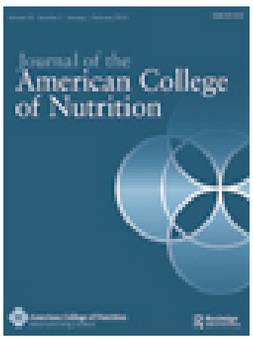

Journal of the American College of Nutrition

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/uacn20

Combating COVID-19 and Building Immune Resilience: A Potential Role for Magnesium Nutrition?

Taylor C. Wallace

To cite this article: Taylor C. Wallace (2020): Combating COVID-19 and Building Immune Resilience: A Potential Role for Magnesium Nutrition?, Journal of the American College of Nutrition, DOI: 10.1080/07315724.2020.1785971

To link to this article: https://doi.org/10.1080/07315724.2020.1785971

JOURNAL OF THE AMERICAN COLLEGE OF NUTRITION
https://doi.org/10.1080/07315724.2020.1785971

Combating COVID-19 and Building Immune Resilience: A Potential Role for Magnesium Nutrition?

Taylor C. Wallace[a,b,c]

[a]Think Healthy Group, Washington, DC, USA; [b]Department of Nutrition and Food Studies, George Mason University, Fairfax, Virginia, USA; [c]Center for Magnesium Education & Research, Pahoa, Hawaii, USA

ABSTRACT

Background: In December 2019, the viral pandemic of respiratory illness caused by COVID-19 began sweeping its way across the globe. Several aspects of this infectious disease mimic metabolic events shown to occur during latent subclinical magnesium deficiency. Hypomagnesemia is a relatively common clinical occurrence that often goes unrecognized since magnesium levels are rarely monitored in the clinical setting. Magnesium is the second most abundant intracellular cation after potassium. It is involved in >600 enzymatic reactions in the body, including those contributing to the exaggerated immune and inflammatory responses exhibited by COVID-19 patients.

Methods: A summary of experimental findings and knowledge of the biochemical role magnesium may play in the pathogenesis of COVID-19 is presented in this perspective. The National Academy of Medicine's Standards for Systematic Reviews were independently employed to identify clinical and prospective cohort studies assessing the relationship of magnesium with interleukin-6, a prominent drug target for treating COVID-19.

Results: Clinical recommendations are given for prevention and treatment of COVID-19. Constant monitoring of ionized magnesium status with subsequent repletion, when appropriate, may be an effective strategy to influence disease contraction and progression. The peer-reviewed literature supports that several aspects of magnesium nutrition warrant clinical consideration. Mechanisms include its "calcium-channel blocking" effects that lead to downstream suppression of nuclear factor-Kβ, interleukin-6, c-reactive protein, and other related endocrine disrupters; its role in regulating renal potassium loss; and its ability to activate and enhance the functionality of vitamin D, among others.

Conclusion: As the world awaits an effective vaccine, nutrition plays an important and safe role in helping mitigate patient morbidity and mortality. Our group is working with the Academy of Nutrition and Dietetics to collect patient-level data from intensive care units across the United States to better understand nutrition care practices that lead to better outcomes.

ARTICLE HISTORY
Received 13 May 2020
Accepted 16 June 2020

KEYWORDS
Magnesium; COVID-19; coronavirus; COVID-19; nutrition; potassium; vitamin D; hypokalemia; hypomagnesemia; inflammation; cytokine

Introduction

In December 2019, the viral pandemic of respiratory illness caused by COVID-19, otherwise known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), from Wuhan, China began sweeping its way across the globe. The current pandemic has led to >7 million confirmed cases and >400,000 deaths worldwide (1). Nutritional care is critical and if not promptly and adequately implemented, malnutrition will negatively impact patients with the infection. Several researchers and scientific groups, notably the Society of Critical Care Medicine (SCCM) and the American Society for Parenteral and Enteral Nutrition (ASPEN) have recently re-emphasized generalized recommendations for nutrition therapy in COVID-19 patients requiring ICU care (2, 3). Multiple micronutrients (e.g., vitamins C and E, copper, zinc, thiamin, carnitine and others), protein and fluid balance are likely all involved in mitigating and treating the inflammatory response induced by COVID-19. However, two unique characteristics exhibited by COVID-19 patients are particularly relevant to magnesium nutrition and warrant further investigation: (1) a cytokine storm manifesting an elevation of interleukin-6 (IL-6) (4) and C-reactive protein; and (2) hypokalemia (5). This perspective encourages that constant monitoring (and documentation) of magnesium status and repletion, when appropriate, may influence immune resilience, as well as patient morbidity and mortality.

Pathology and management of coronaviruses

COVID-19 is a spherical or pleomorphic enveloped, positive-sense, single-stranded RNA betacoronavirus of the family *Coronaviridae* and the order *Nidovirales* (6). Coronaviruses are a large family of viruses that typically cause mild to moderate upper-respiratory tract infections and less common gastro-intestinal infections (7). Most of

CONTACT Taylor C. Wallace, PhD, CFS, FACN taylor.wallace@me.com Think Healthy Group, Inc., 1301 20th Street, NW, #413, Washington, DC 20036
Supplemental data for this article can be accessed at https://doi.org/10.1080/07315724.2020.1785971.

Table 1. Inflammatory mediators stimulated by angiotensin II.

NF-κB	Nuclear factor- κB
I κB	Inhibitor- κB
NADPH oxidase	Reduced nicotinamide-adenine dinucleotide phosphate dehydrogenase
p47(phox)	p47 protein component of NADPH oxidase
TNF-α	Tumour necrosis factor- α
IL-6	Interleukin-6
MCP-1	Monocyte chemoattractant protein-1
ICAM-1	Intracellular adhesion molecule-1
VCAM-1	Vascular cell adhesion molecule-1
ROS	Reactive oxygen species
$O_2^{\cdot}$	Superoxide
TF	Tissue factor
PAI-1	Plasminogen activator inhibitor-1
AP-1	Activator protein-1
MMP	Matrix metalloproteinase
CRP	C-reactive protein
SAA	Serum amyloid A

the hundreds of coronaviruses identified to date circulate predominantly among animals such as pigs, camels, bats and cats (8). Scientists have traditionally considered coronaviruses in humans to be "inconsequential pathogens" due to their minute clinical manifestations (e.g., common cold) in otherwise healthy people(7). However, over the past two decades coronaviruses capable of causing widespread clinical complications and mortality have begun to emerge in humans (9). Four of seven coronaviruses that sicken people have been well documented to cause mild to moderate disease (9). Three coronaviruses have caused more serious, even fatal, disease: 1) SARS-CoV emerged in 2002 causing 8,000 cases with a 10% death rate, 2) Middle East Respiratory Syndrome (MERS)-CoV emerged in 2012 causing 2500 cases with a 36% fatality rate; and 3) the current COVID-19 outbreak emerging in late 2019 (9, 10).

