



The role of zinc in the prevention and treatment of nonalcoholic fatty liver disease

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ABSTRACT

The zinc element is an essential nutrient for human health. Zinc is involved in the glucose, lipid, and protein metabolism and antioxidant processes in biological pathways. Zinc deficiency can lead to several chronic liver diseases. Nonalcoholic fatty liver disease (NAFLD) is one of the most common liver diseases where zinc deficiency plays a critical role in pathogenesis. Human and animal studies showed that both NAFLD risk factors (i.e., insulin resistance, diabetes mellitus, dyslipidemia, obesity, hypertension) and NAFLD itself are associated with decreased blood levels of zinc. Additionally, endoplasmic reticulum stress and inflammation due to unfolded protein response, inadequate dietary zinc intake, and decreased zinc absorption from the gastrointestinal tract can result in zinc deficiency leading to NAFLD. Herein, we reviewed the mechanistic links between zinc deficiency and NAFLD development and the role of zinc in the prevention and treatment of NAFLD.

1. Introduction

In 2016, the World Health Organization estimated that there were more than 1.9 billion adult overweight people, of whom more than 650 million were obese [1]. The healthcare and economic burdens related to chronic metabolic diseases have been increasing in the US such that one-third of the adult population in the US is now obese [2]. Due to the rising obesity epidemic, one-fourth of the adult population worldwide is affected by nonalcoholic fatty liver disease (NAFLD) [3]. Additionally, cirrhosis secondary to NAFLD is on the verge of becoming the most common indication for liver transplantation, not only in the US but worldwide [4,5]. As such, there is an urgent need for effective interventions to treat NAFLD. These effective interventions should not only be limited to weight reduction, exercise, and control of risk factors (e.g., obesity, insulin resistance, dyslipidemia), but also repletion of essential micronutrients. Among several micronutrient deficiencies in NAFLD [6], zinc deficiency appears to play the most pivotal role in NAFLD development. This review aims to identify the mechanistic links

between NAFLD and zinc deficiency, determine the role of zinc in the prevention and treatment of NAFLD, and underline the key points in supplementation and laboratory evaluation of zinc element.

2. Conditions associated with zinc deficiency in NAFLD

NAFLD is a significant cause of cirrhosis and liver cancer due to the rising global obesity epidemic [7]. Patients with NAFLD were shown to have significantly reduced serum zinc concentrations compared with controls [8]. Additionally, lower zinc concentrations were reported to be associated with higher stages of hepatic fibrosis in subjects with biopsy-proven NAFLD [9]. A cross-sectional study conducted among 300 subjects with NAFLD defined by NAFLD liver fat score [10] showed that significant hepatic fibrosis estimated by the fibrosis-4 index [11] was associated with reduced zinc levels [12]. In contrast to the results of these studies, a study that evaluated subjects with NAFLD who underwent bariatric surgery showed no significant correlation between serum zinc levels and the severity of hepatic steatosis, steatohepatitis, and

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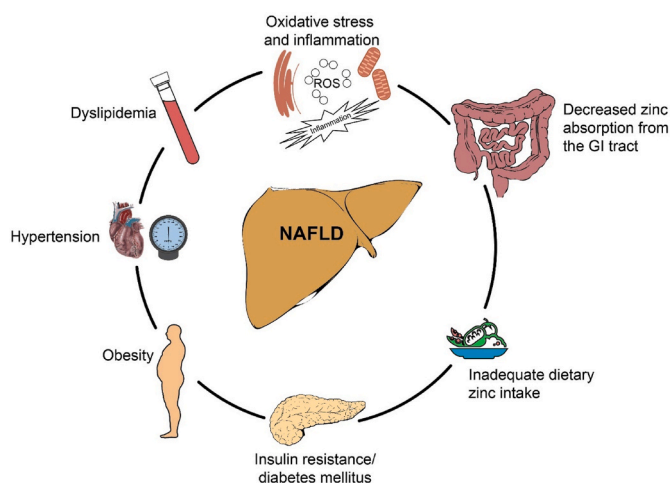


Fig. 1. Several conditions can be associated with zinc deficiency, including oxidative stress and inflammation increasing the demand for zinc supplementation, insulin resistance, diabetes mellitus, obesity, hypertension, dyslipidemia, decreased zinc absorption from the gastrointestinal tract, and inadequate dietary zinc intake. NAFLD=Nonalcoholic fatty liver disease; ROS = Reactive oxygen species, GI = Gastrointestinal (with permission from Baylor College of Medicine).

fibrosis [13]. Regarding the animal studies, zinc supplementation in rats with diet-induced NAFLD reduced the severity of hepatic steatosis in the periportal areas, reduced lipid deposition in hepatocytes, improved glucose metabolism and insulin signaling, and reduced liver injury [14–16].

