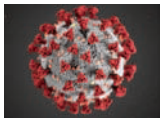

Magnesium and Vitamin D Deficiency as a Potential Cause of Immune Dysfunction, Cytokine Storm and Disseminated Intravascular Coagulation in COVID-19 Patients

by James J. DiNicolantonio, PHarmD & James H. O'Keefe, MD

Patients with COVID-19 who received the magnesium and vitamin D and B12 had an 87% lower risk for requiring oxygen therapy and an 85% lower risk for needing intensive care support.

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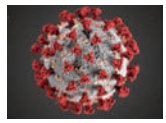
Abstract

Magnesium and vitamin D each have the possibility of affecting the immune system and consequently the cytokine storm and coagulation cascade in COVID-19 infections. Vitamin D is important for reducing the risk of upper respiratory tract infections and plays a role in pulmonary epithelial health. While the importance of vitamin D for a healthy immune system has been known for decades, the benefits of magnesium has only recently been elucidated. Indeed, magnesium is important for activating vitamin D and has a protective role against oxidative stress. Magnesium deficiency increases endothelial cell susceptibility to oxidative stress, promotes endothelial dysfunction, reduces fibrinolysis and increases coagulation. Furthermore, magnesium deficient animals and humans have depressed immune responses, which, when supplemented with magnesium, a partial or near full reversal of the immunodeficiency occurs. Moreover, intracellular free magnesium levels in natural killer cells and CD8 killer T cells regulates their cytotoxicity. Considering that magnesium and vitamin D are important for immune function and cellular resilience, a deficiency in either may contribute to cytokine storm in the novel coronavirus 2019 (COVID-19) infection.

Introduction

Approximately half of adults in the United States do not consume the recommended dietary allowance for magnesium.[1] It has been estimated that up to 30% of a given population has subclinical magnesium deficiency based on serum levels and magnesium deficiency can be as high as 80-90% in certain populations when utilizing magnesium load testing.[1] Many factors contribute to magnesium deficiency, including diets with refined and processed foods, chronic disease states (kidney disease, gastrointestinal disorders, cancer), medications (diuretics, insulin, proton pump inhibitors), stress, strenuous exercise, and vitamin D deficiency to name a few.[1] Thus, subclinical



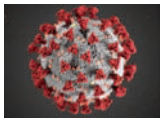
magnesium deficiency is relatively common among the general population and a deficiency in magnesium could impair immune function. This review will cover the potential mechanisms by which magnesium and vitamin D deficiency could drive immune dysregulation contributing to cytokine storm and ultimately endothelial dysfunction in COVID-19 giving rise to disseminated intravascular coagulation (DIC).

Supplementing COVID Patients with Magnesium and Vitamin D May Improve Outcomes

A recent study from Singapore highlights the potential role of magnesium for improving coronavirus (COVID) outcomes.[2] The study was an observational cohort study of consecutive hospitalized COVID-19 patients aged 50 and above in a tertiary academic hospital. Between January 15 and April 15, 2020, 43 consecutive COVID-19 patients aged 50 and above were included in the study. Seventeen patients received magnesium 150 mg, vitamin D3 1,000 IU, and vitamin B12 500 mcg once daily, and 26 patients did not. Baseline demographic characteristics did not significantly differ between the groups. Those who received the magnesium plus vitamin D and B12 had an 87% lower risk for requiring oxygen therapy and an 85% lower risk for needing intensive care support. Moreover, those who did not receive the vitamin/mineral supplement had a 3.5-fold higher rate of needing oxygen therapy throughout hospitalization versus those who received the vitamin/mineral supplement (61.5% vs. 17.6%, p=0.006). The authors concluded, "Magnesium, vitamin D, and B12 combination in older COVID-19 patients was associated with a significant reduction in proportion of patients with clinical deterioration requiring oxygen support and/or intensive care support."[2]

In a preprint, vitamin D insufficiency was identified in 84.6% of severe COVID-19 patients in the intensive care unit.[3] Thus, supplementing COVID-19 patients with vitamin D, especially if they are vitamin D deficient and utilizing concomitant magnesium, which is required to activate vitamin D[4] could provide benefit. Moreover, a recent pilot randomized clinical study in 50 hospitalized COVID-19 patients showed that calcifediol, a hydroxylated analog of vitamin D, significantly reduced the need for intensive care unit treatment compared to those who did not receive calcifediol.[5] This again further supports the idea that vitamin D may be beneficial in COVID-19 patients. To be fair, the group that did not receive calcifediol had a higher percentage of individuals with hypertension and diabetes at baseline, both of which are risk factors for poor COVID-19 outcomes. Thus, this pilot clinical trial would need to be replicated in larger clinical study to confirm these results.

