

EDITORIAL

Intra-nasal zinc level relationship to COVID-19 anosmia and type 1 interferon response: A proposal

Abstract

Anosmia is common among COVID-19 patients and anosmia assessment is proposed to be useful in the early diagnosis and prognosis of patients. Data on the pathogenesis of anosmia during COVID-19 suggest potential olfactory nerve involvement. Zinc is an essential micronutrient that regulates the immune responses, and zinc deficiency is known to induce anosmia and ageusia. We previously proposed that a drop in nasal zinc level is a normal nasal immune response to acute viral infections, including SARS-CoV-2 infection, and play a role in the pathogenesis of anosmia. The drop in the local zinc level in response to SARS-CoV-2 may lead to lower type 1 interferons and shift toward Th2 immune responses; if prolonged, it may lead to increased viral replication and more severe disease. In people who are at risk for baseline systemic zinc deficiency, such as the elderly and those with chronic diseases such as, chronic lung disease, diabetes, cardiovascular disease, and cancer, SARS-CoV-2 infection-induced drop in nasal zinc level may be more severe and prolonged and lead to an insufficient anti-viral nasal immune response and control the spread of the virus systemically and to the lungs. A better understanding of the clinical implications of baseline systemic zinc deficiency on anosmia and nasal immune responses may allow the development of new treatment strategies to slow down or stop the systemic invasion of SARS-CoV-2.

KEYWORDS

anosmia, comorbidity, COVID-19, deficiency, diabetes, elderly, immune system, interferon, SARS, zinc

A significant portion of the common cold and COVID-19 patients develop anosmia and taste dysfunction, and the pathogenesis is thought to be multi-factorial, including inflammation, obstruction, and neuro-epithelial damage.¹

Wessels et al has recently proposed that zinc deficiency is a predisposing factor for SARS-CoV-2 infection.² As with every infection, the virus further decreases the serum and nasal zinc; which may reach a critically low level.² We have recently proposed that the local drop in nasal zinc levels may induce transient anosmia due to decreased function of zinc-dependent metalloenzyme carbonic anhydrase (CA); which maintains taste and smell function.³ The drop in zinc level may also lead to a shift toward Th2 cytokine predominance with decreased Th1 cytokine production.⁴ Recent data suggest that early type 1 interferon response is important to control SARS-CoV-2 replication.^{5,6} Here we build on to our initial proposal³ and suggest that SARS-CoV-2 infection of the nasal epithelium may have differential effects on the olfactory nerve function and nasal immune responses among people with normal baseline zinc level and those who are zinc deficient. People with baseline zinc deficiency may have prolonged anosmia and blunted interferon type 1 responses and more severe COVID-19 (Figure 1).

As an essential micronutrient and the second most abundant trace element in the human body after iron, zinc (Zn) is taken in through food and distributed throughout the whole body.⁷ It plays a role in every aspect of an immune response, including thymus health.⁷ Zinc deficiency is well-known to cause anosmia and taste dysfunction.⁸

During immune activation and infections, zinc is redistributed in tissues and immune system cells.^{7,9,10} This is important to mount appropriate host defenses against invading pathogens.

A local shift in Zn homeostasis in the nose during common colds may lead to a local Th2 phenotype.¹¹ Early Th2 immune responses in the nasopharynx during viral upper respiratory tract infections may have various effects. Among people with a history of chronic rhinitis, where the predominant cytokine environment is Th2, there is a persistence of seasonal human coronaviruses HCoV-NL63 (uses ACE-2 receptor), OC43, and 229E in the nose without symptoms.^{12,13} This may potentially suggest that COVID-19 positive people with chronic rhinitis may be at higher risk for asymptomatic shedding.

The data show that, in some patients, Zn supplementation reduces the risk for respiratory infections, and high dose zinc lozenge

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2020 The Authors. *Laryngoscope Investigative Otolaryngology* published by Wiley Periodicals LLC, on behalf of The Triological Society.

