

Zinc as nutritional intervention and prevention measure for COVID-19 disease

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ABSTRACT

The present spread of severe acute respiratory syndrome coronavirus 2, provoking COVID-19 disease, progresses rapidly worldwide. In current absence of a curative treatment and an effective, safe vaccine, there is a pressing need to focus on identifying and correcting deficits in immune function in order to reduce risk of severe progress of the disease and to lower the number of infections and fatalities. This paper evaluates the most recent literature on zinc status related to antiviral immunity and its possible role in COVID-19. It is concluded that zinc is a critical factor for antiviral immunity. There is ample evidence suggesting that zinc depletion, also prevalent in high-income nations, compromises immune functions. Notably, major risk groups for COVID-19, the elderly, men more than women, obese individuals and patients with diabetes are all at risk of zinc deficiency. Moreover, various widely used antihypertensive drugs and statin therapy have been reported to negatively influence zinc status. As zinc depletion impairs antiviral immunity, it is hypothesised to increase susceptibility for COVID-19. Therefore, dietary preventive measures and prompt implementation of zinc supplementation for risk groups should be considered. Large-scale studies are urgently needed to investigate the role of micronutrients and antiviral immunity, in particular drug-micronutrient immunity interaction.

INTRODUCTION

The current spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), provoking COVID-19 disease, progresses rapidly thereby urgently challenging the healthcare system worldwide. In the absence of curative treatment as well as an effective and safe vaccine at the moment, there is a pressing need to focus on identifying and correcting deficits in immune function, especially for those at risk for COVID-19. The elderly and people with comorbid conditions show increased risk of severe progression.¹ Zinc status, known to be a critical factor for antiviral immune response,²⁻⁴ may have the potential to influence the course of the viral infection in individuals. Here, it is argued that particularly adult populations at risk of disturbed zinc homeostasis have increased risk of severe progression of COVID-19.

Moreover, nutritional, immunological and clinical data suggest that zinc status may play a pivotal role in preventing and controlling COVID-19 disease. This opens up possibilities for targeted dietary preventive and nutritional intervention measures to improve antiviral immune response.

Zinc in antiviral immunity

Zinc is involved in generating innate as well as acquired antiviral immune response.²⁻⁶ First of all, zinc is essential for the barrier function of mucosal epithelium due to its antioxidant and anti-inflammatory activity. It also regulates tight junction proteins that are important for the maintenance of mucosal membrane integrity.^{5,7} Reduction of mucosal integrity and loss of tight junction cohesion aggravates viral inflammation. These deteriorations result in alveolar oedema, due to leakage of high weight proteins and water, resulting in acute respiratory distress syndrome.⁷

Proliferation, differentiation, maturation and functioning of leucocytes including lymphocytes are all regulated by zinc.⁷ Zinc ions regulate intracellular signalling pathways in both innate and adaptive immune cells. Hereby zinc acts directly by binding reversibly to regulating proteins or indirectly by modulating enzymes, such as phosphates, involved in signalling pathways. Production of reactive oxygen species (ROS) and cytokines depend on zinc availability.^{3,6} ROS production is required for intracellular killing of pathogens as well as for the formation of neutrophil extracellular traps, released by granulocytes to neutralise pathogens.^{3,6} Zinc treatment in vitro has demonstrated to increase interferon α (IFN α) production by leukocytes, enhancing its antiviral activity.⁷

Due to involvement of zinc in various immune functions, zinc deficiency results in:

- ▶ Reduced activity of immune cells like impaired phagocytosis.^{3,8,9}
- ▶ Decreased critical neutrophil functions.^{3,8,9}



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- ▶ Weakened natural killer cell function.^{3 8 9}
- ▶ Reduced lymphocyte number and activation.^{3 5}
- ▶ Diminished antibody production.⁶
- ▶ Imbalanced T helper cells cytokine secretion with decreased IFN γ production.^{6 10} IFNs are immunostimulatory cytokines with antiviral activity.²
- ▶ Increased thymic atrophy and consequent risk of infection.⁵

On the other hand, excess of zinc can also impair immune response by inhibiting T-lymphocyte and B-lymphocyte function, reducing intracellular pathogen destruction in macrophages or inducing an overload of regulatory T-cells.^{3 6 11} This demonstrates that a balanced zinc homeostasis is critical for adequate immune functions.

