

Therapeutic supplementation with zinc in the management of COVID-19–related diarrhea and ageusia/dysgeusia: mechanisms and clues for a personalized dosage regimen

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Zinc supplementation is indicated for diarrhea and taste disorders, which are both features of COVID-19. Nevertheless, this strategy has not been tested for the treatment of these secondary complications in the current pandemic. Through an updated review, a practical appraisal was considered as a means of providing a medical nexus of therapeutic zinc regimens as an adjunct in the management of COVID-19–related diarrhea and ageusia/dysgeusia. While diarrhea and taste disorders are consequences of COVID-19, zinc supplementation is useful for non-COVID-19 patients with these clinical problems. The overwhelming evidence for supplementing with zinc in diarrhea and pneumonia is associated with the treatment of children, while for taste disorders the use of supplementing with zinc is more examined in adults. Whereas COVID-19 is more prevalent in adults, precautions should be exercised not to translate the zinc dosage used for children with diarrhea and taste disorders into the current pandemic. Therapeutic doses of zinc used for adults (~50–150 mg/day of elemental zinc) could be included in the treatment strategies for COVID-19, but this proposal should be examined through randomized studies.

INTRODUCTION

Low zinc serum levels are a concern in the management of hospitalized patients,^{1–4} so much so that hospitalization (in addition to intensive care and age greater than 60 years) is a risk factor for serum zinc deficiency.¹ Also, serum zinc deficiency is correlated with noninvasive ventilation,¹ which is frequently required in the current coronavirus disease 2019 (COVID-19) pandemic, as confirmed by a meta-analysis that found a prevalence of 19% for noninvasive ventilation among approximately 6500 patients with COVID-19.⁵

Zinc is an essential micronutrient with recognized roles in many cellular processes, such as the immune response, protein synthesis, and cell growth and

differentiation.^{6–10} In vitro, it is not surprising that zinc plays an antiviral role by inhibiting coronavirus RNA polymerase activity.¹¹ Such a mineral not only has a role in protecting the respiratory epithelium against oxyradicals and other harmful agents related to inflammatory diseases of the airways and lungs,¹² but it also assists in intestinal epithelial wound healing by enhancing the restitution of epithelial cells.¹³ More specifically, intracellular zinc has an essential role in maintaining the intestinal epithelial tight junction barrier via the regulation of occludin proteolysis and claudin-3 transcription.¹⁴ As zinc is involved in modulation of the intestinal transport of water and electrolytes, a dysregulation in this facet is a plausible cause of diarrhea,^{15,16} which has been considered a hallmark symptom of COVID-19.¹⁷

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Gastrointestinal symptoms are reported in 15% of patients with COVID-19, and include diarrhea and loss of appetite, as confirmed by a meta-analysis published in *The Lancet*.¹⁸ Notably, zinc supplementation is a widely used approach in the treatment of diarrhea and of taste disorders (ie, ageusia/dysgeusia)^{19,20}; eg, zinc supplementation has been used in the recovery of taste function since the 1980s.²¹ Therefore, in this review, the pragmatic background of zinc supplementation has been reviewed to assess its potential as an adjuvant in the treatment of COVID-19–related diarrhea and taste disorders.

Epidemiological zinc status

In terms of epidemiology, the National Health and Nutrition Examination Survey (NHANES) results can shed light on zinc status, at least in the US population. Employing an analysis based on the results of NHANES 2011–2014 ($n = 4347$), 1 study showed that serum zinc did not change in response to zinc provided in the diet or in supplements, but males had higher concentrations when compared with females (84.9 ± 0.8 vs 80.6 ± 0.6 $\mu\text{g}/\text{dL}$, $P < 0.0001$).²² In consonance with these findings, a large French study (7448 women and 4926 men) found that serum zinc concentrations were higher in men than in women (87.6 , 95% CI: 63.4 – 111.8 $\mu\text{g}/\text{dL}$ vs 84.3 , 95% CI: 60.1 – 108.5 $\mu\text{g}/\text{dL}$; $P < 0.0001$).²³ Women also presented with a lower serum zinc level compared with men in low-income countries, eg, in South Asian developing countries (66 $\mu\text{g}/\text{dL}$ for nonpregnant females and 70 $\mu\text{g}/\text{dL}$ for males).²⁴ In countries of Latin America and the Caribbean (Mexico, Colombia, Ecuador, and Guatemala), women (12–49 years old) and children (<6 years old) had a zinc deficiency prevalence of 19%–56%.²⁵