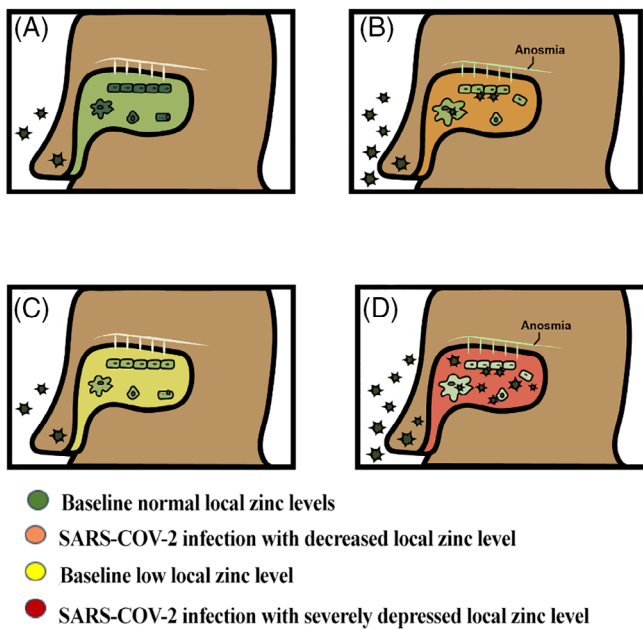


FIGURE 1 SARS-CoV-2 infection in the nose, when compared with healthy individuals A, may lead to a drop in local zinc levels, B, and may lead to anosmia. In patients who are already zinc deficient, C, such as patients with diabetes, vegetarians or elderly patients, intranasal zinc levels may be low at baseline and become severely depressed due to SARS-CoV-2 infection, D. This may lead to ineffective immune responses in the nose with higher virus replication. A, Healthy (normal local zinc levels). B, During COVID-19 (low local zinc levels). C, Zinc deficient person (low zinc levels at baseline). D, Zinc deficient COVID-19 infected person (severely low local zinc levels)

treatment of four COVID-19 patients (ages between 26 and 63 years old, with a history of exposure to confirmed COVID-19 patients) at George Washington University has shown clinical benefit.^{11,14} We propose that during acute HCoV and SARS-CoV-2 infections an appropriate local host immune response may include an initial temporary Zn accumulation in the immune cells with a drop in nasopharyngeal Zn level.¹⁵ This transient nonproductive immune response may induce type 2 cytokines (such as IL4 and IL13) with reduced ACE-2 expression, sneezing, anosmia, and poor taste early on to prevent the virus from establishing a productive infection (Figure 1). Subsequently, with the virus's entry into the cells and the onset of active replication, a type I innate immune response will be activated with type 1 interferon release and suppress SARS-CoV-2 replication and improve the outcome in infected patients.⁵ In *in vitro* experiments, interferon- β -1a treatment of Vero E6 cells 1 hour after SARS-CoV-2 infection inhibited viral replication and clinical trials showed promising results.⁶ Recently, data from a phase 2 double-blind placebo-controlled clinical trial with interferon- β -1a treatment inhaled once daily within 3 days of symptom onset showed favorable results among 101 COVID-19 hospitalized or high-risk patients (ie, those with diabetes or elderly) treated by nine specialists, and lowered the risk of developing the severe disease among 79% of those treated compared with placebo.¹⁶

The broader immune system activation will control and clear the viral replication and induce memory immune responses. Since the nasal mucosa is in continuum with the larger mucosal system (gastrointestinal [GI], respiratory, urinary, and genital tracts), appropriate nasal immune activation will prepare the lungs for a proper immune response to the virus in case there is aspiration or inhalation due to high viral load.¹⁷ In animal models, activation of the nasal mucosa by viral antigens was shown to prime the immune environment in the lungs by increasing the infiltration with activated macrophages in the absence of direct pulmonary infection.¹⁷ A recent community-based cohort study conducted in London, UK, among 567 participants, showed that 69.8% of those with complete anosmia were more likely to develop IgG antibody against SAR-CoV-2 as compared with 23.6% of those who had partial or 6.6% who had no anosmia.¹⁸ Most patients, 52.1%, with anosmia had mild disease with no lower respiratory symptoms such as cough.¹⁸ The data supports our proposal that anosmia is an indication of an appropriate immune response to viral infections in the nasopharynx. The article went on to conclude that the acute loss of smell should be used as a criterion for the processes of containing the spread of SAR-CoV-2.¹⁸ This further demonstrates the importance of identifying anosmia in patients in regard to postural infections such as SAR-CoV-2.

