

Zinc as a Neuroprotective Nutrient for COVID-19–Related Neuropsychiatric Manifestations: A Literature Review

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ABSTRACT

The outbreak of the pandemic associated with Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) led researchers to find new potential treatments, including nonpharmacological molecules such as zinc (Zn²⁺). Specifically, the use of Zn²⁺ as a therapy for SARS-CoV-2 infection is based on several findings: 1) the possible role of the anti-inflammatory activity of Zn²⁺ on the aberrant inflammatory response triggered by COroNaVirus Disease 19 (COVID-19), 2) properties of Zn²⁺ in modulating the competitive balance between the host and the invading pathogens, and 3) the antiviral activity of Zn²⁺ on a number of pathogens, including coronaviruses. Furthermore, Zn²⁺ has been found to play a central role in regulating brain functioning and many disorders have been associated with Zn²⁺ deficiency, including neurodegenerative diseases, psychiatric disorders, and brain injuries. Within this context, we carried out a narrative review to provide an overview of the evidence relating to the effects of Zn²⁺ on the immune and nervous systems, and the therapeutic use of such micronutrients in both neurological and infective disorders, with the final goal of elucidating the possible use of Zn²⁺ as a preventive or therapeutic intervention in COVID-19. Overall, the results from the available evidence showed that, owing to its neuroprotective properties, Zn²⁺ supplementation could be effective not only on COVID-19–related symptoms but also on virus replication, as well as on COVID-19–related inflammation and neurological damage. However, further clinical trials evaluating the efficacy of Zn²⁺ as a nonpharmacological treatment of COVID-19 are required to achieve an overall improvement in outcome and prognosis. *Adv Nutr* 2022;13:66–79.

Statement of Significance: By summarizing the available literature on, and exploring the possible role of, zinc in SARS-CoV-2 infection, the present review suggests how Zn²⁺ supplementation may be effective in COVID-19–related neurological complications.

Keywords: zinc, micronutrient, supplementation, COVID-19, SARS-CoV-2, neuropsychiatry, neuroprotection, inflammation

Introduction

Zinc (Zn²⁺) is an essential trace element in both humans and animals, and it is implicated in a wide range of metabolic and signaling pathways in the body (1). Among micronutrients, Zn²⁺ is the second most abundant trace element in the

human body and the effects of its deficiency have been known since the 1960s (2). Scientific data reported that Zn²⁺ plays a central role in the immune system and the brain (1).

Regarding its function in the immune system, several studies have described Zn²⁺ as a crucial factor in the response to pathogens, because it is an essential trace element not only for the host's immune defense but also for pathogens' survival and the propagation of virulence, all functions modulating the competitive balance between the host and the invading pathogens (3, 4).

Furthermore, Zn²⁺ has been found to play a central role in brain functioning. Indeed, it represents one of the most prevalent metal ions in the brain and participates in the regulation of neurogenesis, neuronal migration, and

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Abbreviations used: ACE-2, angiotensin-converting enzyme-2; AD, Alzheimer disease; CNS, central nervous system; COVID-19, COroNaVirus Disease 19; CSF, cerebrospinal fluid; DC, dendritic cell; HCQ, hydroxychloroquine; ICU, intensive care unit; MS, multiple sclerosis; MT, metallothionein; NALT, nasopharynx-associated lymphoid tissue; PD, Parkinson disease; RCT, randomized clinical trial; SARS-CoV, Severe Acute Respiratory Syndrome coronavirus.

differentiation, thereby determining cognitive development and maintaining healthy brain function (5). For this reason, Zn²⁺ deficiency during pregnancy can lead to specific damage in the brain of the offspring, which has been observed not only in animal models but also in humans (6).

Moreover, several strands of evidence have showed that alteration in brain Zn²⁺ status has been involved in different types of neuropsychiatric disorders, such as neurodevelopmental diseases (e.g., autism spectrum disorders), neurodegenerative disorders [e.g., Alzheimer disease (AD), Parkinson disease (PD)] (7, 8), and mood disorders (9), as well as neuronal damage associated with traumatic brain injury, stroke, and seizure (10).

According to the WHO, Zn²⁺ deficiency affects about one-third of the world's population, representing the fifth leading cause of mortality and morbidity in developing countries (11). Worldwide, Zn²⁺ deficiency accounts for ~16% of lower respiratory tract infections, 18% of malaria, and 10% of diarrheal diseases (12). Although severe Zn²⁺ deficiency is rare, mild to moderate deficiency is more common worldwide (12). Subsequently, considering the importance of Zn²⁺ for the immune and nervous system, a deficiency of this element could lead to a worse outcome in the response toward infection and sepsis and to an increased susceptibility to the development of different neuropsychiatric diseases.

Since April 2020, the COroNaVirus Disease 19 (COVID-19) pandemic, caused by Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) (13), has led to >150 million cases worldwide and >3 million deaths (14). Briefly, the SARS-CoV-2 infection manifests itself with heterogeneous clinical pictures, which can vary from asymptomatic or low-symptomatic forms, up to severe forms of interstitial pneumonia associated with the severe acute respiratory syndrome and multiorgan failure. Moreover, mounting evidence suggests the presence of long-term COVID-19-related complications, including neurological and psychiatric manifestations (15). Notably, the outbreak of a new pandemic has caused researchers to conduct investigations on new potential treatments against this RNA virus, including non-pharmacological molecules. Specifically, in the worldwide race toward the identification of a COVID-19 therapeutic strategy, one of the first studies on the topic reported the potential activity of Zn²⁺ against SARS-CoV-2, mainly due to the immunomodulant and antiviral effects of this micronutrient (16).