Juxtaposed with sex, age is a variable that must be considered when assessing zinc status, since its circulating levels are more susceptible to shifts upon aging than to changes in habitual zinc intake, as there is progressive reduction in the absorption of zinc and epigenetic factors throughout senescence.^{26,27} In a study involving 1090 healthy elderly subjects (74.6 ± 8.7 years old) from 5 European countries (Italy, Greece, Poland, France, and Germany), age was an independent predictor of low plasma zinc levels.²⁸ Late-onset disorders, such as Alzheimer's disease, are associated with zinc deficiency,²⁹ but in an Australian cohort consisting of 1084 subjects, decreased serum zinc levels were considered an effect of aging and not of Alzheimer's disease per se.³⁰

Ultimately, particular zinc deficiency risk groups deserve special attention, and include vegetarian/vegan and alcoholic individuals, patients undergoing medical procedures (dialysis/hemodialysis, bariatric surgery, and radiation treatment), and people with infectious

diseases, mainly due to gastrointestinal problems.³¹ In view of this latter aspect, the topics below assist in the clinical rationale concerning zinc status and its role in possible regimens against COVID-19.

Zinc deficiency in patients with COVID-19

Some observational studies have shown pronounced associations between zinc deficiency and COVID-19–related critical illness.^{2,4} In a new observational study consisting of 269 patients admitted to the intensive care unit, 214 (80%) had serum zinc deficiency and 152 (57%) suffered from severe acute respiratory distress syndrome caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).² Patients with zinc deficiency ($n = 214$) were 14 times more likely to have severe acute respiratory distress syndrome when compared with those with normal zinc concentration ($n = 55$).² It ought to be noted that the patients were older (mean 74 years old) and needed invasive mechanical ventilation,² a typical condition found in critically ill patients with COVID-19.³² Another observational study showed significantly lower zinc levels in COVID-19 patients ($n = 47$) when compared with the levels in healthy controls ($n = 45$), with a median of 74.5 $\mu\text{g}/\text{dL}$ (interquartile range 53.4 – 94.6) vs 105.8 $\mu\text{g}/\text{dL}$ (interquartile range 95.7 – 120.9).⁴ Fifty-seven percent ($n = 27$) of the individuals with COVID-19 had zinc deficiency and were almost 6 times more likely to develop complications (odds ratio = 5.54 , 95% CI 1.56 – 19.6) when compared with COVID-19 patients with normal zinc. Taking this comparison into account, COVID-19 patients with hypozincemia had a longer hospital stay of 7.9 days (vs 5.7 d) and a higher need to receive corticosteroid therapy (12 vs 2 patients).

In the above study, C-reactive protein (CRP) concentrations were not significantly different between groups; nonetheless, it should be noted that there were clinically higher CRP concentrations in COVID-19 patients with low zinc compared with those affected by this phenomenon but with normal zinc levels, achieving a CRP level related to serious infection (ie, >10 mg/L of CRP) and 3 times higher than the other group (11.0 mg/L, 3.5 – 48.5 vs 3.6 mg/L, 1.3 – 35.8).⁴ Importantly, higher CRP concentrations are a good predictor of early severe COVID-19,^{33,34} and zinc supplementation can attenuate the laboratory values of this protein in a multitude of diseases.^{35,36} Moreover, although the clinical diagnosis of diarrhea is imperative in medical practice,^{37,38} CRP is an associated biomarker of inflammatory diarrhea,^{39,40} which is a secondary event related to COVID-19.⁴¹ The prevalence of diarrhea in COVID-19 and the promise of therapeutic zinc regimens for mitigating this complication are discussed below.

COVID-19–related diarrhea: a rationale for supplementing zinc?

