The Potential Impact of Zinc Supplementation on COVID-19 Pathogenesis

Inga Wessels 1†, Benjamin Rolles 2† and Lothar Rink 1*

1 Institute of Immunology, Faculty of Medicine, RWTH Aachen University, Aachen, Germany; 2 Department of Hematology, Oncology, Hemostaseology and Stem Cell Transplantation, Faculty of Medicine, RWTH Aachen University, Aachen, Germany

During the current corona pandemic, new therapeutic options against this viral disease are urgently desired. Due to the rapid spread and immense number of affected individuals worldwide, cost-effective, globally available, and safe options with minimal side effects and simple application are extremely warranted. This review will therefore discuss the potential of zinc as preventive and therapeutic agent alone or in combination with other strategies, as zinc meets all the above described criteria. While a variety of data on the association of the individual zinc status with viral and respiratory tract infections are available, study evidence regarding COVID-19 is so far missing but can be assumed as was indicated by others and is detailed in this perspective, focusing on re-balancing of the immune response by zinc supplementation. Especially, the role of zinc in viral-induced vascular complications has barely been discussed, so far. Interestingly, most of the risk groups described for COVID-19 are at the same time groups that were associated with zinc deficiency. As zinc is essential to preserve natural tissue barriers such as the respiratory epithelium, preventing pathogen entry, for a balanced function of the immune system and the redox system, zinc deficiency can probably be added to the factors predisposing individuals to infection and detrimental progression of COVID-19. Finally, due to its direct antiviral properties, it can be assumed that zinc administration is beneficial for most of the population, especially those with suboptimal zinc status.

Keywords: zinc, COVID-19, SARS-CoV2, 2019-nCoV, coronaviridae, zinc deficiency, impaired immune system

INTRODUCTION

The significance of the trace element zinc for the development and function of the immune system across all kinds of species has been proven in numerous studies (1–3). As zinc deficiency results in altered numbers and dysfunction of all immune cells, subjects with suboptimal zinc state have an increased risk for infectious diseases, autoimmune disorders, and cancer (3–6). In addition to malnutrition, risk groups for zinc deficiency include the elderly and patients with various inflammatory and autoimmune diseases, which will be discussed in detail later in the article (7, 8). As mild zinc deficiency is largely sub-clinical, it is unnoticed in most people. However, the World Health Organization (WHO) assumes that at least one third of the world population is affected by zinc deficiency (9). The fact that zinc deficiency is responsible for 16% of all deep respiratory infections world-wide (9) provides a first strong hint on a link of zinc deficiency with the risk of infection and severe progression of COVID-19 and suggests potential benefits of zinc supplementation.
The most common symptoms of COVID-19 are impaired smell and taste, fever, cough, sore throat, general weakness, pain as aching limbs, runny nose, and in some cases diarrhea (10). In the subsequent chapters, we will associate most of those symptoms with altered zinc homeostasis and explain how zinc might prevent or attenuate those symptoms, as summarized in Figure 1, and thus should be regarded as promising cost-effective, globally available therapeutic approach for COVID-19 patients, for which minimal to no side effects are known.

**ZINC PROTECTS THE HUMAN BODY FROM ENTERING OF THE VIRUS**

The entry of infectious agents into the human body is prevented by tissue barriers equipped with cilia and mucus, anti-microbial peptides like lysozymes and interferons. Regarding SARS-CoV2, the angiotensin-converting enzyme 2 (ACE2) and the cellular protease TMPRSS2 are the major mechanism for entering the cells (11).

a) Mucociliar clearance of viruses is affected by zinc
Infections with coronaviruses go along with damage of the ciliated epithelium and ciliary dyskinesia consecutively impairing the mucociliar clearance (12). It was shown that physiological concentrations of zinc increase ciliary beat frequency (13). Moreover, zinc supplementation in zinc deficient rats had a positive effect on the number and the length of bronchial cilia (14) (Figure 1.4). Improved ciliary clearance does not only improve the removal of virus particle, it also reduces the risk of secondary bacterial infections, as discussed later. Alterations of the extracellular matrix, as monitored by increased epidermal growth factor and proliferating cell nuclear antigen (PCNA) immunostaining of rat lungs during zinc deficiency have also been described (15).

b) Zinc is essential for preserving tissue barriers
Disturbances in the integrity of the respiratory epithelia facilitate the entry of the virus as well as co-infecting pathogens and can lead to pathogens entering the blood stream. An ex-vivo model of the chronic obstructive pulmonary disease (COPD) showed that decreasing zinc levels raised the leakage of the epithelium of the respiratory tract (16), while zinc supplementation improved lung integrity in a murine model of acute lung injury in vivo (17). Increased apoptosis and E-cadherin/beta-catenin proteolysis were amongst the underlying mechanisms (17–19). The expression of tight junction proteins like Claudin-1 and ZO-1 was found to be zinc-dependent, offering another explanation for zinc’s positive effects on lung integrity (16). In addition, an inhibitory effect of zinc on LFA-1/ICAM-1 interaction weakened inflammation in the respiratory tract via reduction of leukocyte recruitment (20). Furthermore, high zinc levels improved the tolerance of the lung towards damage induced by mechanical ventilation (21) (Figure 1.4).

c) Zinc-dependent alterations in gene expression by pneumocytes could affect viral entering
ACE-2, mainly expressed on pneumocytes type 2, is a zinc-metalloenzyme. Zinc binds to its active center and is thus essential for its enzymatic activity. If zinc binding also affects the molecular structure of ACE-2 and thereby its binding affinity to the virus, remains to be tested (22, 23). However, this is likely as zinc is important for stabilizing protein structures and altering substrate affinity of various metalloproteins (24, 25). Finally, zinc homeostasis might affect ACE-2 expression, as zinc-dependent expression was reported for other zinc-metalloenzyme such as metallothionein and metalloproteinas (26). This suggestion is strengthened by the finding that ACE-2 expression is regulated by Sirt-1 (27, 28). As zinc decreases Sirt-1 activity, it might decrease ACE-2 expression and thus viral entry into the cell (Figure 1.2).

A lack of adequate secretion of type I and type II interferons was reported for COVID-19 patients (29). For human interferon alpha (IFN-α) it was shown that zinc supplementation can reconstitute its expression by leukocytes and potentiates its anti-viral effect via JAK/STAT1 signaling as observed for rhinovirus-infected cells (30, 31). However, as it was suggested that SARS-CoV2 might take advantage of the interferon-dependent expression of ACE2, which was recently addressed by Ziegler et al. (32), the overall effects of zinc need to be carefully evaluated in future studies.

