median, 64 µg/dL) compared to UC (median, 69 µg/dL) and normal controls (median, 77 µg/dL). Additionally, the prevalence rate of ZD was significantly higher in CD (60.2%) than in normal controls (37.2%), but not significantly different from UC (51.7%) [66]. Another study conducted on 165 pediatric patients with IBD (under 17 years; 87 CD and 78 UC) surveyed the prevalence and predictors of anemia and micronutrient deficiencies at diagnosis and 1-year follow-up. The prevalence of zinc deficiency was found to be 10% at diagnosis and 6% at follow-up, while anemia was prevalent in 57% of patients at diagnosis and 25% at follow-up [67].

Although recent literature indicates the potential benefits of zinc supplementation for CD, zinc products have not undergone FDA inspection and validation specifically for CD. There are no specific guidelines regarding zinc supplementation for CD beyond emphasizing the significance of maintaining a balanced and adequate nutritional intake. The daily intake of zinc above the current recommended daily allowance is suggested in specific GI diseases at risk of ZD.

In summary, the evidence from epidemiological studies indicates that regular zinc intake via diets can reduce the risk of developing IBD. ZD poses significant risks for adverse disease-specific outcomes, hospitalizations, and surgeries in IBD patients. Addressing ZD in patients with IBD, particularly those with CD, seems to be crucial in managing the condition and maintaining overall health. Zinc supplementation may offer potential benefits in managing inflammation in UC, but further research is needed to fully understand its effects and mechanisms of action. The prevalence of ZD is notably high in pediatric IBD patients, underscoring the importance of addressing nutritional deficiencies in this vulnerable population.

4. Celiac Disease

Patients with celiac disease exhibit deficiencies in various vitamins and minerals, including zinc [69][70]. Research has shown that both untreated and clinically remitted celiac disease patients have reduced plasma zinc levels [71]. ZD was documented with a prevalence as high as 67% in newly diagnosed adult patients with celiac disease, and it can affect up to 64% of pediatric patients with the condition [72][73]. ZD was found to correlate with villous atrophy in celiac disease patients. A study reported that 60% of patients with partial villous atrophy, 80% with subtotal villous atrophy, and 92% with total villous atrophy were deficient in zinc [74]. Stenberg et al. proposed that ZD, particularly in the intestinal mucosa, may activate the enzyme transglutaminase-2 (TG2), which is normally inhibited by zinc. This activation, in turn, leads to the formation of a TG2-thioester intermediate–deamidated gliadin complex, which acts as a “neo-antigen”, triggering an immune response in genetically susceptible individuals, resulting in inflammation and villous atrophy [75].

The management of celiac disease primarily involves a lifelong gluten-free diet (GFD). However, numerous studies have reported nutritional deficiencies and imbalances associated with GFD. In pediatric patients, studies have shown decreased intakes of magnesium, zinc, selenium, and folate on a GFD, leading to potential nutritional inadequacies in this population [76]. Regardless of the GFD, children with celiac disease are at risk of insufficient calcium, vitamin D, iron, and fiber intake [77]. These imbalances may be exacerbated during GFD. Specifically, children with celiac disease on a GFD may experience altered intake of magnesium, zinc, folate, and high glycemic index foods.

A narrative review examining celiac disease patients on a long-term GFD with good compliance (over 2 years) revealed that micronutrient deficiencies were common, with up to 40% of subjects experiencing zinc deficiency [78]. Children with untreated celiac disease and enteropathy exhibited significantly reduced serum zinc levels, which subsequently returned to normal upon adopting GFD [79][80]. Supplementation of zinc along with GFD did not result in additional increases in plasma zinc levels [81]. While certain studies did not detect variations in zinc absorption between individuals with untreated celiac disease and control groups, there is evidence suggesting disrupted zinc homeostasis in celiac disease patients [82][83]. Improved zinc turnover and reduced loss of endogenous zinc were observed after starting a GFD. Additionally, the “exchangeable zinc pool” (zinc pools in the body that can exchange with serum zinc) was found to be significantly decreased in celiac disease patients [83][84]. Interestingly, some celiac disease patients may experience ZD despite having normal zinc absorption [82].

