JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Coronavirus Pandemic

Vitamins and minerals: A means for surviving the COVID-19 pandemic or just a myth?

Eman El Sabbagh[1], Mohammad El-Sayed[1], Tamer Elbaz[1]

[1] Hepato-gastroenterology and Endemic Medicine Department, Faculty of Medicine, Cairo University, Cairo, Egypt

Abstract

A novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) that was initially reported from Wuhan, China in December 2019, was declared a pandemic by the WHO in March 2020. Considering the current COVID-19 pandemic, where there are no specific effective preventive or therapeutic drugs available, a healthy immune system is one of the most important tools that should be considered. Vitamins and minerals supplements have been well known to help the immune system in battling viral infections in general. Physicians worldwide are largely interested in vitamin and mineral supplements to help them battle COVID-19 whether through protection or treatment. Dietary supplementations especially vitamin D, vitamin C, and Zinc offer good prophylactic and therapeutic support to the currently available treatment regimens. They are relatively safe and were proven to aid recovery in other respiratory infections. Further studies should be encouraged especially those examining their role in prophylaxis from COVID-19 while maintaining current recommendations for social distancing and proper protective gear.

Key words: Vitamin C; vitamin D; zinc; COVID-19; supplements.

J Infect Dev Ctries 2022; 16(5):782-786. doi:10.3855/jidc.14692

(Received 14 January 2021 – Accepted 31 May 2021)

Introduction

A novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), which was initially reported from Wuhan, China in December 2019, was declared a pandemic by the WHO in March 2020 [1]. The organism responsible for the pandemic is SARS-CoV-2, RNA virus of subgenus *Sarbecovirus*. It is similar to the SARS virus and binds to the human angiotensin converting enzyme (hACE-2) receptor and causes constitutional and respiratory symptoms [2].

The spectrum of illness ranges from mild disease (with no or mild pneumonia) in 81% patients with a usual recovery period of around 2 weeks, to severe illness (with signs including dyspnea, hypoxia, or > 50% lung involvement on imaging within 24–48 hours) in 14% of the patients with a recovery period of around 3–6 weeks. In 5% of the cases, critical illness develops with acute respiratory distress syndrome (ARDS), sepsis, septic shock, or Multi-organ dysfunction syndrome (MODS) [3]. Rapid containment of this pandemic needs urgent advancement in our knowledge concerning its transmission, incubation period, clinical signs and symptoms, proper management, and prevention.

Considering the current COVID-19 pandemic, where there are no specific effective preventive or therapeutic drugs available, a healthy immune system is one of the most important tools that should be considered. Vitamins and minerals supplementation has been well known to help the immune system battle viral infections in general. Since the nutritional status is an important factor influencing the outcome of patients with COVID-19, physicians worldwide are largely interested in vitamin and mineral supplements to help them battle COVID-19 whether through protection or treatment [4].

Vitamin D

There are several ways by which vitamin D may reduce the risk of microbial infection and death. A recent review suggested the role of vitamin D in reducing common cold risk through three possible categories: physical barrier, cellular natural immunity, and adaptive immunity [5]. Vitamin D can help to maintain tight junctions, gap junctions, and adherens junctions (e.g., by E-cadherin) [6]; these tight junctions prevent viruses that invade cells through disruption of junction integrity.

Vitamin D also enhances the cellular innate immunity through the induction of antimicrobial peptides, such as human cathelicidin which exhibits direct antimicrobial activities against a spectrum of

microbes [7], LL-37, and defensins [6]. Vitamin D is believed to increase natural antibody production as well as strengthen immunity by inducing monocyte differentiation and inhibiting lymphocyte proliferation. In addition, it may enhance the phagocytic activity of macrophages [8].

Vitamin D can reduce the cytokine storm induced by the innate immune system partly by reducing the production of pro-inflammatory Th1 cytokines, such as tumor necrosis factor α and interferon γ, so the administration of vitamin D reduces the expression of pro-inflammatory cytokines and increases the expression of anti-inflammatory cytokines by macrophages [6].