Diarrhea is a common symptom in patients with COVID-19, with an incidence rate of 2%–50% of cases.⁴² Angiotensin-converting enzyme-2 (ACE2) is greatly expressed in organs of the digestive tract, such as the upper esophagus, liver, and colon, with SARS-CoV-2 having 10–20 times higher affinity for the ACE2 receptor compared with the previous coronavirus.⁴² Severe COVID-19 is known to cause a cytokine storm by triggering the production of granulocyte monocyte colony-stimulating factor alongside interleukin (IL)-2, IL-6, IL-7, and tumor necrosis factor- α .⁴³ In addition to the damaged gastrointestinal epithelium directly caused by SARS-CoV-2, the use of antibiotics for secondary bacterial infections may lead to diarrhea as an untoward effect during the treatment of COVID-19.⁴³

Additionally, levels of fecal calprotectin—a biomarker commonly used to distinguish inflammatory bowel disease from irritable bowel syndrome—are generally elevated in patients with COVID-19, especially in the presence of gastrointestinal symptoms,⁴⁴ indicating a higher number of neutrophils in bowel inflammation.⁴⁵ The level is not only a specific tool for screening neutrophils during gut inflammation, but fecal calprotectin is a calcium- and zinc-binding protein at the molecular level.⁴⁵ Regarding the latter activity, its biological association with zinc underpins the need to study the use of zinc supplementation for COVID-19–induced diarrhea, since zinc transporters mediate the activity of zinc in barrier function and in the integrity of intestinal epithelial cells by preserving and regenerating tight junctions, the mucus layer, and antimicrobial molecules that fight against luminal pathogens,^{13,46,47} whereas zinc deficiency is associated with an increased risk of gastrointestinal infections, adverse effects on the structure and function of the gastrointestinal tract, and impaired immune function.^{6,48–50} Besides, zinc may shorten the period of diarrhea by improving the absorption of water and electrolytes.⁵¹

In a systematic review with an emphasis on developing countries, zinc supplementation reduced the average duration of childhood diarrhea by ~20%.¹⁹ In light of this concrete evidence, zinc supplementation is regarded as a cost-effective approach for reducing the duration of acute childhood diarrhea,⁵² and the 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.^{6,53,54} Although zinc supplementation as a means of mitigating diarrhea is geared toward children in developing countries, it could be time to test the applicability of this strategy in COVID-19–related diarrhea regardless

of income and age, due to the vast consequences of the pandemic.

The biological rationale for using zinc supplementation to mitigate COVID-19–related diarrhea can be seen clearly in [Figure 1](#).^{46,55–63}

COVID-19–related ageusia/dysgeusia: a rationale for supplementing zinc?

Zinc is involved in the taste function in humans by modulating the taste buds and the brain, seemingly favoring the information transmission from taste cells to gustatory nerve fibers.²¹ Correspondingly, oral zinc administration can stimulate food intake via its effect on neuropeptides in the hypothalamus, hence providing insights into the treatment of taste disorders.⁶⁴ COVID-19–related changes in smell or taste perception could be caused by COVID-19 itself or could occur in conjunction with zinc deficiency reducing odorant receptor levels in response to innate immune signaling.³¹

The oral cavity can act as a gateway for SARS-CoV-2 infection, leading to the development of taste disorders.^{65,66} More specifically, the suggested mechanism for taste alteration caused by SARS-CoV-2 is related to the ability of the virus to bind to the ACE2 receptor, a receptor that is highly expressed on the surface of the tongue and in the oral mucosa.^{65,66} A systematic review published in the middle of the pandemic showed a prevalence of ~33% and ~20% for dysgeusia and ageusia, respectively, in infected patients,⁶⁷ whereas a more recent meta-analysis, including a total of 817 patients, showed that almost half of the patients with COVID-19 (49.8%, 95% CI: 8.2%–91.5%) had ageusia/dysgeusia.⁶⁵