Nonetheless, although the possible role of Zn²⁺ in the therapy of SARS-CoV-2 infection has also been studied (17–19), no clinical trials have been conducted so far on the possibility of using Zn²⁺ to prevent neurological complications in COVID-19 patients. Indeed, alongside lung involvement, several studies have described neurological complications as a result of COVID-19 to include taste and smell disturbances (20) as well as, in severe cases, alterations of the state of consciousness, delirium (21), encephalitis (22), and cerebrovascular events (23). All of these neurological complications are because SARS-CoV-2 could have a neurotoxic impact caused by different aspects, which include

the invasion of the central nervous system (CNS), both through the sensory neurons of the olfactory mucosa, CNS inflammation, autoimmune processes involving molecular mimicry, or immunological cross-reactions, and a pro-coagulative state. In this context, Zn²⁺ may not only show antiviral and immunomodulant properties but also exert a neuroprotective function. This hypothesis could represent the basis for future trials, testing its efficacy as an agent against the brain damage underlying common neurologic and behavioral symptoms of COVID-19 (24).

In this context, we aim to provide a narrative review of existing data, by reporting the functions of Zn²⁺ in different systems of the human body (in both physiologic and pathologic conditions). Then, in the context of the COVID-19 pandemic, we will analyze the role of Zn²⁺ both in patients at risk of developing COVID-19 and in affected patients, thus overviewing the antiviral and immunomodulatory effects of Zn²⁺.

Current Status of Knowledge

Zinc status and human health

Zn²⁺ is a ubiquitous trace element that is present in the human body in amounts of ~2–3 g, therefore representing the second most abundant trace metal in humans after iron (2). Within the body, Zn²⁺ is distributed unequally throughout different organs and tissues, because 90% of Zn²⁺ is found in the muscles and bones (25). Although Zn²⁺ is a prominent constituent of the human body, it cannot be stored, therefore representing an essential nutrient whose daily food intake is fundamental to achieving and maintaining the adequate plasma and tissue concentrations required to support all its functions. The current RDA [which is the average daily amount of intake sufficient to meet the nutrient requirements of nearly all (97%–98%) healthy individuals] in adults is 8 mg/d for women and 11 mg/d for men (26). Red meat is the richest source of Zn²⁺, followed by seafood, legumes, and fowl. The Zn²⁺ found in plants is less available for absorption, because phytates (which are present in plant-based foods) bind it and inhibit its absorption (2).

Only 0.1% of the total Zn²⁺ is renewed daily, after absorption by the small intestine. Later Zn²⁺ is distributed by plasma, where it is bound entirely to proteins, such as albumin, 2-macroglobulin (A2M), and transferrin (27). Although dietary Zn²⁺ intake fluctuates, homeostasis mechanisms need to maintain constant intracellular and plasma concentrations (within the reference range of 11–25 μmol/L or 0.7–1.6 mg/L) to provide Zn²⁺-specific functions (28). Despite the fact that plasma Zn²⁺ is <1% of the total body content, it represents a primary source accessible to all human cells. On the other hand, 99% of the total body Zn²⁺ is intracellular and it is distributed between cellular nuclei, specific vesicles retaining Zn²⁺ (called zincosomes), and the cytoplasm (27), which is largely bound by zinc-chelating proteins [called metallothioneins (MTs)] (29).

Based on these data, over the years, several studies explored Zn²⁺ functions in human physiology, describing its

pre-eminent role in maintaining human health. More specifically, Zn^{2+} plays 3 major biological roles in the organism: catalytic, structural, and regulatory (30). Zn^{2+} has a catalytic or structural function in 10% of human proteins, and it reversibly binds other proteins, according to their roles in the different processes of Zn^{2+} metabolism (regulation, transport, transfer, sensing, signaling, and storage) (31). Zn^{2+} also contributes to different cell functions, such as proliferation, differentiation, survival (32), stabilization of the cell membrane (33), redox regulation (34), and apoptosis (35).

From a nutritional point of view, Zn^{2+} deficiency is the fifth largest health risk factor in developing countries and the 11th largest in the world, being responsible for a substantial proportion of the leading causes of death and disability according to the WHO (11). In the early 1960s, for the first time Prasad reported the existence of Zn^{2+} deficiency in humans; nowadays, the most important cause of Zn^{2+} deficiency is malnutrition, which affects >17% of the world population (36). In addition, other less frequent causes of Zn^{2+} deficiency are represented by 1) inadequate intake due to gastrointestinal diseases (e.g., Crohn disease or acrodermatitis enteropathica) or pancreatic diseases (alcoholic pancreatitis, cystic fibrosis); 2) reduced absorption; 3) increased losses of biological fluids (such as gastrointestinal fluid, skin losses, wound exudate, urine, dialysate); 4) increased need owing to a systemic illness resulting in increased oxidative stress (e.g., infection); 5) aging; and 6) drugs and intravenous fluids with effects on Zn^{2+} homeostasis, in particular steroids, penicillamine, EDTA, ethambutol, and certain antibiotics (37).

Adverse effects on health can emerge not only from Zn^{2+} deficiency but also from deficiency of copper secondary to Zn^{2+} excess. Supplementing Zn^{2+} is a major determining factor of toxicity, especially if the form of Zn^{2+} in the supplement is readily bioavailable (2). Considering that different Zn^{2+} supplements contain varying concentrations of elemental Zn^{2+} (Zn^{2+} citrate is ~34% Zn^{2+} in weight, Zn^{2+} sulfate is ~22% Zn^{2+} in weight, and Zn^{2+} gluconate is ~13% Zn^{2+} in weight), Zn^{2+} intake should probably not exceed 20 mg Zn^{2+} daily in adults (2).

Finally, Zn^{2+} has a critical effect on human homeostasis, immune function, oxidoreductive balance, cellular apoptosis, and aging. Therefore, it is not surprising that Zn^{2+} is associated with significant disorders of great public health interest. Indeed, in many chronic diseases including cardiovascular diseases (38), several malignancies (in particular prostate, mammary, and pancreatic gland cancers) (39, 40), age-related neurological degenerative disorders (41), chronic liver diseases (42), and autoimmune diseases (43), the concurrent Zn^{2+} deficiency may complicate the clinical picture, thus affecting immunological status, increasing oxidative stress, and leading to the generation of inflammatory cytokines.