DPP4/CD26 receptor expression, which has recently been shown to interact with the S1 domain of the COVID-19 spike glycoprotein, was found to be significantly reduced in vivo upon correction of vitamin D deficiency [9].

Optimization of vitamin D may attenuate some of the critical downstream immunological sequelae responsible for poorer clinical outcomes in COVID-19 infection, such as prolonged interferon-gamma response, and persistent interleukin 6 elevation, a negative prognostic indicator in acutely-ill pneumonia patients, including COVID-19 [9].

As evidence of its potential role, a recent meta-analysis involving data from eight observational studies concluded that subjects with a serum vitamin D concentration < 50 nmol/L (i.e., < 20 ng/mL) had a 64% increased risk of community-acquired pneumonia [10].

Many retrospective studies determined a correlation between vitamin D levels with COVID-19 severity and mortality. A study on 9,212 cases by Daneshkhah *et al.* showed an inverse correlation between high CRP and 25(OH)D and a notable OR of 3.4 with 95%CI (2.15 to 5.4) for high CRP in severe COVID-19 patients [11]. Among 186 COVID-19 patients, Smet *et al.* showed lower median 25(OH)D (18.6 ng/mL, IQR 12.6-25.3 among COVID-19 patients versus 21.5 ng/mL, IQR 13.9-30.8; $p = 0.0016$) and higher vitamin D deficiency rates (58.6% versus 45.2%, $p = 0.0005$) [12]. Raharusun *et al.* concluded that when controlling for age, sex, and comorbidities, vitamin D status strongly correlated with COVID-19 mortality outcomes [13]. Otherwise, Hastie *et al.* found no association between 25(OH)D and COVID-19 infection after adjusting for potential confounders [14].

It has been hypothesized that there is therapeutic potential for melatonin at the respiratory system level. This may be mediated through the blockade of nuclear factor-κappa beta (NF-κβ), overexpression of c-Fos, and down-regulation of matrix metalloproteinases-3 (MMP-3), which modulates pro-fibrotic and pro-inflammatory cytokines [15]. COVID-19 infection may be attacking the melatonin synthetic pathway resulting in reduced melatonin levels at a time when melatonin is most needed [16]. Also, it has been suggested that elder age is associated with low melatonin levels which in turn make them a worse prognosis for COVID-19 infection. Many reports suggest taking melatonin may help improve the consequences of some of the comorbidities associated with poor prognosis for COVID infection such as obesity, diabetes, and hypertension [17]. A clinical trial is also undergoing to investigate the use of melatonin in the prophylaxis of COVID-19 infection among healthcare workers (ClinicalTrials.gov Identifier: #NCT04353128) [18]. The use of oral melatonin is considered safe with a large safety margin, with minor side effects such as headache and drowsiness [19]. It was suggested that a daily dose of around 40 mg one hour before sleep given to healthcare providers may help protect them from COVID-19 by helping to maximize the immune response, along with its anti-inflammatory and antioxidant effects. The dose is modified according to the severity of the illness [17].

The combination of vitamin D with melatonin supplements could offer an attractive synergistic option for the prevention and treatment of pulmonary infection caused by COVID-19 since they share the same signaling pathways related to anti-inflammatory, immunomodulatory, antioxidant, anti-fibrotic, as well as anti-apoptotic effects, with a particular focus at the lung tissue level [15]. A therapeutic algorithm proposed that patients admitted to a hospital with mild COVID symptoms will be treated in wards using melatonin 50mg orally twice daily for 7 days in addition to hydroxychloroquine 400 mg twice daily on day 1 followed by 200 mg twice daily for the next 4 days. As well as supportive care. Patients admitted to the hospital with respiratory symptoms and $SpO_2 < 94\%$ on room air or requiring oxygen supplementation should be treated in an ICU with melatonin 200mg orally twice daily for 7 days, hydroxychloroquine 400mg twice daily on day 1 followed by 200 mg twice daily for 4 days in addition to supportive care and escalation of respiratory support [17].