Several conditions in patients with NAFLD can be associated with zinc deficiency, including oxidative stress and inflammation increasing the demand for zinc supplementation, insulin resistance, diabetes mellitus, obesity, hypertension, dyslipidemia, decreased zinc absorption from the gastrointestinal tract, and inadequate dietary zinc intake (Fig. 1).

2.1. Zinc deficiency associated with oxidative stress and inflammation

Endoplasmic reticulum stress that leads to unfolded protein response, and thereby oxidative stress and inflammation play a central role in the development of NAFLD [17]. The endoplasmic reticulum stress occurs when the demand for protein folding exceeds the capacity of the endoplasmic reticulum resulting in the accumulation of unfolded and/or misfolded proteins [18,19]. Several factors can stimulate endoplasmic reticulum stress (e.g., obesity, hyperlipidemia, hyperglycemia), which is expected to occur specifically in the cells that produce proteins in large amounts (e.g., pancreatic beta cells and adipocytes) [17–19]. The endoplasmic reticulum stress induces an unfolded protein response, an adaptive response to reduce protein folding demand, inducing endoplasmic reticulum-associated degradation for cell survival [17–19]. When endoplasmic reticulum stress is unresolved, chronic unfolded protein response can lead to inflammation via the activation of the endoplasmic reticulum sensors, including protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK), inositol-requiring enzyme 1 α (IRE1 α), and activating transcription factor-6 (ATF6) that in turn trigger the formation of intracellular reactive oxygen species (ROS), and activation of nuclear factor- κ B and JUN N-terminal kinase [18,19]. While hepatic steatosis was suggested to result from chronic unfolded protein response in the hepatocytes, steatohepatitis and hepatocellular carcinoma were suggested to result from terminal and resistant unfolded protein response, respectively [17]. An adequate zinc supply plays a central role in the adaptation of the endoplasmic reticulum to oxidative stress and attenuation of inflammation. Indeed, zinc supplementation was shown to reduce oxidative stress and downregulate

inflammatory cytokines (e.g., tumor necrosis factor- α) [20–23]. As mentioned above, zinc deficiency originates from increased demand in endoplasmic reticulum stress, but also zinc deficiency itself can induce endoplasmic reticulum stress [24,25]. Homma et al. [25] showed that zinc deficiency exposed the Derlin-1 binding region of the copper-zinc superoxide dismutase (SOD1) and led to SOD1-Derlin-1 interaction, and this, in turn, triggered the endoplasmic reticulum stress response and upregulated expression of ZIP14, which is the zinc transporter abundant in the hepatocytes. In addition to the critical role of zinc, two major zinc transporter groups, including zinc transporter (ZnT) that regulates efflux of zinc from the cytoplasm and Zrt-, Irt-like protein (ZIP) that regulates the influx of zinc into the cytoplasm, were shown to be involved in the attenuation of oxidative stress and inflammation [26, 27]. Among the zinc transporters, hepatic ZIP14-mediated zinc transport was reported to play a critical role in the adaptation of the cells to the endoplasmic reticulum stress [26].

2.2. Zinc deficiency associated with diabetes mellitus

Patients with NAFLD can have zinc deficiency associated with diabetes mellitus. According to a cross-sectional study conducted among 2839 patients with type 2 diabetes mellitus, nearly 70% of patients had NAFLD diagnosed by ultrasound [28]. A more recent study showed that the prevalence of NAFLD diagnosed by magnetic resonance imaging was 76% in patients with insulin-naïve type 2 diabetes mellitus and only 8.8% in patients with type 1 diabetes mellitus [29]. Zinc plays a key role in insulin synthesis, storage, secretion, and signaling [30]. Pancreatic beta cells store insulin in the form of zinc-insulin crystals [30], and therefore pancreas has the highest zinc concentration per tissue wet weight compared with other organs [30,31]. The zinc concentration was found to be 50% lower in the pancreas of diabetic patients compared with the pancreas of non-diabetic patients [32]. Additionally, several studies showed that serum zinc concentration was lower in patients with type 1 or type 2 diabetes mellitus than patients without diabetes [33–35].

