Zinc and respiratory tract infections: Perspectives for COVID-19 (Review)

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Abstract. In view of the emerging COVID-19 pandemic caused by SARS-CoV-2 virus, the search for potential protective and therapeutic antiviral strategies is of particular and urgent interest. Zinc is known to modulate antiviral and antibacterial immunity and regulate inflammatory response. Despite the lack of clinical data, certain indications suggest that modulation of zinc status may be beneficial in COVID-19. *In vitro* experiments demonstrate that Zn^{2+} possesses antiviral activity through inhibition of SARS-CoV RNA polymerase. This effect may underlie therapeutic efficiency of chloroquine known to act as zinc ionophore. Indirect evidence also indicates that Zn^{2+} may decrease the activity of angiotensin-converting enzyme 2 (ACE2), known to be the receptor for SARS-CoV-2. Improved antiviral immunity by zinc may also occur through up-regulation of interferon α production and increasing its antiviral activity. Zinc possesses anti-inflammatory activity by inhibiting NF-κB signaling and modulation of regulatory T-cell functions that may limit the cytokine storm in COVID-19. Improved Zn status may also reduce the risk of bacterial co-infection by improving mucociliary clearance and barrier function of the respiratory epithelium, as well as direct antibacterial effects against *S. pneumoniae*. Zinc status is also tightly associated with risk factors for severe COVID-19 including ageing, immune deficiency, obesity, diabetes, and atherosclerosis, since these are known risk groups for zinc deficiency. Therefore, Zn may possess protective effect as preventive and adjuvant therapy of COVID-19 through reducing inflammation, improvement of mucociliary clearance, prevention of ventilator-induced lung injury, modulation of antiviral and antibacterial immunity. However, further clinical and experimental studies are required.

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Contents

1. Introduction

Zinc is an essential metal being involved in a variety of biological processes due to its function as a cofactor, signaling molecule, and structural element. It is involved in the

regulation of carbohydrate and lipid metabolism, as well as the functioning of the reproductive, cardiovascular, and nervous system (1). At the same time, the most critical role of zinc is demonstrated for the immune system. Briefly, zinc regulates proliferation, differentiation, maturation, and functioning of leukocytes and lymphocytes (2). Zinc plays a signaling role involved in the modulation of inflammatory responses (3). It is also a component of nutritional immunity (4). Correspondingly, alteration of zinc status significantly affects immune response resulting in increased susceptibility to inflammatory and infectious diseases including acquired immune deficiency syndrome, measles, malaria, tuberculosis, and pneumonia (5). Earlier data demonstrate that populational Zn status is associated with the prevalence of respiratory tract infections in children and adults (6,7).

In view of the high prevalence of zinc deficiency worldwide (up to 17%), its impact on population health is considered as a significant issue (8). Moreover, certain groups of people, including infants, especially preterm ones, and elderly, are considered to be at high risk of zinc deficiency and its adverse effects (9).

Under zinc deficiency condition, organisms are more susceptible to toxin-producing bacteria or enteroviral pathogens that activate guanylate and adenylate cyclases, stimulating chloride secretion, causing diarrhea and diminishing absorption of nutrients, thus exacerbating an already compromised mineral status. In addition, zinc deficiency may impair the absorption of water and electrolytes, delaying the termination of normally self-limiting gastrointestinal disease episodes (10). During chronic deficiency, the production of pro-inflammatory cytokines increases, influencing the outcome of a large number of inflammatory, metabolic, neurodegenerative and immune diseases (11). Diseases such as rheumatoid arthritis, diabetes (12), atherosclerosis and obesity (13), impaired cognitive function (14), as well as age-related macular degeneration (AMD) may be due to zinc deficiency, worsening chronic inflammation and triggering oxidative stress.