In a randomized clinical trial investigating patients with idiopathic dysgeusia, zinc gluconate supplementation at 140 mg/day (20 mg/d of elemental zinc; $n = 26$) for 3 months improved gustatory function and reduced the severity of dysgeusia when compared with placebo ($n = 24$).⁶⁸ In another randomized clinical trial with a larger sample size ($n = 109$), in contrast, of patients suffering from taste disorders, supplementing elemental zinc at 68 mg/day (300 mg/d of polaprezinc, a zinc L-carnosine complex) for 12 weeks, but not at 34 mg/day (150 mg/d of polaprezinc), was better than placebo for improving gustatory sensitivity, curing 18 of 28 patients.⁶⁹ Importantly, medical oncologic patients often suffer from taste disorders, mainly during radiation therapy, and in a randomized, placebo-controlled trial ($n = 35$), zinc sulfate at 50 mg 3 times a day for 5–9 weeks prevented radiation-induced taste changes in adult patients with head-and-neck cancer.⁷⁰

Taking into account that a localized change in the cellular zinc homeostasis of oral gustatory cells as a result of infection by the SARS-CoV-2 is conceivable,⁷¹ this could

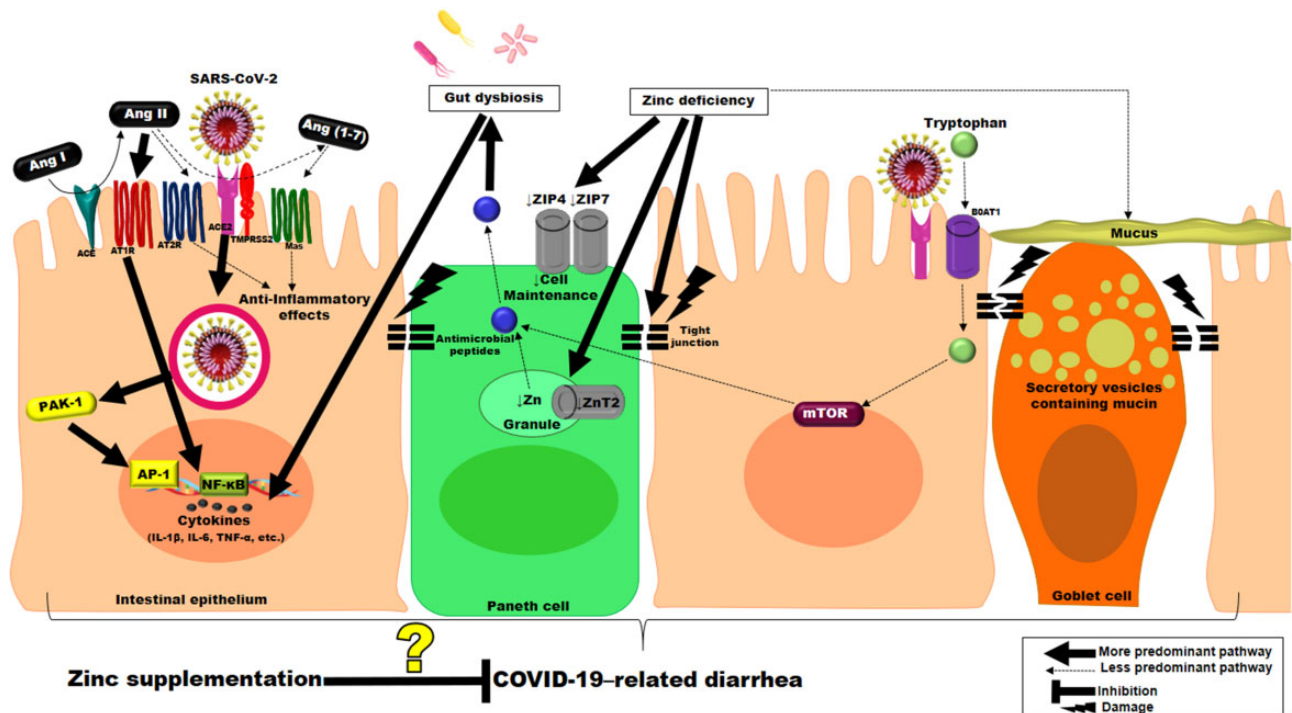


Figure 1 Biological rationale for supplementing with zinc to mitigate COVID-19-related diarrhea. The gut is affected by both SARS-CoV-2 and zinc deficiency, each of which affects the intestinal epithelium and related cells.⁵⁵ SARS-CoV-2 binds to the ACE2 receptor and hence blocks the binding of Ang II to this receptor.⁵⁶ As a consequence, the conversion of Ang II to Ang(1-7) is decreased, reducing the anti-inflammatory effects mediated by the Mas receptor.^{57,58} In addition, the binding of Ang II to AT1R is increased relative to its binding to AT2R, thereby leading to a higher production of pro-inflammatory cytokines.⁵⁷ After endocytosis, SARS-CoV-2 per se triggers the production of pro-inflammatory cytokines via PAK-1 and AP-1.^{59,60} Zinc deficiency, in turn, affects the tight junction, while reducing the maintenance of Paneth cells via an impaired action of zinc transporters (eg, ZIP4 and ZIP7).^{46,61} Moreover, low zinc content in the granule alongside reduced action of ZnT2 leads to less formation of antimicrobial peptides, which are crucial elements for a healthy gut microbiota composition,^{46,61} whereas there is more stimulus for the production of pro-inflammatory cytokines upon dysbiosis.