**ZINC DIRECTLY INHIBITS VIRAL REPLICATION**

As a virus, SARS-CoV2 is highly dependent on the metabolism of the host cell. Direct antiviral effects of zinc have been demonstrated in various cases, which was reviewed in great detail (33–37). Examples include coronaviridae, picornavirus, papilloma virus, metapneumovirus, rhinovirus, herpes simplex virus, varicella-zoster virus, respiratory syncytial virus, human immunodeficiency virus (HIV), and the hepatitis C virus (34, 35, 37–39). It was suggested that zinc can prevent fusion with the host membrane, decreases the viral polymerase function, impairs protein translation and processing, blocks viral particle release, and destabilizes the viral envelope (35, 37, 40). Low-dose zinc supplementation together with small concentrations of the zinc ionophores pyrithione or hinokitol decreased RNA synthesis in influenza, poliovirus, picornavirus, the equine arteritis virus, zinc can enhance the effect of chloroquine, another known zinc ionophore, while zinc ionophores like epigallocatechinate gallate or quercetin remain to be tested (42–45). There are close similarities of SARS-CoV2 and other coronaviridae like SARS-CoV and Middle East respiratory syndrome-coronavirus (MERS-CoV) (46). Also, the alcohol-aversive drug disulfiram can bind the papain-like proteases of SARS-CoV and MERS-CoV resulting in release of cysteine-bound zinc that results in protein destabilization (47). Detailed studies on zinc’s effect specifically on SARS-CoV2 are highly required (Figure 1.3).
Wessels et al. Zinc Supplementation in COVID-19 Pathogenesis

FIGURE 1 | Viral mechanism of COVID-19 and how they might be opposed by zinc data. (1) There is an impressive intersection of known risk factors for zinc deficiency (blue circle) and the predisposition for a severe COVID-19 infection (red circle). (2,3) Zinc (Zn) supplementation might already prevent the viral entry and also suppresses its replication, while it supports the anti-viral response of the host cells. (4) As zinc is known to increase ciliary length and movements and also sustains tissue integrity, entrance of the virus is impeded. (5–10) The importance of zinc on the development and function of the immune cells is manifold. It should be underlined, that zinc’s effects should not generally be described as activating or inhibiting, as zinc in various cases normalizes overshooting immune reactions and balances the ratios of the various immune cell types. Zinc thus prevents for example that high levels of inflammatory mediators including reactive oxygen and nitrogen species destroy the host tissue. (11) On first view it appears contradicting, that zinc increases activation induced production of reactive oxygen species in platelets, while it is generally considered as anti-oxidative. However, in case of platelets, up to a certain threshold, ROS production is essential, as it can prevent the formation of platelet aggregates. In summary, zinc therefore might be able to prevent vascular complications observed in COVID-19 patients. Details for each point can be found in the text. ACE2, angiotensin converting enzyme 2; AG, antigen; IFN, interferon; IFNR, interferon receptor; ISRE, interferon-sensitive response element; APC, antigen presenting cell; IKK, IκB kinase; IL, interleukin; iNOS, inducible nitric oxide synthase; IFP3, IFN regulatory factor 3; MHC, major histocompatibility complex; MEK1/2, mitogen-activated protein kinase kinase 1/2; NADPH oxidase, nicotinamide adenine dinucleotide phosphate oxidase; NFAT, nuclear factor of activated T-cells; NF-κB, nuclear factor kappa B; PKR, protein kinase R; Akt, protein kinase B; iPK, phosphatidylinositol-3 kinases; ROS, reactive oxygen species; RdRP, RNA-dependent RNA polymerase; RNase L, ribonuclease L; Sirt-, Sirtuin 1; STAT, signal transducer and activators of transcription; TCR, T cell receptor; Tc, cytotoxic T cell; TH, helper T cell; TGF, transforming growth factor; TRAM, TRIF-related adaptor molecule; TRIF, TIR-domain-containing adapter-inducing interferon-β; TLR, toll-like receptor; TNF, tumor necrosis factor; Zip, Zrt- and Irt-like protein; ZO-1, zona occludens.

ZINC BALANCES THE IMMUNE RESPONSE DURING INFECTIOUS DISEASES

One of the hallmarks of COVID-19 is an imbalanced immune response (48). Due to hyper-inflammation, immune products including pro-inflammatory cytokines like interleukin (IL)-6, C-reactive protein (CRP), tumor necrosis factor (TNF)α and IL-1β (summarized as cytokine storm or cytokine release syndrome), reactive oxygen, and nitrogen species in connection with the recruitment of high numbers of strongly activated immune cells to the lungs, the destruction of the tissue, permanent lung damage and death due to systemic inflammation, and organ failure are expected, while the anti-inflammatory response is insufficient (48–52). A high number of patients develop an acute respiratory distress syndrome (ARDS) accompanied by high alveolar leakage leading to alveolar and interstitial edema with severely limited oxygen exchange (53). Advanced SARS-CoV2 infections are characterized by a systemic involvement with organ complications and accompanying cytokine storm (52, 54).

There is no doubt on the anti-inflammatory and anti-oxidative properties of zinc and underlying mechanisms have been the focus of numerous studies (1–3, 6, 55–60). A detailed description of zinc metabolism in airway epithelium and during inflammation of the airways has been published by Zalewski et al. (61). On the other hand, zinc deficiency was associated with elevated levels of pro-inflammatory mediators, increased reactive oxygen species (ROS) levels and pre-disposing for severe progression of inflammatory diseases, especially those affecting the lung, often reversible by zinc supplementation (6, 17, 56, 62–66) (Figures 1.5,1.6). As one example, exposure to organic dust increased lung damage, inflammation and
macrophage hyper-activation in animals with zinc deficiency, predisposing these animals to pulmonary fibrosis, while zinc supplementation 24h before induction of acute lung injury significantly attenuated the inflammatory reaction and tissue damage (17, 67). Regarding systemic inflammatory diseases the number of studies showing benefits of especially preventive zinc supplementation is constantly increasing (17, 18, 58, 65, 68). Amongst the underlying mechanism, zinc’s role as second messenger and importance in regulating intracellular signaling as detailed in Figure 1 were described as well as zinc’s effects on the epigenome (56, 57, 69–74).