Zinc deficiency in diabetes mellitus is multifactorial. Zinc deficiency in type 2 diabetes mellitus could be secondary to increased oxidative stress and hyperinsulinemia, all of which increase the demand for zinc and result in intracellular depletion of zinc [18,36,37]. Specifically, hyperinsulinemia can deplete pancreatic zinc stores, inducing more insulin secretion, further reducing pancreatic zinc levels [36]. This vicious cycle in the form of exacerbation of hyperinsulinemia in diabetic patients can be overcome by zinc supplementation and reducing insulin production by the pancreatic beta cells [36,37]. A randomized, double-blind, placebo-controlled trial conducted in 200 adult subjects with prediabetes showed that the subjects who received 20 mg of zinc daily had decreased blood glucose levels, improved insulin resistance, and beta-cell function, and reduced progression to diabetes compared with the subjects who received placebo [38]. A meta-analysis that included placebo-controlled trials, showed that zinc supplement alone without co-supplements significantly lowered the fasting and 2-h post-prandial glucose levels, homeostatic model assessment for insulin resistance (HOMA-IR), and hemoglobin A1c [39].

Zinc deficiency in diabetes mellitus also can occur secondary to dysfunction of zinc transporters [30,40]. The gene SLC30A8 encodes for the zinc efflux transporter ZnT8 that plays a key role in zinc storage and insulin secretion in pancreatic beta cells [30,40]. The polymorphic variants of the gene SLC30A8, including rs13266634 and rs11558471, were shown to be associated with type 2 diabetes mellitus and glucose-increasing effect, respectively [41–43]. According to the results of a large meta-analysis that included 14 cohort studies, a higher daily zinc intake was shown to be associated with lower fasting glucose levels in subjects who had polymorphic variant rs11558471 of the gene SLC30A8 [42].

Zinc deficiency in diabetic patients also can result from hyperzincuria [44] that appears to be secondary to glycosuria, hyperglycemia

and/or decreased zinc absorption [45–47]. McNair et al. [45] showed a positive correlation between urinary zinc excretion and the degree of glycosuria in diabetic patients. Kinlaw et al. [46] reported a positive correlation between urinary zinc excretion and serum glucose levels in patients with type 2 diabetes mellitus. Additionally, they showed that patients with type 2 diabetes mellitus and proteinuria had a higher urinary zinc excretion than those without proteinuria [46]. Escobar et al. [47] showed that the levels of metallothionein were higher in the liver and small intestine of the rats with streptozotocin-induced diabetes compared with the control rats and attributed the decreased zinc absorption and hyperzincuria to the increased zinc intake secondary to hyperphagia in diabetic rats rather than diabetes-induced defect in zinc transport [47].

2.3. Zinc deficiency associated with obesity

Zinc appears to play an essential role in appetite regulation and obesity prevention through its interaction with the leptin hormone [48]. Leptin, a hormone that is secreted by adipocytes, inhibits hunger, controls energy balance, and thereby regulates body weight [49]. Zinc supplementation in rats that had high-fat/high-fructose diet-induced obesity significantly reduced leptin and insulin levels along with body weight and abdominal fat pad [50]. Liu et al. [51] reported a similar negative association between leptin and zinc levels showing that zinc deficiency enhanced leptin production and macrophage infiltration in the adipocytes of the high-fat diet-induced obese mice. Maxel et al. [52] showed that obese subjects had a downregulated zinc influx transporter ZIP14 expression compared with non-obese subjects and an upregulated ZIP14 expression after losing weight. Additionally, ZIP14 gene expression had a negative correlation with leptin gene expression and blood leptin levels [52].

A cross-sectional study conducted using US National Health and Nutrition Examination Survey 2011–2014 (NHANES) database showed a negative correlation between serum zinc levels and body mass index in children and adolescents [53]. A randomized, double-blind, placebo-controlled trial showed that adult obese subjects who had 30 mg of zinc daily for 15 weeks and a restricted-calorie diet had significantly reduced body weight, body mass index, waist circumference, and appetite score compared with obese subjects who had placebo and a restricted-calorie diet [54]. Another randomized, double-blind, placebo-controlled trial showed that adult obese or overweight subjects who had 30 mg of zinc daily and a restricted-calorie diet for 12 weeks had significantly reduced waist circumference, alanine aminotransferase, and gamma-glutamyl transpeptidase levels compared with obese subjects who had placebo and a restricted-calorie diet [55].