Respiratory failure due to acute respiratory distress syndrome is the leading cause of mortality in patients diagnosed with COVID-19 (11). The nosocomial spread of COVID-19 can be explained through basic virology: the predominant human cell receptor for the virus is the angiotensin-converting enzyme 2 (ACE2), which is mainly expressed in a variety of endothelial cells lining the lung, intestine, kidney and blood vessels (12, 13). ACE2 has recently been shown to be expressed in the oral cavity mucosa and highly enriched within epithelial cells of the tongue (14). This may help explain the potential route of infection given the high expression of ACE2 in type II alveolar cells of the lung and epithelial cells of the upper esophagus (14–17). Most infected individuals experience mild to moderate respiratory illness and recover without requiring special treatment; however, older individuals and those with underlying medical conditions such as obesity, type-2 diabetes and cardiovascular disease are more likely to develop serious and life-threatening illness (18). Available clinical data suggest that there is a mild to severe cytokine release among patients, which increases both morbidity and mortality rates. ACE2 is commonly known for its blood pressure lowering effects, since it catalyzes the hydrolysis of angiotensin II, a vasoconstrictor peptide. Inhibition of ACE2 enhances angiotensin II, with resultant proinflammatory effects due to increases in NADPH oxidase, reactive oxygen species (ROS), phosphorylation of inhibitor-κB (IκB) and nuclear factor-κB (NF-κB), and inflammatory cytokines (e.g., TNFα, IL-6, MCP-1, etc), as well as decreases in endothelial nitric oxide (eNOS) and nitric oxide (NO) bioavailability (19). Table 1 describes inflammatory mediators stimulated by angiotensin II. Release of the virus from the alveolus occurs with an increase in cell permeability and destruction of epithelial cells (20). It then activates both the innate and adaptive immune system. Macrophages and other immune cells capture the virus and as explained above release a large number of cytokines and chemokines, most notably interleukin-6 (IL-6) and C-reactive protein (CRP). Large numbers of erythrocytes and inflammatory exudates then enter the alveoli, eventually causing dyspnea and respiratory failure (20–23). Pulmonary fibrosis and hypertension are common when the proinflammatory cytokine IL-6 is expressed in the lungs (24). High expression of IL-6 other inflammatory cytokines have also been well documented in patients with both SARS-CoV and MERS-CoV (25–27). IL-6 plays an important role in cytokine release and its importance to human metabolism, autoimmune cell differentiation, and disease treatment has been recently reviewed by experts in the field (24). It has broad effects on cells of the immune system and often displays hormone-like attributes that affects homeostatic processes in the body (24). CRP production by the liver is regulated by cytokines, particularly IL-6. IL-6 is now being considered as a prominent target for COVID-19 drug interventions; several pharmacologists and medical experts have suggested Tocilizumab, a drug approved for the treatment of rheumatoid arthritis and juvenile idiopathic arthritis, as a likely effective drug for patients with COVID-19 (28, 29). Tocilizumab works by blocking the IL-6 transduction pathway.

Cytokine-induced malnutrition

Profound metabolic changes occur due to the actions of proinflammatory cytokines, including but not limited to TNF-α, IL-1, IL-6, IL-8, and CRP, all of which seem to be drastically elevated in moderate to severe COVID-19 cases (30, 31). These changes have long been documented to influence energy, fat, carbohydrate, protein, and micronutrient metabolism (32). At the same time, the body's antioxidant defenses become depleted in response to the elevated cytokines, resulting in upregulation of the inflammatory process and localized tissue damage. The immune response exerts a high metabolic and nutritional cost upon the body. Aside from negative nitrogen and mineral balance, overt symptoms such as fever and loss of appetite are directly and indirectly caused by proinflammatory cytokines (33). Thus, the body of an individual infected with COVID-19 primarily relies on essential vitamins and minerals contained within to support its biochemical needs.

Magnesium in human health

Magnesium is the fourth most abundant cation in the human body and the second most abundant intracellular

cation (next to potassium) (34). It is currently among the four nutrients prioritized for Dietary Reference Intake (DRI) reevaluation (35). Enzymatic databases list over 600 enzymes for which magnesium serves as a cofactor, and an additional 200 in which it may act as an activator (36–38). Total body magnesium content is about 24 g (2000 mEq or 1 mol [24 mg magnesium = 2 mEq = 1 mmol]) in a normal human adult. Bone serves as a reservoir and contains 50% to 60% of the body's magnesium (39, 40); approximately one-third of skeletal magnesium is exchangeable when dietary intakes are low (41). The remaining body magnesium is intracellular, with approximately 27% and 20% residing in muscle and soft tissue, respectively (39). Extracellular magnesium accounts for only about 1% of total body magnesium, which is found primarily in the serum and red blood cells (41–43). In the serum, about 32% of magnesium is bound to the protein albumin and ~55% is as the free ionized cation (iMg^{2+}), which is the bioactive form (41, 44).

There is a substantial body of scientific evidence that demonstrates an individual's magnesium requirement and status are affected by multiple factors, including to sex, age, race, body weight, lean body mass, energy needs, and the intake of other minerals, particularly sodium and calcium (45). Approximately 48% of the population in the United States has been shown to consume less than the estimated average requirement (EAR) (46), while three-fourths fail to meet the recommended dietary allowance (RDA) (47). It should be noted that these estimates are based on values published by a the National Academies of Sciences, Engineering and Medicine (NASEM) DRI Committee in 1997 and are based on average body weight values for men and women that are lower than the current population average (48, 49). Racial and ethnic differences in magnesium intake also exist (50).

Hypomagnesaemia if not properly diagnosed and treated can be a severe and potentially fatal complication. Deficiency can be present despite normal total serum magnesium levels (45, 51). Normal total serum magnesium concentrations range between 1.7 – 2.2 mg/dL (or 1.5 – 1.9 mEq/L or 0.75 – 0.95 mmol/L), regardless of age (39, 42). However, this reference interval was established using distribution of total serum magnesium among participants enrolled in the NHANES I (1974 – 1974) dataset, rather than clinical outcomes (42). Whole blood iMg $(2)^{+}$ has recently been suggested as a more sensitive measure of acute oral intake of magnesium compared to total serum and urinary magnesium and may therefore be preferred for assessing patient status (52). Normal iMg $(2)^{+}$ values range between 0.42 and 0.59 mmol/L (53), although this interval has not been universally adopted and again, is based on distribution in the normal "healthy" population vs. the relation of iMg^{2+} with clinical outcomes. Hypomagnesemia is a relatively common occurrence in clinical medicine that often goes unrecognized since magnesium levels are rarely monitored in the clinical setting. Prevalence (measuring total serum magnesium) varies from one study to another, with a wide range from 11 to 61% (54–59). Many studies have showed good relationships between iMg^{2+} and total serum magnesium in healthy adult populations, however total serum magnesium seems to be a weak predictor of ionized hypomagnesemia in hospitalized or critically ill patients. More than half of patients admitted to the intensive care unit (ICU) with ionized hypomagnesemia have normal serum magnesium status (n = 446) (53). 60% of critically ill children with ionized hypomagnesemia were shown to have normal total serum magnesium status, although the study population was relatively small (n = 24) (60). Measuring whole blood iMg^{2+} is likely the superior marker of status in COVID-19 patients given the enhanced sensitivity to changes in oral intake (52) and demonstrated association with commonly used medications such as diuretics (53) that are more likely to be taken by subpopulations at increased risk of infection.