Furthermore, leukocytosis with neutrophilia and lymphopenia, especially affecting CD8+ T cells, were associated with poor prognosis of COVID-19 and the recovery of inflammation-induced destruction of the lung (75, 76). Similar changes in lymphopoiesis and myelopoiesis have been described in zinc deficient rodents, which were normalized when zinc was supplemented (17, 19). Circulating and lung-resident T cells from COVID-19 patients showed increased expression of markers for T cell exhaustion like Tim-3 and PD-1 (77). The extent of these changes had an impact on the patient’s prognosis (50). During the past decades, an immense literature was generated on the need of zinc for lymphocyte development and function and that zinc supplementation (6, 19, 63, 64, 78, 79) can reverse lymphopenia. Enumerating all findings and underlying mechanisms is beyond the scope of this article, and a lot of aspects have been discussed in related publications (36) but as one of the many key roles of zinc in the context of T cell function, zinc is indispensable in the signal cascade of the T cell receptor and IL-2 as a second messenger (78, 80) (Figure 1.9). The B cell compartment also strongly benefits from a balanced zinc homeostasis, as zinc is required for B cell maturation and function (72, 81) (Figure 1.8). Also important to mention, but neglected by previous related articles, is that there is evidence (82, 83) that SARS-CoV2 can directly infect T cells as well as B cells and impair their cell specific function. This could explain the impact of SARS-CoV2 infection on lymphoid tissues like the human spleen and lymph nodes (84). However, as data are limited to in vitro experiments, this needs to be verified in vivo as well as if zinc affects the virus-induced changes in T and B cells.

Additionally, granulocytes play a vital role during the inflammation-induced destruction of the lung (85). Recent evidence suggests that lipopolysaccharide-induced hyper-activation, recruitment and formation of neutrophil extracellular traps are attenuated by zinc supplementation in vivo and that cytokine expression, phagocytosis and burst, chemotaxis and degranulation, and intracellular signaling are zinc regulated (17, 86, 87) (Figure 1.5). Important defense mechanisms of the innate immunity include the toll like receptors. For instance, in silico data suggest that toll-like receptor (TLR)-4 can potentially recognize outer components of SARS-CoV2’s like the viral spikes (88), while intracellular receptors including TLR3, TLR7/8, and TLR9 can recognize viral dsRNA, ssRNA, and unmethylated CpG DNA respectively (89–92). Intranasal pretreatment with a TLR3 agonist and, to a lesser extent, with TLR9, TLR7/8, or TLR4 agonists, provided a high level of protection against infections by SARS coronavirus and influence virus in mice, suggesting that TLR signaling can induce protective antiviral immunity (93). This might be a completely novel approach to consider regarding COVID-19 as well. Zinc is an essential regulator in TLR-4 and TLR-3-induced signaling in innate immune cells (94). Thus, zinc deficiency potentially disturbs the innate immune response toward SARS-CoV2, enabling the virus to easily spread throughout the host without an adequate immune response (Figure 1.6).

Clinical improvement of COVID-19 patients was correlated to an increase of CD14+ monocytes and NK cells in the recovery phase (48). For a physiological inflammatory response and phagocytic activity macrophages need sufficient intracellular zinc levels (1). In addition, for NK cells and cytotoxic T cells it was shown that zinc supplementation increased their cytotoxicity toward target cells (1, 2, 95) (Figures 1.7, 1.10).

In summary zinc’s (re-)balancing power regarding immune cell numbers and functions might be highly beneficial in regard to therapy of COVID-19.

**ZINC SUPPLEMENTATION IN RESPIRATORY INFECTIONS**

Our suggested benefits of zinc supplementation to prevent and treat COVID-19 are supported by a row of successful supplementation studies focusing on respiratory tract infection, of which we listed some selected publications in Table 1. In most cases, prophylactic zinc supplementation was more effective than therapeutic proceedings (106–108, 111). Up to 30% of the everyday respiratory infections, briefly named “common cold,” are due to infections with coronaviruses (112). Studies showed reduced symptom severity, reduced frequency, and duration of the common cold after zinc administration (99, 100, 113, 114) depending on dosage, zinc compound and the start time after initial symptoms (115). Most importantly, zinc supplementation of children revealed significant benefits in various studies (96, 106) and reduced 15% pneumonia-specific morality and 19% of pneumonia morbidity in developing countries (116).

**RISK GROUPS AND SYMPTOMS OF COVID-19 AND ZINC DEFICIENCY REVEAL A LARGE OVERLAP**

As illustrated in Figure 1.1, the intersection between risk groups of COVID-19 and zinc deficiency is impressive. In patients with chronic obstructive pulmonary disease (COPD), bronchial asthma, cardiovascular diseases, autoimmune diseases, kidney diseases, dialysis, obesity, diabetes, cancer, atherosclerosis, liver cirrhosis, immunosuppression, and known liver damage low serum zinc levels are regularly observed (4, 117). At the same time, these groups are particular at risk for COVID-19 (10, 51, 118, 119). For example 57.5% elderly and nursing home residents in the U.S., for which high incidence of respiratory tract infections is described, showed significantly decreased zinc intake levels and are considered subjects with high risk regarding COVID-19 (120). Moreover, other studies showed that serum zinc levels were inversely correlated with pneumonia and cystic
### TABLE 1 | Selected zinc supplementation studies in respiratory infections.

| Compound | Conc. [mg/d] | Duration | Disease | Effect | References |
|----------|--------------|----------|---------|--------|------------|
| **Treatment** |              |          |         |        |            |
| Zinc bis-glycinate | 30 (elemental) | Max 7 days/dis-charge from the hospital | Lower RTI (Children) | Reduction of days of ALRI and shorter hospital stay | (96) |
| Zinc acetate | 20 | 5d | Lower RTI (children) | Increased recovery rates (boys) | (97) |
| Zinc gluconate | 10 | 6 mo | Lower RTI (children) | Decreased episodes of infection, more infection free days | (98) |
| Zinc gluconate | 60–313 | Until symptoms are gone | Common cold | Variable results but generally reduced duration if supplementation started within first 24 h | Meta-study of 16 studies (99) |
| Zinc acetate | 76.8–102.4 | Until symptoms are gone | Common cold | <75 mg/day: reduced duration; zinc acetate better than gluconate | Meta-study of 7 studies (100) |
| Gluconate nasal gel | 2.1 | | | | |
| SULFITE nasal spray | 0.044 | | | | |
| Zinc acetate vs. zinc gluconate | 80–92 | Until symptoms are gone | Common cold | | Meta-study of 16 studies (99) |
| Zinc gluconate | 192–207 | | | | |
| Zinc gluconate | 30 (elemental) | 12 mo | Cystic fibrosis (children) | Reduced duration of antibiotics | (101) |
| **Prophylactic** |              |          |         |        |            |
| Zinc sulfate | 20 (elemental) | 2 wk/6 mo follow-up | Lower RTI (children) | Reduced morbidity | (102) |
| Zinc sulfate | 20 to ZD children | 14d, 6 mo follow-up | Upper and lower RTI (children) | Decreased incidence and duration of upper and lower RTI | (103) |
| Zinc oxide | 5 | 12 mo | Upper RTI (children) | Decreased incidence | (104) |
| Zinc gluconate | 10 | 6 mo | Lower RTI | Decreased incidence | (105) |
| Zinc acetate, gluconate, methionine, sulfate | Min 70 mg/wk | >3 mo | Lower RTI | Decreased incidence (depending on criteria) | Meta-study of 10 studies (106) |
| Zinc in mineral mix | 6 8g–7.5 (m) | 12 mo | Naturally occurring pneumonia | Decreased incidence and duration, decreased duration of antimicrobial therapy | (107) |
| Zinc sulfate | 60–90 | 12 mo | Ventilation associated pneumonia | Decreased incidence | (108) |
| Zinc gluconate | Up to 12x 23 mg/d | Until symptoms are gone | Common cold | Decreased clinical score | (109) |
| Zinc sulfate | 15 | 7 mo | Common cold | Decreased incidence | (110) |
| **Murine models** |              |          |         |        |            |
| Zinc-enriched rodent diet | ZD: 50 ppm–ZS: 100 ppm | 18d ZD followed by 3d ZS | Sepsis-induced ALI | Decrease in inflammation, lung damage, and mortality (vs. ZD mice) | (68) |
| Zinc aspartate | 30 µg/mouse | 24 h | Acute lung injury (LPS inhalation), mice | Decreased hyper-inflammation, tissue damage | (17) |