Vitamin C

There is a widespread belief that vitamin C boosts the immune system and can aid in the treatment or prevention of respiratory infections. Vitamin C is best known for its antioxidant properties. During infections,

vitamin C levels get depleted and patients usually need supplementation up to intravenous administration of gram doses of vitamin C during severe sepsis [20]. A Cochrane systematic review concluded that 1-2 g of vitamin C per day is a safe and inexpensive way to reduce the duration and severity of the common cold [21].

Vitamin C is known to support various cellular functions of both the innate and the adaptive immune system, including modifying susceptibility to various viral infections, as well as influencing inflammation. In addition, vitamin C treatment can help in restoring the stress response. It can decrease IL-6 and block the release of IL-6 from the endothelium induced by endothelin-1 (ET-1) in humans [22]. A randomized placebo-controlled study showed that vitamin C (500 mg twice daily) improves the inflammatory status by reducing IL-6 and C-reactive protein in hypertensive and/or diabetic obese patients [23]. Vitamin C may inhibit the ability of neutrophils to form neutrophil extracellular traps, which was a contributor to organ damage and mortality in COVID-19 [24]. Additionally, vitamin C may have beneficial effects on thrombotic or thromboembolic diseases which are commonly found in COVID-19 patients [22].

It was also already established that vitamin C can be used as a nonspecific treatment for severe viral respiratory tract infection during the outbreak of SARS-CoV-1 (2003) acting as an essential micronutrient for humans and a free radical scavenger. Since vitamin C inhibits the increase of a range of inflammatory cytokines, it may be therapeutically superior to other blockers that block individual cytokine mediators [22].

Several new COVID-19 related clinical trials have been started or are announced since February 2020 to investigate the therapeutic effect of vitamin C alone or in combination with one or more other substances e.g. vitamin D, zinc (gluconate), hydroxychloroquine (sulphate), azithromycin [22]. A clinical trial is being conducted to test for the beneficial effects of IV vitamin C in ICU admitted COVID-19 patients where 140 patients will be treated with a placebo control or intravenous vitamin C at a dose of 24 g/day for 7 days and observed for requirements for mechanical ventilation and vasopressor drugs, organ failure scores, ICU length of stay, and 28-day mortality [25]. A Chinese trial stated that more than 50 patients with moderate to severe COVID-19 were successfully managed with large doses of IV vitamin C (10,000-20,000 mg/d), leading to a shorter mean hospital length of stay compared to untreated patients [26]. However, such high doses shouldn't be taken orally due to gastrointestinal adverse events (nausea, vomiting, heartburn, abdominal cramps). Also, high doses of vitamin C may be associated with the formation of kidney stones, particularly in those with high oxalate levels from the start [27]. However, a systemic review by Baladia *et al.* did not find any of the 95 studies to meet their selection criteria, and hence there was no evidence to support or refute the use of vitamin C in the treatment of patients with COVID-19. Still, there are ongoing studies that might be of value [28].

Glycyrrhizic acid (GA) is a major phytonutrient found in licorice roots. It has antimicrobial, anti-inflammatory as well as hepatoprotective properties. It has been recently reported for its binding capability with angiotensin-converting enzyme 2 (ACE2) to prevent SARS-CoV-2 infection [29]. Curcumin (CC) and its analogs are widely used for their anti-inflammatory, anti-cancer, cardiovascular regulation, respiratory, and immune system benefits, in addition, they can suppress multiple cytokines [29]. A system biology analysis revealed that a combination of vitamin C, GA, and CC is predicted to help in regulating immune response against COVID-19 infections and inhibiting excessive inflammatory response to prevent the onset of cytokine storm. However, further in vitro/in vivo experiments are warranted for validation [29].

Zinc

Zinc is a trace mineral that has been suggested to inhibit viral replication as well as inhibit attachment to the nasopharyngeal mucosa. In vitro studies suggested that zinc modifies the effects of several respiratory pathogens, including rhinovirus, respiratory syncytial virus, and SARS-COV [27]. Zinc ions are closely associated with the normal development, differentiation, and function of immune cells. Therefore, it is considered to be critical for both innate and acquired (humoral) antiviral responses [30]. Zinc deficiency is associated with decreased antibody production, low activity of the natural killer cell, decreased cytokine production by monocytes, the chemotaxis and oxidative burst of neutrophil granulocytes, atrophy of the thymus, and lymphopenia [31]. Its deficiency has been responsible for 16% of all deep respiratory infections worldwide [32].