⁶² SARS-CoV-2 itself also reduces the formation of antimicrobial peptides due to the inhibition of BOAT1, which decreases the influx of tryptophan, a fundamental amino acid that activates the mTOR complex so that antimicrobial peptides can be generated.⁶³ Zinc deficiency also affects the Goblet cell by reducing the production of mucus, and this is another way in which the gut barrier integrity can be damaged.⁴⁶ In summary, the pathophysiological processes aforementioned may imply diarrhea, while zinc supplementation can be hypothesized as a tool to mitigate this clinical problem. *Abbreviations:* ACE2, angiotensin-converting enzyme 2; Ang(1-7), angiotensin(1-7); Ang I, angiotensin I; Ang II, angiotensin II; AT1R, angiotensin II receptor type 1; AT2R, angiotensin II receptor type 2; BOAT1, broad neutral amino acid transporter; COVID-19, coronavirus disease 2019; mTOR, mechanistic target of rapamycin; NF-κB, nuclear factor-kappa B; PAK-1, p21-activated kinase 1; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNF-α, tumor necrosis factor alpha; ZIP4, zinc transporter 4 precursor; ZIP7, zinc transporter 7 precursor; ZnT2, zinc transporter-2.

be one of the causes of COVID-19-related ageusia/dysgeusia. Correspondingly, the aforementioned background provides insights regarding the need to consider zinc supplementation for COVID-19-related ageusia/dysgeusia, which is of pivotal relevance since impaired taste function is associated with all forms of malnutrition, that is, undernutrition per se, overweight, obesity, and inadequate vitamins or minerals caused by low intake of vegetables and fruits, which collectively lead to worsening prognosis and recovery from illness.⁷²⁻⁷⁴

Figure 2⁷⁵⁻⁸⁴ describes the potential mechanisms for COVID-19-related ageusia/dysgeusia, and illustrates how the effects of zinc supplementation could be useful for the alleviation of this complication.

Clues for a personalized dosage regimen of oral zinc

Apart from diarrhea and taste disorders, zinc supplementation may be a tool for use against pneumonia, a disease that affects people in the extremes of age.⁸⁵⁻⁸⁷ Inadequate zinc stores are suggestive of an increased risk for pneumonia in the elderly.⁸⁸ As such, in elderly nursing home residents with low serum zinc levels, after a year receiving 50% of the recommended dietary allowance for zinc, a higher risk of pneumonia and a longer duration of pneumonia episodes were observed, as well as increased use and duration of antibiotics for managing pneumonia.⁸⁹ Based on evidence such as this, Barnett et al⁸⁸ suggested a daily dose of at least 30 mg of