Clinical magnesium deficiency due to low dietary intake in otherwise healthy people is relatively uncommon since the kidneys tightly regulate urinary excretion (42, 61). This type of deficiency is easily diagnosed due to obvious symptoms such as weakness, confusion, and if extreme, convulsions and uncontrollable muscle contractions (34). Subclinical magnesium deficiency has been shown to be a more common occurrence in healthy populations and is associated with an increase in low-grade chronic inflammation. Limiting dietary intake in animals demonstrates similar results on low-grade chronic inflammation (62). Several markers of endothelial dysfunction and systemic inflammation (e.g., IL-6, TNF-α, soluble intracellular adhesion molecule 1, soluble vascular cell adhesion molecule 1, and CRP) have shown inverse relationships with low magnesium intake (42). Recent systematic reviews of randomized, controlled trials illustrate inverse relationships of magnesium supplementation with circulating CRP levels, with larger magnitudes of effect among individuals with elevated inflammatory status (63,64). Co-supplementation of magnesium and zinc have also been shown to lower circulating CRP levels in women with polycystic ovary syndrome, in addition to enhancing plasma antioxidant capacity and downregulating genes controlling the expression of IL-1 and TNF-α (65). Magnesium has a known "calcium-channel blocking" effect – the mineral can inhibit calcium (Ca^{+2}) influx in immunocompetent cells, which limits nuclear factor-κB (NF-κB) activation, cytokine production and resulting systemic inflammation (62, 66). The hallmark downstream effect of NF-κB activation is the production of proinflammatory cytokine IL-6. IV infusion of magnesium has been proposed as an emergent treatment for use in acute asthma exacerbations (primarily an inflammatory disease) given the nutrient's demonstrated role in attenuating neutrophil respiratory burst and superoxide (O_2-) production (67). Short-term exposure to magnesium sulfate has been shown to effectively reduce the frequency of monocytes producing TNF-α and IL-6 under constructive and toll-like receptor stimulated conditions, decreasing cytokine gene and protein expression (66).

Magnesium as a modulator of IL-6 levels

Experimentally induced magnesium deficiency in rodent models has been widely shown to elicit an inflammatory response, characterized with increases in plasma hs-CRP and

IL-6 levels (42, 62, 68). Cross-sectional studies also indicate inverse relationships between magnesium intake, status and serum IL-6 concentration (69, 70). However, knowledge of the relationship between magnesium and IL-6 is limited as a comprehensive or systematic review of the literature is currently absent. To support this perspective, methods for conducting systematic review outlined by the National Academy of Medicine's Standards for Systematic Reviews (71) were independently employed to identify clinical and prospective cohort studies in the peer-reviewed scientific literature. Detailed methods can be found in Supplementary Tables 1–2 and Supplementary Figure 1. A total of 11 clinical studies that administered magnesium in oral (n = 6) and intravenous (n = 5) form, as well as 1 prospective cohort study were identified from the literature search (Supplemental Table 3) (72–83). Magnesium intake or infusion was associated with significant decreases in IL-6 across diverse patient populations, in all but three studies; however most did not have adequate statistical power. Of the three studies not showing statistically significant decreases in IL-6, two showed borderline statistical significance ($p = 0.08$) with participants having very low baseline levels (79, 81). A third study in liver transplant patients showed that 35 mg/kg magnesium sulfate infusion increased IL-6 after 30-minutes and noted that while normomagnesemia has a protective role against harmful inflammatory reactions that over-normalization of magnesium status can cause peripheral vasodilation and should be avoided. Only two of the included studies had patients with significantly elevated IL-6 levels from a clinical perspective (73, 76). Rashvand et al., 2019 showed modest ~12% improvements in IL-6 after oral administration of 500 mg magnesium per day as magnesium oxide for 2-months in type-2 diabetic patients, as compared to the placebo. Interestingly, co-administration of magnesium and choline showed a ~17% reduction in IL-6 in this multi-arm RCT with a parallel design (73). Mojtahedzadeh et al. 2016 administered 10 g intravenous magnesium sulfate 36-hours post-surgical correction of acute aortic aneurysm in a RCT with a parallel design (n = 18). Even though large differences in IL-6 were noted, particularly after 12-hours, baseline levels were almost double in the intervention vs. control and both groups showed large decreases in IL-6 over the 36-hour period (76). Magnesium infusions present a greater risk compared to dietary intake, but allow for more rapid repletion during an emergency situation, such as initiation of a cytokine storm. Dietary intake of magnesium through food and modest supplementation during the early stages of infection (when symptoms are mild) is safe and may have potential to benefit the patient. Both scenarios require future clinical research and our team will be collaborating with the Academy to collect patient level data on this topic through the Academy of Nutrition and Dietetics Health Informatics Infrastructure (ANDHII).

Electrolyte interrelationships: Hypokalemia and hypomagnesemia

Hypokalemia has been shown to be largely prevalent among critically ill COVID-19 patients (5). A recent report from China showed that 93% of severe and critically ill patients suffering from COVID-19 had hypokalemia (5); unfortunately magnesium status was not assessed among this population. The major imbalance in the renin-angiotensin system caused by the downregulation of ACE2 is a critical element of unfavorable evolution in patients with COVID-19. Hypokalemia appears to be a biomarker of imbalance, where diminished urinary potassium loss and response to intravenous potassium indicate restored ACE2 functionality (84). Supportive of this notion, severe hypokalemic patients administered 3 g potassium per day of (average 34 g during hospital stay) reported that patients responded well to the when they were inclined to recovery (5). Hypokalemia, defined as a serum potassium concentration of less than 3.5 mEq/L, is one of the most frequent fluid and electrolyte abnormalities documented in the clinical setting. Hypokalemia is a common finding in patients with hypomagnesemia; about half of patients with clinically defined potassium deficiency also have depleted magnesium levels (85), although as previously discussed the serum level used to define deficiency has varied across studies (0.6 to 0.75 mmol/L) with some being more conservative than others. Hypomagnesemia contributes to the development and severity of hypokalemia by reducing intracellular potassium concentrations and promoting renal potassium wasting (86). Intracellular potassium concentrations have been suggested to decrease in the presence of hypomagnesemia since low magnesium impairs the function of the sodium-potassium ATPase pump. The renal outer medullary potassium (ROMK) channel exacerbates potassium wasting during magnesium deficiency through increased distal potassium secretion. It should be noted that low intracellular magnesium (caused by magnesium deficiency) does not necessarily cause hypokalemia alone, as increases in distal sodium delivery and aldosterone levels may also have a prominent role in exacerbating potassium wasting during magnesium deficiency (86). Huang and Kuo (2007) provide an extensive review of the scientific literature (86).

Certain medications (e.g., antibiotics, beta 2-receptor antagonists, diuretics, insulin, glucocorticoids, laxatives, etc) may also cause hypokalemia through a variety of mechanisms including intracellular potassium shifting, increased renal loss, and decreased intestinal uptake (87). Deficiency in magnesium in critically ill patients can not only lead to secondary hypokalemia but also hypocalcemia, accompanied by severe neuromuscular and cardiovascular clinical manifestations. Concurrent magnesium deficiency aggravates hypokalemia and renders it refractory to potassium treatment (86). If the patient is hypomagnesemic or has borderline low-normal serum concentrations, treating hypomagnesemia concomitantly with the hypokalemia is appropriate to prevent serum potassium levels from falling below the normal range after discontinuation of potassium therapy. In critically ill patients with mild to moderate hypomagnesemia, administration of 1 g (8 mEq) of intravenous magnesium will increase serum concentrations by 0.15 mEq/L within 18 to 30 hours (Table 2) (88). Severe cases may require treatment with a higher dosage. Since magnesium slowly distributes into the tissues and

Table 2. Intravenous dosing of potassium and magnesium in patients with normal renal function.