However, several recent studies testing vitamin D supplementation confirm its possibility for utility in COVID-19 patients. The SHADE study gave 60,000 IU/day of vitamin D as a nano-liquid or placebo to 40 asymptomatic or mildly symptomatic COVID patients with vitamin D deficiency.[6] Vitamin D supplementation was given for up to 14 days until a vitamin D blood level of 50 ng/ml was achieved. By day 21, three times as many patients in the vitamin D group were SARS-CoV2 negative (62.5%) vs. placebo (20.8%) ($p < 0.018$, for the difference). Thus, this randomized controlled trial suggests that vitamin D supplementation in vitamin D deficient asymptomatic or mildly symptomatic COVID patients helps to clear the virus quicker. Another study, this time a preprint multicenter, double-blind, randomized controlled trial, gave a single dose of 200,000 IU of vitamin D3 in 240 hospitalized patients with severe COVID.[7] These individuals were far out in their course of COVID, with an average of 10.2 days after symptom onset. Importantly, their average baseline vitamin D levels were not deficient but were insufficient. Despite this, mechanical ventilation was cut in half in the vitamin D group (7%) compared to placebo (14.4%), which just missed statistical significance (p=0.090). Importantly, at baseline, the vitamin D group had a higher percentage of sore throat ($p = 0.026$) and nearly significantly more patients with diabetes ($p = 0.058$). This may have prevented the results from reaching statistical significance.



Magnesium Deficiency Leads to Immune Dysregulation

It was recently discovered that intracellular free magnesium regulates the cytotoxic functions of natural killer (NK) and $CD8^+$ T cells[8] and that decreased intracellular free magnesium causes defective expression of the natural killer activating receptor NKG2D on NK and $CD8^+$ T cells and impairs their cytolytic responses. Decreased intracellular free magnesium levels also causes defective expression of programmed cell death 1 in both NK and $CD8^+$ T cells.[9]

Cytotoxic T cells, also known as $CD8^+$ T cells or killer T cells, kill viruses in a way that leads to a silent apoptotic death.[10] However, when $CD8^+$ T cells lose their cytotoxic activity, this puts a burden on the innate immune cells, such as macrophages and neutrophils, which kill viruses in a proinflammatory way. Furthermore, the reduction in $CD8^+$ T cell viral killing, alongside greater innate immune cell viral killing, leads to an increased death of healthy bystander cells leading to a greater proinflammatory response.[10] Thus, a reduction in $CD8^+$ T cell cytotoxicity appears to be a primary underlying contributor of immune dysfunction and proinflammatory killing that likely increases the risk of cytokine storm in the lungs. Indeed, the functional exhaustion of cytotoxic lymphocytes, such as T lymphocytes and natural killer cells, are correlated with COVID-19 disease progression.[11] Thus, strategies that can improve $CD8^+$ T cell cytotoxicity may have utility by improving RNA viral clearance and reducing inflammatory cytokine storms in the lungs.

Tissue factor expression is a principle initiator of the coagulation cascade and nuclear factor-kappa beta (NF-KB) signaling increases tissue factor expression.[12] This can be inhibited with magnesium supplementation.[13, 14] Lastly, magnesium, likely through its ability to inhibit NF-KB, decreases inflammatory cytokine production from monocytes.[15] Additionally, magnesium deficiency primes leukocyte and macrophage inflammatory responses by increasing cellular calcium levels.[16] All of this suggests that a deficiency in magnesium promotes chronic low-grade inflammation, increased inflammatory responses during viral infections and a pro-thrombotic state.