2.4. Zinc deficiency associated with hypertension

Although multiple hypotheses were proposed for zinc deficiency-induced hypertension, a murine study shed light on its mechanism. Williams et al. [56] showed that zinc deficiency-induced hypertension by upregulating the $\text{Na}^+ - \text{Cl}^-$ cotransporter and increasing sodium reabsorption, which was reversed by zinc repletion and administration of hydrochlorothiazide, an inhibitor of $\text{Na}^+ - \text{Cl}^-$ cotransporter. According to a meta-analysis that included data from nine randomized clinical trials, zinc supplementation significantly reduced systolic blood pressure without any significant effect on diastolic blood pressure [57].

2.5. Zinc deficiency associated with dyslipidemia

According to the results of a randomized, double-blind, placebo-controlled trial, obese subjects who received zinc gluconate 30 mg daily had reduced triglyceride levels compared with obese subjects who received placebo; however, they had no significant reduction in other lipid profile biomarker levels compared with the placebo group [58]. A meta-analysis that included nine randomized controlled trials showed

that patients with type 2 diabetes mellitus who had zinc supplementation had a significantly reduced triglyceride and total cholesterol levels compared with patients with type 2 diabetes mellitus who had placebo; however there was no significant improvement on high-density lipoprotein and low-density lipoprotein levels with zinc supplementation [59]. In contrast to the findings of these studies conducted in subjects with obesity and type 2 diabetes mellitus, a study conducted in healthy subjects showed that zinc supplementation lowered HDL levels, potentially increasing the risk of cardiovascular disease [60].

2.6. Zinc deficiency associated with decreased absorption from the gastrointestinal tract

In humans, zinc is absorbed from the small intestine [61]. The absorption of zinc was shown to be concentration-dependent, occurring at the highest rate in the jejunum and at the lowest rate in the ileum [61]. In rats, the highest zinc absorption was reported in the ileum [62]. While the resection of the distal small intestine resulted in a compensatory increase of zinc absorption in the proximal small intestine, the resection of the proximal small intestine did not increase zinc absorption in the distal small intestine [62]. Given zinc absorption in the small intestine, zinc deficiency can occur in patients with impaired small bowel absorption (e.g., short bowel syndrome, Crohn's disease, severe diarrhea) [62,63]. Zinc deficiency also occurs in patients with exocrine pancreatic insufficiency [64]. Taken altogether, zinc deficiency secondary to impaired small bowel absorption and pancreatic exocrine insufficiency may be playing a role in the development of NAFLD after pancreatectomy and pancreatoduodenectomy. In fact, several studies showed that patients undergoing pancreatectomy or pancreatoduodenectomy developed post-op NAFLD [65–67].

Besides the impaired small bowel absorption, pancreatic exocrine insufficiency, and pancreatoduodenectomy that can result in impaired zinc absorption, several other factors (e.g., low protein diet, toxic levels of cadmium, phytic acid in fiber-rich diet) also can reduce the zinc absorption from the gastrointestinal tract [68]. Specifically, patients with type 2 diabetes mellitus often have an increased fiber intake in their diet to achieve a better control on their blood glucose and lipid levels [69]. The phytic acid in a fiber-rich diet (e.g., beans, nuts, grains, and seeds) can reduce zinc absorption [68]. A cross-sectional study conducted in healthy and diabetic patients showed a positive association between dietary fiber and (calcium)(phytic acid)/zinc molar ratio [70]. It is unknown whether phytic acid-induced zinc deficiency results in NAFLD, and the results of the animal studies are conflicting. Omoruyi et al. [71] observed that there was no significant change in the lipid profile of the phytic acid-treated diabetic rats compared with the lipid profile of the normal control rats and untreated diabetic rats. Also, they showed that phytic acid-fed diabetic rats had significantly increased alanine aminotransferase, alkaline phosphatase, and inflammatory biomarker levels, including interleukin-1 beta and interleukin-6 [71]. In contrast, Sekita et al. [72] showed that phytic acid improved high sucrose-induced hepatic steatosis in rats by altering the gut microbiota and downregulating the genes regulating lipogenesis.