In individuals who are zinc deficient at baseline, such as the elderly, nursing home residents, those with chronic obstructive pulmonary disease (COPD), bronchial asthma, cardiovascular diseases, autoimmune diseases, kidney diseases, dialysis, obesity, diabetes, cancer, atherosclerosis, liver damage/cirrhosis and immunosuppression, there may be a nonproductive immune response, insufficient Th1 response and inadequate type 1 interferon release with faster disease progression, invasive disease and worse outcome.² Among people with low baseline zinc levels but no comorbidities, there may be prolonged asymptomatic shedding and invasive disease but less severe outcome.²

Anosmia may be an indicator of acute viral infection, early non-productive immune response, and COVID-19 prognosis. Yan CH and colleagues from the University of California San Diego observed that patients with anosmia were less likely to require hospitalization and that COVID-19 resolved together with the resolution of anosmia.¹⁹ Another study from Iran suggested that patients with anosmia were less likely to have fever, cough, and dyspnea compared with those without anosmia (87.9% vs 37.38%, 67.7% vs 18.98% and 18.6% vs 14.38%, respectively) and hospitalization rate was low (1.1%) among patients with anosmia.²⁰

In healthy people with a viral infection, zinc levels dropped below average in 60% of those tested and stayed low for several weeks.²¹ Among patients admitted to the intensive care unit with critical illness and sepsis, serum zinc levels were low; which correlated with increased cytokine levels and worse cardiovascular outcomes.²² In the mouse model, dietary zinc deficiency was shown to potentiate ventilator-induced lung injury.²³ Wessels et al have recently demonstrated that zinc supplementation improved the clinical outcome in mouse acute lung injury models.²⁴ Baseline serum zinc level may be measured among people admitted to the hospital with signs and

symptoms of COVID-19 and planned for intubation, and those who are deficient may be treated.²⁵ It would be useful to look at the clinical and anosmia outcome of zinc supplementation among people of different age groups, with and without comorbidities, and are at risk for zinc deficiency at baseline as well.^{23,24} Smell and taste decline with aging and by certain treatments, such as chemotherapy. Aliani et al investigated the impact of oral zinc supplementation on anosmia in the elderly; the results were inconclusive.²⁵ Lyckholm et al investigated whether oral zinc supplementation would restore taste and smell dysfunction due to chemotherapy.²⁶ There was no significant difference between the control group and the group receiving zinc supplementation.²⁶ The potential reason behind the failure of oral zinc supplementation to restore smell and taste in these two studies may be due to the fact that the mechanisms of anosmia in the elderly and those who are undergoing chemotherapy are different from those with acute viral infection. For example, during chemotherapy treatment, there is both direct damage to the neuronal cells and suppression of the carbonic anhydrase enzyme. In addition, patients undergoing chemotherapy tend to take various other medications which can induce anosmia. During aging, there are many factors that can induce anosmia. Chronic rhinitis is associated with anosmia and occurs more frequently in the older individuals, and certain medications such as beta-blockers and ACE inhibitors that induce anosmia are more commonly prescribed to older individuals.²⁷

In another randomized, double-blind, placebo-controlled crossover study, Henkin et al looked at the effects of zinc sulfate supplementation on taste and smell dysfunction among 106 patients with taste and smell dysfunction secondary to a variety of etiological factors.²⁸ They did not observe a significant difference in anosmia between zinc sulfate vs placebo treatment groups.²⁸ This could be explained by the fact that the study enrolled patients with more than 10 different underlying conditions, each with a small sample size, and the pathogenesis of anosmia may be different in each one of these cohorts and may not be related to low local zinc levels. In addition, almost half of the enrolled patients had post influenza related anosmia; which could have improved over time regardless of zinc supplementation, even during placebo period. Future studies assessing the impact of zinc supplementation on anosmia and COVID-19 outcome should consider patient demographics, other underlying conditions.

Nasal and salivary zinc levels may be compared with assess whether there is appropriate gastrointestinal absorption and penetration into the nasal mucosa; however, local nasal and oral mucosal zinc levels may be low despite normal systemic zinc levels. Clinical studies assessing the effect of zinc supplementation on oro-nasopharyngeal Sars-CoV-2 responses should collect data on medication exposure. For example, an angiotensin-converting enzyme (ACE) inhibitor commonly used for the treatment of hypertension, captopril, may decrease zinc levels over a period of 6 months and this may be associated with respiratory side effects of ACE inhibitors.²⁹

Direct intra-nasal zinc administration has been shown to induce olfactory nerve damage and anosmia.³⁰ Since SARS-CoV-2 is found not only in the nose but also in the mouth and gastrointestinal tract, the clinical trials assessing the effect of zinc supplementation on

SARS-CoV-2 response may compare the effect of supplementation with oral zinc formulations at maximum daily dosages recommended by the FDA with placebo.³¹ The study groups may be younger individuals (<65 years of age) who are at risk for systemic zinc deficiency prior to COVID-19, such as people with diabetes or those with poor nutrition. Prolonged use of thiazide diuretics could deplete zinc tissue levels.³² Studies may compare the rate of anosmia and COVID-19 outcome between people who are on medications that lower systemic zinc levels such as ACE inhibitors and thiazide diuretics those who are not.