Coronaviridae were considered as the etiological agent in 6-29% of respiratory infections (15,16), although the severity of the disease varies significantly on the particular virus and its virulence (17). The viruses from the *Coronaviridae* family are zoonotic viruses that can be transmitted from animals to humans. The bat is considered the reservoir for these viruses, but other intermediate animals can also transmit the virus to humans (18). COVID-19 is a coronavirus disease caused by the novel 2019-nCoV virus (now called SARS-CoV-2) that appeared for the first time in Wuhan, China at the end of 2019 (19). Despite a close relation other two highly pathogenic coronaviruses, MERS-CoV and SARS-CoV (20), SARS-CoV-2 expanded to the majority of countries (21). On 11 March 2020, WHO characterized COVID-19 as a pandemic (22). Currently, the prevalence of COVID-19 exceeds 1,521,200 cases resulting in 92,700 deaths worldwide (23).

COVID-19 predominantly affects the respiratory system resulting in pneumonia and acute respiratory distress syndrome (24), leading to the requirement of mechanical ventilation (25). In turn, advanced age, acute respiratory distress syndrome (ARDS) and mechanical ventilation are known to be associated with higher COVID-19 mortality (26). The risk is also increased by modern life in which individuals are exposed to a multitude of chemicals, even in low doses that in the long-term predispose to chronic diseases and metabolic disturbances (27-31). Preexisting chronic metabolic diseases including diabetes, cardiovascular diseases (32), and obesity (33) are considered as risk factors for increased COVID-19 susceptibility and mortality. It is proposed that the elderly are at higher risk of COVID-19 due to impaired immune function (34).

Due to the clearly demonstrated role of zinc in immunity (2), and impaired zinc status in ageing (35), metabolic diseases including diabetes, obesity, and cardiovascular diseases (13), it is speculated that zinc compounds may be used as an adjunct therapy in COVID-19 treatment (36) for increasing antiviral resistance (37). Of note, zinc was earlier suggested as the potential agent for immune support and prevention of H1N1 influenza ('swine flu') (38).

In view of lack of clinical data on preventive and/or therapeutic efficiency of zinc in COVID-19, as well as primary involvement of the respiratory system, in this review, we will discuss recent clinical data on the role of zinc in protection against bronchopulmonary infections, as well as the existing indications of the direct impact of zinc on nCoV-2019.

2. Zinc and COVID-19

In view of the global COVID-19 pandemic, potential protective effect of zinc is of particular interest. Zinc is considered as the potential supportive treatment in therapy of COVID-19 infection due to its immune modulatory effect, as well as direct antiviral effect (36). However, the existing data will be only mechanistically discussed in this review, as direct data on anti-COVID-19 effects of zinc are absent to date.

Specifically, Zn^{2+} cations especially in combination with Zn ionophore pyrithione were shown to inhibit SARS-coronavirus RNA polymerase (RNA dependent RNA polymerase, RdRp) activity by decreasing its replication (39). These important findings demonstrate that Zn^{2+} may be considered as the particular antiviral agent in COVID-19 treatment. Of note, recent trials have indicated efficiency of chloroquine antiviral activity as a treatment of COVID-19 (40), although the intimate mechanisms of its antiviral activity require further investigation (41). Earlier findings demonstrate that chloroquine is a zinc ionophore increasing Zn^{2+} flux into the cell (42). Moreover, the authors also propose that chloroquine-mediate zinc influx may underlie anticancer activity of the compound (42). Similarly, it was hypothesized that increasing intracellular Zn^{2+} concentration by chloroquine may also mediate its antiviral effect against SARS-CoV-2. In this view zinc supplementation without chloroquine might have similar positive effects without adverse side-effects of chloroquine treatment (43). Hypothetically, such an effect may be also observed using other zinc ionophores like quercetin and epigallocatechin-gallate (44) with substantially lower toxicity, although clinical trials supported by experimental *in vitro* studies are required to support this hypothesis.

