



REVIEW

# COVID-19: Zinc and Angiotensin-Converting Enzyme 2 (ACE2) Deficiencies as Determinants of Risk and Severity of Disease: A Narrative Review

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## ABSTRACT

A growing body of evidence supports the premise that deficiencies of zinc and angiotensin-converting enzyme 2 (ACE2, a zinc enzyme) determine severity of coronavirus disease 2019 (COVID-19). ACE2 is part of the renin-angiotensin system (RAS) and acts as a feedback control system moderating blood pressure, keeping blood pressure within normal limits. For a virus to infect a person, the virus has to get inside the person's cells. The virus that causes COVID-19 uses ACE2 to get into the cell. Think of this like an invader from outer space attacking your car by getting in through your cruise control; the RAS is like the cruise control of your car. What happens next depends on how robust your cruise control is. If your cruise control is young and healthy perhaps very little happens; your car may slow down or speed up a bit. But if your cruise control is in poor condition the attack might disrupt the entire speed control system; your car may brake suddenly or speed out of control and crash. Feedback control systems (natural or man-made) are designed to keep dynamic systems in control, but under

certain situations can drive the system completely out of control. The RAS is composed of two feedback loops: the ACE loop provides amplification, increasing pro-inflammatory cytokines and blood pressure; the ACE2 loop provides fine control and mitigates the vasoconstrictive, pro-inflammatory, and thrombotic actions of the ACE loop. Usually, there is balance, but in the setting of COVID-19, underlying deficiencies of zinc and ACE2 can lead to an imbalance. Exacerbated by the severe downregulation of ACE2 seen with viral entry, a "tipping point" is reached with loss of control of the RAS system resulting in increased angiotensin II (Ang II) causing downstream vasoconstriction, inflammation, and thromboses. These, in turn, lead to complications often seen in "severe COVID-19" such as acute respiratory distress syndrome (ARDS) or cytokine storm, often seen in high-risk patients in the second week of illness. This model suggests that supplemental zinc could replenish zinc in ACE2, stabilize the ACE2 axis, and prevent disruption of the RAS. This would prevent the vasoconstrictive, inflammatory, and thrombotic actions of Ang II, thus preventing the severe COVID-19 complications which cause the high morbidity and mortality seen in high-risk patients with underlying zinc deficiency. Zinc supplements are available, easy to use, and relatively safe. Randomized clinical trials are needed to confirm safety and efficacy of zinc supplementation to decrease severity of and

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morality from COVID-19 in high-risk patients. Since replenishment of zinc and active ACE2 in patients in whom these are deficient may take weeks, supplementation in high-risk populations prior to COVID infection may be required. Such supplementation should not replace vaccination but may be useful in populations for whom vaccination is not available or for populations exposed to viral variants to which available vaccines have insufficient coverage.

**Keywords:** Angiotensin-converting enzyme 2 (ACE2); COVID-19; Future treatments; Narrative review; Pathophysiology; Renin–angiotensin system (RAS); SARS-CoV-2; Zinc; Zinc deficiency

### Key Summary Points

Angiotensin-converting enzyme 2 (ACE2) is a key component of the renin–angiotensin system (RAS)

SARS-CoV-2 virus uses ACE2 for cell entry

These two facts can explain high-risk populations, symptoms, and clinical progression

High-risk groups likely to be zinc or ACE2 deficient

ACE2 and zinc deficiency leads to imbalance of the RAS, predominance of ACE adverse axis. Exacerbated by downregulation of ACE2 with viral entry leads to Ang II-mediated increase in vasoconstrictive, inflammatory, and thrombotic actions leading to severe sequelae (e.g., ARDS, cytokine storm)

Randomized clinical trials needed to confirm efficacy and safety of zinc supplementation to decrease severe sequelae and mortality of COVID-19, especially in those unable or unwilling to access vaccination or those who may be at increased risk from viral variants that are insufficiently covered by available vaccines.