In addition, Zinc can affect monocyte signal transduction and secretion of pro-inflammatory cytokines, and interfere with the binding of leukocyte function-associated antigen-1 to ICAM-1, hence suppressing the inflammatory reaction. Zinc also improves cell resistance to apoptosis through inhibition of caspases-3, −6, and −9, and increases the Bcl-2/Bax

ratio; this may increase the number of T helper cells available for combating infections. Zinc alters the capillary epithelium, inhibits transcapillary movement of plasma proteins, and reduces local edema, inflammation, exudation, and mucus secretion. Finally, Zinc may protect or stabilize the cell membrane thus contributing to the inhibition of the entry of viruses into the cell [31].

News reports are starting to emerge claiming that zinc may have a role in COVID-19 management, and this may be based on prior knowledge that some coronaviruses can cause the common cold. It is suggested that in coronavirus, zinc achieves its effects through interference with viral polyprotein processing [33]. Since COVID-19 infection goes along with the damage of the ciliated epithelium and ciliary dyskinesia, zinc supplement would help battle such infection as it was shown that physiological concentrations of zinc increases ciliary beat frequency. Furthermore, zinc will help boost the immune system to battle other bacterial and fungal coinfections which contribute to the mortality risk in COVID-19 infected patients [34]. Importantly, there is a functional association between zinc and ROS (reactive oxygen species) production in platelets, indicating that zinc could decrease thrombus formation in a clinical context, a critical complication that has been described in COVID-19 patients [35].

On the contrary, Caruso *et al.* reported that three of the studies reviewed found no therapeutic advantage for zinc lozenges or nasal sprays in common cold outcomes and just one study has shown a positive outcome with zinc nasal gel [36]. Wessels *et al*., have concluded that prophylactic zinc supplementation was more effective than therapeutic supplementation. Studies have shown decreased symptom severity, reduced frequency, and duration of the common cold (30% of which are assumed to be due to coronaviruses) after zinc administration especially in children [34]. A few trials are currently registered to test zinc as part of a regimen to treat COVID-19 (NCT04335084, NCT04342728, NCT04351490) [37-39].

Conclusions

Dietary supplements offer good prophylactic and therapeutic support to the currently available treatment regimens. They are relatively safe and were proven in other respiratory infections to improve the outcome. Further studies should be encouraged especially those examining their role in prophylaxis from COVID-19 while maintaining current recommendations for the social distancing and proper protective gear.