Another Zn-related approach to modulation of COVID-19 may include targeting Zn ions in the structure of viral proteins. Particularly, it has been demonstrated that disulfiram-induced Zn^{2+} release from papain-like protease in MERS-CoV and SARS-CoV resulting in protein destabilization (45). In view of

the presence of similar critical Zn-containing sites, Zn-ejector drugs (e.g., disulfiram) may be considered as potential antiviral agents (46) and components of targeted oxidation strategy in anti-SARS-CoV-2 treatment (47).

SARS-CoV-2 similarly to SARS-CoV requires angiotensin-converting enzyme 2 (ACE2) for entry into target cells (48). Therefore, modulation of ACE2 receptor was considered as the potential therapeutic strategy in COVID-19 treatment (49). Speth *et al* (50) demonstrated that zinc exposure (100 μM) was shown to reduce recombinant human ACE-2 activity in rat lungs. Although this concentration is close to physiological values of total zinc, the modulating effect of zinc on SARS-CoV-2-ACE2 interaction seem to be only hypothetical (51).

Although neither coronavirus HCoV 229E (52) nor HCoV-OC43 (53) infection caused a significant reduction in ciliary beat frequency, HCoV 229E induced ciliary dyskinesia resulting in impaired mucociliary clearance. The latter may not only alter viral particle removal, but also predispose to bacterial co-infection as observed for influenza virus (54). In turn, Zn supplementation was shown to improve ciliary length in bronchial epithelium of Zn-deficient rats (55), as well as increase ciliary beat frequency *in vitro* (56). Therefore, zinc may hypothetically ameliorate nCoV-2019-induced dysfunction of mucociliary clearance. Generally, zinc was shown to be essential for respiratory epithelium due to antioxidant and anti-inflammatory activity (57), as well as regulation of tight junction proteins ZO-1 and Claudin-1 (58), thus increasing its barrier functions. In turn, downregulation of tight junction protein complexes e.g., ZO-1 and Claudin-1 and reduction in barrier function aggravates viral and bacterial inflammatory processes (59). In addition, loss of TJ perm selectivity in the airways results in an un-controlled leakage of high molecular weight proteins and water into the airways, which results in the formation of alveolar edema and ARDS (60).

3. Zn and respiratory viruses

Despite limited data on the direct effect of zinc on SARS-CoV-2 and COVID-19, its antiviral effects were demonstrated in other viral diseases. Zinc was shown to have a significant impact on viral infections through modulation of viral particle entry, fusion, replication, viral protein translation and further release for a number of viruses including those involved in respiratory system pathology (37,61). Specifically, increasing intracellular Zn levels through application of Zn ionophores such as pyrithione and hinokitiol significantly alters replication of picornavirus, the leading cause of common cold (62). These findings generally correspond to the earlier indications of suppressive effect of zinc on rhinovirus replication originating from the early 1970s (63). In addition, Zn treatment was shown to increase interferon α (IFNα) production by leukocytes (64) and potentiate its antiviral activity in rhinovirus-infected cells (65). As antiviral activity of IFNα is mediated through JAK1/STAT1 downstream signaling and up-regulation of antiviral enzymes [e.g., latent ribonuclease (RNaseL) and protein kinase RNA-activated (PKR)] involved in viral RNA degradation and inhibition of viral RNA translation (66), recent findings allow to propose that these mechanisms may be stimulated by Zn^{2+}.

These findings along with the existing data on the role of zinc in immunity raised interest to the potential use of zinc in prevention and/or treatment of common cold. A systematic review by Singh and Das (67) published in Cochrane database revealed a significant reduction in common cold duration, as well as the incidence rate ratio of developing common cold (IRR=0.64 (95% CI: 0.47-0.88), P=0.006) in response to zinc supplementation. The results of meta-analysis demonstrated that Zn supplementation in the dose >75 mg/day significantly reduced duration of common colds (68), with Zn acetate being the most effective form (69).