Conc, concentration; d, day; mo, months; ref, reference; RTI, respiratory tract infection; ZD, zinc deficiency; ZS, zinc supplementation; wk, week.

Single studies are not included in the meta-studies.

fibrosis (121, 122). On the other hand, zinc supplementation was able to reconstitute immune function in elderly and zinc deficient individuals (107, 123), which remains to be addressed for SARS-CoV2 infections (36). In this regard, the low response of older patients with low serum zinc to a 23-valent pneumococcal polysaccharide vaccination compared to those with higher zinc level (124), should be mentioned. However, zinc's role in the response to vaccination is generally discussed controversially and no data are available for vaccination against any corona virus.

Several studies indicate that there is an association between chemosensory dysfunctions and COVID-19 (125–133). Smell or taste is largely decreased, which might be a good disease biomarker (133). It was suggested that this might either be due to direct destruction of sensory cells by the virus, as ACE-2 is highly
expressed by the oral mucosa, or by viral entry into the brain and neuronal pathologies as was described for other SARS-CoV (133, 134). Zinc deficiency was related to significantly reduced taste sensitivity and impaired salivary secretion in humans and animals, which might involve zinc’s importance for the action of carbonic anhydrase (135–140). Results from supplementation studies largely describe improvements in chemosensory functions (140, 141), but some studies did not find any effects (142) or even more severe disturbances when very high zinc concentrations were used (143). This is possibly due to investigating olfactory diseases of various origins, the lack of controlled trials and inclusion of observable studies. Thus, the benefits of zinc supplementation alone or in combination with common medical strategies should be tested for taste and smell diseases according to the available guidelines (144).

About 50% of patients that died of COVID-19 had bacterial or fungal co-infections (145), underlining the importance of sustaining the immune function by a sufficient zinc supply (1, 2, 36). In animal experiments it was shown that zinc restriction made mice highly susceptible to bacterial infection with *Streptococcus pneumoniae* (146). As mentioned earlier, marginal zinc deficiency affects one third of the worldwide population and most subjects with COVID-19 are at risk of zinc deficiency (Figure 1). During physiological inflammatory responses, zinc is additionally redistributed to the tissues, resulting in serum hypozincemia (1, 65). In combination with the pre-existing suboptimal zinc supply, this will decrease serum zinc levels to critically low values and thereby significantly increase the susceptibility for co-infections with detrimental progression. In critically ill patients persistent low serum zinc was associated with recurrent sepsis and serum zinc levels were inversely correlated with mortality from sepsis (62), underlining the potential benefits of monitoring the zinc status of the patients and implementing zinc supplementation into therapy of COVID-19.

Vascular complications resulting from atherosclerosis development, microangiopathic organ failure, and venous thromboembolism were found as a major cause of death in COVID-19 patients (147–149), suggesting an important role of disease-induced coagulopathy, which, however, needs further investigation. Zinc influences thrombocyte aggregation and coagulation (150). Recently, a functional association between zinc and ROS production in platelets was described, indicating that zinc could decrease thrombus formation in a clinical context (151). Complications of SARS-CoV2 infections also include tissue damage affecting the gastrointestinal system (152), the liver (153), heart (154), nervous system (155), kidneys (156), blood vessels (149), and the skin (157). In this regard it should be mentioned that a balanced zinc homeostasis is essential for wound healing and tissue recovery after mechanical and inflammation-mediated damage (158, 159), adding more potential benefits of zinc supplementation of COVID-19 patients (Figure 1.11).

**CONCLUSION**

In this perspective, we reviewed the most important literature on the role of zinc homeostasis during viral infections, focusing on the potential benefits of zinc supplementation to prevent and treat SARS-CoV2 infections. Although data specifically on SARS-CoV2 are unfortunately still pending and randomized controlled studies have not been conducted, the enumerated evidence from the literature strongly suggests great benefits of zinc supplementation. Zinc supplementation improves the mucociliary clearance, strengthens the integrity of the epithelium, decreases viral replication, preserves antiviral immunity, attenuates the risk of hyper-inflammation, supports anti-oxidative effects and thus reduces lung damage and minimized secondary infections. Especially older subjects, patients with chronic diseases and most of the remaining COVID-19 risk groups would most likely benefit. Although studies are needed testing the effect of zinc as therapeutic option for established disease, preventive supplementation of subjects from risk groups should begin now, as zinc is a cost-efficient, globally available and simple to use option with little to no side effects. The first clinical trials on zinc supplementation alone and in combination with other drugs such as chloroquine have been registered (124, 160–162). Thus, first results and treatment regimens regarding zinc supplementation for COVID-19 risk groups and patients can be anticipated soon.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article-supplementary material, further inquiries can be directed to the corresponding author/s.

**AUTHOR’S NOTE**

LR is a member of ZINC Net.

**AUTHOR CONTRIBUTIONS**

IW, BR, and LR drafted and corrected the text, table, and figure. All authors contributed to the article and approved the submitted version.