Furthermore, accurate modulation of the inflammatory response is required for achieving an adequate antiviral immune response.⁶ Hereby, zinc is crucial to counteract excessive inflammatory reactions by improving control of regulatory transcriptional factor, nuclear factor- κ B (NF- κ B), resulting in a reduced production of pro-inflammatory cytokines.^{3 4 7 8} Zinc signals can increase intracellular levels of zinc finger protein A20, which inhibits activation of NF- κ B through a negative feedback loop, downregulating proinflammatory factors as well.^{3 6 10} Zinc may also limit excessive inflammatory response by modulating regulatory T-cell functions.⁷

Moreover, zinc has proven direct antiviral activity towards a wide variety of viruses^{2 3}; enhancing antiviral immunity. Zinc deficiency results in a compromised immune system along with reduced zinc availability for direct antiviral action, increasing susceptibility for viral infections.^{2 5 8 9 12} Hence, zinc-deficient populations are more likely to acquire pneumonia^{5 7 13} and viral infections as documented for hepatitis C and HIV.² Some studies suggest that zinc may also improve antibacterial immune response to *Streptococcus Pneumoniae*, which can provoke coinfection in viral pneumonia.^{2 7} In addition, the anti-inflammatory effects of zinc also aid to limit tissue damage in case of pneumonia and decrease the risk of sepsis.^{3 7}

The increased knowledge about the role of zinc in viral immunity has resulted in clinical studies, showing evident therapeutic effect of zinc supplementation in viral infections like common cold⁷ and herpes simplex.^{2 3} Presently, zinc is recommended by WHO as first-line treatment, with oral rehydration solution, for acute gastroenteritis in children because of its clinically proven efficacy to reduce diarrhoea.¹⁴ The question is to what extent zinc is also involved in antiviral immunity in case of COVID-19.

Who are at risk of zinc deficiency?

Emerging characteristics regarding COVID-19 show that patients most at risk of fatal outcome of COVID-19 are the elderly, those with cardiovascular disease, diabetes, chronic respiratory disease, hypertension, overweight and cancer. Male show increased risk compared with female.^{1 15 16} Comparing these outcomes to the risk groups for low zinc status then the following can be

noticed: the elderly population, more at risk of severe COVID-19 disease,^{1 15} is also more at risk of zinc deficiency.^{2 3 11 12} A cross-sectional population survey among a random sample of elder participants, aged 67–87 years, found 10.1% zinc deficient, in line with previous studies. The prevalence was significantly higher as age increased and notably more men (13.1%) than women (7.3%) were zinc depleted.¹⁷ A zinc-poor diet, increased alcohol-intake and disease-state can all contribute to zinc depletion.^{2 17}

Concerning diabetes, a meta-analysis including 52 studies on micronutrients in diabetes demonstrated significantly lower zinc status for patients with diabetes (n=20 183) compared with controls.¹⁸ The results of this study are consistent with other studies that observed zinc depletion in up to 77% of patients with type 2 diabetes^{19–21} or found an inverse correlation between blood glucose and zinc levels.²² Furthermore, research demonstrates that obesity predisposes for zinc deficiency. Studies have revealed reduced serum zinc levels in up to 28% of obese individuals prior to bariatric surgery and in 36%–51% of patients afterwards. Another study in Spain among 115 morbid obese women found 74% of them zinc deficient.²³ In conclusion, these studies suggest a strong correlation between age, diabetes, overweight and zinc status.