Certain studies also revealed the association between Zn status and respiratory syncytial virus (RSV) infection. Particularly, it has been demonstrated that whole blood zinc was significantly lower in children with RSV pneumonia (70). Impaired zinc metabolism in perinatal alcohol exposure is associated with immunosuppression and altered alveolar macrophage activity resulting in increased susceptibility to RSV infection (71). In turn, Zn compounds were shown to inhibit respiratory syncytial virus replication and RSV plaque formation with a more than 1,000-fold reduction at 10 μm Zn preincubation (72).

It is also notable that zinc deficiency was associated with higher mortality and adverse long-term outcome in influenza-MRSA bacterial superinfection (73), also underlining the importance of considering the risk of bacterial coinfection.

Despite the presence of experimental findings on the protective effect of zinc supplementation against respiratory virus infections, clinical and epidemiological data are still to be elaborated and systematized.

4. Pneumonia in adults and the elderly

Zinc is essential for the immune system and elderly people have an increased probability for zinc deficiency (74). Low Zn status was considered as the potential risk factor for pneumonia in elderly. Particularly, subjects with high serum Zn (>70 μg/dl, i.e., approx. 10.8 μmol/l) were characterized by reduced incidence of pneumonia [0.52 (0.36, 0.76), P<0.001], as well as lower disease duration and antibiotic administration as compared to low-Zn (<70 μg/ml) group (75), being also related to all-cause mortality (76). Serum Zn levels were 15% lower in cases of community-acquired pneumonia and advanced age, being also associated with pneumonia severity as evaluated by CURB-65 scores (77). The incidence of severe pneumonia was significantly higher in Irani patients with low Zn status, although the mean duration of fever, tachycardia, and tachypnea only tended to be longer, although not significant (78). Correspondingly, serum Zn levels were found deficient at the onset of acute respiratory failure with the lowest values observed in septic shock patients. However, no association between serum Zn values and day-30 mortality or period of stay in intensive care unit was observed (79).

The results of systematic analysis also confirmed the efficiency of intake of at least 75 mg/day Zn in reduction of pneumonia symptom duration but not severity, with the response being more pronounced in adults than in children (80). At the same time, certain studies failed to reveal any improvement in pneumonia when administered along with standard antibiotic treatment, although the period of supplementation was only 4 days (81).

A detailed study by Boudreault *et al* (82) demonstrated that low plasma Zn predisposes to ventilator-induced injury in intensive care, being related to the role of metallothionein system in lung protection. These data corroborate the results of the experimental study demonstrating aggravation of ventilation-induced lung injury in Zn deficient rats (83).

In Indian patients high plasma zinc levels were found to be associated with reduced mortality from sepsis as well as lower 48-h SOFA scores (84). Moreover, persistent low serum Zn levels were associated with increased risk of recurrent sepsis in critically ill patients (85).

Altogether, the existing data demonstrate an association between zinc status and pneumonia in adults and elderly, as well as its complications including respiratory failure, ventilator-induced injury, and sepsis.

5. Pediatric respiratory infections

Initial reports have postulated nearly exceptional susceptibility of elderly to SARS-CoV-2 infection allowing to propose natural resistance to COVID-19 in children (86). However, detailed analysis of the pediatric COVID-19 cases (87) and the emerging Russian experience indicate that children may be also severely affected by SARS-CoV-2. In view of high incidence of Zn deficiency in infants, the existing data on the association between Zn status and pneumonia in children is also discussed.

High incidence of pneumonia in developing countries has been considered as the consequence of zinc deficiency in the population (7). The incidence of low serum zinc in children with severe pneumonia was 80% (88). Correspondingly, a 2-fold lower level of serum Zn was observed in pediatric acute lower respiratory infection patients (89). Significantly lower serum zinc levels were observed in children with pneumonia complicated by sepsis, mechanical ventilation, and cases of lethality (90). Generally, indications of low zinc status in children with pneumonia provide a rationale for preventive Zn supplementation.

