ROLE OF DIETARY ZINC IN *Clostridioides difficile* INFECTION

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BACKGROUND AND OBJECTIVE

➢ *Clostridioides difficile* (*C. difficile*) infection (CDI) is associated to nosocomial diarrhea. Zinc (Zn) is an essential micronutrient acquired through the diet and is recommended by the World Health Organization (WHO) in cases of acute diarrhea. This review aimed to verify the association between zinc and CDI.

METHOD

A search was performed in the PubMed database → Descriptors: Zinc and *C. difficile*

Published from December 2016 to July 2020 → Six publications were included in the review

RESULTS

Three studies were performed in humans through a case study and two retrospective cohort studies. The case study reported low serum zinc levels (36 µg / dL) in an adult patient with recurrent CDI receiving vancomycin and zinc supplementation, which in turn prevented new recurrent CDI episodes. [1]

In a retrospective cohort study performed with 113 patients, Zinc was the most common micronutrient deficiency in patients with CDI. In another retrospective cohort study performed with 127 patients, low zinc levels were associated with higher rates of CDI recurrence after fecal microbiota transplantation (FMT) when controlling for risk factors for FMT failure, and zinc supplementation in the setting of zinc deficiency was associated with a reduced recurrence rate. [4,5]

In contrast, a preclinical study using CDI model in mice demonstrated that high zinc levels in the diet (1000 mg / kg) increased the severity of the disease, increasing the activity of the toxin and altering the immune response in mice. [2]

The protein calprotectin (CP), a heterodimeric protein that has the ability to bind to zinc and is an important indicator of inflammation, was also investigated for the limitation of Zn *to C. difficile.* It was observed that mice with CP deficiency were unable to contain the growth of *C. difficile.* Other research has shown that a putative zinc transporter, ZupT, is employed by *C. difficile* as a strategy to survive CP-mediated metal limitation and also compete for essential nutrients in the CDI.[3,6]

CONCLUSION

In human with CDI, zinc supplementation showed to plays an important role in reducing recurrence of CDI. While in mice, zinc has been associated to increase the severity of disease induced by CDI. Future work is needed to better understand the response of *C. difficile* to zinc.

REFERENCES

1. Parvataneni S, Dasari AR. Zinc Level and Its Role in Recurrent *Clostridium difficile* Infection: A Case Report and Literature Review. *J Investig Med High Impact Case Rep*. 2020;8:2324709620941315. doi:10.1177/2324709620941315.
2. Zackular JP, Moore JL, Jordan AT, et al. Dietary zinc alters the microbiota and decreases resistance to *Clostridium difficile* infection [published correction appears in Nat Med. 2016 Dec 6;22(12):1502]. *Nat Med*. 2016;22(11):1330-1334. doi:10.1038/nm.4174.
3. Lopez CA, Beavers WN, Weiss A, et al. The Immune Protein Calprotectin Impacts *Clostridioides difficile* Metabolism through Zinc Limitation. *mBio*. 2019;10(6):e02289-19. Published 2019 Nov 19. doi:10.1128/mBio.02289-19.
4. Niccum BA, Stein DJ, Behm BW, Hays RA. Zinc Deficiency and the Recurrence of *Clostridium difficile* Infection after Fecal Microbiota Transplant: A Retrospective Cohort Study. *J Nutr Metab*. 2018;2018:9682975. Published 2018 Oct 10. doi:10.1155/2018/9682975.
5. Shin JH, Chaplin AS, Hays RA, et al. Outcomes of a Multidisciplinary Clinic in Evaluating Recurrent *Clostridioides difficile* Infection Patients for Fecal Microbiota Transplant: A Retrospective Cohort Analysis. *J Clin Med*. 2019;8(7):1036. Published 2019 Jul 16. doi:10.3390/jcm8071036.
6. Zackular JP, Knippel RJ, Lopez CA, et al. ZupT Facilitates *Clostridioides difficile* Resistance to Host-Mediated Nutritional Immunity. *mSphere*. 2020;5(2):e00061-20. Published 2020 Mar 11. doi:10.1128/mSphere.00061-20.