2.7. Zinc deficiency associated with inadequate dietary zinc intake

Several reports link the development of obesity to empty calorie intake (e.g., solid fat, added sugars) [73–75] which can result in micronutrient deficiency. According to a cross-sectional study using the NHANES database, almost 40% of total caloric intake in children between the ages of 2 and 18 was from solid fats (e.g., pizza, whole milk, regular cheese, fatty meats, grain desserts) and added sugars (e.g., soda, fruit drinks, candy, grain and dairy desserts) [75]. A survey conducted among 645 children between ages 1 and 5 revealed a negative relationship between milk intake and sweetened beverages (i.e., juice drinks, soda, and added sugar beverages), leading to multiple nutrient deficiencies [76]. A 26-week randomized, double-blind,

Table 1

Summary of human studies that used zinc supplementation in subjects with nonalcoholic fatty liver disease (NAFLD) risk factors and conditions associated with NAFLD.

NAFLD risk factor/condition associated with NAFLD	Study	Study population	Study design	Zinc supplementation (intervention)	Study duration	Summary of study outcome
Oxidative stress and inflammation	Prasad et al. (2004) [20]	Healthy subjects, age range: 19–50 years	Randomized, placebo-controlled	Zinc gluconate 45 mg daily	8 weeks	Reduction in lipid peroxidation products and downregulation of inflammatory cytokines in the intervention group
	Prasad et al. (2007) [23]	Healthy subjects, age range: 55–87 years	Randomized, double-blinded, placebo-controlled	Zinc gluconate capsule (15 mg elemental zinc), one capsule before breakfast, and two capsules at bedtime	12 months	Reduction in the incidence of infections, tumor necrosis factor- α , and oxidative stress markers in the intervention group
	Bao et al. (2008) [21]	Subjects with sickle cell disease, mean age (SD): 32.9 (9.7) years	Randomized, placebo-controlled	Zinc acetate 25 mg three times a day	3 months	Reduction in oxidative stress, and inflammatory cytokines, increase in red blood cell, and hemoglobin/hematocrit in the intervention group
Diabetes mellitus/insulin resistance	Ranasinghe et al. (2018) [38]	Subjects with prediabetes, mean age (SD): 51.8 (7.3) years	Randomized, double-blinded, placebo-controlled	Zinc 20 mg daily	12 months	Reduction in blood glucose level, insulin resistance, total cholesterol, low-density lipoprotein, and progression to diabetes, and improvement in beta-cell function in the intervention group
	Wang et al. (2019) [39]	Varies by study	Meta-analysis of 20 randomized, placebo-controlled trials	Varies by study	Varies by study	Reduction in fasting and 2-h postprandial glucose levels, homeostatic model assessment for insulin resistance (HOMA-IR), and hemoglobin A1c in the intervention group
	Kanoni et al. (2011) [42]	Subjects without type 2 diabetes mellitus, age range as mean (SD): 11.2 (0.7)–74.8 (2.9)	Meta-analysis of 14 cohort studies	Average total zinc intake from food sources and supplements: 13.8 mg daily, range: 8.7–17.3 mg daily	Varies by study	Inverse correlation between fasting glucose levels and total zinc intake in subjects with SLC30A8 rs11558471 variant
Obesity	Khorsandi et al. (2019) [54]	Subjects with obesity, mean age (SD) in zinc group: 35.63 (3.2), in placebo group: 32.95 (1.7) years	Randomized, double-blind, placebo-controlled	Zinc 30 mg daily	15 weeks	Reduction in body weight, body mass index, waist circumference, and appetite score in the intervention group
	Fathi et al. (2020) [55]	Overweight and obese subjects, age range: 18–65 years	Randomized, double-blind, placebo-controlled	Zinc 30 mg daily	12 weeks	Reduction in waist circumference, alanine aminotransferase, and gamma-glutamyl transpeptidase levels in the intervention group
Hypertension	Mousavi et al. (2020) [57]	Subjects with type 2 diabetes mellitus, prediabetes, diabetic retinopathy, polycystic ovary syndrome, hypertension, obesity, and subjects on hemodialysis, age range as mean: 25–57 years	Meta-analysis of 9 randomized, controlled trials	Varies by study (elemental zinc 5–150 mg daily)	Varies by study (1–12 months)	Reduction in systolic blood pressure in the intervention group
Dyslipidemia	Hooper et al. (1980) [60]	Healthy male subjects, age range: 23–35 years	Zinc sulfate 440 mg daily	Zinc sulfate 440 mg daily	5 weeks	Reduction in high-density lipoprotein levels
	Payahoo et al. (2013) [58]	Subjects with obesity, age range: 18–45 years	Randomized, double-blind, placebo-controlled	Zinc gluconate 30 mg daily	1 month	Reduction in triglyceride levels in the intervention group
	Asbaghi et al. (2020) [59]	Subjects with type 2 diabetes mellitus	Meta-analysis of 9 randomized, controlled trials, age range as means: 48.2–65.9	Varies by study (zinc sulfate 30–660 mg daily, zinc gluconate 50–240 mg daily)	Varies by study (6–52 weeks)	Reduction in triglyceride and total cholesterol levels in the intervention group