**REFERENCES**

1. Wessels I, Maywald M, Rink L. Zinc as a gatekeeper of immune function. *Nutrients*. (2017) 9:1286. doi: 10.3390/nu9121286
2. Gammoh NZ, Rink L. Zinc in infection and inflammation. *Nutrients*. (2017) 9:624. doi: 10.20944/preprints201705.0176.v1
3. Roohani N, Hurrell R, Kelishadi R, Schulin R. Zinc and its importance for human health: an integrative review. *J Res Med Sci*. (2013) 18:144–57.
4. Wessels I, Rink L. Micronutrients in autoimmune diseases: possible therapeutic benefits of zinc and vitamin D. *J Nutr Biochem*. (2020) 77:108240. doi: 10.1016/j.jnutbio.2019.108240
5. Haase H, Schomburg L. You’d better zinc-trace element homeostasis in infection and inflammation. *Nutrients*. (2019) 11:2078. doi: 10.3390/nu11092078

6. Prasad AS. Effects of zinc deficiency on Th1 and Th2 cytokine shifts. *J Infect Dis*. (2000) 182(Suppl. 1):562–8. doi: 10.1086/315195

7. Suita S, Ikeda K, Nagasaki A, Hayashida Y. Zinc deficiency during total parenteral nutrition in childhood. *J Pediatric Surg*. (1978) 13:5–9. doi: 10.1016/S0022-3468(78)80202-4

8. Hotz C, Brown KH. Identifying populations at risk of zinc deficiency: the use of supplementation trials. *Nutr Rev*. (2001) 59:80–4. doi: 10.1111/1753-4887.2001.tb06992.x

9. World Health Organization. The World Health report 2002. *Midwifery*. (2003) 19:72–3. doi: 10.1054/midw.2002.0343

10. Eurosurveillance ET. Updated rapid risk assessment from ECDC on coronavirus disease 2019 (COVID-19) pandemic: increased transmission in the EU/EEA and the UK. *Euro Surveill*. (2020) 25:2003121. doi: 10.2807/1560-7917.ES.2020.25.10.2003121

11. Hoffmann M, Kleine-Weber H, Krüger N, Müller M, Drosten C, Pöhlmann S. The novel coronavirus 2019 (2019-nCoV) uses the SARS-coronavirus receptor ACE2 and the cellular protease TMPRSS2 for entry into target cells. *bioRxiv*. (2020) 10.1101/2020.01.31.929042. [Epub ahead of print]

12. Chilvers MA, McKean M, Rutman A, Myint BS, Silverman M, O’Callaghan. Zinc supplementation reconstitutes the production of interferon-alpha by leukocytes from elderly persons. *J Interferon Cytokine Res*. (1997) 17:469–72. doi: 10.1089/jir.1997.17.469

13. Ziegler CGK, Allon SJ, Nyquist SK, Mbanfo IM, Miao VN, Tzouanas CN, et al. SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues. *Cell*. (2020) 181:1016–35.e19. doi: 10.1016/j.cell.2020.04.035

14. IShida T. Review on the role of Zn2+ ions in viral pathogenesis and the effect of Zn2+ ions for host-cell virus growth inhibition. *AJSR*. (2019) 2:28–30. doi: 10.34297/AJSR.2019.02.000566

15. Krenn BM, Gaudernak E, Holzer B, Lanke K, van Kuppevelt FJ, Seipel J. Antiviral activity of the zinc ionophores pyrithione and hinokitol against picornavirus infections. *J Virol*. (2009) 83:58–64. doi: 10.1128/JVI.01543-08

16. Read SA, Obeid S, Ahlenstiel C, Ahlenstiel G. The role of zinc in antiviral immunity. *Adv Nutr*. (2019) 10:696–710. doi: 10.1093/advances/nmy013

17. Skalny AV, Rink L, Ajsuakova OP, Aschner M, Gritsenko VA, Aleksenko SI, et al. Zinc and respiratory tract infections: perspectives for COVID19 (Review). *Int J Mol Med*. (2020) 46:17–26. doi: 10.3892/ijmm.2020.5475

18. Suara RO, Crowe JE. Effect of zinc salts on respiratory syncytial virus replication. *Antimicrob Agents Chemother*. (2004) 48:783–90. doi: 10.1128/AAC.48.3.783-790.2004

19. Cai H, Zhang Y, Ma Y, Sun J, Liang X, Li J. Zinc binding activity of human IFN-alpha tenfold. *J Interferon Cytokine Res*. (2001) 21:471–4. doi: 10.1089/10799900152434330

20. Cakman I, Kirchner H, Rink L. Zinc supplementation reconstitutes the production of interferon-alpha by leukocytes from elderly persons. *J Interferon Cytokine Res*. (1997) 17:469–72. doi: 10.1089/jir.1997.17.469

21. Haase H, Schomburg L. You’d better zinc-trace element homeostasis in infection and inflammation. *Nutrients*. (2019) 11:2078. doi: 10.3390/nu11092078

22. Prasad AS. Effects of zinc deficiency on Th1 and Th2 cytokine shifts. *J Infect Dis*. (2000) 182(Suppl. 1):562–8. doi: 10.1086/315195

23. Christianson DW, Alexander RS. Carboxylate-histidine-zinc interactions in protein structure and function. *J. Am. Chem. Soc.* (1989) 111:6412–9. doi: 10.1021/ja00189a065

24. Cox E. Zinc-dependent protein folding. *Curr Opin Chem Biol*. (2000) 4:162–5. doi: 10.1016/S1367-5931(99)00070-8

25. Cao J-W, Duan S-Y, Zhang H-X, Chen Y, Guo M. Zinc deficiency promoted fibrosis via ROS and TIMP/MMPs in the myocardium of mice. *Biol Trace Elem Res*. (2019) 196:145–52. doi: 10.1007/s11161-019-01902-4

26. Wessels et al. Zinc Supplementation in COVID-19 Pathogenesis
46. Liu J, Zheng X, Tong Q, Li W, Wang B, Sutter K, et al. Overlapping and discrete aspects of the pathology and pathogenesis of the emerging human coronaviruses SARS-CoV, MERS-CoV, and 2019-nCoV. *J Med Virol.* (2020) 92:491–4. doi: 10.1002/jmv.25709

47. Lin M-H, Moses DC, Hsieh C-H, Cheng S-C, Chen Y-H, Sun C-Y, et al. Disulfiram can inhibit MERS and SARS coronavirus papain-like protease via different modes. *Antiviral Res.* (2018) 150:155–63. doi: 10.1016/j.antiviral.2017.12.015

48. Wen W, Su W, Tang H, Le W, Zhang X, Zheng Y, et al. Immune cell profiling of COVID-19 patients in the recovery stage by single-cell sequencing. *Cell Discov.* (2020) 6:31. doi: 10.1038/s41421-020-00187-y