Dosing of potassium chloride		
Serum K (mEq/L)	Dose (mEq)	Laboratory Work
3.5 – 3.9[a]	40 (x 1)	Assess basal metabolic profile and check magnesium status next morning.
3.0 – 3.4	40 (x 2)	Assess basal metabolic profile and check magnesium status next morning; may wish to assess potassium status 2-hours after second 40 mEq bolus, especially if losses are suspected to be high. Reassess
2.0 – 2.9	40 (x 3+)	Assess potassium status 2-hours after second 40 mEq infusion and reassess; may need 1 – 2 additional boluses; repeat. Check magnesium status. Reassess.
Dosing of Magnesium Gluconate		
Serum Mg (mg/dL)	**Dose (g/kg)**	
1.6 – 1.8	0.05	
1.0 – 1.5	0.1	
<1.0	0.15	

Adapted with permission from Dickerson 2001 (89).

[a]Some clinicians choose not to provide any potassium for a serum concentration of 3.5–3.9 mEq/L, depending on the clinical scenario.

Note: These doses are based on "average sized" adults and should not be used for patients with renal impairment or adrenal insufficiency. Always examine magnesium status in any patient who is hypokalemic. Increase the amount of potassium in the IV/parental nutrition solutions if possible. Be sure to check arterial pH level to ascertain whether any aberrations in serum potassium are due to an abnormal pH.

is rapidly excreted by the kidneys, infusion time is crucial. Magnesium administration should be carefully done in patients with moderate to severe CKD at dose reductions of 50-75%. Suggested intravenous dosing guidelines for patients of average size with normal renal function are given in Table 2, adopted from Dickerson 2001 (89).

Vitamin D, respiratory infections, and the role of magnesium

Vitamin D has been shown to reduce the risk of infections through multiple mechanisms including the induction of cathelicidins and defensins that reduce viral replication rates and concentrations of several proinflammatory cytokines that lead to inflammation and injury of the lungs (90). A high-quality systematic review and meta-analysis of 25 RCTs recently showed supplementation to protect against respiratory infection. Patients who were "*very vitamin D deficient*" and those not receiving a bolus dose experienced the most benefit (91). Supplementation with 20 μg (800 IU) per day was shown to be the most effective with a goal of raising serum 25(OH)D levels to $\geq$ 25 nmol/L. No additional benefits were shown with higher levels of supplementation (91). Since the onset of COVID-19, a growing number of retrospective observational investigations of patient medical records from around the globe have consistently identified low vitamin D status to be prevalent in those with COVID-19 (92–98). A study of 20 European countries found vitamin D status to be related to risk of mortality from infection (94). Status was also shown to be lower among older patients (94), which is consistent with the previously published vitamin D literature (99). Serum 25-dihydroxyvitamin D (25OHD) levels below 30 ng/mL were strongly associated with an increase in COVID-19 mortality in Indonesia. India provided consistent data to that from Indonesia indicating that serum 25OHD levels <30 ng/mL to be strongly associated with risk of death from COVID-19, after controlling for age, gender and comorbidities (97). Data from the Philippines indicate that for each standard deviation increase in serum 25OHD the odds of having a mild vs. critical outcome increased by 19.61 times (OR: 0.126, $p < 0.001$, n = 212) (96). The underlying mechanisms for which vitamin D status influences risk of COVID-19 infection, severity and mortality has not been fully elucidated. The most notable hypothesis is the potential link of vitamin D as an inverse endocrine regulator of the renin-angiotensin system. In animal studies vitamin D acts as a down-regulator of renin (100). Vitamin D receptor (VDR) knockout mice have significantly elevated renin and angiotensin II concentrations. These mice also develop hypertension and target-organ-damage (101, p. 25) similar to patients with severe COVID-19.

CRP has been suggested to be a valuable biomarker to anticipate the COVID-19 disease progression in non-severe adult cases. Elevated CRP levels have been shown to rise in non-severe patients prior to disease progression (102). Vitamin D has been suggested to suppress CRP and the cytokine storm in COVID-19 patients. CRP has also been suggested to be a surrogate marker for vitamin D deficiency (98). It is also noteworthy to mention that the active form of vitamin D (calcitriol or 1,25-dihydroxycholecalciferol) is a steroid hormone that acts as an immune system modulator by down-regulating expression of inflammatory cytokines, while enhancing macrophage function (99).

Several steps in vitamin D metabolism are dependent on magnesium as a cofactor, such as:

- Binding of vitamin D to vitamin D binding protein (VDBP)
- 25(OH)D synthesis
- 1,25(OH)D synthesis
- 25-hydroxylase synthesis

- Vitamin D receptor (VDR) activation for cellular effects (103, 104)

Magnesium deficiency can decrease parathyroid hormone synthesis and secretion, and also the number of available VDRs in target cells (104–108). Serum 1,25(OH)D often remains low in patients with magnesium deficiency despite vitamin D intake (103, 104, 109, 110). The role of magnesium in vitamin D activation and function has recently described in detail by experts in the field (111).

A recent retrospective observational investigation of COVID-19 patients found significantly fewer hospitalized patients age ≥50 years receiving daily oral vitamin D_3 (1000 IU), magnesium (150 mg), and vitamin B12 (500 μg) supplementation for up to 14-days (n = 3/17) required subsequent oxygen therapy compared to controls (16/26). Multivariate analyses showed supplementation to be a significant protective factor against clinical deterioration after adjusting for age, gender and comorbidities (HR: 0.152, 95% CI: 0.025 − 0.930, $p = 0.041$) (112).

Clinical recommendations

Concurrent vitamin D and magnesium supplementation may be critical for prevention and treatment of COVID-19. Consuming nutrient-dense foods that follows patterns current recommended U.S. dietary guidelines is critical for supporting immune system resilience. Normal healthy individuals taking precaution to prevent infection or those experiencing mild COVID-19 symptoms may consider daily supplementation with ≤350 mg of magnesium, particularly if dietary intake is low. Modest daily over-the-counter supplementation with vitamin D_2 or D_3 should remain under the current UL of 4000 IU per day (99), unless otherwise prescribed by a credentialed medical professional.

Critical care teams in the ICU may wish to consider magnesium infusion in COVID-19 patients with moderate to severe hypokalemia, cytokine storm, or suspected hypomagnesemia. Usual adult dose for treating hypomagnesemia is 1 g (8 mEq) of intravenous magnesium every 6-hours for 4 doses (mild hypomagnesemia) or as much as 250 mg/kg within a 4-hour period (severe hypomagnesemia). Appropriate diluents include 5% dextrose or 0.9% sodium chloride. Caution should be used to prevent exceeding renal excretory capacity (separate recommendations may exist for patients with impaired kidney function). When possible, whole blood ionized magnesium (vs. serum magnesium) has been demonstrated to be a more sensitive indicator of magnesium of a patient's status (52). Clinicians should also use treatment with magnesium as concurrent with potassium repletion, when appropriate. See additional suggestions for intravenous potassium and magnesium repletion in Table 2. Monitor and replete a patient's 25OHD status to ≥30 ng/mL through your institution's standard protocol(s).

