

# SIGNIFICANCE OF ZINC IN CURRENT PANDEMIC

## EVIDENCE SERIES



*Reviewed by:*

**Dr JC Suri**  
 MD, DNB, DTCD, FNCCP  
 Director & Head  
 Department of Pulmonary, Critical  
 Care & Sleep Medicine  
 Fortis Flt. Lt. Rajan Dhall Hospital,  
 Vasant Kunj, New Delhi

## ZINC AND ITS ANTIVIRAL EFFECTS: POTENTIAL IMPLICATIONS

### PROLOGUE

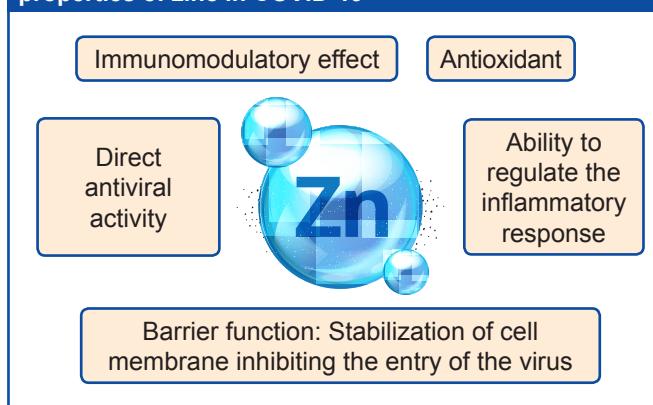
- Today, the world witnesses one of the greatest health burdens in the form of the COVID-19 pandemic.
- There is constant effort to mitigate the detrimental effect of this pandemic, and any attempt with whatsoever positive results is expected to be of benefit, in terms of both the individual clinical health and overall public health.
- Especially, a cost-effective, easily available, and safe option with little-to-no side effects and simple applications are desperately needed.
- In this context, zinc is an important trace element which is involved in various biological processes due to its role as a cofactor, signaling molecule, and structural component.
- Moreover, zinc exhibits potent immunoregulatory and antiviral properties.<sup>1</sup>

### POTENTIAL MECHANISMS FOR ANTIVIRAL EFFECTS OF ZINC IN COVID-19

- A broad range of direct and indirect antiviral properties of zinc has been demonstrated in numerous viral species, including several nidoviruses, for which SARS-CoV-2 causing COVID-19 belongs.
- Thus, it suggests that antiviral effects of zinc may be realized in SARS-CoV-2 as well; and zinc supplementation may be of benefit for prophylaxis and treatment of COVID-19.<sup>2</sup>
- Figure 1 illustrates the possible actions by which zinc might be effective in the therapy of COVID-19.<sup>2,3</sup>



**Figure 1: Potential antiviral and immunomodulatory properties of zinc in COVID-19<sup>2,3</sup>**



## ZINC DIRECTLY INHIBITS VIRAL REPLICATION

- As a virus, SARS-CoV-2 is highly dependent on the metabolism of the host cell.
- Zinc supplementation might prevent the viral entry and also suppress its replication, while supporting the anti-viral response of the host cells.<sup>4</sup>
- Zinc-mediated blockade of viral entry and suppression of its replication is facilitated through inhibition of the RNA dependent RNA polymerase (RdRp) of the virus.
- Evidence also suggests that zinc minimizes the Sirtuin 1 (SIRT-1) induced angiotensin-converting enzyme 2 (ACE-2) receptors expression, thus decreasing the probability of SARS-CoV-2 binding to ACE2 receptors.
- Zinc also modulates the antiviral immunity through up-regulation of interferon alpha (IFN $\alpha$ ) production by leucocytes, which may also help to limit SARS-CoV-2 infection.

- Zinc, by up-regulating IFN $\alpha$  production, indirectly increases the synthesis of antiviral proteins like latent ribonuclease (RNaseL) and protein kinase RNA-activated (PKR), which along with IFN $\alpha$ -induced JAK1/STAT1 signaling can degrade viral RNA and inhibit its translation (Figure 2).<sup>3,5</sup>