Drug use and zinc balance

For most of the comorbid groups affected by COVID-19, we may assume that they include a relative high percentage of vulnerable patients with serious cardiovascular or respiratory dysfunction. Therefore, these patients clearly are at risk of severe COVID-19 disease. However, the relative high percentage of patients with hypertension struck by fatal outcome is striking: the in China reported case fatality rate for the hypertension group (6.0%) is nearly as high as for the chronic lung disease group (6.3%).¹ The high risk for hypertensive patients is difficult to explain solely by their pathological condition, considering hypertension in itself appears not directly associated with compromised immune functions, unless it is accompanied by organ damage, like kidney failure. Thus, it seems likely that other factors are involved. Unfortunately, data on the clinical characteristics of the risk groups as well as their prognostic factors are limited as the pandemic is still in progress.

An important issue is the use of antihypertensive pharmaceuticals and their possible effect on immune functions. With regard to zinc, various antihypertensive drugs have been reported to negatively influence zinc balance, resulting in a potentially reduced antiviral immune response.

First, thiazide diuretics, widely used in hypertensive therapy, can result in significantly increased urinary zinc excretion^{24–26} and consequently reduce tissue zinc concentrations.²⁶ A study on the long-term use of hydrochlorothiazide (≥ 6 months) resulted in significant lower serum zinc levels in 20 out of 39 subjects when compared with controls.²⁴ Patients with hypertension (n=36) on

monotherapy with diuretics, most of them using thiazide-like diuretics, were found to have significant lower zinc concentration in serum and erythrocytes after 3 months of therapy when compared with baseline levels in a randomised trial.²⁵

Furthermore, long-term use of some ACE-inhibitors like captopril (50–150 mg/day), verapamil (240 mg/day) and ramipril (5 mg/day) can significantly lower serum zinc levels.²⁴ Serum zinc concentrations were also decreased in subjects (n=14) after using ACE-inhibitors for 3 months. In this study, dietary zinc intake was controlled during the test period. In the same study, a significant decrease of erythrocyte zinc concentration was also observed in patients with hypertension (n=18) on calcium antagonists (Ca-antagonists)²⁵ in contrast to a previous study (n=20) in which no such changes were found. However, dietary zinc intake monitoring was not reported.²⁴

In addition, some angiotensin 2 receptor blockers (ARBs) proved to have a potential to lower zinc levels as well. A 3-month treatment with valsartan (80 mg/day) has revealed to reduce serum zinc and erythrocyte zinc levels significantly in hypertensive patients. Stand-alone therapy with losartan (50.0 mg/day) in 17 hypertensive patients for 4 weeks resulted in significantly increased urinary zinc excretion and zinc depletion.²⁴ However, no alterations in serum and erythrocyte zinc level were found in 12 patients with hypertension after 3 months of treatment with ARBs, although drug dosages were not reported.²⁴ Meanwhile, studies done on beta-blockers remain inconclusive about their effect on zinc metabolism.^{24 25 27 28}

It should be noted that most of the studies on antihypertensive drugs and zinc status lasted between 4 weeks and 6 months. That is considerably shorter than the actual situation in which hypertensive patients usually take these drugs for years. Moreover, mainly monotherapy was investigated, while in medical practice the use of two or more antihypertensive drugs is often applied. One drug could have an additive effect on the other drug in lowering zinc levels as was shown for the combination losartan (50.0 mg/day)/hydrochlorothiazide (12.5 mg/day).²⁴

Moreover diuretics, ACE inhibitors, ARBs and Ca-antagonists are also extensively used for other cardiovascular disorders, either separate or combined with additional drugs. For instance, statins are widely used for treating dyslipidaemia in cardiovascular disease. Long-term statin therapy is associated with 10%–45% higher risk for new-onset type 2 diabetes,²⁹ which can induce zinc depletion. Hence, many cardiovascular patients using antihypertensives or statins, which can affect zinc balance,^{30 31} may be at increased risk of zinc deficiency (table 1). For numerous other cardiovascular drugs, sufficient data on zinc metabolism are lacking.