49. Cheng ZJ, Shan J. 2019 Novel coronavirus: where we are and what we know. *Infection.* (2020) 48:153–63. doi: 10.1007/s10157-020-01401-y

50. Chen G, Di Wu, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest.* (2020) 130:2620–9. doi: 10.1172/JCI137244

51. Guan W-L, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med.* (2020) 382:1708–20. doi: 10.1056/NEJMoa2002323

52. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. *Acute respiratory distress syndrome.* *Lancet.* (2020) 396:1033–49. doi: 10.1016/S0140-6736(20)30578-6

53. Matthay MA, Zemans RL, Zimmerman GA, Arabi YM, Beilte JR, Mercaat A, et al. Acute respiratory distress syndrome. *Nat Rev Dis Primers.* (2019) 5:18. doi: 10.1038/s41775-019-0186-9

54. Wichmann D, Sperhake J-P, Lütgehetmann M, Steurer S, Edler C, Heinemann A, et al. Autopsy findings and venous thromboembolism in patients with COVID-19: a prospective cohort study. *Ann Intern Med.* (2020) 173:623–32. [Epub ahead of print].

55. Beck FW, Prasad AS, Kaplan J, Fitzgerald JT, Brewer GJ. Changes in cytokine production and T cell subpopulations in experimentally induced zinc-deficient humans. *Am J Physiol.* (2017) 272:E1002–7. doi: 10.1152/ajpendo.1997.272.6.E1002

56. Wessels I, Haase H, Engelhardt G, Rink L, Uciechowski P. Zinc deficiency adversely influences interleukin-4 and interleukin-6 signaling. *J Biol Regul Homeost Agents.* (2013) 27:661–71.

57. Maywald M, Wessels I, Rink L. Zinc signals and immunity. *Int J Mol Sci.* (2018) 19:2222. doi: 10.3390/ijms18102222

58. Maywald M, Meurer SK, Weiskirchen R, Rink L. Zinc supplementation augments TGF-beta-dependent regulatory T cell induction. *Mol Nutr Food Res.* (2020) 64:172–9. doi: 10.1002/mnfr.201810008

59. Liu J, Li S, Liu J, Liang B, Wang X, Wang H, et al. Longitudinal study of NLRP3 inflammasome activity in critically ill COVID-19 patients: a prospective cohort study. *Antiviral Res.* (2020) 180:104735. doi: 10.1016/j.antiviral.2020.104735

60. Prasad AS, Meftah S, Abdallah J, Kaplan J, Brewer GJ, Bach JF, et al. Zinc supplementation leads to immune modulation and improved survival in mice involves zinc transporter Zip14 and can be overcome by zinc deficiency. *Am J Physiol Gastrointest Liver Physiol.* (2015) 309:G768–78. doi: 10.1152/ajpgi.00179.2015

61. Besecker BY, Exline MC, Holleyfield J, Phillips G, Disivasto RA, Wevers MD, 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) 93:1356–64. doi: 10.3945/ajcn.110.008417

62. Knoell DL, Smith DA, Sapkota M, Heires AJ, Hanson CK, Smith LM, et al. Insufficient zinc intake enhances lung inflammation in response to agricultural dust exposure. *J Nutr Biochem.* (2019) 70:56–64. doi: 10.1016/j.jnutbio.2019.04.007

63. Liu J, Zheng X, Tong Q, Li W, Wang B, Sutter K, et al. Overlapping and discrete aspects of the pathology and pathogenesis of the emerging human coronaviruses SARS-CoV, MERS-CoV, and 2019-nCoV. *J Med Virol.* (2020) 92:491–4. doi: 10.1002/jmv.25709

64. Bao S, Liu M-J, Lee B, Besecker B, Lai J-P, Guttridge DC, et al. Zinc modulates the innate immune response in vivo to polymicrobial sepsis through regulation of NF-kappaB. *Am J Physiol Lung Cell Mol Physiol.* (2020) 298:L744–54. doi: 10.1152/ajplung.00368.2019

65. Wessels I, Cousins RJ. Zinc dyshomeostasis during polymicrobial sepsis in mice involves zinc transporter Zip14 and can be overcome by zinc supplementation. *Am J Physiol Gastrointest Liver Physiol.* (2015) 309:G768–78. doi: 10.1152/ajpgi.00179.2015
Hemilä H. Zinc lozenges and the common cold: a meta-analysis comparing...J Virol. (2002) 76:8729–36. doi: 10.1128/JVI.76.17.8729-8736.2002

Kurt-Jones EA, Popova L, Klinn W, Haynes LM, Jones LP, Tripp RA, et al. Pattern recognition receptors TLR4 and CD14 mediate response to respiratory syncytial virus. Nat Immunol. (2000) 1:398–401. doi: 10.1038/77833

Alexopoulos L, Holt AC, Medzhitov R, Flavell RA. Recognition of double-stranded RNA and activation of NF-kB by Toll-like receptor 3. Nature. (2001) 413:732–8. doi: 10.1038/35099560

Heil F, Hemmi H, Hochrein H, Amenzheimer F, Kirschning C, Akira S, et al. Species-specific recognition of single-stranded RNA via toll-like receptor 7 and 8. Science. (2004) 303:1526–9. doi: 10.1126/science.1093620

Zhao J, Wohlford-Lenane C, Zhao J, Fleming E, Lane TE, McCray PB, et al. Intranasal treatment with poly(I:C) protects aged mice from lethal respiratory virus infections. J Virol. (2012) 86:11416–24. doi: 10.1128/JVI.01410-12

Brieger A, Rink L, Haase H. Differential regulation of TLR-dependent MyD88 and TRIF signaling pathways by free zinc ions. J Immunol. (2013) 191:1808–17. doi: 10.4049/jimmunol.1301261

Rolloes B, Maywald M, Rink L. Influence of zinc deficiency and supplementation on NK cell cytotoxicity. J Funct Foods. (2018) 48:322–8. doi: 10.1016/j.jff.2018.07.027

Rerkspapphol S, Rerkspapphol L. A randomized controlled trial of zinc supplementation in the treatment of acute respiratory tract infection in Thai children. Pediatr Rep. (2019) 11:7954. doi: 10.4081/pr.2019.7954

Mahalanabis D, Lahiri M, Paul D, Gupta S, Gupta A, Wahed MA, et al. Randomized, double-blind, placebo-controlled clinical trial of the efficacy of treatment with zinc or vitamin A in infants and young children with severe acute lower respiratory infection. Am J Clin Nutr. (2009) 79:430–6. doi: 10.1093/ajcn/79.3.430