Zinc and the immune system

The maintenance of Zn^{2+} homeostasis is essential for the overall functioning of the immune system. During

inflammation, an adequate status is essential in acute-phase responses, because Zn^{2+} is momentarily transferred from serum into organs (especially the liver), possibly causing transient serum hypozincemia (44). The transient intracellular transferring of Zn^{2+} constitutes a defensive mechanism against Zn^{2+} -dependent extracellular microorganisms. Moreover, Zn^{2+} is important in the maintenance of the structural and functional integrity of mucosal cells in innate barriers (45), thus Zn^{2+} deficiency has been specifically found to cause failure in the intestinal epithelial cell barrier, which in turn can be responsible for numerous downstream effects (e.g., diarrhea) and also lead to gut flora translocation and, finally, to sensitization to sepsis (46).

Zn^{2+} deficiency affects innate immunity in different ways. It reduces polymorphonuclear cell chemotaxis and phagocytosis (47), monocyte adhesion, and maturation of macrophages (48), natural killer cells (49), and dendritic cells (DCs). Zn^{2+} deficiency is reported to influence cytokine release, affecting the generation of cytokines such as IL-2, IL-6, and TNF- α (50). On the other hand, with regards to adaptive immunity, Zn^{2+} deficiency causes thymic atrophy with subsequent T-cell lymphopenia, reduced differentiation of T-cells, increased pre-T-cell death (51), an unpaired balance between Th1 (decreased) and Th2 (less affected) (49), as well as a reduced Th17 subset (52). B-cell maturation and antibody production are less affected by Zn^{2+} deficiency (53).

Zinc and neuronal and blood-brain barrier modulation

Zn^{2+} plays a fundamental role in brain functioning, in the formation and migration of neurons as well as the formation of neuronal synapses (54). In particular, there are several homeostatic systems (Zn^{2+} transporters, Zn^{2+} -importing proteins, MTs, lysosomes, and mitochondria) permitting neurons to maintain extracellular and intracellular Zn^{2+} at concentrations that are nontoxic in different brain regions, comprising those implicated in the physiopathology of depression (e.g., hippocampus, amygdala, and the whole cerebral cortex) (55). Moreover, owing to its essential role in regulating brain functions, many disorders have been associated with Zn^{2+} deficiency, including neurological diseases, such as AD (7), PD (8), multiple sclerosis (MS) (56), and ischemic brain injury (10), as well as psychiatric disorders, such as depression (9, 57) and schizophrenia (58).

Furthermore, Zn^{2+} is known to be a neuroactive substance detectable in specific regions of the CNS (i.e., the olfactory bulb and the hippocampus) (59). It is especially localized in synaptic terminals (where Zn^{2+} can lead to membrane depolarization), acting in different conditions both as an excitatory and an inhibitory modulator (60). Several evidence-based studies showed a potential neurotoxic action of an excessive concentration of Zn^{2+} both in vitro and in vivo, with a role in neuronal damage associated with cerebral ischemia, epilepsy, and trauma (61). Interestingly, besides this literature describing that Zn^{2+} overload is clearly

related to adverse neurological outcomes, some studies reported the crucial role of Zn^{2+} in the maintenance of brain homeostasis and physiology by also showing that the lack of this micronutrient could be associated with brain damage. Indeed, after a traumatic brain injury, patients are at risk of a moderate to severe Zn^{2+} deficiency, which determines an increase in urinary Zn^{2+} excretion and consequently a low serum Zn^{2+} (62). In support of the hypothesis that Zn^{2+} deficiency might have a pathogenetic role in neuronal damage, rat models have shown that a moderate Zn^{2+} deficiency significantly correlates with cell death at the site of cortical injury for both necrosis and apoptosis, persisting ≤ 4 wk after the trauma (63).

Addressing the question concerning the role of Zn^{2+} in the maintenance of brain homeostasis, a significant chapter is represented by the studies that describe the blood–brain barrier (BBB) modulatory function of Zn^{2+} . The BBB is a fundamental anatomical structure, ensuring protection to the brain from undesired substances circulating in the bloodstream. The BBB may break down in certain conditions like convulsive seizures and other CNS insults (i.e., ischemia) (64). At the state of the art, the relation between Zn^{2+} homeostasis and BBB-permeability regulation remains unclear.

However, recent results suggest a fine regulation between Zn^{2+} and the BBB, postulating that Zn^{2+} concentrations in the CNS controlled by the BBB may lead to changes in the BBB itself, especially regarding permeability.

Specifically, a study carried out by Yorulmaz et al. (65) found that the administration of Zn^{2+} treatment in murine models had a proconvulsant effect and increased BBB permeability, possibly changing the prooxidant/antioxidant balance and neuronal excitability during seizures. Similar results were obtained in cellular studies, where a Zn^{2+} overload exacerbated BBB permeability in cultured cells modeling a BBB under ischemia (66), which could be caused by damage of tight junctions and intercellular structures essential for BBB integrity (67).

Moreover, some results suggested that Zn^{2+} deficiency might increase BBB permeability. In an MRI study on male rats under Zn^{2+} deficiency, a more permeable BBB was present, leading to higher amounts of MRI-visible free water and thus edema (68). Consistent results were found in a study carried out by Song et al. (69), which showed that Zn^{2+} protects the integrity of the BBB by inhibiting the decline of occludin and F-actin in endothelial cells in rats exposed to aluminum (69).

In conclusion, overall the results highlight that neither an excess nor a lack of Zn^{2+} is desirable in the brain and that both conditions may lead to a brain insult, possibly resulting in higher BBB permeability.

However, future studies are needed to explore the role of systemic Zn^{2+} supplementation or central Zn^{2+} chelation in CNS damage (70). In this perspective, the development of new therapeutic strategies for the treatment of CNS insults should take into account Zn^{2+} as a new therapeutic target.