Patients with genetically low intracellular free magnesium levels secondary to a magnesium transporter deficiency, have uncontrolled chronic Epstein-Barr virus expression and an increased risk of lymphoma.[8] When these individuals are supplemented with magnesium L-threonate, there is a partial restoration in $CD8^+$ T cell cytotoxicity and near complete restoration in NK cell cytotoxicity, along with a reduction in Epstein-Barr viral load and an increase in intracellular free magnesium levels.[8] Thus, genetic intracellular magnesium deficiency leads to acquired human immunodeficiency and can essentially be reversed through magnesium supplementation. Intracellular free magnesium levels also play a key role in the control of hepatitis B viral infection. Indeed, as already discussed, decreased intracellular free magnesium levels causes defective expression of programmed cell death 1 in both NK cells and $CD8^+$ T cells.[9] Lastly, low intracellular free magnesium levels have been found in patients with Type 2 diabetes, which may partially explain their increased susceptibility to RNA viruses.[17]

Magnesium Deficiency Increases Oxidative Stress and Cytokine Storm

Magnesium deficiency leads to increased oxidative stress and intracellular glutathione depletion.[18] There is also an increase in inflammatory cytokine release from monocytes, macrophages and leukocytes during magnesium deficiency,[15,16] whereas magnesium supplementation reduces these effects,[15] which may be due to reduced Nuclear Factor Kappa-Beta (NF-KB) activation. Moreover, magnesium deficiency increases the susceptibility of tissues to oxidative stress[19] and decreases antioxidant defenses,[20] which may increase damage to pulmonary alveoli from cytokine storms during magnesium deficiency. Moreover, magnesium deficiency increases proinflammatory cytokines leading to endothelial dysfunction.[21] Thus, having a low magnesium status may increase the risk for inflammatory cytokine storms, damage to the endothelium and trigger the coagulation cascade leading to disseminated intravascular coagulation (DIC).

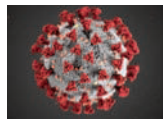


Table 1: Reasons why Magnesium and Vitamin D Deficiency may lead to Immune Dysfunction, Cytokine Storm and Disseminated Intravascular Coagulation in COVID-19 patients

Low intracellular free magnesium levels in NK and $CD8^+$ T cells reduces their cytotoxicity.
Patients with genetically low intracellular free magnesium, who are supplemented with magnesium, have a partial or near complete reversal of dysfunctional NK and $CD8^+$ T cells and a reduced viral load.
Dysfunctional $CD8^+$ T cell cytotoxicity leads to increased proinflammatory death in virally infected cells and healthy bystander cells, as opposed to silent apoptotic death, increasing the risk of cytokine storm in the lungs.
Magnesium activates vitamin D into the hormone calcitriol.
Active vitamin D is required to boost the expression of cathelicidins.
Magnesium deficiency slows fibrinolysis and increases coagulation and thrombosis.
Low magnesium status increases damage to tissues and cellular membranes and reduces antioxidant defense systems leading to increased oxidative stress and damage.
Magnesium deficient animals have a depressed immune response.[45]

Magnesium Deficiency Increases Endothelial Dysfunction and Coagulation

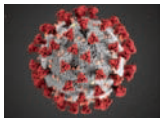
Magnesium deficiency increases the susceptibility of endothelial cells to oxidative damage and promotes endothelial dysfunction,[18, 21] whereas magnesium supplementation improves endothelial function.[22] Magnesium also has antithrombotic effects,[23, 24] reducing ex vivo platelet aggregation and increasing in vivo blood clotting times.[25] Lower serum magnesium is associated with increased thrombotic risk and slowed fibrinolysis[26-28] and low intracellular magnesium promotes platelet-dependent thrombosis.[29] Moreover, magnesium has antithrombotic effects and reduces mortality in in vivo experiments of induced pulmonary thromboembolism.[30] All of this suggests that magnesium deficiency in patients with COVID-19 increases the risk of disseminated intravascular coagulopathy.

Magnesium is Required to Activate Vitamin D

Magnesium is needed to move vitamin D around in the blood and to activate vitamin D.[4] Magnesium deficiency can also reduce active vitamin D (1,25 dihydroxyvitamin D) levels and impair parathyroid hormone response.[31] This may lead to "magnesium-dependent vitamin-D-resistant rickets."[32] Magnesium is also required to inactivate vitamin D when levels become too elevated.[4] Thus, optimal magnesium status is required for optimal vitamin D status.[33] Both magnesium and vitamin D are important to the immune system independently. Together, they may be beneficial in COVID-19 infection because magnesium is necessary to activate vitamin D.