## INTRODUCTION

This is a narrative review focusing on the role of zinc and the zinc enzyme angiotensin-converting enzyme 2 (ACE2) in the renin–angiotensin system (RAS). ACE2 is the portal to cell entry for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), thus linking the RAS to viral infection. Review of the literature has revealed an emerging consistent narrative that explains much that we see in risk factors, symptoms, and course of disease in COVID-19. The conceptual framework encompassing this narrative points to a pathophysiologic mechanism of disease. The true value of this approach will be if therapeutic interventions based on this framework are safe and effective in decreasing severity and mortality of COVID-19. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by the author.

## SYMPTOMS AND DEMOGRAPHICS

Anosmia and ageusia previously considered pathognomonic of zinc deficiency [1, 2] are now also considered early symptoms of COVID-19, suggesting a shared mechanism.

Individuals age older than 65, of male sex, and minority race or ethnicity are at high risk of contracting COVID-19 and once infected are at a higher risk of disease progression and death [3–6]. They are also at increased risk of developing hypertension and of progression to severe hypertension. These same groups also have been shown to have higher rates of ACE2 deficiency [7], suggesting that ACE2 deficiency plays a role in the response to COVID and in development of hypertension. Risk groups for COVID-19 and zinc deficiency largely overlap [8].

## CHRONIC CONDITIONS OF RISK FOR COVID-19

The Centers for Disease Control and Prevention (CDC) has noted risk of severe COVID-19

including rehospitalization in patients with any of five chronic conditions: chronic obstructive pulmonary disease (COPD), heart failure, diabetes with chronic complications, chronic kidney disease, and obesity [9]. Zinc deficiency has been implicated in COPD [10], heart failure [11], diabetes [12], and chronic kidney disease and obesity [13].

## SOCIOECONOMICS

Patients at high risk of SARS-CoV-2 infection, disease progression, and death include racial and ethnic minorities [4]. These increased risks have been attributed to societal and racial inequities [14].

Baseline ACE2/zinc deficiency is hypothesized as a biochemical mediator of the socioeconomic conditions and diet to which high-risk individuals have been subject and also provides a logical mechanism as to how socioeconomic factors can impact individual risk.

## ACE2 AND RAS

ACE and ACE2 are key components of the RAS providing homeostasis of blood pressure (BP) (Table 1). For details, see [15, Table 1] and [16].

ACE and ACE2 are homologous zinc metalloenzymes, each with an N-terminal signal sequence, a hydrophobic transmembrane section, and a cytoplasmic section [17]. Zinc is

required to catalyze peptide hydrolysis [18; for ACE, prior to discovery of ACE2]. Activity of ACE is dependent on adequate dietary zinc. Adding zinc to the serum from zinc-deficient animals restored ACE activity and adding EDTA inhibited activity, reversible with zinc but not copper [19].

## VIRAL ENTRY

SARS-CoV-2 utilizes epithelial cell ACE2 as a cellular entry receptor [7]. The viral spike glycoprotein S binds to the host cell ACE2 receptor [20, 21]. This is followed by release of the viral genome into the cell, accompanied by severe downregulation of the ACE2 receptor [7].

## ACE “ADVERSE” VS. ACE2 “PROTECTIVE” AXES OF RAS

The major difference between ACE and ACE2 is the specificity of their carboxypeptidases—the ACE carboxypeptidase removes a single amino acid from inactive angiotensin (Ang) to yield active angiotensin II (Ang II). The carboxypeptidase of ACE2 removes two amino acids. The major substrate of ACE2 is Ang II; ACE2 degrades (active) Ang II to generate (vasodilatory) Ang 1–7 and Ang 1–9.