The studies on coronavirus seroconversion have shown that nasal immunoglobulin responses are essential in controlling viral replication and disease severity.³³ Data are needed on the relationship between the occurrence of anosmia, nasal and serum zinc levels, nasal and serum anti-SARS-CoV-2 immune responses, as well as COVID-19 severity and prognosis. A better understanding of the mechanisms of zinc's role in anosmia may also help develop criteria for early zinc supplementation, antiviral, convalescent plasma, recombinant antibody treatment, and immunization with or without adjuvanted vaccines that may be more effective among those immune deficient.

CONFLICT OF INTEREST

There are no conflicts of interest.

Ozlem Equils MD, FAAP¹ 
 Klaudi Lekaj¹
 Arthur Wu MD, FARS²
 Sahar Fattani¹ 
 Gene Liu MD, MMM, FACS²
 Lothar Rink PhD³

¹MiOra, Public Health Education Foundation, California, Los Angeles, USA

²Cedars-Sinai Medical Center, Division of Otolaryngology, California, Los Angeles, USA

³Institute of Immunology, RWTH Aachen University Hospital, Aachen, Germany

Correspondence

Ozlem Equils, MiOra Foundation, 17328 Ventura Blvd. No 190, Los Angeles, CA 91316.
 Email: ozlem@miora.org

ORCID

Ozlem Equils  <https://orcid.org/0000-0002-8707-9019>

Sahar Fattani  <https://orcid.org/0000-0002-8173-8570>

REFERENCES

- Mullol J, Albid I, Mariño-Sánchez F, et al. The loss of smell and taste in the COVID-19 outbreak: a tale of many countries. *Curr Allergy Asthma Rep.* 2020;20(10):1-5.
- Wessels I, Rolles B, Rink L. The potential impact of zinc supplementation in COVID-19 pathogenesis. *Front Immunol.* 2020;11:1712.