Vitamin D and Its Importance for Immune Health

It is estimated that one billion people worldwide are vitamin D deficient and around half the global population is vitamin D insufficient.[34, 35] Epidemiologically, influenza infection is most common worldwide when vitamin D levels are at their lowest.[36] Vitamin D is a fat-soluble vitamin that plays a major role in immune function. Indeed, vitamin D receptors are expressed on numerous immune cells including B cells, T cells, and antigen presenting cells.[37] Additionally, monocytes, macrophages, dendritic cells, B cells and T cells are capable of converting vitamin D into its active form, calcitriol, modifying the expression of hundreds of genes including those for cytokine production.[36] Indeed, calcitriol has the ability to reduce proinflammatory cytokines and increase anti-inflammatory cytokines.[38] This suggests that maintaining adequate vitamin D levels may be important for reducing inflammatory cytokine storms.



A meta-analysis of 25 randomized controlled trials in over 11,000 participants showed that vitamin D supplementation significantly reduces the risk of acute respiratory infections in the overall population by 12% and in those with profound vitamin D deficiency at baseline (25-hydroxyvitamin D level of < 25 nmol/l) by 70%.[39] These benefits were noted in individuals taking daily or weekly vitamin D supplementation. Another meta-analysis of 11 placebo-controlled trials in 5,660 patients showed that vitamin D supplementation reduced the risk of respiratory tract infections by 36%, with greater benefits in those using once-daily dosing (49% reduction) as compared to bolus doses (14% reduction).[40] Thus, vitamin D supplementation seems to protect against respiratory tract infections with the greatest benefits being found with once daily dosing.

As noted previously, vitamin D insufficiency is highly prevalent in severe COVID-19 patients.[3] This provides sound scientific reasoning for vitamin D supplementation in COVID patients. Patients who have had their vitamin D levels measured in the year before COVID-19 testing, the relative risk of testing positive for COVID-19 was 1.77 times greater for those who were deficient in vitamin D compared to those who were sufficient.[41] Both 25-hydroxyvitamin D_3 and 1,25 dihydroxyvitamin D3 inhibit proinflammatory cytokine release in human monocytes.[34] However, this only seems to occur when vitamin D levels are adequate. Indeed, it was discovered that 15 ng/ml of 25-hydroxyvitamin D_3 (indicating insufficient serum vitamin D levels in humans) was not able to suppress LPS-induced p38 phosphorylation, whereas significant inhibition of LPS-induced p38 phosphorylation was achieved with 30 ng/ml or higher. Importantly, maximum inhibition was achieved with vitamin D levels of 50 ng/ml of 25(OH)D_3. Similarly, a dose-dependent inhibition of LPS-induced p38 activation was observed in human monocytes when the cells were pretreated with active vitamin D. The maximum inhibitory effect was achieved when the cells were preincubated with 0.4 ng/ml of 1,25 dihydroxyvitamin D3.[34] Lipopolysaccharide, can induce inflammatory and procoagulant responses[42] likely through the activation of Toll-like receptor 4 (TLR4).[43] The binding of LPS to TLR4 on monocytes triggers the activation of mitogen-activated protein kinase (MAP kinase), ERK, JNK, p38 and nuclear factor-kappa-B, and regulates proinflammatory cytokine production leading to unresolved inflammation.[34] Mitogen-activated protein kinase phosphatases (MKP) can inactivate MAP kinases and Mitogen-activated protein kinase dual-specificity phosphatase-1 (MKP-1) attenuates p38 activation, which is up-regulated by vitamin D. Furthermore, active vitamin D, which requires magnesium, is needed to boost the expression of antimicrobial cathelicidin peptides, which have numerous antiviral effects.[44] Thus, both vitamin D and magnesium deficiency likely contribute to persistent inflammation independently, and work together, as magnesium is needed to activate vitamin D. Table 1 summarizes the reasons why magnesium and vitamin D deficiency may lead to immune dysfunction, cytokine storm and disseminated intravascular coagulation in COVID-19 patients.

Conclusion

Magnesium and vitamin D supplementation should be considered in the general population with special consideration during the COVID-19 pandemic.

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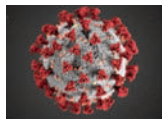

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Disclosure

JJD is Director of Scientific Affairs at Advanced Ingredients for Dietary Products. JHO is an owner of a nutraceutical company. **MM**