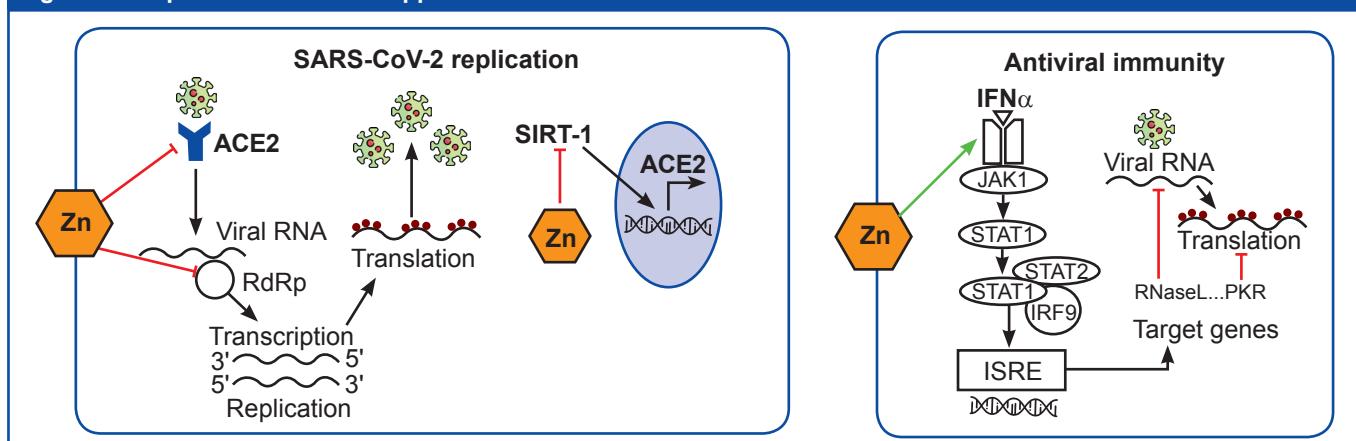
## POOR OUTCOMES IN COVID-19 PATIENTS WITH ZINC DEFICIENCY

- A prospective observational study<sup>6</sup> was conducted with an aim to determine the clinical significance of serum zinc in COVID-19 patients and to establish a correlation with disease severity.
- COVID-19 patients ( $n = 47$ ) had significantly lower zinc levels when compared to healthy controls ( $n = 45$ ): median 74.5  $\mu\text{g}/\text{dL}$  versus 105.8  $\mu\text{g}/\text{dL}$  ( $p < 0.001$ ). Zinc deficiency was reported in 27 (57.4%) of the 47 COVID-19 patients.
- COVID-19 patients with zinc deficiency had higher rates of complications, acute respiratory distress syndrome, corticosteroid therapy, prolonged hospital stay, and mortality versus patients with normal zinc levels (Figure 3).
- Findings of the study suggest that low baseline zinc levels in COVID-19 patients may be associated with more complications, leading to prolonged hospitalization and increased mortality.<sup>6</sup>

## EVIDENCE-BASED EFFICACY OF ZINC SUPPLEMENTATION IN COVID-19

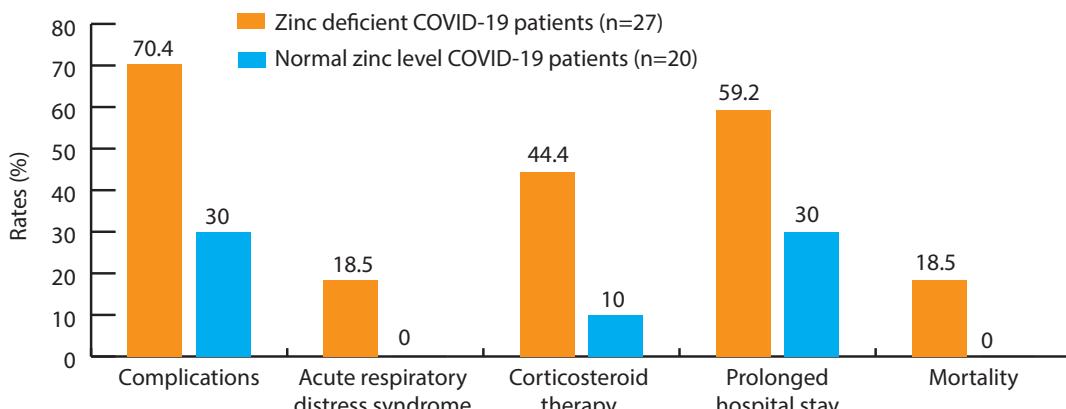
- A multicenter cohort study<sup>7</sup> was conducted to evaluate the impact of zinc with an ionophore hydroxychloroquine (Zn + ionophore) on COVID-19 in-hospital mortality rates.