Zinc and susceptibility for COVID-19

The decline of immune functions with ageing, which is often referred to as ‘immunosenescence’, appears to be

related to lower zinc availability.^{6 8 9 11 12} Mild zinc deficiency, commonly seen with ageing, leads to dysregulation of the adaptive immune system decreasing the specific immune response (B-cell function, production of immunoglobulins) along with the tendency of enhanced production of proinflammatory cytokines, called ‘inflammaging’. In chronic inflammation, there is a continuous sequestration of intracellular zinc and the release of zinc bound to intracellular proteins (metallothioneins) is impeded. As a consequence, intracellular zinc ion bioavailability, indispensable for proper immune function, is reduced.^{6 10} Zinc supplementation partially restores these alterations.^{5 6 8 10 12} Moreover, inflammaging often seen with ageing can affect innate immunity as well. Especially in the early stage of newly acquired viral infections an adequate immune response depends largely on the innate immune system. In particular zinc is critical for its efficient functioning.^{5 6 8} In COVID-19, there are strong indications for downregulation of the innate immune response along with a high inflammatory condition, features similar to those found in SARS and Middle East respiratory syndrome. This may explain why elderly are more at risk of COVID-19 in contrast to young children who benefit from a highly effective innate immune response.³²

Apart from its role in immune functions, zinc has also shown direct antiviral activity for a number of RNA viruses. It was demonstrated that zinc efficiently inhibits the replication of SARS-CoV in cell culture, showing the crucial role of intracellular zinc in inhibiting replication of the virus.³³ This study by de Velthuis *et al* used the zinc ionophore pyrithione, which transports zinc ions in large amounts from the extracellular matrix into the cell, in order to increase intracellular zinc levels. Without zinc, the ionophore was unable to effectively inhibit viral replication. The pharmaceuticals chloroquine and hydroxychloroquine, also known to function as zinc ionophores, are now being tested in several clinical studies for the treatment of COVID-19, although without simultaneous supplementation of zinc. The antiviral properties of these drugs or other zinc ionophores could depend on the availability of zinc, which illustrates that the combination with zinc supplementation could be useful to improve their therapeutic effect in patients with COVID-19.³⁴

In addition papain-like protein 2, a viral protease of SARS-CoV that is fundamental for its virulence, was potentially inhibited by zinc.³⁵ The same viral inhibiting actions of zinc found for SARS-CoV may also apply to SARS-CoV2, since their genome is similar. In case zinc might have direct antiviral activity towards SARS-CoV2, then zinc status will be of an even greater importance to reduce the viral load in COVID-19.

Only a small functional zinc reserve, located in the liver and other tissues, is available to the human body for rapid exchange with the plasma, enough for just a few days. Hence, a systemic increased demand of zinc, increased excretion, low intake or impaired absorption due to disease inevitably results into zinc deficiency.^{6 8 11 12 24}

Table 1 The table describes the findings, reported in studies, regarding serum zinc concentration and intracellular zinc concentration related to the risk factors for COVID-19 (including age, type 2 diabetes and obesity), antihypertensive agents as well as statin therapy