3. Equils O, Lekaj K, Fattani S, Wu A, Liu G. Proposed mechanism for anosmia during COVID-19: the role of local zinc distribution. *J Trans Sci.* 2020;7:1-2. <https://www.oatext.com/pdf/JTS-7-397.pdf>.
4. Prasad AS. Effects of zinc deficiency on Th1 and Th2 cytokine shifts. *J Infect Dis.* 2000;182:S62-S68.
5. Wadman M. Can interferons stop COVID-19 before it takes hold? *Sci Mag.* 2020;369(6500):125-126. <https://doi.org/10.1126/science.369.6500.125>.
6. Clementi N, Ferrarese R, Criscuolo E, et al. Interferon- β -1a inhibition of severe acute respiratory syndrome–coronavirus 2 in vitro when administered after virus infection. *J Infect Dis.* 2020;222:722-725.
7. Wessels I, Maywald M, Rink L. Zinc as a gatekeeper of immune function. *Nutrients.* 2017;9(12):1286.
8. Komai M, Goto T, Suzuki H, Takeda T, Furukawa Y. Zinc deficiency and taste dysfunction; contribution of carbonic anhydrase, a zinc-metalloenzyme, to normal taste sensation. *Biofactors.* 2000;12(1-4): 65-70.
9. Wessels I, Rink L. Micronutrients in autoimmune diseases: possible therapeutic benefits of zinc and vitamin D. *J Nutr Biochem.* 2020;77: 108240.
10. Honscheid A, Rink L, Haase H. T-lymphocytes: a target for stimulatory and inhibitory effects of zinc ions. *Endocr Metab Immune Disord Drug Targets.* 2009;9(2):132-144.
11. Skalny AV, Rink L, Ajsuvakova OP, et al. Zinc and respiratory tract infections: perspectives for COVID 19. *Int J Mol Med.* 2020;46(1): 17-26.
12. Deming ME, Chen WH. COVID-19 and lessons to be learned from prior coronavirus outbreaks. *Ann Am Thorac Soc.* 2020;17:790-794.
13. Cho GS, Moon BJ, Lee BJ, et al. High rates of detection of respiratory viruses in the nasal washes and mucosae of patients with chronic rhinosinusitis. *J Clin Microbiol.* 2013;51(3):979-984.
14. Finzi E. Treatment of SARS-CoV-2 with high dose oral zinc salts: a report on four patients. *Int J Infect Dis.* 2020;99:307-309.
15. Klemens, C., Rasp, G., Jund, F., Hilgert, E., Devens, C., Pfrogner, E., & Kramer, M. F. (2007). Mediators and cytokines in allergic and viral-triggered rhinitis. In *Allergy & Asthma Proceedings* (Vol. 28, No. 4).
16. Synairgen Research Ltd. (2020). Trial of Inhaled Anti-viral (SNG001) for SARS-CoV-2 (COVID-19) Infection. ClinicalTrials.gov identifier NCT04385095.
17. Dwivedy A, Aich P. Importance of innate mucosal immunity and the promises it holds. *Int J Genel Med.* 2011;4:299.
18. Makaronidis J, Mok J, Balogun N, et al. Seroprevalence of SARS-CoV-2 antibodies in people with an acute loss in their sense of smell and/or taste in a community-based population in London, UK: an observational cohort study. *PLoS Med.* 2020;17(10):e1003358.
19. Yan, C. H., Faraji, F., Prajapati, D. P., Boone, C. E., & DeConde, A. S. (2020). Association of chemosensory dysfunction and Covid-19 in patients presenting with influenza-like symptoms. In *International Forum of Allergy & Rhinology.*
20. Bagheri, S. H. R., Asghari, A. M., Farhadi, M., Shamshiri, A. R., Kabir, A., Kamrava, S. K., ... & Ghalehbaghi, B. (2020). Coincidence of COVID-19 epidemic and olfactory dysfunction outbreak. *Medrxiv preprint.*
21. Srinivas U, Abdulla M, Åkesson B, Öckerman PA, Braconier JH, Jeppsson B. Trace element alterations in infectious diseases. *Scand J Clin Lab Invest.* 1988;48(6):495-500.
22. Besecker BY, Exline MC, Hollyfield J, et al. A comparison of zinc metabolism, inflammation, and disease severity in critically ill infected and noninfected adults early after intensive care unit admission. *Am J Clin Nutr.* 2011;93(6):1356-1364.
23. Boudreault F, Pinilla-Vera M, Englert JA, et al. Zinc deficiency primes the lung for ventilator-induced injury. *JCI Insight.* 2017;2(11):1-14.
24. Wessels I, Pupke JT, von Trotha KT, et al. Zinc supplementation ameliorates lung injury by reducing neutrophil recruitment and activity. *Thorax.* 2020;75(3):253-261.
25. Aliani M, Udenigwe CC, Girgih AT, Pownall TL, Bugera JL, Eskin MN. Zinc deficiency and taste perception in the elderly. *Crit Rev Food Sci Nutr.* 2013;53(3):245-250.
26. Lyckholm L, Hedding SP, Parker G, et al. A randomized, placebo controlled trial of oral zinc for chemotherapy-related taste and smell disorders. *J Pain Palliat Care Pharmacother.* 2012;26(2):111-114.
27. Slavin RG. Treating rhinitis in the older population: special considerations. *Allergy, Asthma Clin Immunol.* 2009;5(1):1-4.
28. Henkin R, Schechter PJ, Friedewald WT, Demets DL, Raff MORTON. A double blind study of the effects of zinc sulfate on taste and smell dysfunction. *Am J Med Sci.* 1976;272(3):285-299.
29. Golik A, Zaidenstein R, Dishy V, et al. Effects of captopril and enalapril on zinc metabolism in hypertensive patients. *J Am Coll Nutr.* 1998;17(1):75-78.
30. Davidson DM, Smith WM. The Bradford Hill criteria and zinc-induced anosmia: a causality analysis. *Arch Otolaryngol Head Neck Surg.* 2010; 136(7):673-676.
31. NIH Zinc Factsheet for Health Professionals. 2020. <https://ods.od.nih.gov/factsheets/Zinc-HealthProfessional/#en93>
32. Wester PO. Urinary zinc excretion during treatment with different diuretics. *Acta Med Scand.* 1980;208:209-212.
33. Callow KA, Parry HF, Sergeant M, Tyrrell DAJ. The time course of the immune response to experimental coronavirus infection of man. *Epidemiol Infect.* 1990;105(2):435-446.

How to cite this article: Equils O, Lekaj K, Wu A, Fattani S, Liu G, Rink L. Intra-nasal zinc level relationship to COVID-19 anosmia and type 1 interferon response: A proposal. *Laryngoscope Investigative Otolaryngology.* 2021;6:21–24. <https://doi.org/10.1002/lio2.513>