Shah UB, Abu-Shaheen AK, Malik MA, Alam S, Riaz M, Al-Tannir MA. The efficacy of zinc supplementation in young children with acute lower respiratory infections: a randomized double-blind controlled trial. Clin Nutr. (2013) 32:193–9. doi: 10.1016/j.clinu.2012.08.018

Hulíc D. Zinc nutrition in children with common cold-like infections: an overview. J Am Pharm Assoc. (2003) 44:594–603. doi: 10.1331/1544-3191.45.5.594.Hulic

Hemilä H. Zinc lozenges and the common cold: a meta-analysis comparing zinc acetate and zinc gluconate, and the role of zinc dosage. IRSM Open. (2017) 8:20542704177694291. doi: 10.1177/20542704177694291

Abdulhamid I, Beck FW, Milard S, Chen X, Prasad A. Effect of zinc supplementation on respiratory tract infections in children with cystic fibrosis. Pediatr Pulmonol. (2008) 43:281–7. doi: 10.1002/ppul.20771

Malik A, Tanega DK, Devesanapathy N, Rajeshwari K. Zinc supplementation for prevention of acute respiratory infections in infants: a randomized controlled trial. Indian Pediatr. (2014) 51:780–4. doi: 10.1007/s13312-014-0503-z

Khera D, Singh S, Purhot R, Sharma P, Singh K. Prevalence of zinc deficiency and effect of zinc supplementation on prevention of acute respiratory infections. Turk Thorac J. (2019) 1–14. doi: 10.2139/ssrn.3273670

Martinez-Estevez NS, Alvarez-Guevara AN, Rodriguez-Martinez CE. Effects of zinc supplementation in the prevention of respiratory tract infections and diarrheal disease in Colombian children: A 12-month randomised controlled trial. Allergol Immunopathol. (2016) 44:368–75. doi: 10.1016/j.aller.2015.12.006

Sazawal S, Black RE, Jalla S, Mazumdar S, Sinha A, Bhan MK. Zinc supplementation reduces the incidence of acute lower respiratory infections in preschool and schoolchildren: a double-blind, controlled trial. Pediatrics. (1998) 102:1–5. doi: 10.1542/peds.102.1.1

Roth DE, Richard SA, Black RE. Zinc supplementation for the prevention of acute lower respiratory infection in children in developing countries: meta-analysis and meta-regression of randomized trials. Int J Epidemiol. (2010) 39:795–808. doi: 10.1093/ije/dyp391

Meydani SN, Barnett JB, Dallal GE, Fine BC, Jacques PF, Leka LS, et al. Serum zinc and pneumonia in nursing home elderly. Am J Clin Nutr. (2007) 86:1167–73. doi: 10.1093/ajcn/86.4.11617

Hasanzadeh Kiabi F, Alipour A, Darvishi-Khezri H, Aliashgarian A, Emami Zeydi A. Zinc supplementation in adult mechanically ventilated trauma patients is associated with decreased occurrence of ventilator-associated pneumonia: a secondary analysis of a prospective, observational study. Indian J Crit Care Med. (2017) 21:34–9. doi: 10.4103/0973-5229.198334

Al-Nakib W, Higgins PG, Barrow I, Batstone G, Tyrell DA. Pharyngitis and treatment of rhinovirus colds with zinc gluconate lozenges. J Antimicrob Chemother. (1987) 20:893–901. doi: 10.1093/jac/20.6.893

Kurugol Z, Akilli M, Bayram N, Kutoglu G. The prophylactic and therapeutic effectiveness of zinc sulphate on common cold in children. Acta Paediatr. (2006) 95:1175–81. doi: 10.1111/j.1651-2227.2006.00304.x

Eby GA, Davis DR, Halcomb WW. Reduction in duration of common colds by zinc gluconate lozenges in a double-blind study. Antimicrob Agents Chemother. (1984) 25:20–4. doi: 10.1128/AAC.25.1.20

Godfrey JC, Conant Sloane B, Smith DS, Turco JH, Mercer N, Godfrey NJ. Zinc gluconate and the common cold: a controlled clinical study. J Int Med Res. (1992) 20:234–46. doi: 10.1177/03000605920200305

Kazmaier AG, Gupta MB, Win SS, Pang J. Zinc supplementation reduces common cold duration among healthy adults: a systematic review of randomized controlled trials with micronutrients supplementation. Am J Trop Med Hyg. (2020) 102:42699/jtmh.19-0718

Yakob MY, Theodoratou E, Jabeen A, Imdad A, Eisele TP, Ferguson J, et al. Preventive zinc supplementation in developing countries: impact on mortality and morbidity due to diarrhea, pneumonia and malaria. BMC Public Health. (2011) 11(Suppl. 3):S23. doi: 10.1186/1471-2458-11-S3-S23

Ackland ML, Michalczyk A. Zinc deficiency and its inherited disorders -a review. Genetics. Nutr. (2006) 1:4–9. doi: 10.1007/s80833-006-00592-0

Petilli CM, Jones SA, Yang I, Rajagopalan H, O'Donnell LF, Chernyak Y, et al. Factors associated with hospitalization and critical illness among 4,103 patients with COVID-19 disease in New York city. JAMA Sci Rep. (2020) 4:202139. doi: 10.1001/jamasci.2020.102159

Briefel RR, Bloistosky K, Kennedy-Stephenson J, McDowell MA, Ervin DT, Wrigg JD. Zinc intake of the U.S. population: findings from the third National Health and Nutrition Examination Survey, 1988-1994. J Nutr. (2000) 130:1367S–73S. doi: 10.1093/jn/130.5.1367S

Krogh D, Hegsted DM, Hendricks JH, et al. The metabolism of dietary cholesterol.2. J Biol Chem. (1948) 174:109–14. doi: 10.1016/S0021-9258(18)5367S-0

Wessels et al. Zinc Supplementation in COVID-19 Pathogenesis

Frontiers in Immunology | www.frontiersin.org 9 July 2020 | Volume 11 | Article 1712
A Study of Hydroxychloroquine and Zinc in the Prevention of COVID-19 Infection in Military Healthcare Workers. (2020). Available online at: https://ClinicalTrials.gov/show/ (accessed May 15, 2020).