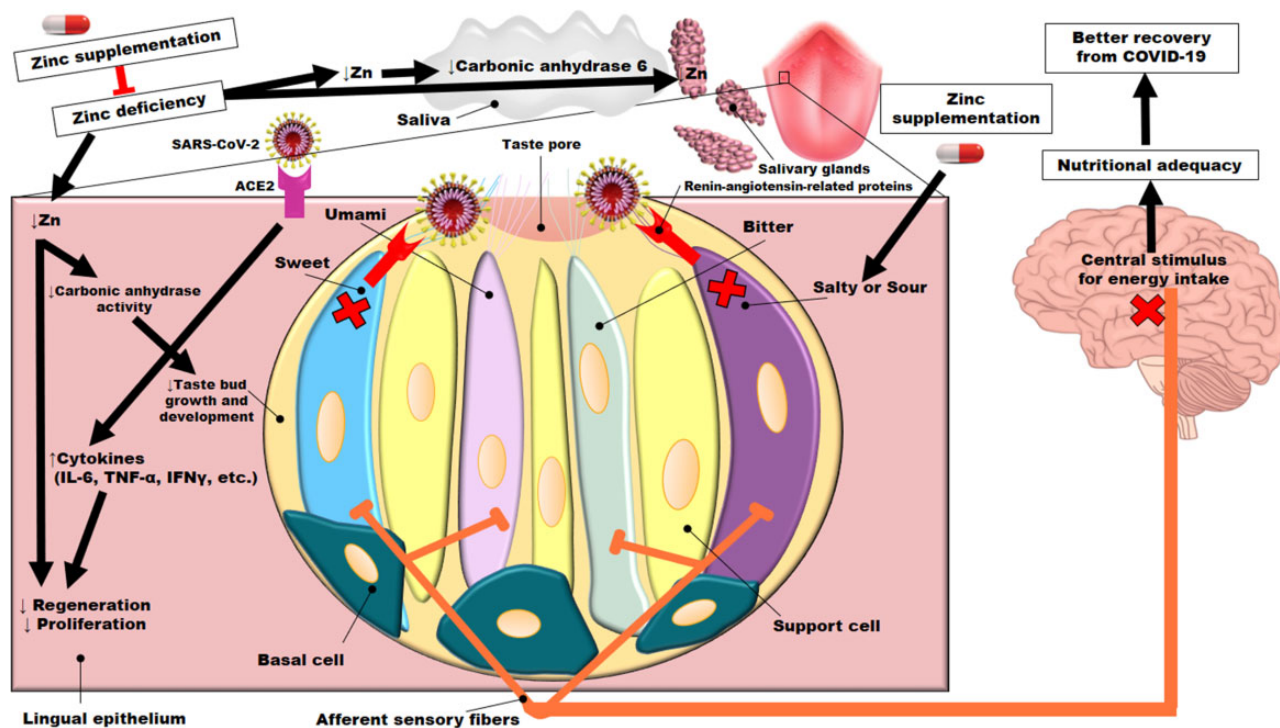


Figure 2 Potential mechanisms of COVID-19-related ageusia/dysgeusia and zinc supplementation. SARS-CoV-2 affects the lingual epithelium by binding to the ACE2, thereby triggering pro-inflammatory cytokines, which may decrease the regeneration and proliferation of tongue cells.⁷⁵ Renin-angiotensin-related proteins are expressed in taste buds, modulating the perception of salty and sweet flavors⁷⁶; given that SARS-CoV-2 penetrates the taste cells via renin-angiotensin-related proteins, the virus can inhibit salty and sweet tastes, decreasing the central stimulus for energy intake and hence affecting nutritional adequacy and the recovery from COVID-19. During zinc deficiency, the zinc content in the lingual epithelium would be expected to be low, affecting its regeneration and proliferation as the main consequences.^{77,78} In addition, low zinc content in such a tissue can decrease carbonic anhydrase activity.⁷⁹ Insofar as zinc content in the salivary glands may decline during zinc deficiency,^{80,81} low salivary zinc content is particularly linked to decreased activity of carbonic anhydrase 6, also called gustin, whose enzyme is a trophic factor that promotes the growth and development of taste buds.^{82,83} Thus, zinc supplementation could be a reasonable approach for reversing the harmful effects of zinc deficiency in this scenario or a booster for the perception of salty taste,^{81,84} which can be considered the pivotal taste for stimulating energy intake from salt meals and ultimately ameliorating nutritional adequacy and recovery from COVID-19. *Abbreviations:* ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

elemental zinc to improve immune function and reduce the risk of infections, but compelling evidence is scarce.