In normal functioning, the ACE positive feedback loop leads to amplification of Ang II and increased BP, inflammation, and

**Table 1** Renin–angiotensin system overview

Axis	Adverse/ protective	Substrate	Product	Feedback	Actions in RAS	Receptor	Downstream signal
ACE	Adverse	(Inactive) Ang	(Active) Ang II	+	Amplifies	AT1	↑ Vasoconstriction, inflammation, thromboses
ACE2	Protective	(Active) Ang II	(Vasodilatory) Ang 1–7	–	Modulates ACE, fine control	Mas	Mitigates pro- inflammatory actions of ACE

*Ang* angiotensin, *Ang II* angiotensin II, *Ang 1–7* angiotensin 1–7

thrombosis. The ACE2 negative feedback loop modulates the ACE loop, dampening the vasoactive, inflammatory, and thrombogenic actions of the ACE axis, regulating the RAS [22–24] providing homeostasis and smooth fine control, Table 1 (see also [15, Table 1]) and [7].

With zinc deficiency ACE2 activity is decreased which can lead to decrease of the “preventive” Ang 1–7 and Ang 1–9 and predominance of the ACE “adverse” Ang II. Upon SARS-CoV-2 infection, ACE2 is further decreased with viral cell entry, leading to loss of control.

Supplemental zinc could reverse this with preservation of the ACE2 axis, mitigation of the effects of the ACE axis with decreased inflammation, vasoconstriction, and thromboses [25].

## HYPOTHESIS: DEFICIENCIES OF ZINC AND ACE2, DYSREGULATION, AND THE TIPPING POINT

Building on work of others [7, 17, 26] a hypothesis has emerged that deficiencies of ACE2 and zinc can explain the high-risk groups for COVID-19. Furthermore, clinical exacerbation that occurs in many high-risk patients at approximately day 8–9 (the beginning of the second week of illness) is thought to represent a “tipping point” with increasing oscillations, dysregulation, and disruption of the “Yin/Yang” balance [26] usually maintained by the RAS (Table 1). This loss of control and predominance of the ACE “adverse” axis [27] is signaled downstream by Ang II acting via the AT1 receptor to increase vasoconstriction, inflammation, and thromboses. In the lung, Ang II hyperactivity could result in multifocal pneumonia, acute respiratory distress syndrome (ARDS), thromboses, or (systemically) cytokine storm [7, 25, 27, 28].

Others [29] have stressed the cytokine actions with little mention of the failed RAS.

Loss of control in feedback systems occurs when perturbations or delays exceed the limits of the system [15].

## ZINC AND ACE2 DEFICIENCY IN PATIENTS WITH COVID-19

In one series of hospitalized patients with COVID-19, 57.4% were zinc deficient at the time of hospitalization compared to healthy controls [30]. Patients with COVID-19 who were zinc deficient at time of hospitalization were compared with those with normal zinc levels at hospitalization. Those showing zinc deficiency had increased complications (OR 5.54), ARDS (18.5% vs. 0%,  $p = 0.06$ ), and mortality (18.5% vs. 0%,  $p = 0.06$ ).

Verdecchia and colleagues [7] noted that the groups with higher rates of disease progression with COVID-19 (advanced age, male sex) have higher rates of ACE2 deficiency.

## TIME COURSE OF COVID-19: ACUTE EXACERBATION AND COMPLICATIONS

Many patients with COVID-19 do relatively well in the first week after onset but then (especially high-risk patients) may experience an acute exacerbation, often with ARDS or other sequelae in the second week. Liu and colleagues [31] reviewed the clinical histories of 276 patients and selected 24 patients meeting predefined criteria of confirmed COVID-19 pneumonia. They noted clinical exacerbation (defined as moving from the general ward to the intensive care unit) at 8.8 days after disease onset. With exacerbation, patients had more clinical symptoms, and an increase in number of lung lobes involved, with multifocal lesions in 100%. Complications seen in the second week of illness include multifocal pneumonia, ARDS, thromboses, or cytokine storm. Berlin et al. [32] have reviewed this “severe COVID-19” starting approximately 1 week after onset of illness.