Zinc and neuropsychiatric disorders

Nowadays, most of the studies investigating the correlation between Zn^{2+} status and mental disorders have been focused on depression, whereas the relation between Zn^{2+} and other psychiatric disorders is still uncertain (71). Indeed, since the late 1980s, Zn^{2+} deficiency was mainly found to be correlated with depression in animal and human samples (72) and several brain homeostatic systems have been linked to the maintenance of extra- and intracellular Zn^{2+} at nontoxic concentrations, including in brain regions involved in the physiopathology of depression (73). Moreover, to verify the hypothesis of Zn^{2+} deficiency relating to the pathogenesis of depression, peripheral blood Zn^{2+} concentrations have been measured in numerous studies of depressed and nondepressed subjects. A meta-analysis of 17 observational studies found that blood Zn^{2+} concentrations were lower in depressed subjects than in control subjects (9). In addition, a systematic review summarizing the results of just 4 randomized clinical trials (RCTs) reported that, overall, the results showed that Zn^{2+} as an adjunct to antidepressant treatment might result in more rapid or more effective symptomatic improvement (57). However, despite this evidence, the potential mechanisms underlying the association between low serum Zn^{2+} and depression remain unclear, although they may involve the regulation of endocrine (74, 75), neurotransmitter (76–78), and neurogenesis (79–81) pathways.

Importantly, studies have also been performed on other psychiatric disorders, although to a much lesser extent. Specifically, a recent meta-analysis found significantly lower serum Zn^{2+} concentrations in schizophrenic patients than in controls (58). Moreover, a study found a higher prevalence of Zn^{2+} deficiency in patients with other psychiatric diagnoses, such as psychosis, than in patients with depression (71).

The role of Zn^{2+} has also been studied in different neurological disorders. Indeed, it has been reported that Zn^{2+} could be fundamental in the pathogenesis of different neurodegenerative diseases, such as AD (7) and PD (8). Specifically, the role of Zn^{2+} in the pathogenesis of AD is still controversial because it has been found that Zn^{2+} may act as a contributor of AD pathogenesis, inducing the oligomerization of $A\beta P$ (β -amyloid protein), and as a protector, limiting $A\beta P$ -induced neurotoxicity (82). Moreover, although a meta-analysis indicated that serum Zn^{2+} concentrations were significantly decreased in AD patients compared with healthy controls, no significant difference in Zn^{2+} concentrations between AD patients and healthy controls was observed when only the age-matched studies were considered (41). With regards to PD patients, different meta-analyses showed that both serum and cerebrospinal fluid (CSF) Zn^{2+} concentrations were significantly lower in these patients than in healthy controls (8, 83, 84). Although low serum Zn^{2+} concentrations could be considered a risk factor for PD by increasing oxidative stress (which has been linked to the pathogenesis of PD) (8), Zn^{2+} deficiency could also be a consequence of this disease, because Zn^{2+} concentrations inversely correlated with PD duration (83).

TABLE 1 In vitro studies on zinc assessing the antiviral efficacy on Coronaviridae¹

Coronavirus	Antiviral effect	Zinc	Reference
Feline infectious peritonitis virus (FIPV)	Inhibition of viral polyprotein cleavage	Zn ²⁺	Wang et al. (111)
Mouse hepatitis virus (MHV)	Inhibition of viral polyprotein cleavage	ZnCl ₂	Denison et al. (105)
	Inhibition of viral polyprotein cleavage	ZnCl ₂	Shi et al. (106)
Severe acute respiratory syndrome coronavirus (SARS-CoV)	Inhibition of viral polyprotein cleavage	Zn ²⁺ , N-ethyl-N-phenylthiocarbamic acid	Han et al. (107)
	Inhibition of viral polyprotein cleavage	Zn, hydroxypyridine-2-thione Zn Zn ²⁺ , 1-hydroxypyridine-2-thione Zn	Hsu et al. (108)
	Inhibition of RdRp activity by affecting template binding	ZnOAc ₂ + PT	te Velthuis et al. (109)
Transmissible gastroenteritis virus (TGEV)	Inhibition of viral replication after viral adsorption	ZnCl ₂ , ZnSO ₄	Wei et al. (110)

¹PT, pyrithione; RdRp, RNA-dependent RNA polymerase.

Finally, an altered Zn²⁺ homeostasis has also been linked with the pathogenesis of MS, a chronic inflammatory immune-mediated disease of the CNS. Specifically, a meta-analysis showed lower concentrations of Zn²⁺ in the plasma of MS patients than in controls, although just 1 study (of the 6 studies measuring CSF Zn²⁺ concentrations included in the meta-analysis) found a significant difference between patients with MS and controls (56). Therefore, these findings point toward the hypothesis that local alterations of Zn²⁺ may be actively involved in the pathogenesis of MS, ultimately suggesting the need for further studies to investigate the relation between plasma Zn²⁺ concentrations and different MS subtypes.

Zinc and infectious diseases

Starting from the observation that Zn²⁺ deficiency could provoke a disruption in both the humoral and cell-mediated immune responses, consequently increasing the susceptibility to infection, numerous studies have been carried out to disentangle the role of Zn²⁺ in infectious diseases. Specifically, the results of such studies showed that in both animal models and humans, Zn²⁺ supplementation during sepsis had conflicting outcomes, whereas prophylactic administration proved to have positive effects (3). Contrarily, several studies exploring adjunctive Zn²⁺ supplementation for the treatment of pneumonia (85) and diarrhea (86) (performed especially in children) showed no beneficial effects. The contrasting results could be explained by the fact that Zn²⁺ is an essential element not only for the host but also for the pathogen; in fact, this ion is fundamental for the survival, propagation, and disease establishment of several microbes. Moreover, the redistribution of Zn²⁺ during the acute phase of sepsis is probably essential to ensure transcription and translation of the acute-phase proteins, and to protect from oxidative stress and inflammation, supporting the hypothesis of the association between a lack of Zn²⁺ and a worse outcome of infectious diseases (3). Therefore, the decision to administer Zn²⁺ during an infection must consider the