Particularly, Zn supplementation in developing countries reduced pneumonia morbidity by 19% (RR=0.81; 95% CI: 0.73, 0.90), whereas a 15% decrease in pneumonia-specific mortality was not significant (91). A recent systematic review and meta-analysis published in Cochrane database demonstrated that Zn supplementation significantly reduced the incidence and prevalence of pneumonia in children by 13 and 41% (92).

In contrast to the demonstrated preventive effects of Zn supplementation, data on the therapeutic effect of zinc in treatment of childhood pneumonia are conflicting (93). Despite the earlier observed reduction of treatment failure risk (94) and case fatality [RR=0.67 (95% CI: 0.24-0.85)] (95) in children with severe pneumonia, a more recent study demonstrated that Zn supplementation in 2-24 months old children with radiologically verified pneumonia did not result in significant improvement of risk reduction of treatment failure (96). Moreover, Zn supplementation in Zn-deficient children with pneumonia until achievement of normal serum Zn levels did not improve clinical appearance of the disease (97).

A number of studies revealed the potential efficiency of Zn supplementation in prevention of non-specified acute lower respiratory infections including bronchitis, bronchiolitis, pneumonitis. Specifically, supplementation with 10 mg zinc gluconate in Zn-deficient children resulted in a nearly twofold reduction of the number of episodes of acute lower respiratory infections as well as the time to recovery (98). In addition, Zn supplementation (30 mg/day) in Thai children significantly reduced severity of acute lower respiratory tract infections resulting in faster disease cessation and shorter hospital stay (99). A detailed meta-analysis demonstrated that Zn supplementation significantly decreased the incidence of acute lower respiratory infection defined according to specific clinical criteria in children aged <5 years (100).

In parallel, the impact of Zn supplementation in relation to upper respiratory tract infections was also demonstrated. Particularly, the number of upper respiratory tract infections in Colombian children was reduced by 73% in response to supplementation with 5 mg Zn in a 12-month randomized clinical trial (101). Certain studies also revealed protective effect of zinc supplementation against both acute upper and lower respiratory diseases in children (102,103).

6. Zinc and lung inflammation

Inflammation plays the key role in COVID-19 pathogenesis both at local (pneumonia) and systemic (cytokine storm) levels, and the search for adequate anti-inflammatory agents is of particular importance (104).

Although the role of zinc in regulation of inflammatory response was discussed in detail in a number of reviews (2,5), certain aspects of the regulatory role of zinc in pneumonia pathogenesis and lung inflammation are still to be elucidated. However, the existing data clearly demonstrate that Zn ions may possess anti-inflammatory effects in pneumonia thus limiting tissue damage and systemic effects.

Specifically, Zn deficiency in rats resulted in a significant increase in proinflammatory TNFα and VCAM-1 expression and lung tissue remodeling, being partially reversed by Zn supplementation (105). Zn deficiency also resulted in a significant alteration of lung epithelial cell barrier function through up-regulation of TNFα, IFNγ, and FasR signaling and cellular apoptosis *in vitro* (106). Zn deficiency was shown to up-regulate acute phase response-related genes through stimulation of JAK-STAT signaling in lungs under septic conditions (107). Zinc and nitric oxide (NO)-metallothioneine (MT)-Zn pathways were shown to mediate lung injury in response to LPS or hyperoxia (108).

In turn, Zn pretreatment significantly reduced LPS-induced pulmonary endothelial cell damage and increased cell viability *in vitro*, as well as improved respiratory function as assessed by blood oxygen pressure and saturation (109). It has been demonstrated that Zn pretreatment significantly decreases LPS-induced neutrophil recruitment to the lungs thus reducing acute lung injury in mice (110).

It is also notable that zinc deficiency is associated with inflammatory alterations of lung extracellular matrix predisposing to fibrosis (111). This finding is of particular interest in view of the presence of interstitial pulmonary fibrosis in COVID-19 patients (112).

Certain studies revealed protective effect of zinc against lung injury in systemic inflammation including sepsis.