In a study aimed at determining serum zinc values in 140 samples from 78 children with celiac disease in different phases, abnormally low serum zinc levels were observed in children with acute celiac disease (50% below 2 SD), but not in children receiving a GFD [85]. The results of the study suggest regular measurement of serum zinc concentration in children with celiac disease and support zinc supplementation in patients with reduced zinc values during a period of 2–4 weeks, as ZD could inhibit the recovery of the intestinal mucosa.

Data regarding the effect of zinc supplementation with GFD on the normalization of serum or plasma zinc in celiac disease patients are still limited and controversial. The absence of advantages from zinc supplementation in terms of raising plasma zinc levels in patients adhering to a GFD could be associated with various factors, including the extent of mucosal healing following the initiation of GFD, the pharmacokinetics of zinc, its distribution and storage within the body, as well as the duration of supplementation. Theethira et al. suggested measuring the serum zinc levels of celiac disease patients at diagnosis and repeating the procedure regularly until the levels were normal; zinc supplementation (25–40 mg/day) was recommended until zinc levels were normalized [86].

Significantly lower plasma zinc concentrations were found in celiac children with chronic diarrhea compared to healthy children [87]. ZD can be used as an indicator to suggest the diagnosis of celiac disease in children with short stature, low plasma zinc levels were observed in 54.2% of cases due to celiac disease [88]. Hambidge et al. observed an association between poor growth and unsatisfactory zinc status assessed by low hair-zinc levels [25]. The same association was reported by Halsted et al. in Iranian boys [89]. ZD (decreased plasma zinc levels) was reported in 71.4% of pediatric series with celiac disease (n = 134). In that study, patients with ZD (n = 96) were randomly treated with GFD plus zinc (n = 48) and GFD only (n = 48). The results showed that the group with GFD plus zinc (20 mg elemental zinc) for 4 weeks provided no additional benefit regarding the rise in plasma zinc concentrations. Both groups showed a significant increase in plasma zinc levels after starting GFD for 4 weeks [90].

In summary, the prevalence of ZD is notably high in celiac disease patients, ZD was found to correlate with villous atrophy in celiac disease patients. The beneficial effect of zinc supplementation as adjuvant to the GFD diet in Celiac disease is controversial, further research, including clinical trials investigating the efficacy of different dosages of zinc supplementation in treating celiac disease, is warranted to better understand the potential benefits of zinc in managing the disease.

5. PUD

Zinc is a crucial metabolic requirement for the growth and repair of squamous tissue [10]. Over the past three decades, researchers have observed zinc-mediated suppression of gastric acid production and improvement in gastric ulcer healing [91]. The therapeutic effects of zinc on PUD were described in both animal and human studies [92][93][94][95]. In animal studies, zinc supplementation did not affect the formation of gastric ulcers but was found to delay ulcer healing [93]. Human studies have shown that zinc offers protective action on the gastric mucosa [96][97]. In a clinicopathological study, a possible correlation between serum zinc levels and PUD was identified, along with a plausible mechanism for these findings [96]. The study observed lower serum zinc levels in patients with PUD compared to normal controls, but significantly increased zinc content in the gastric mucosa of PUD patients. These

results indicate that the low serum zinc levels in peptic ulcer patients may be due to a positive shift of zinc from serum to the gastric mucosa.