risks of creating a Zn²⁺ microenvironment that is favorable for pathogen growth (3). Conversely, different shreds of evidence can explain the beneficial effects of prophylactic administration of Zn²⁺. First, Zn²⁺ deficiency, which is hard to define just by its serum concentrations, increases susceptibility to infections that, under normal circumstances, the host would be less vulnerable to. Most notably, inadequate Zn²⁺ intake is associated with new-onset upper respiratory tract and gastrointestinal tract infections in children (87, 88). Moreover, there is substantial evidence that Zn²⁺ supplementation is beneficial for the prevention of acute and persistent diarrhea (89), and of respiratory infections in children with Zn²⁺ deficiency (90, 91). Furthermore, Zn²⁺ has been shown to exert direct inhibitory effects against a variety of viruses (92), including human rhinovirus (93–95) and other picornaviruses (96), herpes simplex virus (97–99), HIV-1 (100), hepatitis C virus (101), hepatitis E virus (102), respiratory syncytial virus (103), and vaccinia virus (104). This effect is also evident in different coronaviruses (19), such as mouse hepatitis virus (105, 106), SARS-CoV (107–109), transmissible gastroenteritis virus (110), and feline infectious peritonitis virus (111) (Table 1). Notably, the use of zinc-ionophores, such as hinokitol, pyrrolidine dithiocarbamate, and pyrithione, can stimulate cellular import of Zn²⁺, thus increasing its intracellular concentrations while reducing the extracellular concentrations and, consequently, the systemic adverse effects. This can be explained considering that, in cell culture studies, high Zn²⁺ concentrations and the addition of zinc-ionophores were found to inhibit the replication of various RNA and DNA viruses (112–119). This evidence was also confirmed for coronavirus in the study of te Velthuis et al. (109). These findings are not surprising because the association of Zn²⁺ and a zinc-ionophore, by stimulating Zn²⁺ uptake, may efficiently inhibit the viral replication, while not causing detectable cytotoxicity. This mechanism may be considered relevant for further studies exploring the activity of Zn²⁺ against SARS-CoV-2, especially in light of the zinc-ionophoric activity of chloroquine (120), which

in the first phase of the pandemic represented one of the most used, yet controversial, molecules in the treatment of COVID-19.

Zinc and COVID-19

SARS-CoV-2 infection, called COVID-19, occurs with heterogeneous clinical manifestations, ranging from asymptomatic cases to severe interstitial pneumonia with severe acute respiratory syndromes and multiorgan failure (121). The outbreak of the pandemic associated with SARS-CoV-2 has caused researchers worldwide to search for new potential treatments against such RNA viruses. In one of the first reviews of the literature (16), Zn^{2+} was cited as one of the potential nonpharmacological agents, based on its immunomodulant and antiviral properties. Subsequently, the hypothesis of using Zn^{2+} as a therapeutic option for SARS-CoV-2 infection has been explored by further scientific data (17–19), which outlined the mechanisms of action by which Zn^{2+} might exert therapeutic activity in COVID-19. From an immunologic point of view, 1 in vitro study showed that 50 μM $ZnCl_2$, in the presence of Ca^{2+} , could increase ciliary beat frequency, consequently boosting mucociliary clearance and therefore the elimination of bacterial and viral particles (122). Moreover, considering the key role that the aberrant inflammatory response plays in COVID-19 pathogenesis (123), the well-recognized anti-inflammatory activity of Zn^{2+} (47) may be an additional benefit from a therapeutic perspective.

Some further specific biological activities of Zn^{2+} may explain its efficacy for the treatment of COVID-19 and its complications. Angiotensin-converting enzyme-2 (ACE-2) is now considered the gateway receptor of SARS-CoV-2 infection in humans (124), and an in vitro study (125) highlighted that in the presence of 100 μM zinc acetate, the metabolism of an artificial substrate of ACE-2 in rat's lungs by recombinant human angiotensin-converting enzyme 2 (rhACE2) was significantly decreased compared with 0 or 10 μM zinc acetate. Moreover, another RCT which tried to assess the effect of zinc supplementation on the immune response to the heptavalent pneumococcal protein conjugate (PNC) vaccine found that a 29-wk supplementation of 5 mg zinc acetate per day enhanced the immune response to 1 of the serotypes (126). This ultimately suggests a protective role of Zn^{2+} supplementation in COVID-19 patients, for whom a high risk of *Streptococcus pneumoniae* co-infection has been recently documented (equivalent to 59.5%) (127).

As for antiviral activity, previous in vitro studies described inhibitory activity of Zn^{2+} against SARS-CoV (107–109) and other coronaviruses (105, 106, 110, 111), which seems to be exerted via various hypothetical mechanisms of action (Table 1). Moreover, the association of Zn^{2+} and a zinc-ionophore might improve this activity (109), which could be of extreme interest especially in light of the zinc-ionophoric activity of chloroquine (109). This conclusion is based on an in vitro study that showed significantly elevated intracellular Zn^{2+} concentrations when chloroquine and $ZnCl_2$ were

added for 1 h to the cell culture medium at various concentrations (109). It was proposed that 1) chloroquine-mediated Zn^{2+} influx may enhance chloroquine anticancer activity, improving the inhibition of autophagy and the induction of apoptosis by chloroquine; and 2) increasing intracellular Zn^{2+} concentration may mediate chloroquine's antiviral effects (109). Therefore, it was proposed that the supplementation of Zn^{2+} with chloroquine could represent a possible therapeutic association (18). It is important to underline that the current guidelines recommend against the use of chloroquine (128), based on different findings that do not support the use of hydroxychloroquine (HCQ) for treatment of COVID-19 among hospitalized adults (129, 130).