Acknowledgments

The author thanks Andrea Rosanoff and Rebecca Costello for their expert input and critique of the draft manuscript prior to submission.

Disclosure statement

TCW declares no funding or support for the work. TCW is a co-investigator on an investigator-initiated unrestricted educational grant from New Capstone, Inc. to study the bioavailability of a new picometer-sized magnesium (ReMag®) supplement. TCW is a Senior Fellow of the Center for Magnesium Education & Research but does not receive financial compensation in this role.

Author contributions

TCW wrote the manuscript and is solely responsible for its contents. He has read, reviewed, and approved the final submission.

ORCID

Taylor C. Wallace http://orcid.org/0000-0002-9403-2745

References

1. Johns Hopkins University. COVID-19 Dashboard by the Center for Systems Science and Engineering. Coronavirus Resource Center; 2020 Apr 21 [accessed 2020 Apr 21]. https://coronavirus.jhu.edu/map.html.
2. Martindale R, Patel JJ, Taylor B, Warren M, McClave SA. Nutrition therapy in the patient with COVID-19 disease requiring ICU care: joint recommendations from SCCM and ASPEN. Crit Care Med.; 2020 [accessed 2020 Apr 21]. https://www.sccm.org/getattachment/Disaster/Nutrition-Therapy-COVID-19-SCCM-ASPEN.pdf?lang=en-US
3. Laviano A, Koverech A, Zanetti M. Nutrition support in the time of SARS-CoV-2 (COVID-19). Nutrition. 2020;74:110834. doi:10.1016/j.nut.2020.110834.
4. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033–4. doi:10.1016/S0140-6736(20)30628-0.
5. Chen D, Li X, Qifa s, Hu C, Su F, Dai J. Hypokalemia and clinical implications in patients with coronavirus disease 2019 (COVID-19). Infectious Diseases (except HIV/AIDS). 2020. doi:10.1101/2020.02.27.20028530.
6. Mousavizadeh L, Ghasemi S. Genotype and phenotype of COVID-19: their roles in pathogenesis. J Microbiol Immunol Infect. 2020. doi:10.1016/j.jmii.2020.03.022.
7. Paules CI, Marston HD, Fauci AS. Coronavirus infections—more than just the common cold. JAMA. 2020;323(8):707. doi:10.1001/jama.2020.0757.
8. Salata C, Calistri A, Parolin C, Palù G. Coronaviruses: a paradigm of new emerging zoonotic diseases. Pathog Dis. 2019;77(9). doi:10.1093/femspd/ftaa006.
9. National Institute of Allergy and Infectious Diseases. Coronaviruses; 2020 [accessed 2020 Apr 13]. https://www.niaid.nih.gov/diseases-conditions/coronaviruses.
10. de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. Nat Rev Microbiol. 2016;14(8):523–34. doi:10.1038/nrmicro.2016.81.
11. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020;46(6):1294–7. doi:10.1007/s00134-020-05991-x.
12. Hamming I, Timens W, Bulthuis M, Lely A, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor