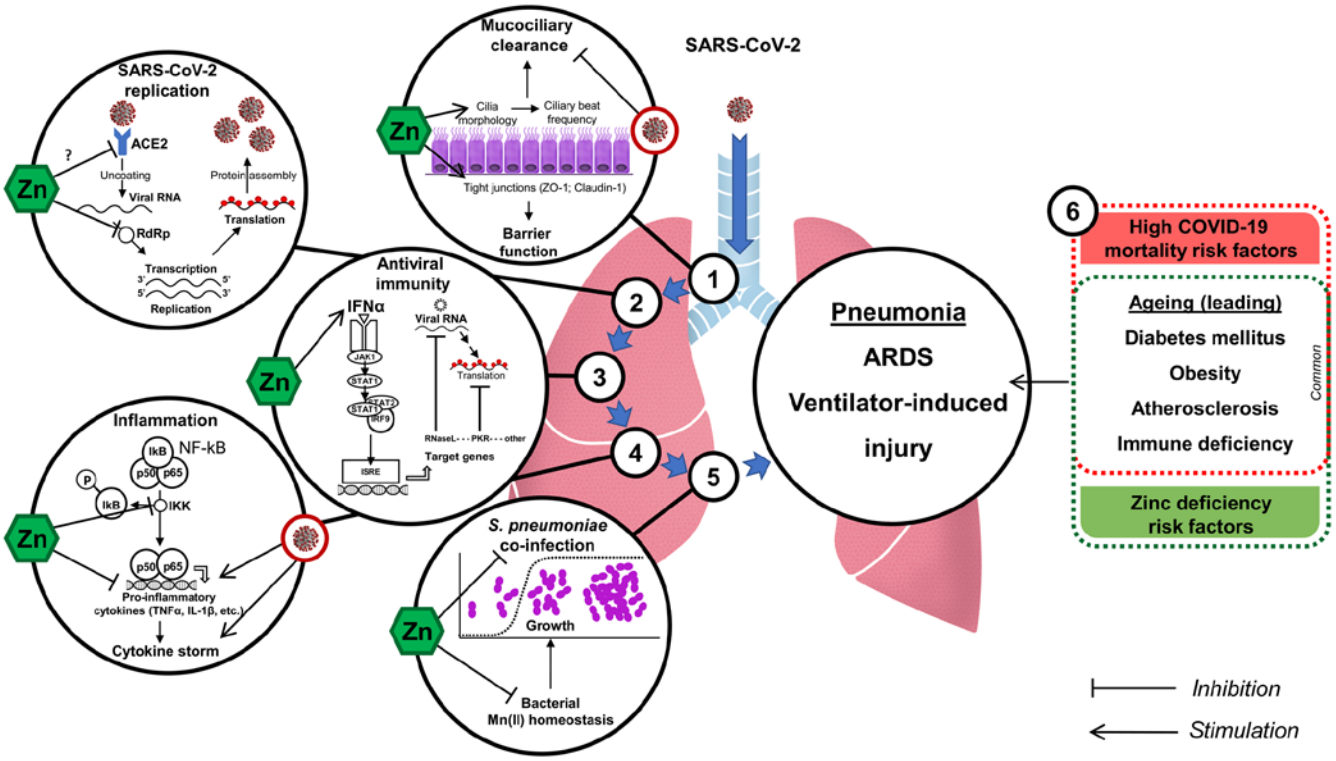

Figure 1. The proposed protective mechanisms of zinc in COVID-19. 1. Zinc significantly improves cilia morphology (54) and increases ciliary beat frequency (55) thus improving mucociliary clearance and removal of bacteria and virus-containing particles. By up-regulating tight junction proteins ZO-1 and claudin-1 (57) and increasing antioxidant activity of respiratory epithelia (56) zinc also increases barrier function of the latter. In turn, coronavirus infection was shown to impair mucociliary clearance (50) predisposing the lung for further viral and bacterial aggression. 2. Zinc may also possess antiviral activity through inhibition of RdRp and blocking further replication of viral RNA as demonstrated for SARS-CoV (38). Indirect evidence also indicates that Zn^{2+} may decrease activity of ACE2 (49), known to be the receptor for SARS-CoV-2 (47). 3. Modulation of antiviral immunity by zinc may also limit SARS-CoV-2 infection at least through up-regulation of IFNα production (63) and increasing its antiviral activity (64). The latter may be mediated through IFNα-induced JAK1/STAT1 signaling and up-regulation of antiviral proteins (RNaseL and PKR) known to degrade viral RNA and inhibit its translation (65). 4. Excessive inflammatory response resulting in overproduction of proiflammatory cytokines and cytokine storm is known to play a significant role in COVID-19 pathogenesis (103). In turn, zinc possesses anti-inflammatory activity through inhibition of IKK activity and subsequent NF-κB signaling resulting in down-regulation of proinflammatory cytokine production (122,124). Modulation of regulatory T-cell functions by Zinc may also limit excessive inflammatory response (125,126) as well as the downregulation of proinflammatory cytokine production (127,123). 5. Given a high risk of bacterial co-infection in viral pneumonia (128), Zn-induced inhibition of *S. pneumoniae* growth through modulation of bacterial Mn(II) homeostasis (137) may also be beneficial. 6. Zinc status is also associated with risk factors for high COVID-19 mortality. Specifically, ageing, immune deficiency, as well as metabolic diseases such as obesity, diabetes, and atherosclerosis, are known to be both risk factors for high disease mortality (31,32) and zinc deficiency (149). In turn, Zn supplementation may have beneficial effect in modulation of at least some of these risk factors. ACE2, angiotensin-converting enzyme 2; IFN, interferon; IKK, IκB kinase; NF-κB, nuclear factor-κB; ARDS, acute respiratory distress syndrome.