**Figure 2: Proposed mechanistic approach to the antiviral effects of zinc in COVID-19<sup>3,5</sup>**



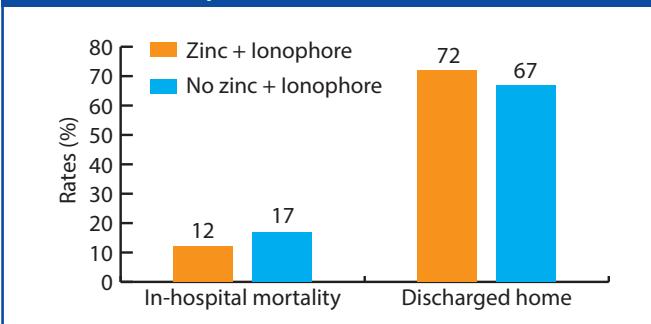
**Abbreviations:** ACE2, angiotensin-converting enzyme 2; RdRP, RNA dependent RNA polymerase; SIRT-1, sirtuin 1; Zn, zinc; IFN, interferon; JAK, Janus kinase; STAT, signal transducers and activators of transcription; IRF, interferon-gene regulatory factors; ISRE, interferon-stimulated response elements; RNaseL, latent ribonuclease; PKR, protein kinase RNA-activated.

**Figure 3: Complications in COVID-19 patients during hospital stay: zinc deficient versus normal zinc level<sup>6</sup>**



- Among a total of 3,473 adult hospitalized patients with SARS-CoV-2 infection, 1,066 (29%) patients received Zn + ionophore beginning at a median of 0.5 days from admission.
- Rates of in-hospital mortality were significantly lower among patients who received Zn + ionophore (12%) compared to those who did not (17%),  $p < 0.001$ .
- Likewise, rates of discharged to home were significantly higher among patients who received Zn + ionophore (72%) compared to those who did not (67%),  $p < 0.003$  (Figure 4).
- No significant interactions were observed for Zn + ionophore with other COVID-19 specific medications.
- The findings demonstrated that among COVID-19 patients, zinc along with an ionophore (hydroxychloroquine) brings about a significant reduction in hospital mortality rates,

**Figure 4: Outcomes in COVID-19 patients who received zinc with an ionophore versus who did not<sup>7</sup>**



along with a 24% reduced risk of in-hospital mortality and increased rates of discharge to home; thus suggesting it to be a potentially effective therapeutic option.<sup>7</sup>

### Dose

Evidence suggests that consuming up to 50 mg of zinc per day might provide a protective role against the COVID-19, possibly by increasing the host resistance against viral infection.

Evidence also suggests that zinc may reduce the risk, duration and severity of SARS-CoV-2 infections, particularly for populations at risk of zinc deficiency including older adults and people with chronic disease co-morbidities.<sup>8-10</sup>

## MUCORMYCOSIS: NEW ADDITION TO THE COVID-19 SPECTRUM

- Recently, several cases of mucormycosis in people with COVID-19 have been increasingly reported worldwide.<sup>11</sup>
- According to clinical experts, there is a dearth of direct link between zinc and mucormycosis, which is seen primarily in patients with uncontrolled diabetes, increased use of corticosteroids, and in immunocompromised situations.<sup>12,13</sup>
- In fact, hyperglycemia is considered the leading risk factor associated with mucormycosis globally, with an overall mortality of 46%. Table 1 illustrates some other important risk factors for mucormycosis in patients with COVID-19.<sup>11</sup>
- The severity of mucormycosis is largely dependent on the patient's immunity and general health.<sup>14</sup>

- Secondary bacterial or fungal infections have been reported in almost 50% of COVID-19-related mortality; this underscores the importance of sustaining the immune function by sufficient zinc replenishment.<sup>4</sup>
- Oral zinc supplementation has been shown to improve glycemic control in patients with diabetes.<sup>15</sup>
- Also, zinc supplementation effectively improves immunity, ameliorates chronic dysfunctional inflammatory responses, supports anti-oxidative effects and thus reduces lung damage and minimizes secondary infections.<sup>4,16</sup>

**Table 1: Risk factors for mucormycosis in patients with COVID-19<sup>11</sup>**

- An ideal environment of low oxygen (hypoxia)
- High glucose (diabetes, steroid-induced hyperglycemia)
- Acidic medium (metabolic acidosis)
- High iron levels (increased ferritins)
- Decreased phagocytic activity of white blood cells due to immunosuppression
- Prolonged hospitalization

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<sup>1</sup> Mossink JP. Zinc as nutritional intervention and prevention measure for COVID-19 disease. *BMJ Nutrition, Prevention & Health* 2020;0. doi:10.1136/bmjnph-2020-000095  
\* Data on file