Furthermore, it should be noted that different meta-analyses have reported that Zn^{2+} supplementation could modulate some of the major risk factors for COVID-19–related mortality (131), such as diabetes, obesity, and atherosclerosis. Indeed, it has been found that 1) several glycemic indicators are significantly reduced by Zn^{2+} supplementation, particularly fasting glucose (132); 2) Zn^{2+} supplementation may decrease circulating leptin concentrations (133); and 3) Zn^{2+} supplementation could exert positive effects on plasma lipid parameters, reducing total cholesterol, LDL cholesterol, and triglycerides (134). Therefore, its preventive administration in selected high-risk patients might improve the clinical prognosis of the infection.

Finally, just a few studies are now available on the use of Zn^{2+} as a therapeutic option in COVID-19 (Table 2). A retrospective observational study (135) was performed on 411 patients taking 220 mg zinc sulfate twice daily in addition to HCQ and azithromycin and 521 patients taking HCQ and azithromycin alone, matched for age, race, sex, tobacco use, and relevant comorbidities. The study revealed that the addition of zinc sulfate increased the probability of patients being discharged from the hospital (OR: 1.53; 95% CI: 1.12, 2.09) and decreased mortality or transfer to hospice for patients who did not require intensive care unit (ICU) treatment (OR: 0.449; 95% CI: 0.271, 0.744), after adjusting for the time at which zinc sulfate was added to the protocol. A multicenter cohort study on 3473 hospitalized adult patients was performed to evaluate the impact of Zn^{2+} on outcome in hospitalized COVID-19 patients (136). Rates of in-hospital mortality were significantly lower among patients (29%) who received Zn^{2+} and an ionophore (HCQ) than among those who did not (12% died compared with 17%). Similarly, rates of discharge were significantly higher among patients who received this combination (72% compared with 67%). Just 1 RCT is currently available evaluating the effect of combining chloroquine/HCQ and zinc in the treatment of 191 COVID-19 patients (137). In this study, zinc supplements did not enhance the clinical efficacy of HCQ, with no significant effect on clinical outcomes (recovery within 28 d, the need for mechanical ventilation, and death). Overall, such results support the start of RCTs investigating the use of Zn^{2+} as a therapeutic option in COVID-19.

TABLE 2 Clinical studies assessing the antiviral efficacy of zinc on Severe Acute Respiratory Syndrome coronavirus 2¹

Reference	Study design	Zinc	Statistical significance	Main results
Carlucci et al. (135)	Retrospective observational study	Zinc sulfate 220 mg PO BID + HCQ 400 mg once followed by 200 mg PO BID + azithromycin 500 mg once daily	–	Decreased length of hospitalization
			–	Decreased duration of ventilation
			–	Decreased ICU duration
			+	Increased rates of discharge home
Frontera et al. (136)	Multicenter cohort study	Zinc sulfate 220 mg (50 mg Zn) PO once daily or BID + HCQ (400 mg BID for 1 d then 200 mg BID for 4 d)	+	Reduced risk of in-hospital mortality or transfer to hospice for non-ICU patients
			+	Increased rates of discharge home
			+	Reduced risk of in-hospital mortality
			–	Decreased length of hospitalization
Abd-Elsalam et al. (137)	Randomized clinical trial	Zinc sulfate 220 mg (50 mg Zn) PO BID + HCQ (400 mg BID for 1 d then 200 mg BID for 5 d)	–	Decreased duration of ventilation
			–	Decreased need for mechanical ventilation
			–	Decreased length of hospitalization
			–	Reduced risk of in-hospital mortality

¹BID, bis in die; HCQ, hydroxychloroquine; ICU, intensive care unit; PO, per os.

Neuropsychiatric complications of COVID-19

Human respiratory coronaviruses have been shown to have neuroinvasive propensity (138), with SARS-CoV virions being found in neurons of the human brain (139, 140). Because SARS-CoV-2 has significant genetic homology with SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) (79% and 50%, respectively), it seems fair to hypothesize that the novel coronavirus may possess a similar neuroinvasive potential (141).

According to the most recent literature, the neuronal retrograde route might represent a main neuroinvasive mechanism of SARS-CoV-2. Following this hypothesis, after the infection of the olfactory neurons of the nasal mucosa, SARS-CoV-2 would be able to reach the olfactory bulb and then the CNS through retrograde axonal transport (142). In particular, neuroepithelial invasion by SARS-CoV-2 may be explained by the high tropism for the sustentacular cells, a cell subpopulation highly expressing the SARS-CoV-2 entry proteins ACE-2 and transmembrane serine protease 2 (TMPRSS2) (143). Other potential neuronal routes of infection are those represented by backpropagation through the trigeminal or vagal nerve fibers. Moreover, the virus has been also hypothesized to reach the brain through a hematogenous route, either via the penetration of a

disrupted BBB or through the transmigration of infected peripheral immune cells (144). Various pathophysiologic mechanisms have also been postulated to explain the neuronal manifestations associated with CNS infection. In a series of 18 brain autopsies in COVID-19 patients, the only evident neuropathological features were those associated with hypoxic damage, thus supporting the notion of cardiorespiratory failure being the major cause of neurological alterations in such patients (145). On the other hand, another series of histopathological examinations of brain specimens performed in 6 patients found evidence consistent with damage of the brain stem nuclei, pan-encephalitis, and meningitis, suggesting a primary CNS involvement of the coronavirus (146). Another possible mechanism through which SARS-CoV-2 could cause neurological manifestations is through the modulation of the cholinergic system. In fact, it has been suggested that the spike protein may have an affinity for the $\alpha 7$ nicotinic acetylcholine receptors (147), which are highly expressed in the olfactory bulb and vagus nerve terminals, 2 putative brain entry points for the virus (148, 149). Thus, involvement of the cholinergic system might explain both the viral neuroinvasion and the associated neuropsychiatric manifestations, because cholinergic activity is a major modulator of inflammatory and coagulative activity (147).

The hypothesis of brainstem invasion and damage by SARS-CoV-2 has been advocated by many authors who noted a discrepancy between the degree of pulmonary involvement and the severity of respiratory insufficiency in some patients (150); therefore, they questioned whether the respiratory failure could be mediated, at least partially, by the impairment of the cardiorespiratory centers located in the brainstem (151).