for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004;203(2):631–7. doi:10.1002/path.1570.
13. Ciaglia E, Vecchione C, Puca AA. COVID-19 infection and circulating ACE2 levels: protective role in women and children. Front Pediatr. 2020;8. doi:10.3389/fped.2020.00206.
14. Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, Li T, Chen Q. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci. 2020;12(1):8. doi:10.1038/s41368-020-0074-x.
15. Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front Med. 2020;14(2):185–92. doi:10.1007/s11684-020-0754-0.
16. Zhao Y, Zhao Z, Wang Y, Zhou Y, Ma Y, Zuo W. Single-cell RNA expression profiling of ACE2, the receptor of SARS-CoV-2. Bioinformatics. 2020. doi:10.1101/2020.01.26.919985.
17. Zhang H, Kang Z, Gong H, et al. The digestive system is a potential route of 2019-NCov infection: A bioinformatics analysis based on single-cell transcriptomes. Microbiology. 2020. doi:10.1101/2020.01.30.927806.
18. World Health Organization. Coronavirus disease (COVID-2019) R&D; 2020 [accessed 2020 Apr 13]. https://www.who.int/blueprint/priority-diseases/key-action/novel-coronavirus/en/.
19. Dandona P, Dhindsa S, Ghanim H, Chaudhuri A. Angiotensin II and inflammation: the effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockade. J Hum Hypertens. 2007;21(1):20–7. doi:10.1038/sj.jhh.1002101.
20. Zhang C, Wu Z, Li J-W, Zhao H, Wang G-Q. The cytokine release syndrome (CRS) of severe COVID-19 and interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality. Int J Antimicrob Agents. 2020;55(5):105954. doi:10.1016/j.ijantimicag.2020.105954.
21. Leiva-Juárez MM, Kolls JK, Evans SE. Lung epithelial cells: therapeutically inducible effectors of antimicrobial defense. Mucosal Immunol. 2018;11(1):21–34. doi:10.1038/mi.2017.71.
22. Knudsen L, Ochs M. The micromechanics of lung alveoli: structure and function of surfactant and tissue components. Histochem Cell Biol. 2018;150(6):661–76. doi:10.1007/s00418-018-1747-9.
23. Brune K, Frank J, Schwingshackl A, Finigan J, Sidhaye VK. Pulmonary epithelial barrier function: some new players and mechanisms. Am J Physiol Lung Cell Mol Physiol. 2015;308(8):L731–45. doi:10.1152/ajplung.00309.2014.
24. Hunter CA, Jones SA. IL-6 as a keystone cytokine in health and disease. Nat Immunol. 2015;16(5):448–57. doi:10.1038/ni.3153.
25. Castilletti C, Bordi L, Lalle E, Rozera G, Poccia F, Agrati C, Abbate I, Capobianchi MR. Coordinate induction of IFN-alpha and -gamma by SARS-CoV also in the absence of virus replication. Virology. 2005;341(1):163–9. doi:10.1016/j.virol.2005.07.015.
26. Shi S-Q, Peng J-P, Li Y-C, Qin C, Liang G-D, Xu L, Yang Y, Wang J-L, Sun Q-H. The expression of membrane protein augments the specific responses induced by SARS-CoV nucleocapsid DNA immunization. Mol Immunol. 2006;43(11):1791–8. doi:10.1016/j.molimm.2005.11.005.
27. Tseng C-T, Perrone LA, Zhu H, Makino S, Peters CJ. Severe acute respiratory syndrome and the innate immune responses: modulation of effector cell function without productive infection. J Immunol. 2005;174(12):7977–85. doi:10.4049/jimmunol.174.12.7977.
28. Navarro G, Taroumian S, Barroso N, Duan L, Furst D. Tocilizumab in rheumatoid arthritis: a meta-analysis of efficacy and selected clinical conundrums. Semin Arthritis Rheum. 2014;43(4):458–69. doi:10.1016/j.semarthrit.2013.08.001.
29. Yokota S, Miyamae T, Imagawa T, Iwata N, Katakura S, Mori M, Woo P, Nishimoto N, Yoshizaki K, Kishimoto T, et al. Therapeutic efficacy of humanized recombinant anti-interleukin-6 receptor antibody in children with systemic-onset juvenile idiopathic arthritis. Arthritis Rheum. 2005;52(3):818–25. doi:10.1002/art.20944.
30. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506. doi:10.1016/S0140-6736(20)30183-5.
31. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'cytokine storm' in COVID-19. J Infect. 2020;80(6):607–13. doi:10.1016/j.jinf.2020.03.037.
32. Beisel WR. Herman Award Lecture, 1995: infection-induced malnutrition-from cholera to cytokines. Am J Clin Nutr. 1995;62(4):813–9. doi:10.1093/ajcn/62.4.813.
33. Grimble RF. Basics in clinical nutrition: main cytokines and their effect during injury and sepsis. e-SPEN Eur e-J Clin Nutr Metab. 2008;3(6):e289–92. doi:10.1016/j.eclnm.2008.07.002.
34. Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. National Academies Press (US); 1997 [accessed 2019 Sep 30]. http://www.ncbi.nlm.nih.gov/books/NBK109825/.
35. U.S. Department of Health and Human Services. Nutrient assessment for DRI review; 2014 [accessed 2020 Apr 13]. https://health.gov/our-work/food-nutrition/dietary-reference-intakes-dris/nutrient-assessment-dri-review.
36. de Baaij JHF, Hoenderop JGJ, Bindels R. Magnesium in man: implications for health and disease. Physiol Rev. 2015;95(1):1–46. doi:10.1152/physrev.00012.2014.
37. Bairoch A. The ENZYME database in 2000. Nucleic Acids Res. 2000;28(1):304–5. doi:10.1093/nar/28.1.304.
38. Caspi R, Altman T, Dreher K, Fulcher CA, Subhraveti P, Keseler IM, Kothari A, Krummenacker M, Latendresse M, Mueller LA, et al. The MetaCyc database of metabolic pathways and enzymes and the BioCyc collection of pathway/genome databases. Nucleic Acids Res. 2012;40(Database issue):D742–53. doi:10.1093/nar/gkr1014.
39. Elin RJ. Assessment of magnesium status. Clin Chem. 1987;33(11):1965–70.
40. Wallach S. Availability of body magnesium during magnesium deficiency. Magnesium. 1988;7(5-6):262–70.
41. Elin RJ. Laboratory tests for the assessment of magnesium status in humans. Magnes Trace Elem. 1991;10(2-4):172–81.
42. Costello RB, Elin RJ, Rosanoff A, Wallace TC, Guerrero-Romero F, Hruby A, Lutsey PL, Nielsen FH, Rodriguez-Moran M, Song Y, et al. Perspective: the case for an evidence-based reference interval for serum magnesium: the time has come. Adv Nutr. 2016;7(6):977–93. doi:10.3945/an.116.012765.
43. Kielstein JT, David S. Magnesium: the "earth cure" of AKI? Nephrol Dial Transplant. 2013;28(4):785–7. doi:10.1093/ndt/gfs347.
44. Vormann J. Magnesium: nutrition and metabolism. Mol Aspects Med. 2003;24(1-3):27–37. doi:10.1016/S0098-2997(02)00089-4.
45. Cao S, Hodges JK, McCabe LD, Weaver CM. Magnesium requirements in children: recommendations for reevaluation and comparison with current evidence for adults. Nutr Today. 2019;54(5):195–206. doi:10.1097/NT.0000000000000363.
46. Moshfegh AJ, Goldman J, Ahuja J, Rhodes D, Lacomb R. What we eat in America, NHANES 2005-2006, usual nutrient intakes from food and water compared to 1997 dietary reference intakes for vitamin D, calcium, phosphorus, and magnesium. U.S. Department of Agriculture, Agriculture Research Service; 2009 [accessed 2019 Aug 1]. https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/0506/usual_nutrient_intake_vitD_ca_phos_mg_2005-06.pdf.
47. World Health Organization, ed. Calcium and magnesium in drinking-water: public health significance. Geneva, Switzerland: World Health Organization; 2009.