Experimental data demonstrate that Zn deficiency increases susceptibility to systemic inflammation and sepsis-induced organ damage including lungs in a murine model of polymicrobial sepsis (113). In a model of polymicrobial sepsis Zn deficiency resulted in increased NF-κB p65 mRNA expression and production in lungs resulting in up-regulation of target genes IL-1β, TNFα, and ICAM-1 (114), whereas Zn supplementation reduced neutrophil infiltration and MPO-mediated oxidative damage (115,116). Modulation of ERK1/2 and NF-κB pathways was shown to be critical for protective effect of zinc in lungs under septic conditions (117).

Correspondingly, patients with sepsis were characterized by low serum Zn levels that may occur due to increased ZIP8 (SLC39A8) mRNA expression. Moreover, serum Zn concentrations inversely correlated with both disease severity and proinflammatory cytokines IL-6, IL-8, and TNFα (118). Reciprocal regulation of ZIP8 and NF-κB expression in response to TNFα or LPS exposure was demonstrated in lung epithelia and alveolar macrophages (119). In addition, ZIP8-deficient mice were characterized by increased airway neutrophil infiltration and elevated CXCL1 and IL-23 production (120).

Zn-mediated respiratory protection was also demonstrated in models of toxic atmospheric pollutant exposure. Particularly, Zn deficiency in agricultural organic dust-exposed animals aggravated neutrophil migration and proinflammatory cytokine (TNFα, IL-6, CXCL1) overproduction, as well as increased IL-23 and CXCL1 expression by macrophages due to NF-κB activation (121). In turn, Zn supplementation in cigarette smoke exposed mice significantly reduced the number of alveolar macrophages in bronchoalveolar lavage (122).

The observed anti-inflammatory effects of Zn in lung tissue seem to be mainly mediated by inhibition of NF-κB signaling through PKA-induced inhibition of Raf-1 and IκB kinase β (IKKβ) (123,124) or A20-dependent inhibition (125). Moreover, Zn-induced modulation of T-cell activity may also play a significant role in limiting inflammatory response (126,127). Lastly, zinc was shown to normalize the overproduction of proinflammatory cytokines induced by zinc deficiency on the epigenetic level (124,128).