The literature is rich in clinical records of neurological complications during the course of COVID-19. One of the earliest reports is by Mao et al. (24), who carried out a cohort study in which the incidence of neurological manifestations and complications was registered. The authors reported that in their sample 36.4% of patients showed ≥ 1 neurological feature, with the most common being dizziness, headache, and impaired consciousness.

Notably, taste and smell disturbances are the most commonly reported neurological complications, ranging from 34% (20) to 86% (152). When olfactory and gustatory functions were measured through psychophysical tests in a sample of 60 COVID-19 patients, all but 1 of them had some degree of measured olfactory dysfunction (153). As previously stated, the occurrence of olfactory disturbances in COVID-19 may be because of the high tropism of SARS-CoV-2 for the olfactory neuroepithelium, potentially leading to a rapid and massive disruption of both peripheral and central olfactory structures, through the retrograde axonal route. Furthermore, a recent review suggests that the early disruption of the olfactory mucosa of SARS-CoV-2 invasion might be a crucial determinant of the further systemic immune response against viral invasion (154). Indeed, the nasopharynx-associated lymphoid tissue (NALT) constitutes the first defense against airborne pathogens, making the nasopharyngeal mucosa not only a local defense barrier but also a gateway between the innate and the adaptive immune response, which enables it to rapidly induce the systemic immune response against pathogens (155). More specifically, NALT is rich in antigen-presenting cells, such as DCs, macrophages, and microfold cells that, together with nasal epithelial ciliated and goblet cells, promptly stimulate the generation of Th1 and Th2 cells and IgA-producing B cells after recognizing pathogenic antigens (154). The ability of NALT to protect against the spread of different pathogens by triggering the systemic immune response is also supported by the evidence of a specific role of the NALT against CNS invasion by neurotropic viruses (156). Therefore both the SARS-CoV-2 neuroinvasivity and the damage to the olfactory mucosa, which leads to the failure of NALT induction of an efficacious systemic immune response, may be complementary mechanisms at the basis of the olfactory disturbances (157) and of other COVID-19 neuropsychiatric complications.

Indeed, multiple reports have described the presence of CNS inflammation in the context of SARS-CoV-2 infection, with encephalitis (22), rhombencephalitis (158), myelitis (159), acute disseminated encephalomyelitis (160), and meningoencephalitis (161) being the most common

neurological complications. These findings fit well with the now well-known notion that a major feature of COVID-19 is represented by the vigorous inflammatory response caused by the viral infection, with high inflammatory indexes and abundant cytokine production (162). Brain involvement in the context of an abnormal cytokine release may be mediated by a profound alteration in the BBB (163), with subsequent proinflammatory activation of neurons and glial cells (164).

However, neuropsychiatric complications of COVID-19 are not solely the consequence of the massive systemic inflammatory response documented in these patients. In this regard, other relatively common neurological conditions described in COVID-19 patients include disorders such as the Guillain-Barré (165–169) and the Miller Fisher syndrome (170). The pathogenetic mechanism most probably involved in the occurrence of such disorders is an autoimmune process involving molecular mimicry or immunological cross-reactions. However, additional preclinical and clinical studies are needed to verify this pathogenetic hypothesis.

In addition, the clinical course of COVID-19 has been associated with a procoagulative state (171) such that antithrombotic prophylaxis is often started in hospitalized patients. Several reports can be found about COVID-19 being complicated by cerebrovascular events, in particular, stroke due to large vessel occlusion. Of note, in a significant number of cases, the age of affected patients was significantly lower than the average age for this condition in the general population. Specifically, in the case series by Tiwari et al. (23) the patients had a median age of 48 y; similarly, Oxley et al. (172) described 5 cases of large-vessel ischemic stroke occurring in young COVID-19 patients in their 30s or 40s (age range: 33–49 y).

Moreover, delirium is reported to be a common manifestation of SARS-CoV-2 infection. In a multicenter cohort study (21) (including 817 older adults with COVID-19 presented to US emergency departments), delirium was a common finding (28%). Interestingly, among the patients with delirium, 16% had delirium as a primary symptom and 37% had no typical COVID-19 symptoms or signs. Several other studies reported that delirium represented a common complication of COVID-19 in hospitalized patients. In a study (173) on 852 hospitalized patients, the prevalence of delirium was 11% and delirium resulted in a marker of severe disease course. In a multicentric retrospective cohort study (174), delirium was present in 25% of 821 patients aged ≥ 70 y; in another study, delirium was present in 33% of hospitalized patients aged 50 y and older (175). Also, delirium was associated with poor hospital outcomes and death, particularly in the intensive care setting, with a percentage of patients as high as 65% showing the presence of delirium when measured through the Confusion Assessment Method for the ICU (CAM-ICU) (176). All these data suggest the clinical importance of including delirium on checklists of presenting signs and symptoms of COVID-19 that guide screening, testing, and evaluation.

Finally, recent findings support that COVID-19 could be associated with psychiatric sequelae. In a recent study on 402 adults surviving COVID-19, 56% were scored in the pathological range in ≥ 1 clinical dimension and the indexes of inflammation were positively associated with depression and anxiety at follow-up (177). A recent meta-analysis also suggested that, in the longer term, neuropsychiatric syndromes may be particularly pronounced in COVID-19 patients (178).

Individuals suffering from various neuropsychiatric conditions have been shown to have an increased risk of developing serious infections owing to several factors that hinder the integrity of the immune system, including lifestyle, immunosuppressive therapies, and socioeconomic conditions (179). For example, it has been shown that long-term immunosuppressant treatments of MS confer an increased risk of infection with SARS-CoV-2 (180). Also, severe psychiatric conditions such as schizophrenia, known to be associated with immunity dysregulations (181), increased the risk of dying from COVID-19 (182).