48. Fryar CD, Gu Q, Ogden CL, Flegal KM. Anthropometric reference data for children and adults: United States, 2011-2014. Vital Health Stat. 2016;3(39):1–46.
49. Fryar CD, Kruszon-Moran D, Gu Q, Ogden CL. Mean body weight, height, waist circumference, and body mass index among adults: United States, 1999-2000 through 2015-2016. Natl Health Stat Rep. 2018;(122):1–16.
50. Ford ES, Mokdad AH. Dietary magnesium intake in a national sample of U.S. adults. J Nutr. 2003;133(9):2879–82. doi:10.1093/jn/133.9.2879.
51. Rude RK, Kirchen ME, Gruber HE, Stasky AA, Meyer MH. Clinical manifestations of magnesium deficiency. Mineral Electrolyte Metab. 1998;24 (5):314–22. doi:10.1159/000057389.
52. Zhan J, Wallace TC, Butts SJ, Cao S, Ansu V, Spence LA, Weaver CM, Gletsu-Miller N. Circulating ionized magnesium as a measure of supplement bioavailability: results from a pilot study for randomized clinical trial. Nutrients. 2020;12(5):1245. doi:10.3390/nu12051245.
53. Soliman HM, Mercan D, Lobo SSM, Mélot C, Vincent J-L. Development of ionized hypomagnesemia is associated with higher mortality rates. Crit Care Med. 2003;31(4):1082–7. doi:10.1097/01.CCM.0000060867.17556.A0.
54. Reinhart RA, Desbiens NA. Hypomagnesemia in patients entering the ICU. Crit Care Med. 1985;13(6):506–7. doi:10.1097/00003246-198506000-00015.
55. Ryzen E, Wagers PW, Singer FR, Rude RK. Magnesium deficiency in a medical ICU population. Crit Care Med. 1985;13(1):19–21. doi:10.1097/00003246-198501000-00006.
56. Rubeiz GJ, Thill-Baharozian M, Hardie D, Carlson RW. Association of hypomagnesemia and mortality in acutely ill medical patients. Crit Care Med. 1993;21(2):203–9. doi:10.1097/00003246-199302000-00010.
57. Huijgen HJ, Soesan M, Sanders R, Mairuhu WM, Kesecioglu J, Sanders GT. Magnesium levels in critically ill patients. What should we measure? Am J Clin Pathol. 2000;114(5):688–95. doi:10.1309/JR9Y-PPTX-AJTC-QDRD.
58. Chernow B, Bamberger S, Stoiko M, Vadnais M, Mills S, Hoellerich V, Warshaw AL. Hypomagnesemia in patients in postoperative intensive care. Chest. 1989;95(2):391–7. doi:10.1378/chest.95.2.391.
59. Guérin C, Cousin C, Mignot F, Manchon M, Fournier G. Serum and erythrocyte magnesium in critically ill patients. Intensive Care Med. 1996;22(8):724–7. doi:10.1007/BF01709512.
60. Fiser RT, Torres A, Butch AW, Valentine JL. Ionized magnesium concentrations in critically ill children. Crit Care Med. 1998;26(12):2048–52. doi:10.1097/00003246-199812000-00039.
61. Ross AC, Caballero B, Cousins RJ, Tucker KL, Ziegler TR. Modern nutrition in health and disease. Wolters Kluwer Health; 2012 [accessed 2020 Apr 13]. https://library.biblioboard.com/content/d7522477-6f1f-4adf-902e-e4d1d17099a5.
62. Nielsen FH. Magnesium, inflammation, and obesity in chronic disease. Nutr Rev. 2010;68(6):333–40. doi:10.1111/j.1753-4887.2010.00293.x.
63. Mazidi M, Rezaie P, Banach M. Effect of magnesium supplements on serum C-reactive protein: a systematic review and meta-analysis. Archiv Med Sci. 2018;14(4):707–16. doi:10.5114/aoms.2018.75719.
64. Simental-Mendia LE, Sahebkar A, Rodriguez-Moran M, Zambrano-Galvan G, Guerrero-Romero F. Effect of magnesium supplementation on plasma C-reactive protein concentrations: a systematic review and meta-analysis of randomized controlled trials. Curr Pharm Des. 2017;23(31):4678–86. doi:10.2174/1381612823666170525153605.
65. Afshar Ebrahimi F, Foroozanfard F, Aghadavod E, Bahmani F, Asemi Z. The effects of magnesium and zinc co-supplementation on biomarkers of inflammation and oxidative stress, and gene expression related to inflammation in polycystic ovary syndrome: a randomized controlled clinical trial. Biol Trace Elem Res. 2018;184(2):300–7. doi:10.1007/s12011-017-1198-5.
66. Sugimoto J, Romani AM, Valentin-Torres AM, Luciano AA, Ramirez Kitchen CM, Funderburg N, Mesiano S, Bernstein HB. Magnesium decreases inflammatory cytokine production: a novel innate immunomodulatory mechanism. J Immunol. 2012;188(12):6338–46. doi:10.4049/jimmunol.1101765.
67. Cairns CB, Krafi M. Magnesium attenuates the neutrophil respiratory burst in adult asthmatic patients. Acad Emerg Med. 1996;3(12):1093–7. doi:10.1111/j.1553-2712.1996.tb03366.x.
68. Nielsen FH. Magnesium deficiency and increased inflammation: current perspectives. J Inflamm Res. 2018;11:25–34. doi:10.2147/JIR.S136742.
69. Chacko SA, Song Y, Nathan L, Tinker L, de Boer IH, Tylavsky F, Wallace R, Liu S. Relations of dietary magnesium intake to biomarkers of inflammation and endothelial dysfunction in an ethnically diverse cohort of postmenopausal women. Diabetes Care. 2010;33(2):304–10. doi:10.2337/dc09-1402.
70. Mahalle N, Garg MK, Kulkarni MV, Naik SS. Relation of magnesium with insulin resistance and inflammatory markers in subjects with known Coronary artery disease. J Cardiovasc Dis Res. 2014;5(1):22–9. doi:10.5530/jcdr.2014.1.4.
71. Institute of Medicine (US) Committee on Standards for Systematic Reviews of Comparative Effectiveness Research. Finding what works in health care: standards for systematic reviews. (Eden J, Levit L, Berg A, Morton S, eds.). National Academies Press (US); 2011 [accessed 2020 Apr 14]. http://www.ncbi.nlm.nih.gov/books/NBK209518/.
72. Bressendorff I, Hansen D, Pasch A. The effect of increasing dialysate magnesium on calciprotein particles, inflammation and bone markers: post hoc analysis from a randomized controlled clinical trial. Nephrol Dial Transplant. 2019. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02005700/full.
73. Rashvand S, Mobasseri M, Tarighat-Esfanjani A. The effects of choline and magnesium co-supplementation on metabolic parameters, inflammation, and endothelial dysfunction in patients with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled trial. J Am Coll Nutr. 2019;38(8):714–721. doi:10.1080/07315724.2019.1599745. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01941545/full.
74. Steward CJ, Zhou Y, Keane G, Cook MD, Liu Y, Cullen T. One week of magnesium supplementation lowers IL-6, muscle soreness and increases post-exercise blood glucose in response to downhill running. Eur J Appl Physiol. 2019;119(11-12):2617–27. doi:10.1007/s00421-019-04238-y.
75. Dmitrasinovic G, Pesic V, Stanic D, Plecas-Solarovic B, Dajak M, Ignjatovic S. ACTH, cortisol and IL-6 levels in athletes following magnesium supplementation. J Med Biochem. 2016;35(4):375–84. doi:10.1515/jomb-2016-0021.
76. Mojtahedzadeh M, Chelkeba L, Ranjvar-Shahrivar M, Najafi A, Moini M, Najmeddin F, Sadeghi K, Barkhordari K, Gheymati A, Ahmadi A, et al. Randomized trial of the effect of magnesium sulfate continuous infusion on IL-6 and CRP serum levels following abdominal aortic aneurysm surgery. Iran J Pharm Res. 2016;15(4):951–6.
77. Zogović D, Pešić V, Dmitrašinović G, Dajak M, Plećaš B, Batinić B, Popović D, Ignjatović S. Pituitary-gonadal, pituitary-adrenocortical hormones and IL-6 levels following long-term magnesium supplementation in male students. J Med Biochem. 2014;33(3):291–8. doi:10.2478/jomb-2014-0016.
78. Chung HS, Park CS, Hong SH, Lee S, Cho M-L, Her Y-M, Sa GJ, Lee J, Choi JH. Effects of magnesium pretreatment on the levels of T helper cytokines and on the severity of reperfusion syndrome in patients undergoing living donor liver transplantation. Magnes Res. 2013;26(2):46–55. doi:10.1684/mrh.2013.0338.
79. Moslehi N, Vafa M, Rahimi-Foroushani A, Golestan B. Effects of oral magnesium supplementation on inflammatory markers in middle-aged overweight women. J Res Med Sci. 2012;17(7):607–14.