7. Zinc and *S. pneumoniae* infection

Although COVID-19 is characterized by viral pneumonia caused by SARS-CoV-2 virus, bacterial co-infection may represent a significant issue due its high incidence in H1N1 influenza-associated pneumonia (129). Specifically, human coronavirus NL63 was associated with increased adherence of *S. pneumoniae* to epithelial cells (130). In turn, *Streptococcus pneumoniae* infection is considered as the most common cause of pneumonia.

Zinc is an essential component of antibacterial immunity (5). Particularly, Zn deficiency was associated with reduced killing activity of phagocytes in pneumococcal infection (131). In turn, Zn supplementation ameliorated the association between nasopharyngeal *S. pneumoniae* carriage and acute lower respiratory infection in children (132). Zn deficiency also predisposed to impaired immune response to Pneumococcal surface protein A, increased nasal *S. pneumoniae* colonization, and severe pneumococcal infection in mice (133) resulting in shorter survival time after infection (134). Correspondingly, patients with better immune response to 23-valent pneumococcal polysaccharide vaccine were characterized by significantly higher serum Zn levels (135). However, no effect (136) or serotype-specific effect (137) of Zn on antibody production in response to polyvalent pneumococcal vaccine was observed. Zn may also exert toxic effect on *S. pneumoniae* reducing its growth through interference with Mn(II) homeostasis and development of cytoplasmic manganese deficiency (138). The latter, in turn, increases bacterial susceptibility to oxygen-dependent killing by neutrophils (139).

A number of studies demonstrated antibacterial effect of zinc oxide nanoparticles (140). Particularly, ZnO was shown to inhibit both growth and biofilm formation by *S. pneumoniae* (141). Similar effect was observed for other bacterial agents involved in etiology of pneumonia, including *K. pneumoniae* (142), methicillin-resistant *S. aureus* (143), and *P. aeruginosa* (144). However, the potential antibacterial application of ZnO-(NPs) may be limited due to their toxicity to human lung cells (145), as well as impairment of phagocytic activity of macrophages in bronchi and lungs (146).

When considering the relationship between *S. pneumoniae* and zinc, one should also note essentiality of Zn ions for bacteria. Specifically, adequate Zn uptake is required for normal bacterial growth and morphology, as well as colonization and virulence (147). Pneumococcal biofilm formation was also shown to be dependent on Zn bioavailability (148).

8. Perspectives and conclusions

The obtained data demonstrate that adequate zinc status of the individual increases immune reactivity. Correspondingly, inadequate zinc supply may predispose to infectious diseases of upper and lower respiratory tract. Although the therapeutic effects of Zn are considered as inconsistent, the existing evidence-based data indicate efficiency of Zn supplementation and improvement of Zn status in prevention of pneumonia and its complications due to anti-inflammatory effect of zinc.

Certain indirect indications of the potential antiviral effect of Zn against nCoV-2019 exist, although their biomedical relevance is yet to be studied. In view of recent data on clinical course of the disease, it appears that adequate Zn status may possess protective effect as adjuvant therapy of COVID-19 through reducing lung inflammation, improvement of mucociliary clearance, prevention of ventilator-induced lung injury, modulation of antibacterial and antiviral immunity especially in elderly (Fig. 1). Further clinical and experimental studies are strongly required to elucidate the potential role of Zn deficiency in COVID-19 susceptibility, as well as effects of Zn supplementation, and the underlying mechanisms.

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Authors' contributions

Conceptualization: AVS, LR, MA, JA, AT, AAT; validation, research, resources, data reviewing, and writing: AVS, LR, OPA, MA, VAG, SIA, AAS, DP, DAS, JA, AT, AAT; figure preparation and edition: AAT; review and editing: AVS, LR, MA, JA, AT, AAT. All authors read and approved the final manuscript.

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Not applicable.

Patient consent for publication

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Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

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