Zinc neuroprotective rationale in COVID-19 neuropsychiatric complications

As already reported in the previous paragraph, COVID-19 is frequently complicated by heterogeneous neuropsychiatric manifestations, whose severity often negatively influences the disease prognosis, in terms of survival rate and neuropsychiatric sequelae (183). In this regard, a retrospective study on a large cohort of COVID-19 survivors found that about one-third of subjects had ≥ 1 neurological or psychiatric consequence 6 mo after SARS-CoV-2 infection, with a higher hazard risk for the severe forms of COVID-19 than for the mild ones (15). Based on these epidemiologic data, the identification of specific treatments that are able to prevent and treat acute and chronic manifestations of neurological and psychiatric disorders occurring after COVID-19 infection appears to be an urgent medical need (184).

However, to date, little is known about the pathogenesis of neuropsychiatric complications of SARS-CoV-2 infection, but the rapidly increasing number of studies published on this topic seems to identify some mechanisms which could explain the CNS's involvement in SARS-CoV-2 infection (163, 185). Interestingly, an imbalanced Zn^{2+} status, in the case of either Zn^{2+} deficit or excess, could play a role in most of the pathogenic mechanisms described so far (47, 50), suggesting a preventive and therapeutic potential of Zn^{2+} status in balancing both SARS-CoV-2 infection and COVID-19 neuropsychiatric manifestations. Concerning the risk of infection and its severity, in the previous paragraphs, we have outlined a dual role of Zn^{2+} , because we reported that its deficiency can either reduce the efficacy of the systemic immune response against pathogens' spread during sepsis (3) or increase the risk of airborne pathogen infection, with a parallel reduced risk of infection observed in clinical studies testing Zn^{2+} supplementation in populations with Zn^{2+} deficiency (90, 91). However, some lines of evidence

seem to indicate excessive Zn^{2+} concentrations as a favoring condition for pathogen replication (3). Similarly, Zn^{2+} affects brain homeostasis by exerting a dual modulation of BBB permeability, which could be altered both by a deficit and by an excess of Zn^{2+} (67). The most recent evidence on SARS-CoV-2 infection recognized in BBB disruption a relevant mechanism of brain damage in the course of the infection, potentially inducing neuroinflammation. In fact, the increased BBB permeability fostered the passage from the bloodstream to the brain tissues of the proinflammatory cytokines overproduced in the so-called "cytokine storm," considered a critical consequence of the aberrant hyperinflammatory response that occurs in the most severe forms of COVID-19 (186). Moreover, a recent animal study demonstrated the capacity of the SARS-CoV-2 spike protein S1 subunit to pass the BBB and reach the brain parenchyma, further supporting the role of BBB integrity in the protection against the CNS viral spread (187). Considering the role of Zn^{2+} in preserving the integrity of the BBB and the anti-inflammatory activity of Zn^{2+} , it seems reasonable to suppose a neuroprotective role of a balanced Zn^{2+} status in the prevention of neuropsychiatric manifestations of COVID-19. Also, the capacity of Zn^{2+} to preserve the integrity of mucosa (45) might represent a possible therapeutic indication for the use of Zn^{2+} in the early phase of COVID-19, possibly weakening the disruption of the nasal mucosa and thus enforcing the adaptive immune response induced by NALT (155). This may, in turn, counter the viral systemic spread. In this perspective, Zn^{2+} supplementation in healthy subjects with a documented laboratory Zn^{2+} deficiency should be tested in clinical trials with the aim to prevent SARS-CoV-2 infections and the development of severe COVID-19.

Furthermore, based on the well-demonstrated anti-inflammatory activity of Zn^{2+} also exerted by reducing the production of proinflammatory cytokines involved in the cytokine storm (50, 162), further clinical studies should consider different dosages of Zn^{2+} supplementation as a therapeutic option, at least in subjects with a documented Zn^{2+} deficiency. Finally, future clinical research should evaluate Zn^{2+} supplementation therapy not only in COVID-19 patients with neurological and psychiatric complications but also in healed subjects manifesting neuropsychiatric long-term consequences.

Conclusions

In the current narrative review, among the nutritional interventions proposed for the treatment and prevention of COVID-19, we focused on Zn^{2+} , whose effects on the immune and nervous systems are well known, encompassing several neuropsychiatric manifestations. According to the aforementioned findings, Zn^{2+} may have 2 different applications in COVID-19: a preventive and a therapeutic one.

Regarding the preventive potential, because Zn^{2+} is fundamental in maintaining a correct balance of the immune system, its deficiency could be considered a predisposing factor to infection. Indeed, many scientific data have so

far demonstrated the association between individual Zn²⁺ status and a predisposition to viral diseases, in particular respiratory tract infections. In this perspective, a Zn²⁺ supplementation may be useful to reduce the risk of COVID-19 infection, especially in a specific population at high risk, such as the elder population, immunosuppressed subjects, and cardiovascular disease patients. Interestingly, these categories at higher risk of COVID-19 are the same ones that have shown Zn²⁺ deficiency. With regards to its therapeutic potential, *in vitro* studies showed that Zn²⁺ could exert a direct antiviral effect against coronaviruses, such as SARS-CoV and equine arteritis virus. This micronutrient may therefore represent a suitable add-on treatment to the drugs currently administered for COVID-19, in consideration of its specific inhibitory effect on SARS-CoV intracellular replication.

Finally, thanks to its neuroprotective properties, Zn²⁺ may have significant effects on COVID-19-related neurological damage and the symptoms of the disease that are increasingly raising interest. Moreover, considering the aforementioned evidence, Zn²⁺ supplementation might have a role as a neuroprotective agent in COVID-19 patients through several mechanisms, including 1) its systemic anti-inflammatory activity, potentially dampening the aberrant and uncontrolled cytokine release that often accompanies the disease course; 2) its ability to modulate BBB function, preventing the increase in permeability seen in COVID-19 patients; and 3) its capacity to preserve the integrity of mucosal cells, weakening the disruption of the nasal mucosa and thus enforcing the adaptive immune response induced by NALT.

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