80. Muroi C, Burkhardt J-K, Hugelshofer M, Seule M, Mishima K, Keller E. Magnesium and the inflammatory response: potential pathophysiological implications in the management of patients with aneurysmal subarachnoid hemorrhage? Magnes Res. 2012; 25(2):64–71. doi:10.1684/mrh.2012.0314.
81. Simental-Mendía LE, Rodríguez-Morán M, Reyes-Romero MA, Guerrero-Romero F. No positive effect of oral magnesium supplementation in the decreases of inflammation in subjects with prediabetes: a pilot study. Magnes Res. 2012;25(3):140–6. doi: 10.1684/mrh.2012.0322.
82. Kim DJ, Xun P, Liu K, Loria C, Yokota K, Jacobs DR, He K. Magnesium intake in relation to systemic inflammation, insulin resistance, and the incidence of diabetes. Diabetes Care. 2010; 33(12):2604–10. doi:10.2337/dc10-0994.
83. Shibata M, Ueshima K, Harada M, Nakamura M, Hiramori K, Endo S, Sato N, Mukaida H, Suzuki T, Suzuki T, et al. Effect of magnesium sulfate pretreatment and significance of matrix metalloproteinase-1 and interleukin-6 levels in coronary reperfusion therapy for patients with acute myocardial infarction. Angiology. 1999;50(7):573–82. doi:10.1177/000331979905000707.
84. Silhol F, Sarlon G, Deharo J-C, Vaïsse B. Downregulation of ACE2 induces overstimulation of the renin–angiotensin system in COVID-19: should we block the renin–angiotensin system? Hypertens Res. 2020. doi:10.1038/s41440-020-0476-3.
85. Whang R, Whang DD, Ryan MP. Refractory potassium repletion. A consequence of magnesium deficiency. Arch Intern Med. 1992;152(1):40–5.
86. Huang C-L, Kuo E. Mechanism of hypokalemia in magnesium deficiency. J Am Soc Nephrol. 2007;18(10):2649–52. doi:10.1681/ASN.2007070792.
87. Veltri KT, Mason C. Medication-induced hypokalemia. P T Peer Rev J Formul Manag. 2015;40(3):185–90.
88. Hammond DA, Stojakovic J, Kathe N, Tran J, Clem OA, Erbach K, King J. Effectiveness and safety of magnesium replacement in critically ill patients admitted to the medical intensive care unit in an academic medical center: a retrospective, cohort study. J Intensive Care Med. 2019;34(11-12):967–72. doi:10.1177/0885066617720631.
89. Dickerson RN. Guidelines for the intravenous management of hypophosphatemia, hypomagnesemia, hypokalemia, and hypocalcemia. Hosp Pharm. 2001;36(11):1201–8. doi:10.1177/001857870103601111.
90. Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, Bhattoa HP. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nutrients. 2020;12(4): 988. doi:10.3390/nu12040988.
91. Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, Dubnov-Raz G, Esposito S, Ganmaa D, Ginde AA, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. BMJ. 2017;i6583. doi:10.1136/bmj.i6583.
92. Meltzer DO, Best TJ, Zhang H, Vokes T, Arora V, Solway J. Association of vitamin D deficiency and treatment with COVID-19 incidence. Infectious Diseases (except HIV/AIDS). 2020. doi:10.1101/2020.05.08.20095893.
93. D'Avolio A, Avataneo V, Manca A, Cusato J, De Nicolò A, Lucchini R, Keller F, Cantù M. 25-Hydroxyvitamin D concentrations are lower in patients with positive PCR for SARS-CoV-2. Nutrients. 2020;12(5):1359. doi:10.3390/nu12051359.
94. Ilie PC, Stefanescu S, Smith L. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. Aging Clin Exp Res. 2020. doi:10.1007/s40520-020-01570-8.
95. Glicio EJ. Vitamin D level of mild and severe elderly cases of COVID-19: A preliminary report. SSRN; 2020.
96. Alipio M. Vitamin D supplementation could possibly improve clinical outcomes of patients infected with coronavirus-2019 (COVID-2019). SSRN Electron J. 2020. doi:10.2139/ssrn.3571484.
97. Raharusun P, Priambada S, Budiarti C, Agung E, Budi C. Patterns of COVID-19 mortality and vitamin D: an Indonesian study. SSRN Electron J. 2020; doi:10.2139/ssrn.3585561.
98. Daneshkhah A, Agrawal V, Eshein A, Subramanian H, Roy HK, Backman V. The possible role of vitamin D in suppressing cytokine storm and associated mortality in COVID-19 patients. Infectious Diseases (except HIV/AIDS); 2020. doi:10.1101/2020.04.08.20058578.
99. Ross AC, Institute of Medicine (U. S.), eds. Dietary reference intakes: calcium, vitamin D. Washington (DC): National Academies Press; 2011.
100. Li YC. Vitamin D: roles in renal and cardiovascular protection. Curr Opin Nephrol Hypertens. 2012;21(1):72–9. doi:10.1097/MNH.0b013e32834de4ee.
101. Li YC, Kong J, Wei M, Chen Z-F, Liu SQ, Cao L-P. 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. J Clin Invest. 2002;110(2):229–38. doi:10.1172/JCI15219.
102. Guyi W, Chenfang W, Quan Z, Fang W, Bo Y, Jianlei L, Yiming L, Tiao L, Siye Z, Chao W, Guobao W, Yanjun Z. C-reactive protein level may predict the risk of COVID-19 aggravation. Open Forum Infect Dis. 2020;7(5). doi:10.1093/ofid/ofaa153.
103. Zittermann A. Magnesium deficit? Overlooked cause of low vitamin D status? BMC Med. 2013;11:229. doi:10.1186/1741-7015-11-229.
104. Reddy P, Edwards LR. Magnesium supplementation in vitamin D deficiency. Am J Ther. 2019;26(1):e124–32. doi:10.1097/MJT.0000000000000538.
105. Rodríguez-Ortiz ME, Canalejo A, Herencia C, Martínez-Moreno JM, Peralta-Ramírez A, Perez-Martinez P, Navarro-González JF, Rodríguez M, Peter M, Gundlach K, et al. Magnesium modulates parathyroid hormone secretion and upregulates parathyroid receptor expression at moderately low calcium concentration. Nephrol Dial Transplant. 2014;29(2): 282–9. doi:10.1093/ndt/gft400.
106. Risco F, Traba ML. Bone specific binding sites for 1,25(OH)2D3 in magnesium deficiency. J Physiol Biochem. 2004;60(3):199–203. doi:10.1007/bf03167029.
107. McCoy H, Kenney MA. Interactions between magnesium and vitamin D: possible implications in the immune system. Magnes Res. 1996;9(3):185–203.
108. Rude RK, Adams JS, Ryzen E, Endres DB, Niimi H, Horst RL, Haddad JG, Singer FR. Low serum concentrations of 1,25-dihydroxyvitamin D in human magnesium deficiency. J Clin Endocrinol Metab. 1985;61(5):933–40. doi:10.1210/jcem-61-5-933.
109. Lemay J, Gascon-Barré M. Responsiveness of the intestinal 1,25-dihydroxyvitamin D3 receptor to magnesium depletion in the rat. Endocrinology. 1992;130(5):2767–77. doi:10.1210/endo.130.5.1315257.
110. Deng X, Song Y, Manson JE, Signorello LB, Zhang SM, Shrubsole MJ, Ness RM, Seidner DL, Dai Q. Magnesium, vitamin D status and mortality: results from US National Health and Nutrition Examination Survey (NHANES) 2001 to 2006 and NHANES III. BMC Med. 2013;11:187. doi:10.1186/1741-7015-11-187.
111. Uwitonze AM, Razzaque MS. Role of magnesium in vitamin D activation and function. J Am Osteopath Assoc. 2018;118(3): 181–9. doi:10.7556/jaoa.2018.037.
112. Tan CW, Ho LP, Kalimuddin S, et al. A cohort study to evaluate the effect of combination vitamin D, magnesium and vitamin B12 (DMB) on progression to severe outcome in older COVID-19 patients. Infectious Diseases (except HIV/AIDS); 2020. doi:10.1101/2020.06.01.20112334.