placebo-controlled trial conducted among 87 obese women showed that multivitamin and mineral supplementation significantly decreased body weight and fat mass, increased resting energy expenditure, and improved lipid profile compared to placebo [77]. Taken together, subjects with NAFLD should be evaluated for adequate zinc and other micronutrients in their diet.

3. Interactions of zinc with other micronutrients: key points to know in zinc supplementation

Human studies demonstrated benefits of zinc supplementation in

subjects with NAFLD risk factors. Table 1 shows several clinical trials and meta-analysis studies where zinc supplementation outcomes were assessed without co-supplements. Zinc has a good safety profile; however, excessive zinc intake can be toxic. A total of daily 150 mg to 450 mg zinc intake can result in copper deficiency and several other complications (e.g., anemia, altered iron metabolism, decreased HDL level, neurotoxicity) [78]. Excess zinc intake can upregulate intestinal metallothionein, a metal-binding protein, displace zinc and bind dietary copper with high affinity, and reduce copper absorption leading to copper deficiency [78,79]. Therefore, blood copper levels should be monitored during zinc supplementation to prevent zinc-induced copper

deficiency [79].

4. Laboratory evaluation of zinc levels: key points to know in the assessment of zinc levels

According to a systematic review, zinc levels in healthy subjects can be reliably evaluated in the plasma, urine, or hair [80]. A study that assessed plasma zinc kinetics showed that after 5-week of zinc depletion in humans, plasma and urine zinc concentrations decreased by 65% and 96%, respectively [81], demonstrating the response of plasma zinc level to zinc depletion. Although blood zinc concentration is reliable to assess zinc status [80], caution is needed in the interpretation of zinc levels as several factors can interfere with blood zinc levels (e.g., inflammation, hypoalbuminemia, fasting, starvation, pregnancy, intravascular hemolysis, myocardial infarction, contamination of biological samples with zinc) [79,82,83]. Hypoalbuminemia can spuriously lower blood zinc levels as albumin is the primary transporter for zinc [79,84]. The systemic inflammatory response also was reported to cause low blood zinc levels, and checking C-reactive protein level was recommended for reliable zinc level in patients with a systemic inflammatory response [79,85]. Although the utility of assessing zinc levels in every patient with NAFLD remains to be further defined, plasma zinc levels should be assessed in subjects with NAFLD who have advanced fibrosis/cirrhosis for identification and treatment of zinc deficiency and interpreted by taking potential interfering factors into account, specifically inflammation and hypoalbuminemia that are common in these patients.

5. Conclusions

Zinc deficiency in patients with NAFLD is associated with multiple factors, including endoplasmic reticulum stress and inflammation, insulin resistance, diabetes, dyslipidemia, obesity, hypertension, decreased absorption from the gastrointestinal tract, and inadequate dietary intake. Several studies have suggested that zinc supplementation has beneficial metabolic effects in patients with the NAFLD risk factors. Plasma zinc levels should be evaluated in patients with NAFLD and NAFLD risk factors, specifically in those with advanced hepatic fibrosis/cirrhosis. Randomized placebo-controlled trials are required to verify the beneficial effects of zinc supplementation in patients with NAFLD, specifically to evaluate the histological improvement of hepatic steatosis and fibrosis.

Author contributions

Mary Barbara, MD contributed to the drafting and writing the manuscript and performed a critical review of the manuscript for important intellectual content. Ayse L. Mindikoglu, MD, MPH contributed to the drafting and writing the manuscript and performed a critical review of the manuscript for important intellectual content.

Declaration of competing interest

None of the authors has a conflict of interest.

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