Cantini et al. [33, Fig. 1] have diagrammed the time course of clinical symptoms and laboratory findings vs. viral load and immune response, showing an inflection at days 5–7 of illness. This inflection is the acute clinical exacerbation, the shift from the ACE2 protective axis to the ACE adverse axis with loss of the

“Yin/Yang” balance as hypothesized above. The role of ACE2 and the shift to pro-inflammatory cytokines are highlighted [33, Fig. 2]. Goletti and Cantini [34] have added measures of severity and shown the relative pathogenesis of viral replication and immune response and stage of disease when different medications are active. Putting zinc supplementation onto this diagram would show most activity prior to symptom onset and early in infection before the day 7–8 inflection.

## TIME COURSE OF COVID-19 DISEASE: RIGHT DRUG AT THE RIGHT PHASE OF DISEASE

Cantini and Goletti [33, 34] also raised an important concept regarding treatments for COVID-19: we have to use the right drug at the right phase of disease. Remdesivir and other antivirals are expected to be active early during active viral replication while dexamethasone or baricitinib act later dampening the SARS-CoV-2-mediated immune response. Zinc supplementation for replenishment of zinc deficiency would be expected to be most beneficial if administered early, to maintain or replenish ACE2 and the ACE2 axis. Late administration, after the acute exacerbation of the “tipping point”, would likely have diminished chance of success, as the pro-inflammatory Ang II “horse” would already be “out of the proverbial barn.”

## KAWASAKI DISEASE AND MIS-C

Late onset inflammatory disease resembling Kawasaki disease has been reported with COVID-19. Because it effects children older than usually seen with Kawasaki disease, it has now been renamed as multisystem inflammatory syndrome in children (MIS-C).

Decreased plasma zinc levels have been reported in children with Kawasaki disease [35]. This zinc deficiency resolved after treatment with intravenous immunoglobulins.

## COVID-19 LONG-TERM COMPLICATIONS

The CDC has described a broad range of long-term complications seen in some patients continuing weeks to months post infection [36]. Complications include cardiovascular inflammation (see also Kawasaki disease, above), lung abnormalities, rash, hair loss, smell and taste problems. Several of these are reminiscent of symptoms of zinc deficiency (see below). Assessment of zinc status should be considered for patients with these long-term complications. Zinc supplementation for those found to be deficient may be of benefit.

### Zinc Deficiency

Serum zinc levels of 84–159 µg/dl are generally considered the normal range; levels 60–83 µg/dl cover deficiency, physiological fluctuation, or drug-related variation; and levels below 59 µg/dl represent zinc deficient; and levels below 30 µg/dl indicate definite deficiency [37]. Serum zinc levels are considered the most reliable means of diagnosing zinc deficiency [37]. However, as much of the total body zinc is protein bound or intracellular there may be situations with clinical manifestations of deficiency despite serum levels being at the lower end of normal [37].

Overt zinc deficiency is not common [8, 38]; however, in a study of older adults (> 60 years old), 20–25% had insufficient zinc intake [38]. Zinc intake may be insufficient, especially in the 2–4% of households that sometimes or often have a food shortage [38]. Foods rich in zinc include oysters and meats. Phytates found in some breads and cereals can bind zinc, thereby decreasing absorption. A US survey found reduced zinc levels in 2–3% of the population [8, 38]. The World Health Organization has estimated that 1/3 of the world population may be zinc deficient [8].

Deficiency can also be seen associated with a variety of diseases or chronic conditions including some with poor intake or absorption (gastrointestinal surgery, ulcerative colitis, Crohn’s disease, alcohol use, vegetarian diet) as well as others with increased loss via the



gastrointestinal tract or kidneys [38]. Zinc deficiency can exacerbate renal disease and hypertension [37]. Estimates from nutritional surveys suggest that 20–25% of older individuals have inadequate zinc intake [39].

Antihypertensives (diuretics, ACE inhibitors, angiotensin 2 receptor blockers), beta blockers, and statins have been associated with zinc deficiency [40]. Zinc deficiency in hypertensives can be corrected with supplemental zinc.

Assessment of zinc status of an individual patient should thus take into account chronic conditions, dietary issues, and medications which may predispose to zinc deficiency [37].