Zinc Supplementation in COVID-19 Pathogenesis

Bhat MH, Mudassir, Rather AB, Dhobi GN, Koul AN, Bhat FA, et al. Zinc levels in community acquired pneumonia in hospitalized patients; a case control study. Egypt J Chest Dis Tuberc. (2016) 65:485–9. doi: 10.1016/j.ectj.2015.12.020

Kamei S, Fujikawa H, Nohara H, Ueno-Shuto K, Maruta K, Nakashima R, et al. Zinc deficiency via a splice switch in zinc importer ZIP2/SLC39A2 causes cystic fibrosis-associated MUC5AC hypersecretion in airway epithelial cells. EbioMedicine. (2018) 27:304–16. doi: 10.1016/j.ebiom.2017.12.025

Haase H, Mochegiani E, Rink L. Correlation between zinc status and immune function in the elderly. Biogerontology. (2006) 7:421–8. doi: 10.1007/s10522-006-9057-3

ClinicalTrials.gov: A Study of Hydroxychloroquine and Zinc in the Prevention of COVID-19 Infection in Military Healthcare Workers. (2020). Available online at: https://ClinicalTrials.gov/show/ (accessed May 15, 2020).

Yan CH, Faraji F, Prajapati DP, Boone CE, DeConde AS. Association of chemosensory dysfunction and Covid-19 in patients presenting with influenza-like symptoms. Int Forum Allergy Rhinol. (2020) 10:806–13. doi: 10.1002/air.22579

Yan CH, Faraji F, Prajapati DP, Ostrander BT, DeConde AS. Self-reported olfactory loss associates with outpatient clinical course in Covid-19. Int Forum Allergy Rhinol. (2020) 10:821–31. doi: 10.1002/air.22592

Soler ZM, Patel ZM, Turner JH, Holbrook EH. A primer on viral-associated olfactory loss in the era of COVID-19. Int Forum Allergy Rhinol. (2020) 10:832–8. doi: 10.1002/air.22602

Moein ST, Hashemian SM, Mansourafshar B, Khorram-Tousi A, Tavbarsi P, et al. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. Clin Infect Dis. (2020) 70:904–9. doi: 10.1093/cid/ciaa330. [Epub ahead of print].

Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in patients with COVID-19: a multicenter European study. Eur Arch Otorhinolaryngol. (2020) 1–11. doi: 10.1007/s00405-020-05965-1

Russell B, Moss C, Rigg A, Hopkins C, Papa S, van Hemelrijck M. Anosmia and ageusia are emerging as symptoms in patients with COVID-19: What does the current evidence say? Eurineuroendocrinology. (2020) 16:16–8. doi: 10.1038/s41641-019-0365-4

Lechien JR, Chiesa-Estomba CM, Dieterle S, Rodriguez A, et al. Olfactory and gustatory dysfunctions in COVID-19: a rapid prospective nationwide classification. Int Forum Allergy Rhinol. (2020) 10:821–31. doi: 10.1002/alr.22578

Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M, Oreni L, et al. Sniffing out the evidence; It’s now time for public health bodies recognize the link between COVID-19 and smell and taste disturbance. Int Forum Allergy Rhinol. (2020). doi: 10.1002/alr.22587. [Epub ahead of print].

Lyckholm B, Holevska Z, Møller L, Bjerregaard G, Kjaeldgaard L, et al. Obstructive sleep apnoea in patients with COVID-19: An immune response, and wound healing. Nutrients. (2017) 10:71–8. doi: 10.3390/nu10030038

Heckmann SM, Hujolid P, Habiger S, Friess W, Wichmann M, Heckmann JG, et al. Zinc gluconate in the treatment of dysgeusia—a randomized clinical trial. J Dent Res. (2005) 84:35–8. doi: 10.1177/154045810500840010

Sturniolo GC, D’Inca R, Parisi G, Giacomazzi F, Montino MC, D’Orodonico A, et al. Taste alterations in liver cirrhosis: are they related to zinc deficiency? J Trace Elem Electrolytes Health Dis. (1992) 6:15–9.

Netland J, Heddinger SP, Parker G, Coyne PJ, Ramakrishnan V, Smith TJ, et al. A randomized, placebo controlled trial of oral zinc for chemotherapy-related taste and smell disorders. J Pain Palliat Care Pharmacother. (2012) 26:111–4. doi: 10.3109/15360288.2012.676618

Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften. Riech- und Schmeckstörungen (017/050). (2016). Available online at: https://www.awmf.org/leitlinien/detail/ll/017-050.html

Cox MJ, Loman N, Bogaert O, G’Rady J. Co-infections: potentially lethal and unexplored in COVID-19. Lancet Microbe. (2020) 1:1e1. doi: 10.1016/S2666-5247(20)30099-4

Eijkokamp BA, Morey JR, Neville SL, Tan A, Pederick VG, Cole N, et al. Dietary zinc and the control of Streptococcus pneumoniae infection. PLoS Pathog. (2019) 15:e1007957. doi: 10.1371/journal.ppat.1007957

Taylor KA, Pugh N. The contribution of zinc to platelet behaviour during haemostasis and thrombosis. Metallomics. (2016) 8:1144–5. doi: 10.1039/C5MT00251F

Lopes-Pires RE, Ahmed NS, Vera D, Gibbons JM, Pula G, Pugh N. Zinc regulates reactive oxygen species generation in platelets. Platelets. (2020). doi: 10.1080/09537104.2020.1724211. [Epub ahead of print].

Fernández Nieto D, Rodríguez-Villa Lario A, et al. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide study. Br J Dermatol. (2020) 183:71–7. doi: 10.1111/bjd.19163

Lin P-H, Sermersheim M, Li H, Lee PH, Steinberg SM, Ma J. Zinc in wound healing modulation. Nutrients. (2017) 10:106. doi: 10.3390/nu10010016
159. Aydemir TB, Sitren HS, Cousins RJ. The zinc transporter Zip14 influences c-Met phosphorylation and hepatocyte proliferation during liver regeneration in mice. *Gastroenterology.* (2012) 142:1536–46.e5. doi: 10.1053/j.gastro.2012.02.046

160. ClinicalTrials.gov. Coronavirus 2019 (COVID-19)- Using Ascorbic Acid and Zinc Supplementation. (2020). Available online at: https://ClinicalTrials.gov/show/NCT04342728 (accessed May 15, 2020).

161. ClinicalTrials.gov. Hydroxychloroquine and Zinc With Either Azithromycin or Doxycycline for Treatment of COVID-19 in Outpatient Setting. (2020). Available from: https://ClinicalTrials.gov/show/NCT04370782 (accessed May 15, 2020).

162. ANZCTR.org.au. High-Dose Intravenous Zinc (HDIVZn) As Adjunctive Therapy in COVID-19 Positive Critically Ill Patients: A Pilot Randomized Controlled Trial. (2020). Available online at: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=379579&isReview=true (accessed May 15, 2020).

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2020 Wessels, Rolles and Rink. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.