The use of omeprazole, which inhibits gastric acid production and raises the pH in the gastroduodenal tract was documented to diminish zinc absorption in the small intestine in humans [97]. Joshaghani et al. reported a decline in serum zinc levels in males following 8 weeks of omeprazole usage, and a similar reduction in zinc absorption was observed when gastric acid production was inhibited by histamine-2 (H-2) blockers [98][99]. A study by Zhang et al. evaluated the role of Helicobacter pylori infection and serum zinc value in gastric diseases, finding that a similar rate of Helicobacter pylori infection was found in gastritis, peptic ulcer, and gastric cancer patients, while serum levels of zinc were significantly reduced in gastritis, peptic ulcer, and gastric cancer patients, compared with healthy controls [100]. The study illustrates that serum zinc level is an indicator of gastric protection against damage.

Frommer et al. demonstrated the effectiveness of zinc in treating gastric ulcers. However, other studies did not find a significant association between zinc supplementation and peptic ulcer treatment [101]. In one report, high-dose zinc supplementation (220 mg/day) showed no significant effect on peptic ulcers, but a better treatment effect was observed in patients with normal zinc levels [102]. Kirchhoff et al. reported that zinc administration (150 or 0.5 mg/kg/day ZnCl) could effectively raise luminal pH in rats, similar to proton pump inhibitor (PPI) medications, by eliminating secretagogue-induced gastric acid secretion without causing the side effects associated with PPIs, such as liver cytochrome P450 inhibition [103].

6. GERD

Excessive exposure to gastric acid is the major cause of GERD and reflux esophagitis. However, an increasing number of patients are experiencing insensitivity to PPI therapy, leading to a recurrence of symptoms. Consequently, finding alternative treatment options has become essential. It was observed that PPI use significantly reduces supplemental zinc uptake, resulting in decreased zinc body stores in males [103][104]. A study evaluating the effects of omeprazole treatment on trace element levels in GERD patients found that serum zinc levels were significantly lower in male patients after 8 weeks of omeprazole treatment, whereas no significant difference was observed in female patients [98]. As a result, it is suggested that zinc supplementation may be considered for male patients undergoing PPI treatment. Long-term PPI therapy in certain individuals, such as infants being treated for colic, may lead to reduced systemic levels of trace elements necessary for development, regeneration, and immune function [104].

Studies have shown that zinc supplementation can inhibit gastric acid secretion in both human and animal models. The authors of one study reported that exposure to a single dose of zinc salt raised intragastric pH for over 3 h, indicating that zinc supplementation effectively reduced secretagogue-induced gastric acid secretion and elevated luminal pH as effectively as PPI, without the side effects associated with hepatic cytochrome P450 inhibition caused by PPI [103]. A clinical trial involving oral zinc gluconate (containing 26.2 mg zinc, twice daily) for 2 weeks in GERD patients on long-term PPI therapy (>6 months) and healthy controls (not on any antacids or neutralizing medication) found that plasma zinc levels in healthy controls increased by 126% after zinc supplementation,

compared to a 37% increase in those on long-term PPI therapy. The study also revealed that those with PPI therapy had a 28% lower plasma zinc level than healthy controls on their normal diet (without zinc supplementation) [104].

However, it is important to note that not all studies have shown positive results for zinc supplementation in GERD treatment [105]. A randomized double-blind study found that zinc supplementation could not significantly lessen the severity of GERD. The study included 140 patients (81 women, mean age 42.8 ± 11.5 years) divided into two groups: non-erosive reflux disorder and erosive reflux disorder. Each group was further divided into drug subgroups (treated with PPI, lifestyle changes, and 220 mg zinc daily) and placebo subgroups (treated with PPI, lifestyle changes, and placebo). Both drug and placebo groups showed a significant decrease in Reflux Disease Questionnaire (RDQ) scores after 3 months ($p < 0.001$), but the difference in RDQ scores between the drug and placebo groups was not statistically significant ($p = 0.086$) [105].

In summary, while some evidence suggests that zinc supplementation may be beneficial for male GERD patients undergoing PPI treatment, further research is required to fully understand its potential as an alternative therapy for GERD and reflux esophagitis. It is essential to consider individual patient factors and conduct well-designed clinical trials to determine the efficacy and safety of zinc supplementation in the treatment of GERD.

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