Furthermore, pneumonia is a major cause of child morbidity and mortality,^{90–92} and a meta-analysis that selected 6 double-blind, placebo-controlled trials ($n = 2216$) showed that supplementing zinc at 70 mg–280 mg for 7–14 days reduced childhood mortality caused by severe pneumonia without changing antibiotic therapy.⁸⁵ These are crucial data in responding to the current pandemic scenario. First, pneumonia reflects COVID-19 severity; second, a high zinc dosage has been used for children and, thus, it is conceivable to supplement zinc at least at an equivalent (but possibly higher) dosage so that it can be an adjuvant in combating COVID-19 pneumonia.

In summary, therapeutic zinc supplementation is well studied and recommended for children with pneumonia and diarrhea,^{19,85} but not for adults. The prevalence of COVID-19 in adults is one of the reasons why

this background cannot be translated fully into the current pandemic. However, the pharmacological dosage of oral zinc (ie, >40 mg/d of elemental zinc) used for the adult clinical population ranges from 220 mg/day to 660 mg/day of chelated zinc, which contains ~ 50 mg–150 mg of elemental zinc⁹³; recommended duration of supplementation varies according to the disease.^{93–95} Thereby, given that zinc is a vital micronutrient with well-known benefits in clinical nutrition, the therapeutic dosage used for adults could be considered in the decision-making strategies for COVID-19. Such a proposal, nevertheless, must be further examined through randomized clinical trials.

In view of the pharmacological spectrum of chloroquine and its metabolite hydroxychloroquine in bringing extracellular zinc to intracellular lysosomes, where it hinders RNA-dependent RNA polymerase activity and coronavirus replication,⁹⁶ at the beginning of the COVID-19 pandemic, zinc supplementation in

combination with these pharmacological agents was hypothesized for prophylaxis and even tested in hospitalized COVID-19 patients.⁹⁷ Notwithstanding the putative effects, such a strategy is currently deemed controversial^{98,99} and, therefore, this review encourages the investigation of zinc supplementation without zinc ionophore medications in the treatment of COVID-19–related gastrointestinal problems.

Finally, a preventive effect of zinc supplementation is bereft of evidence; thus, the basic measures recommended by the World Health Organization, such as vaccination, physical distancing, proper mask-wearing as a normal part of being around other people, and good hygiene practices in general, remain imperative.^{100–102}

Zinc toxicity: when to worry about side effects

Copper deficiency is the main concern regarding zinc administration since the body upon hyperzincemia produces more metallothionein as a means of reducing free zinc concentrations, but at the expense of copper because this metal has a greater affinity with the metallothionein.¹⁰³ Toxic effects caused by zinc consumption are evidenced in extremely high dosage for a long-term regimen (eg, ≥ 1000 mg/d for ≥ 1 year) so that copper deficiency and anemia, and even nephrosis, can occur at the same time.^{104,105} Generally, such untoward effects may be treated with intravenous and/or oral copper therapy.¹⁰⁴ Finally, atypical zinc toxicity can be induced beyond supplementation, as in the case of metal pica,¹⁰⁶ which is a mental disorder that leads to tremendous overdoses of minerals in virtue of the ingestion of metal objects (coins, bolts, etc.) and, calamitously, can be followed by sudden death.¹⁰⁷

CONCLUSION/TAKE-HOME MESSAGE

- Zinc is a vital element and cost-effective supplement with a myriad of evidence geared toward the clinical setting.
- There is a concrete scientific basis supporting the effectiveness of supplementing with zinc in the management of pneumonia and diarrhea, which are an associated critical illness and a common symptom, respectively, of COVID-19, but this recommendation is for children without COVID-19.
- Several studies encourage zinc supplementation for adults with taste disorders.
- Given the prevalence of COVID-19–related diarrhea and ageusia/dysgeusia, therapeutic zinc supplementation for adults (220 mg/d–660 mg/d chelated zinc or 50 mg–

150 mg of elemental zinc) could be regarded and/or investigated as an adjuvant due to its recognizable effects against diarrhea and taste disorders.

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