White spots in the fingernails are sometimes seen with zinc deficiency [41].

### Excess Zinc

Zinc excess also has its associated toxicities [38, 42]. Zinc in doses as low as 60 mg/day can antagonize intestinal absorption of copper resulting in anemia and neurological symptoms. Low dose copper has been added to some zinc supplements to prevent this [38]. Excess zinc supplementation 150–450 mg/day has been associated with disruption of iron and immune function.

Zinc has been used to treat acne, the common cold (with mixed results), as a denture adhesive, for treatment of infant diarrhea, wound healing, and to delay progression of age-related macular degeneration [38, 43]. Excesses resulting in a US Food and Drug Administration warning have occurred with intranasal formulations for the common cold causing anosmia and zinc-containing denture adhesives.

### Zinc Supplementation

The Food and Nutrition Board (FNB) of the Institute of Medicine of the National Academies has established recommended dietary allowances (RDAs) for zinc of 8 mg for adult women and 11 mg for adult men. They have also established tolerable upper intake levels (ULs) of 40 mg for both adult women and men. These limits are not meant to apply to those receiving zinc for medicinal treatment while under observation.

Prolonged intake above the ULs has increased risk of adverse health effects [38]. Zinc replacement for zinc deficiency with 30 mg/day zinc is generally considered safe. Zinc replacement is usually continued for 3–4 or sometimes to 6 months [37]. Response is better than 70% if therapy is initiated soon after onset of zinc deficiency but is less in the elderly if treatment is delayed.

The AREDS studies for delaying progression of macular degeneration have provided long-term safety data on zinc supplementation; 3640 patients were randomized to (1) antioxidants plus zinc 80 mg/day and copper daily 2 mg/day, (2) zinc and copper without antioxidants, (3) antioxidants alone, and (4) inactive placebo. After the initial 5-year study participants were followed for an additional 5 years. Ten years after initial enrollment 70% of patients were taking zinc 80 mg/day with copper 2 mg/day for an average of 6.3 years. This exposure was associated with a statistically significant increased rate of genitourinary hospitalizations [44], most commonly for benign prostatic hyperplasia, urinary tract infection, urinary lithiasis, and renal failure. There were no prostate or other cancers with the zinc supplementation.

Optimal dosing and duration for treatment of zinc deficiency in COVID-19 has not been established; 30 mg/day is considered safe while 80 mg/day zinc with 2 mg/day copper while monitoring for genitourinary events might be appropriate for clinical trials. Zinc 80 mg/day with copper 2 mg/day increased serum zinc by 17% in a year [45].

### NIH COVID-19 Treatment Guidelines, Zinc

The National Institutes of Health (NIH) has published COVID-19 Treatment Guidelines including a section on zinc supplementation, last updated February 11, 2021 [46].

The panel reviewed available data from three studies: one randomized control study in severe patients [47] and two observational studies in PCR-confirmed [48] and SARS-CoV-2-infected hospitalized patients [49]. All three included zinc supplementation together with use of

hydroxychloroquine (used as an ionophore). Only one [49] included an arm of zinc alone. The randomized controlled trial showed no benefit from combination. Frontera et al. [49] reported 24% reduction in in-hospital mortality with combination, but no benefit from zinc or hydroxychloroquine alone. The NIH COVID-19 Treatment Guidelines Panel recommendations were:

- There are insufficient data to recommend either for or against the use of zinc for the treatment of COVID-19.
- The COVID-19 Treatment Guidelines Panel (the Panel) *recommended against* using zinc supplementation above the recommended dietary allowance for the prevention of COVID-19, except in a clinical trial.