References

1. Cucinotta D, Vanelli M (2020) WHO declares COVID-19 a pandemic. Acta Bio Medica Atenei Parmensis 91: 157–160.
2. Sharma R, Agarwal M, Gupta M, Somendra S, Saxena SK (2020) Clinical characteristics and differential clinical diagnosis of novel coronavirus disease 2019 (COVID-19). In: Saxena SK (ed) coronavirus disease 2019 (COVID-19): epidemiology, pathogenesis, diagnosis, and therapeutics. Springer, Singapore, 55–70.
3. Wu Z, McGoogan JM (2020) Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72,314 cases from the Chinese center for disease control and prevention. JAMA 323: 1239.
4. Chowdhury AI (2020) Role and effects of micronutrients supplementation in immune system and SARS-Cov-2 (COVID-19). Asian Journal of Immunology 4: 47–55.
5. Rondanelli M, Miccono A, Lamburghini S, Avanzato I, Riva A, Allegrini P, Faliva MA, Peroni G, Nichetti M, Perna S (2018) Self-care for common colds: the pivotal role of vitamin D, vitamin C, zinc, and echinacea in three main immune interactive clusters (physical barriers, innate and adaptive immunity) involved during an episode of common colds—practical advice on dosages and on the time to take these nutrients/botanicals in order to prevent or treat common colds. Evidence-Based Complementary and Alternative Medicine 2018: 1–36
6. Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, Bhattoa HP (2020) Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nutrients 12: 988.
7. Herr C, Shaykhiev R, Bals R (2007) The role of cathelicidin and defensins in pulmonary inflammatory diseases. Expert Opin Biol Ther 7: 1449–1461.
8. Charan J, Goyal JP, Saxena D, Yadav P (2012) Vitamin D for prevention of respiratory tract infections: A systematic review and meta-analysis. J Pharmacol Pharmacother 3: 300–303.
9. McCartney DM, Byrne DG (2020) Optimisation of Vitamin D Status for Enhanced Immuno-protection Against Covid-19. Ir Med J 113: 58
10. Zhou Y-F, Luo B-A, Qin L-L (2019) The association between vitamin D deficiency and community-acquired pneumonia: A meta-analysis of observational studies. Medicine (Baltimore) 98: e17252.
11. Daneshkhah A, Agrawal V, Eshein A, Subramanian H, Roy HK, Backman V (2020) The possible role of vitamin D in suppressing cytokine storm and associated mortality in COVID-19 patients. medRxiv 2020.04.08.20058578.
12. Smet DD, Smet KD, Herroelen P, Gryspeerdt S, Martens GA (2020) Vitamin D deficiency as risk factor for severe COVID-19: a convergence of two pandemics. medRxiv 2020.05.01.20079376.
13. Raharusun P, Priambada S, Budiarti C, Agung E, Budi C (2020) Patterns of COVID-19 mortality and vitamin D: an Indonesian study. SSRN Electronic Journal.
14. Hastie CE, Mackay DF, Ho F, Celis-Morales CA, Katikireddi SV, Niedzwiedz CL, Jani BD, Welsh P, Mair FS, Gray SR, O'Donnell CA, Gill JMR, Sattar N, Pell JP (2020) Vitamin D concentrations and COVID-19 infection in UK Biobank. Diabetes Metab Syndr 14: 561–565.
15. Martín Giménez VM, Inserra F, Tajer CD, Mariani J, Ferder L, Reiter RJ, Manucha W (2020) Lungs as target of COVID-19 infection: Protective common molecular mechanisms of