Type of study	n=no of subjects N=no of studies	Serum zinc concentration	Intracellular zinc concentration
Increasing age			
Observational ⁴⁵	n=853	↓ in 31% of subjects	–
Review ⁸	N=20	↓ significant with increasing age	↓ significant in 1 study
Observational ¹⁷	n=1521	↓ significant with increasing age	–
Type 2 diabetes**			
Observational ²²	n=82	↓ related to higher glycated hemoglobin	↓ related to higher glycated haemoglobin
Meta-analysis ¹⁸	n=20183	↓ significant versus control groups	–
Cross-sectional ²¹	n=33	↓ in 77 % of the subjects	–
Observational ¹⁹	n=31	↓ in 27% versus control group (n=31)	–
Cross-sectional ²⁰	n=252	↓ in 68% versus control group 6.4% (n=188)	–
Obesity			
Observational ²³	n=115	↓ in 74% of subjects seeking bariatric surgery	–
Review ²³	N=3	↓ in 28% before bariatric surgery ↓ in 36–51% postbariatric surgery	–
Diuretics			
Clinical Trial ⁴⁶	Cloпамide 5 mg/day, 16 weeks (n=8)	↓ significant versus baseline	↑ in WBC, ↓ in RBC
Clinical Trial ⁴⁷	Hydrochlorothiazide 25–50 mg /day, 6 months (n=39)	↓ significant in 51% of treatment group	–
Clinical Trial ⁴⁸	Hydrochlorothiazide, 25 mg, ≥3 months (n=9)	↔ versus controls	–
Clinical Trial ²⁵	Indapamide (n=29), Torasemide (n=5), Spironolacton (n=2), 3 months	↓ significant compared with baseline zinc level	↓ significant compared with baseline
ACE-inhibitors			
Clinical Trial ⁴⁹	Captopril, 266±34 mg/day, >6 months (n=11)	↓ significant versus baseline	–
Clinical Trial ⁵⁰	Captopril, 75 mg/day, >3 months (n=6)	↔ versus other groups	↓ significant versus baseline
Clinical Trial† ²⁸	Captopril, 50–150 mg/day, 6 months, (n=10)	↓ significant versus baseline	↔ versus baseline
Clinical Trial ⁵¹	Captopril, 6 months (n=16)‡	↔ versus baseline	↓ significant versus baseline
Clinical Trial ⁵¹	Enalapril, 6 months (n=18)‡	↔ versus baseline	↓ significant versus baseline
Clinical Trial ⁵⁰	Enalapril, 20 mg/day, >3 months (n=7)	↔ versus controls	↔ versus controls
Clinical Trial† ²⁸	Verapamil, 240 mg/day, 6 months (n=10)	↓ significant versus baseline	↔ versus baseline
Clinical Trial ²⁷	Ramipril, 5 mg/day, 3 months (n=20)	–	↓ significant versus baseline
Clinical Trial ²⁵	Perindopril (n=9), Captopril (n=3), Ramipril (n=2), 3 months	↓ versus baseline	↔ versus baseline
Calcium-antagonists			
Clinical Trial ²⁵	Amlodipine (n=13), Nifedipine (n=5), 3 months	↔ versus baseline	↓ significant versus baseline
Clinical Trial ²⁷	Amlodipine, 10 mg/day, 3 months (n=20)	–	↔ versus baseline
Angiotensin 2 receptor blockers			
Clinical Trial ²⁷	Valsartan, 80 mg/day, 3 months (n=20)	↓ significant versus baseline	↓ significant versus baseline
Clinical Trial‡ ⁵²	Losartan, 50 mg/day, 4 weeks (n=17)	↓ non-significant versus baseline	↔ versus baseline
Clinical Trial ²⁵	Losartan (n=8), Valsartan (n=2), Telmisartan (n=2), 3 months	↔ versus baseline	↔ versus baseline

Continued

Table 1 Continued

Type of study	n=no of subjects N=no of studies	Serum zinc concentration	Intracellular zinc concentration
Beta blockers			
Clinical Trial ²⁷	Metoprolol, 100 mg/day, 3 months (n=22)	↔ versus baseline	↔ versus baseline
Clinical Trial† ²⁸	Atenolol, 50–150 mg/day, 6 months (n=10)	↓ significant versus baseline	↔ versus baseline
Clinical Trial* ²⁵	Bisoprolol (n=7), Metoprolol (n=7), Nebivolol (n=4)	↔ versus baseline	↔ versus baseline
Statin therapy			
Review ²⁹	Statin therapy, various large scale studies N = 29	10–45% increased relative risk for type II diabetes (see above:**)	–
Clinical Trial ³¹	Simvastatin (n=11), Atorvastatin (n=9), 10 mg/day, 4 months	↓ significant versus baseline	–
Clinical Trial ³⁰	Fluvastatin (n=20), 80 mg/day, 8 weeks	↓ significant versus baseline	–

↓ decreased, ↑ increased, ↔ no change, – unreported data.

*Randomised clinical trial, dietary zinc intake controlled,

†Modified diet to improve lipid profile during test-period.

‡Dietary zinc intake monitored during test-period.

RBC, red blood cells; WBC, white blood cells.

