BMC Nutrition

RESEARCH Open Access

The effects of zinc supplementation on the metabolic factors in patients with non-alcoholic fatty liver disease: a randomized, double-blinded, placebo-controlled clinical trial

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Abstract

Background Non-alcoholic fatty liver disease (NAFLD) is associated with metabolic factors including obesity, dyslipidemia, insulin resistance, oxidative stress, and elevated inflammatory factors. Zinc (Zn) supplementation has been investigated as a potential adjunctive therapy in managing NAFLD outcomes.

Methods In this randomized, double-blinded, controlled clinical trial, 50 overweight or obese participants with NAFLD were randomized into 2 groups of 25 and received either 30 mg of daily Zn or a placebo for 8 weeks. Both groups were invited to follow a balanced energy-restricted diet and physical activity recommendations.

Results Based on the between-group comparison, Zn supplementation caused a significant increase in the Zn level ($P < 0.001$) and a significant decrease in weight ($P = 0.004$), body mass index (BMI) ($P = 0.002$), waist circumference ($P = 0.010$), aspartate transaminase (AST) ($P = 0.033$), total cholesterol (TC) ($P = 0.045$), and low-density lipoprotein cholesterol (LDL-C) ($P = 0.014$), but it had no significant effect on alanine transaminase (ALT), fasting blood sugar (FBS), insulin, homeostasis model assessment of insulin resistance (HOMA-IR), high-density lipoprotein (HDL), triglyceride (TG), high-sensitivity C-reactive protein (hs-CRP), malondialdehyde (MDA), and total antioxidant capacity (TAC) ($P > 0.05$).

Conclusion The results of the present study indicated that 8-week supplementation of 30 mg daily Zn may increase the Zn serum level and decline anthropometric parameters, AST, TC, and LDL-C in NAFLD patients, so further research is suggested in the future.

Trial registration The trial was retrospectively registered at IRCT.ir as IRCT20191015045113N1 (December/8/2019).

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inactivation of the glycogen synthase kinase-3β (GSK-3β) enzyme. This enzyme is a protein kinase related to IR, and Zn inactivates GSK-3β by the PI3 / AKT signaling pathway. Moreover, Zn has beneficial effects on IR due to leptin. Various studies have shown that leptin depletion can be considered a factor in increasing IR as described in the previous part [22, 23].

The effects of Zn on the hs-CRP

Inflammation causes damage to the hepatocytes and the progression of liver disease [34]. Based on the results of the present study, consuming the Zn supplement had no significant effect on the hs-CRP level. Although the results of some studies were in line with those of our study [10, 14], some studies showed inconsistent results and Zn intake reduced the level of hs-CRP [13, 35, 36]. Gut-liver axis can play an effective role in liver disease and increase inflammatory factors [37]. According to studies, Zn supplementation can have positive effects on the gut-liver axis by reducing endotoxemia, reducing oxidative stress and the production of inflammatory cytokines, stabilizing the intestinal defense barrier, and exerting positive effects on hepatocyte apoptosis [38, 39]. Foster and Samman in their study found that Zn supplementation in higher doses equal to 45 mg/d can reduce pro-inflammatory factors. However, at low doses, the effects were different, so even at doses less than 10 mg/d, they had the opposite effect and increased the inflammatory mediators. Consequently, they reported a dose-dependent response of inflammatory factors to the Zn supplementation [40]. As a result, it can be said that one of the possible reasons for the insignificancy of Zn supplementation on inflammatory factors and also discrepancies in the results of different studies in comparison with our research could be the selected dose of 30 mg/d in our study and different doses in other studies.

The effects of Zn on the oxidative stress

MDA as a marker of fat oxidation and TAC are components of oxidative stress that play an important role in NAFLD. Although we observed a decrease in the MDA level and an increase in TAC in this study, these changes were not statistically significant. While some previous studies were in line with the present study and Zn supplementation did not have a significant effect on MDA [36, 41], in some studies, this factor was significantly reduced [13, 14]. Regarding the TAC, the results of a previous study were similar to those of our study [14], while in some other studies a significant increase in TAC was observed by means of Zn intake [10, 36]. Zn increases the antioxidant activation of proteins, molecules, and enzymes such as glutathione, catalase, and superoxide dismutase and reduces the activity of oxidant-promoting enzymes such as nitric acid synthetase [42, 43]. The difference in the duration of the intervention, the dose of supplementation with Zn as well as the serum Zn level in the studies are likely to be the possible reasons for not relevant effect of Zn supplementation on oxidative stress factors.

Strengths and limitations of the study

Measuring serum Zn and controlling the confounding effect of food intake by prescribing both groups a low-calorie diet were the strengths of this study. The short duration of the study and small sample size were the limitations of this study. Furthermore, the results of this study cannot be generalized to the entire society and these results should be assessed by future studies.

Conclusion

Taking 30 mg/d of Zn supplement in addition to a balanced, energy-restricted diet for 8 weeks may increase the Zn serum level and decrease the weight, BMI, waist circumference, AST, TC, and LDL-C in NAFLD patients, so further studies are recommended in the future.

Acknowledgements

The authors would like to thank the Vice-Chancellor of Research and Technology of Shiraz University of Medical Sciences, Shiraz, Iran for the financial support of this study, and also the Center for Development of Clinical Research of Nemazee Hospital and Dr. Nasrin Shokrpour for editorial assistance. Moreover, the authors also honestly thank the staff and patients of Motahari and Imam Reza Clinics, Shiraz University of Medical Sciences, Shiraz, Iran who contributed to this study.

Authors' contributions

M.H.E. supervised the study. M.H.E. and S.M.A.R. conceived and designed the study. S.M.A.R. collected the data and wrote the draft. F.M. analyzed the data and wrote the draft. F.E. accomplished clinical counseling and referral of patients and data collecting. H.G. analyzed and interpreted data. N.M. collected the data and prepared the draft. All the authors approved the final version of the manuscript and critically revised it. The authors would like to thank also Center for Development of Clinical Research of Namazee Hospital and Dr. Nasrin Shokrpour for editorial assistance.

Funding

This study was financially supported by the Vice-Chancellor of Research and Technology of Shiraz University of Medical Sciences, Shiraz, Iran.

Data Availability

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran (Code: IR.SUMS.REC.1397.105). This study was also performed based on the declaration of Helsinki and good clinical practice guidelines. The informed consent form was completed for all the patients.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.