## RECENT STUDIES

Arentz et al. [50] conducted a literature search of eight databases and four clinical trial registries yielding 1627 records of interest. They summarized that direct evidence of benefit of zinc for prevention or treatment of SARS-CoV-2 infection is not yet available; however, indirect evidence from the literature suggests that zinc supplementation may be useful to reduce the “risk, duration, and severity” of SARS-CoV-2 in older patients and those with chronic conditions known to be associated with zinc deficiency. They suggest that these high-risk individuals should have an assessment of zinc status as part of the COVID-19 clinical workup. Those found to have low or borderline zinc levels or those with evidence of insufficient intake or excess loss of zinc should be considered for zinc supplementation.

Thomas et al. [51] randomized 214 newly diagnosed ambulatory patients to open-label zinc (50 mg zinc gluconate daily), ascorbic acid, both, or neither for 10 days of treatment. There was no significant difference in the time to 50% decline in symptoms between the treatments and hospitalizations and deaths did not differ across the treatments. The 10-day duration of treatment may have been insufficient. The study was limited to ambulatory patients; this

may have led inadvertently to underrepresentation of zinc-deficient patients most likely to benefit from zinc supplementation [52].

## PROPOSAL: RANDOMIZED CLINICAL TRIALS

Randomized clinical trials (RCTs) are needed to confirm the benefit of zinc to decrease incidence and severity of COVID-19 in high-risk uninfected patients.

Assessment of zinc status in those with long-term complications of COVID-19 should also be considered. For both these groups, supplementation for those found to be zinc deficient may be beneficial.

The accumulating evidence above and the fact that zinc supplements are available, easy to use, well studied, and relatively safe suggests that randomized clinical trials for high-risk groups could be initiated now.

Zinc supplementation should not be a substitute for COVID-19 vaccination. However, zinc assessment and supplementation for those found to be zinc deficient may be of benefit for those unable or unwilling to access vaccination or those who may be at increased risk from viral variants that are insufficiently covered by currently available vaccines.

## LIMITATIONS

This manuscript presents an internally consistent narrative to explain a number of observations of COVID-19, especially those occurring in high-risk patients. Most of the steps reflect clinical conditions described in the literature correlated to laboratory findings. Zinc serum levels may not reveal all deficiencies, and correlation does not guarantee causality. The optimal duration of zinc supplementation to replenish ACE2 in the setting of COVID has not been established. If supplementation longer than a week is required, initiation after COVID infection may be too late; zinc deficient patients at risk of COVID may have to be identified and zinc supplementation initiated prior to infection. Other models of pathophysiology of

COVID-19 have been proposed [53]. What a consistent narrative can help us with is to guide us in design and implementation of randomized clinical studies. Hopefully new data will help clarify pathophysiological mechanisms and help us find new interventions to control this pandemic.

## CONCLUSIONS

A growing body of evidence supports the premise that deficiencies of zinc and the zinc enzyme ACE2 are determinants of risk and severity of COVID-19. Focusing on the role of ACE2 in the RAS and in viral cell entry provides us a useful conceptual framework, revealing a cohesive and consistent narrative. Anosmia, demographics of high-risk groups, and the actions of the RAS point to deficiencies of zinc and ACE2 playing a role in COVID-19 exacerbation in high-risk individuals. In COVID-19 the baseline deficiency of ACE2 with further depletion due to the viral cell entry results in loss of control of the normal balance of the RAS and predominance of the ACE “adverse” axis. This in turn results in downstream increases in vasoconstriction, inflammation, and thromboses, leading to clinical sequelae of COVID-19 such as ARDs, thromboses, MIS-C, cytokine storm, etc.

RCTs are needed to confirm safety and efficacy of zinc supplementation to decrease incidence and severity of COVID-19 in high-risk patients.

Patients with clinical findings suggestive of zinc deficiency (poor diet, other risk factors [37]) should be considered for clinical and laboratory assessment and supplementation for those found to be zinc deficient. This may be of benefit especially for those unable or unwilling to access vaccination or those who may be at increased risk from viral variants that are insufficiently covered by currently available vaccines. If RCTs confirm the proposed benefit of zinc replacement therapy in high-risk zinc-deficient patients, this would open a new window of attack to prevent the increased vasoconstriction, inflammation and thromboses seen in severe COVID.

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