Consequently, antiviral immune response diminishes. The frequently reported, yet unpublished, sudden worsening in COVID-19 disease could result from an abruptly depleted zinc-pool in already mild zinc deficient patients. In this respect, the loss of taste and smell, often reported by patients with COVID-19,^{36 37} may be due to increased viral load. Yet, these are also known early symptoms of zinc deficiency.^{9 17 19 24 38 39}

Nutritional and clinical aspects

Foods abundant in zinc are fish, seafood, egg, meat, seeds, nuts, whole cereals and legumes.^{40 41} In contrast, refined cereal products lack zinc. The bioavailability of zinc is higher when obtained from animal sources compared with vegetable sources and further depends on diet composition. A high dietary intake of phytates, certain fibres and lignin can bind zinc and therefore reduce zinc absorption. Phytates are more present in plant foods like unrefined cereal products and legumes.^{3 6 9} Besides, high calcium or iron intake may interfere with zinc absorption.^{6 9 40} In addition, people with malabsorption as a result of gastrointestinal surgery,²³ digestive disorders (like chronic diarrhoea, ulcerative colitis or Crohn's disease) or various other chronic illnesses are at risk of getting insufficient zinc.⁴¹

The recommended dietary allowance (RDA) of zinc for adults in Europe is 11 mg/day for men and 8 mg/day for women with a tolerable upper intake level (UL) of 40 mg/day for both males and females. Different recommendations instead apply for children depending on their age: for ages 4–8 years the RDA is 5 mg/day (UL is 12 mg/day), for ages 9–13 years the RDA is 8 mg/day (UL=23 mg/day) and for ages 14–18 years the RDA is 11 mg/day for males and 9 mg/day for females (UL is 34 mg/day for both sexes).⁵ Dosages considered as safe

for oral supplementation in adults are between 10 and 12 mg/day. Excessive dosages resulting in total daily dietary intakes reaching above the ULs, especially for prolonged periods of time, should be avoided. An overdose of zinc can induce copper deficiency and zinc accumulation has toxic effects.^{2 6 10} Bioavailability of oral zinc supplements differs depending on their chemical composition. Zinc gluconate, citrate and picolinate are better absorbed compared with zinc oxide.⁴⁰ Forms of zinc bound to amino acid compounds like aspartate, histidine and cysteine show higher bioavailability in comparison to zinc sulphate, chloride or acetate, with zinc oxide having the lowest uptake.⁶

Regarding interactions with medications, zinc supplements can interfere with the gastrointestinal absorption of tetracycline and quinolone antibiotics, inhibiting the absorption of both zinc and the antibiotic. Separating the moment of ingestion by taking the antibiotic at least 2 hours before or 4–6 hours after taking the zinc supplement minimises this interaction. Zinc supplements can also reduce the absorption of penicillamine, an antirheumatic drug. Individuals can minimise this interaction by taking penicillamine at least 2 hours before or after ingestion of the zinc supplement.⁴¹ As far as can reasonably be ascertained, there are no other relevant effects of zinc on drugs.

Since zinc might decrease blood sugar in people with type 2 diabetes, it is important to monitor their blood sugar levels closely when starting zinc supplementation. The dose of diabetes medication might need adjustments.⁴²

Summary and conclusion

Epidemiological research and observational studies provide indications for zinc depletion in high-risk groups for COVID-19. Various widely used hypotensive

drugs and statins can affect zinc balance, worsening zinc homeostasis in already mild zinc-deficient individuals. As disturbed zinc homeostasis results in compromised immune functions, it is hypothesised to increase susceptibility for COVID-19. Therefore, correcting low zinc status in risk groups could play a pivotal role in preventing and controlling COVID-19 disease. Studies have shown that zinc depletion in hypertension can be corrected by dietary adjustments or zinc supplementation,^{43 44} with the added benefit of improving glycaemic regulation and reducing inflammation.^{6 43 44}

In conclusion, there is an urgent need to implement dietary recommendations for all populations at risk of zinc depletion. In addition, prompt implementation of zinc supplementation should be considered in high-risk groups for zinc deficiency. These preventive and nutritional intervention measures have the potential to improve antiviral immune response for COVID-19 as well as for any future viral outbreaks. Large-scale studies are urgently needed to investigate the role of micronutrients in antiviral immunity, particularly drug-micronutrient immunity interaction.

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