vitamin D and melatonin as a new potential synergistic treatment. Life Sci 254: 117808.
16. Grunewald ME, Shaban MG, Mackin SR, Fehr AR, Perlman S (2020) Murine coronavirus infection activates the aryl hydrocarbon receptor in an indoleamine 2,3-dioxygenase-independent manner, contributing to cytokine modulation and proviral TCDD-inducible-PARP expression. J Virol 94: e01743-19.
17. Reiter RJ, Abreu-Gonzalez P, Marik PE, Dominguez-Rodriguez A (2020) Therapeutic algorithm for use of melatonin in patients with COVID-19. Front Med (Lausanne) 7: 226.
18. Instituto de Investigación Hospital Universitario La Paz (2021) Multicenter randomized controlled trial of the efficacy of melatonin in the prophylaxis of SARS-coronavirus-2 infection among high risk contacts. clinicaltrials.gov. Available https://clinicaltrials.gov/ct2/show/NCT04353128. Accessed: 24 April 2022.
19. Colunga Biancatelli RML, Berrill M, Mohammed YH, Marik PE (2020) Melatonin for the treatment of sepsis: the scientific rationale. J Thorac Dis 12: S54–S65.
20. Carr AC, Rosengrave PC, Bayer S, Chambers S, Mehrtens J, Shaw GM (2017) Hypovitaminosis C and vitamin C deficiency in critically ill patients despite recommended enteral and parenteral intakes. Crit Care 21: 300.
21. Hemilä H, Chalker E (2013) Vitamin C for preventing and treating the common cold. Cochrane Database Syst Rev CD000980.
22. Feyaerts AF, Luyten W (2020) Vitamin C as prophylaxis and adjunctive medical treatment for COVID-19? Nutrition 79–80: 110948.
23. Ellulu MS, Rahmat A, Patimah I, Khaza'ai H, Abed Y (2015) Effect of vitamin C on inflammation and metabolic markers in hypertensive and/or diabetic obese adults: a randomized controlled trial. Drug Des Devel Ther 9: 3405–3412.
24. Barnes BJ, Adrover JM, Baxter-Stoltzfus A, Borczuk A, Cools-Lartigue J, Crawford JM, Daßler-Plenker J, Guerci P, Huynh C, Knight JS, Loda M, Looney MR, McAllister F, Rayes R, Renaud S, Rousseau S, Salvatore S, Schwartz RE, Spicer JD, Yost CC, Weber A, Zuo Y, Egeblad M (2020) Targeting potential drivers of COVID-19: Neutrophil extracellular traps. J Exp Med 217: e20200652.
25. Carr AC (2020) A new clinical trial to test high-dose vitamin C in patients with COVID-19. Crit Care 24: 133.
26. Cheng RZ (2020) Can early and high intravenous dose of vitamin C prevent and treat coronavirus disease 2019 (COVID-19)? Med Drug Discov 5: 100028.
27. Adams KK, Baker WL, Sobieraj DM (2020) Myth busters: dietary supplements and COVID-19. Ann Pharmacother 54: 820–826.
28. Baladia E, Pizarro AB, Ortiz-Muñoz L, Rada G (2020) Vitamin C for COVID-19: A living systematic review. Medwave 20: e7978.
29. Chen L, Hu C, Hood M, Zhang X, Zhang L, Kan J, Du J (2020) A novel combination of vitamin C, curcumin and glycyrrhizic acid potentially regulates immune and inflammatory response associated with coronavirus infections: a perspective from system biology analysis. Nutrients 12: 1193.
30. Overbeck S, Rink L, Haase H (2008) Modulating the immune response by oral zinc supplementation: a single approach for multiple diseases. Arch Immunol Ther Exp (Warsz) 56: 15–30.
31. Kumar A, Kubota Y, Chernov M, Kasuya H (2020) Potential role of zinc supplementation in prophylaxis and treatment of COVID-19. Med Hypotheses 144: 109848.
32. World health report (2002) Reducing risks, promoting healthy life. Available: https://www.who.int/publications-detail-redirect/9241562072. Accessed 26 Apr 2022.
33. Denison MR, Zoltick PW, Hughes SA, Giangreco B, Olson AL, Perlman S, Leibowitz JL, Weiss SR (1992) Intracellular processing of the N-terminal ORF 1a proteins of the coronavirus MHV-A59 requires multiple proteolytic events. Virology 189: 274–284.
34. Wessels I, Rolles B, Rink L (2020) The potential impact of zinc supplementation on COVID-19 pathogenesis. Front Immunol 11: 1712.
35. Lopes-Pires ME, Ahmed NS, Vara D, Gibbins JM, Pula G, Pugh N (2021) Zinc regulates reactive oxygen species generation in platelets. Platelets 32: 368–377.
36. Caruso TJ, Prober CG, Gwaltney JM (2007) Treatment of naturally acquired common colds with zinc: a structured review. Clin Infect Dis 45: 569–574.
37. ProgenaBiome (2021) A randomized, double-blind, placebo-controlled phase IIa study of hydroxychloroquine, vitamin C, vitamin D, and zinc for the prevention of COVID-19 infection. Available: https://clinicaltrials.gov/ct2/show/NCT04335084. Accessed: 24 April 2022.
38. Desai M (2021) Coronavirus Disease 2019- Using ascorbic acid and zinc supplementation (COVIDAtoZ) research study a randomized, Open Label Single Center Study. clinicaltrials.gov. Available: https://clinicaltrials.gov/ct2/show/NCT04342728. Accessed: 24 April 2022.
39. University Hospital, Lille (2021) Impact of zinc and vitamin D3 supplementation on the survival of institutionalized aged patients infected with COVID-19. clinicaltrials.gov. Available: https://clinicaltrials.gov/ct2/show/NCT04351490 Accessed: 24 April 2022.

Corresponding author

Dr. Eman El Sabbagh
Assistant lecturer
Hepato-gastroenterology and Endemic Medicine Department,
Faculty of Medicine, Cairo University,
Cairo 12111, Egypt
Tel number: +0201223566200
Fax:(+202) 5326543
Email: eman.elsabbagh@kasralainy.edu.eg

Conflict of interests: No conflict of interests is declared.